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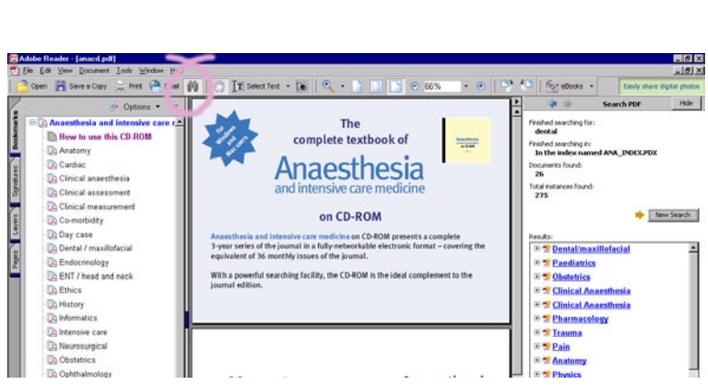

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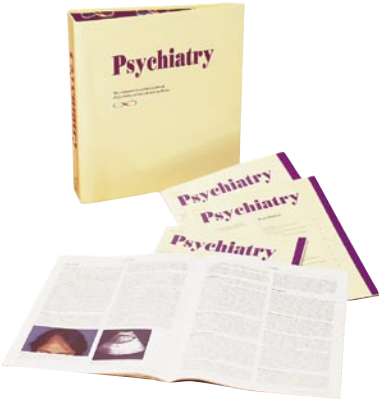

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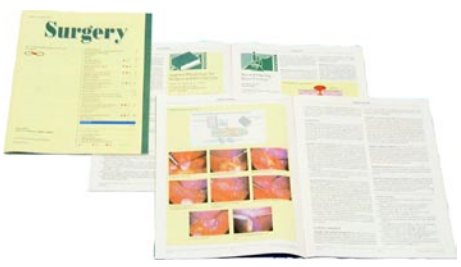

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Anatomy

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The Abdominal Wall and Inguinal Region

John Craven

John Craven was formerly Consultant Surgeon at York District Hospital, York, UK. He trained in Manchester, Uganda and Cardiff. He is past chairman of the primary examiners of the Royal College of Surgeons of England.

Abdominal wall

There is only superficial fascia over the anterior abdominal wall. It is generally fatty but in the lower abdomen there is a deeper membranous layer (Scarpa's fascia) which blends inferiorly with the fascia lata of the upper thigh, invests the penis and scrotum (or labia), before gaining attachment to the ischiopubic rami and the perineal membrane. These attachments define the clinical picture that develops after injury to the posterior urethra when blood and/or urine may extravasate deep to this membranous layer into the perineum and lower abdomen but not into the thigh.

Laterally the anterior abdominal wall consists of three sheet-like muscles in layers, an outer external oblique, a middle internal oblique and an inner transversus abdominis. Each becomes aponeurotic anteriorly and these aponeuroses fuse to form a sheath around the rectus abdominis.

These four muscles form an elastic wall supporting the abdominal viscera. They assist in expiration and expulsive efforts such as defecation, micturition and parturition. They are supplied by the lower five intercostal nerves, the subcostal nerve and the first lumbar nerve. Deep to the muscles lie the transversalis fascia and the peritoneum. The skin of the abdominal wall is supplied by the sixth thoracic to the first lumbar nerves. T6 supplies the epigastric region, T10 the umbilical region and L1 the groin.

Rectus abdominis

These are paired vertical muscles lying in the midline anteriorly enclosed in fibrous sheaths. They extend from the 5th, 6th and 7th costal cartilages and the xiphoid to the pubic crests.

External oblique

From the outer surfaces of the lower eight ribs the fibres descend obliquely downwards to the iliac crest, with a free posterior border. Anteriorly it becomes aponeurotic to form the anterior layer of the rectus sheath and thereby gain attachment to the linea alba, a midline condensation of fibrous tissue, and through it to the body of the pubis. The pubic crest forms the base of a triangular defect in the aponeurosis, the superficial inguinal ring. Between the pubic tubercle and the iliac crest the lower aponeurotic border is thickened to form the inguinal ligament. To the ligament's inner surface is attached laterally the internal oblique and, deep to that, the transverse abdominis.

Internal oblique

Laterally, the internal oblique is attached to the thoracolumbar fascia, the anterior part of the iliac crest and the lateral part of the inguinal ligament. Posteriorly the muscle gains attachment to the costal margin but most fibres pass medially, become aponeurotic and this aponeurosis splits to enclose the upper two-thirds of the rectus abdominis. Inferiorly, the aponeurosis passes anterior to the rectus. Those fibres arising from the inguinal ligament pass medially and arch over the spermatic cord to unite with the transverse abdominis aponeurosis to form the conjoint tendon which gains attachment to the upper surface of the pubis.

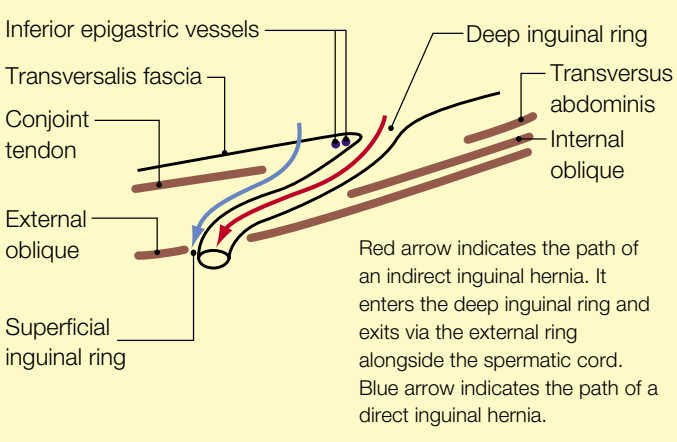
Transversus abdominis

Laterally, the transversus abdominis is attached to the inner surface of the lower six costal cartilages, the thoracolumbar fascia, the anterior iliac crest and the lateral part of the inguinal ligament. Medially, the fibres become aponeurotic and form the posterior part of the rectus sheath. Inferiorly, the aponeurosis blends with that of the internal oblique to form the conjoint tendon.

The inguinal region

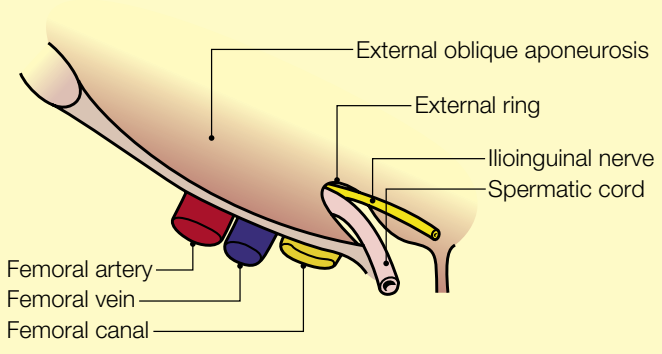
The inguinal canal (Figures 1 and 2) is an oblique path through the lowest part of the anterior abdominal wall. It extends from the deep inguinal ring, a deficiency in the transversalis fascia just above the midpoint of the inguinal ligament, to the superficial inguinal ring, a deficiency in the external oblique aponeurosis, lying above and medial to the pubic tubercle.

Horizontal section through the inguinal canal



1

Inguinal canal showing anterior wall



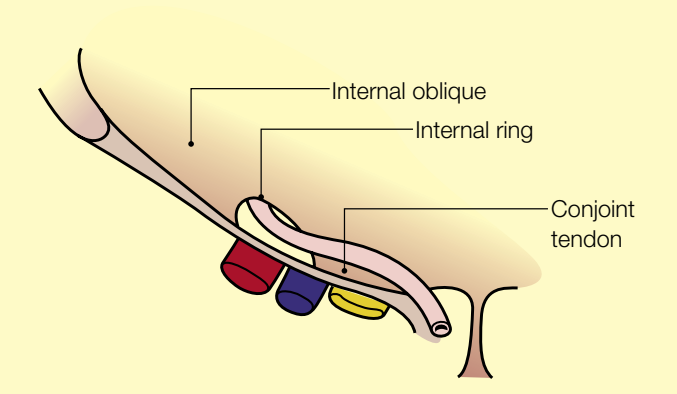
2

It is covered anteriorly by the external oblique aponeurosis which is reinforced laterally by the muscle fibres of internal oblique.

Its posterior wall is formed by transversalis fascia throughout but this is reinforced by the conjoint tendon medially.

Its floor is the re-curved edge of the inguinal ligament and its roof the lowest fibres of internal oblique (Figure 3).

Inguinal canal with external oblique removed

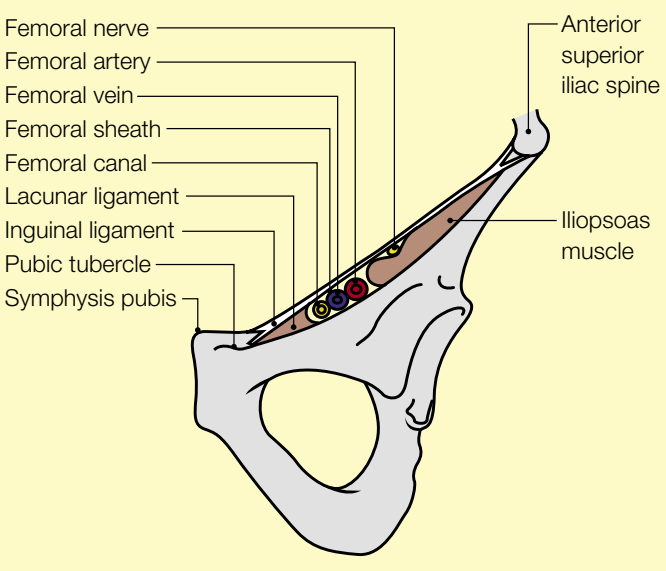


3

It contains the ilioinguinal nerve and the spermatic cord in the male and the round ligament of the uterus in the female.

The femoral artery lies deep to the inguinal ligament which separates it from the deep inguinal ring and its pulsation can be found at the midinguinal point, half-way between the anterior superior iliac spine and the symphysis pubis. Medial to the artery is the femoral vein. Both vessels are invested in a fascial sheath, the femoral sheath which also contains, medial to the vein, the femoral canal (Figure 4).

Structures lying deep to the inguinal ligament



4

Hernias

Hernias are common in the inguinal region. Congenital inguinal hernias, present from birth, are caused by the persistence of a patent peritoneal sac within the spermatic cord. The hernial sac pursues an oblique course through the length of the inguinal canal and is known as an indirect inguinal hernia. From middle age onwards the direct inguinal hernia is common. It results from weakness in the posterior wall of the inguinal canal. It presents as a forward protrusion of the peritoneal sac. Femoral hernias are less common. They occur via the femoral sheath through the narrow unyielding femoral ring immediately below the inguinal ligament. ◆

Anatomy of Tracheostomy and Laryngotomy

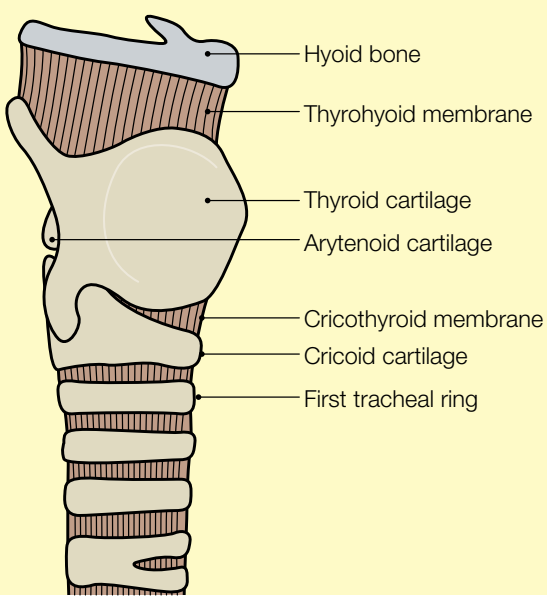
Anil Patel

Anil Patel is Consultant Anaesthetist at the Royal National Throat, Nose and Ear Hospital, London. He qualified from University College, London, and trained in anaesthesia at Guy's Hospital, London.

Knowledge of the anatomy of the upper respiratory pathway is essential for the safe practice of tracheostomy, in which a hole is made in the anterior tracheal wall, and laryngotomy or cricothyroidotomy, in which a hole is made through the cricothyroid membrane.

The larynx consists of articulating cartilages linked together by ligaments. It lies opposite the 4th, 5th and 6th cervical vertebrae. The thyroid notch of the thyroid cartilage can be palpated anteriorly and the cricoid cartilage below this (Figure 1). The cricothyroid ligament lies between the thyroid and cricoid cartilage.

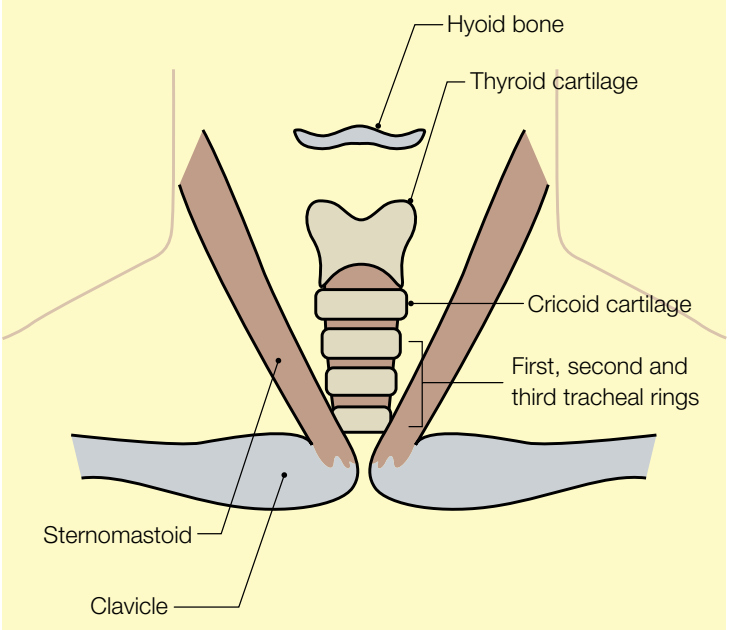
Anatomy of the trachea



1

The trachea starts at the lower end of the cricoid cartilage at the level of the 6th cervical vertebrae and descends through the superior mediastinum to terminate at the bifurcation at the 4th thoracic vertebrae (Figure 2).

Features of the throat



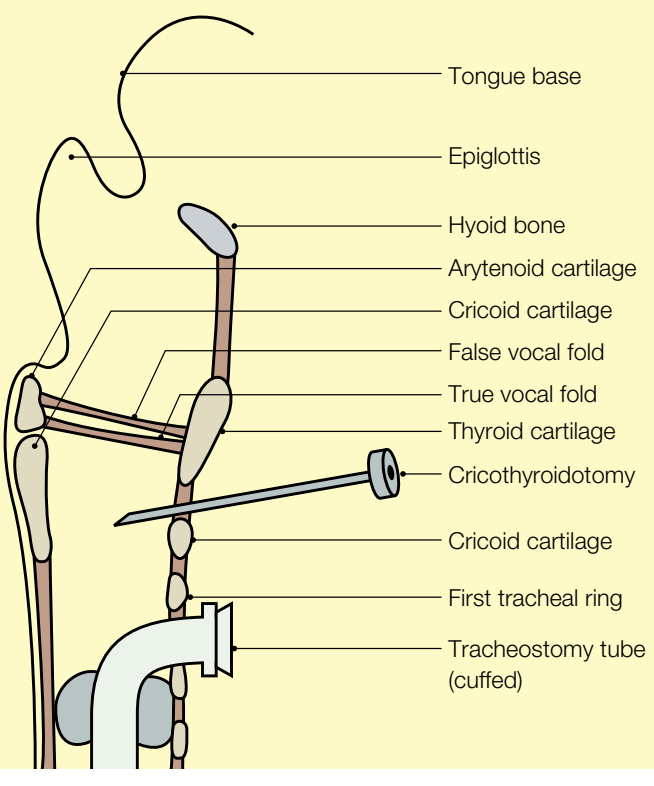
2

Anterior relations – anteriorly in the neck the trachea is covered by skin, superficial fascia, deep fascia, thyroid isthmus overlying 2nd, 3rd and 4th tracheal rings and lower in the neck strap muscles (sternohyoid and sternothyroid).

The blood supply of the larynx is from the superior and inferior laryngeal artery branches of the superior and inferior thyroid artery, respectively. Venous drainage is into superior and inferior thyroid veins.

Laryngotomy or cricothyroidotomy (Figure 3) – an incision is made through the skin, fascia and avascular cricothyroid membrane to enter the upper airway.

Position for cricothyroidotomy and tracheostomy



3

Tracheostomy (Figure 3) – an incision is made midway between the cricoid ring and suprasternal notch, the strap muscles are separated in the midline and retracted laterally, the thyroid isthmus is retracted upwards or divided and a circular window created between 2nd and 3rd or 3rd and 4th tracheal rings. ◆

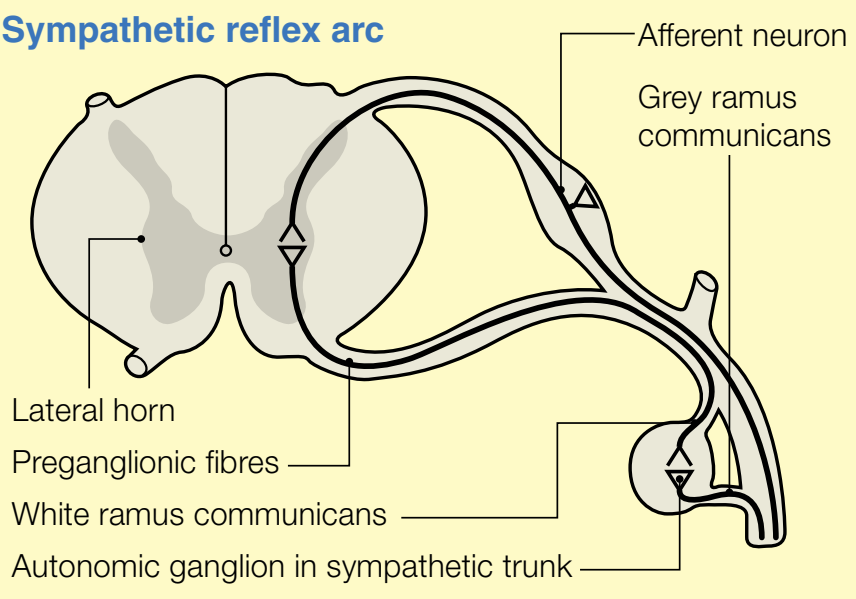
The Autonomic Nervous System

John Craven

John Craven was formerly Consultant Surgeon at York District Hospital, York, UK. He trained in Manchester, Uganda and Cardiff. He is past chairman of the primary examiners of the Royal College of Surgeons of England. His particular interest is gastric cancer.

The autonomic nervous system supplies viscera, glands and smooth and cardiac muscle. Its fibres arise in the lateral columns of the spinal cord, synapsing with peripheral ganglion cells before supplying these structures (Figure 1). The two complementary parts of the autonomic nervous system (sympathetic and parasympathetic) leave the CNS at different sites and usually have opposing effects on the structure they supply through endings that are mainly adrenergic or cholinergic. The sympathetic system prepares the body for 'fight or flight' and the parasympathetic system controls its vegetative function.

Sympathetic reflex arc

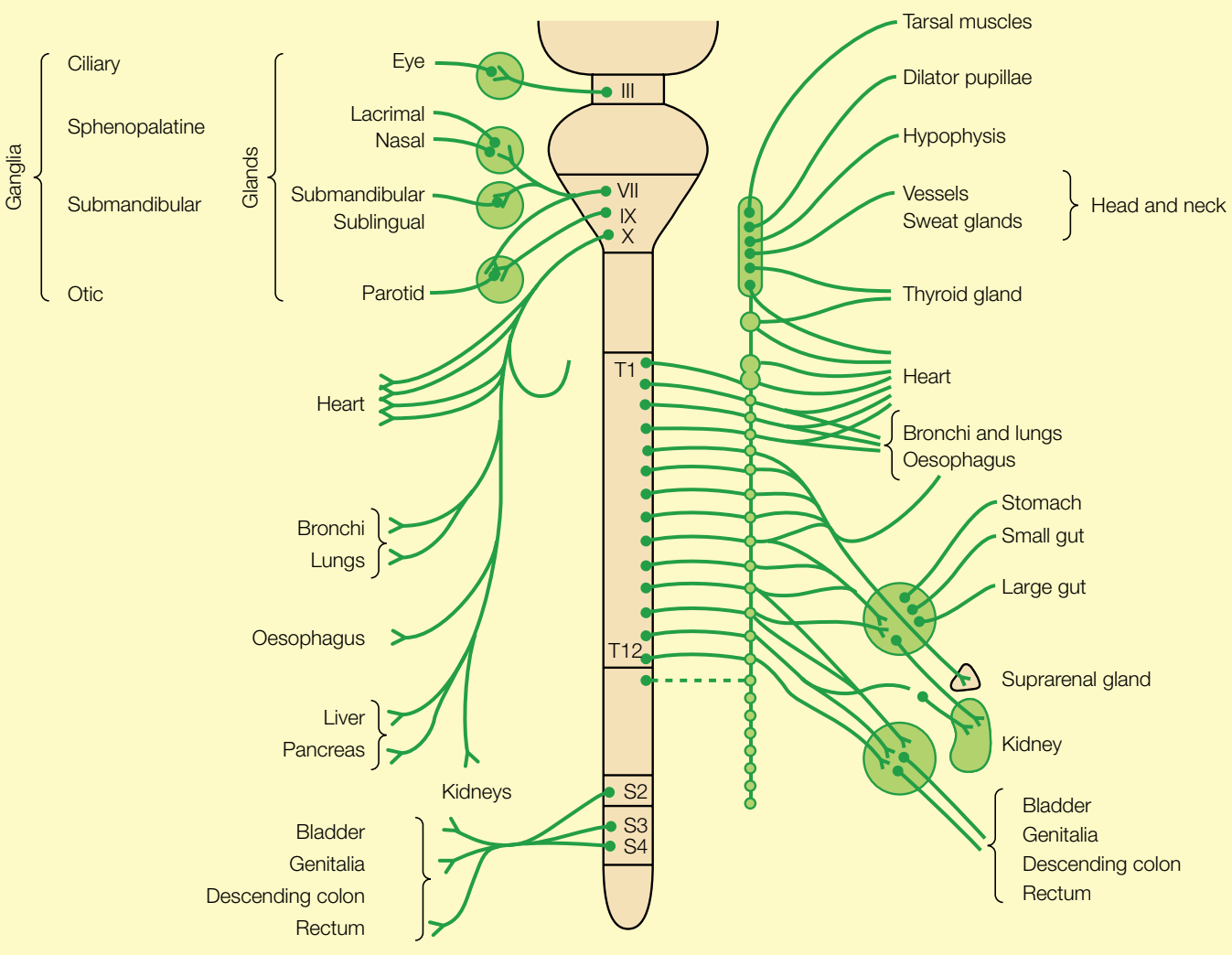


1

Sympathetic system
In the sympathetic system preganglionic fibres arise from the lateral columns in segments T1–L2, passing for a short distance in the anterior roots of the corresponding spinal nerves before leaving as white, myelinated, rami communicantes to join the sympathetic trunk.

The paired sympathetic trunks consist of ganglia and nerve fibres, and extend from the base of the skull to the coccyx. There are three cervical, eleven thoracic, four lumbar and four sacral ganglia and from each pass somatic and visceral fibres (Figure 2).

The autonomic nervous system



2

Somatic fibres are distributed as grey, non-myelinated, postganglionic rami communicantes to each of the 31 spinal nerves supplying vasoconstrictor fibres to arterioles, secretory fibres to sweat glands and pilomotor fibres to the skin. Grey fibres, unlike the white preganglionic fibres, do not run up or down the sympathetic trunk.

Visceral fibres pass to the:

- thoracic viscera and synapse in the cervical and upper thoracic ganglia; their postganglionic fibres pass to the viscera via the cardiac, oesophageal and pulmonary plexuses
- abdominal viscera and pass through the ganglia without synapsing, to enter one of the splanchnic nerves before synapsing in one of the prevertebral plexuses in the abdomen
- adrenal medulla and through the trunk without synapsing, travelling in the greater splanchnic nerve through the coeliac plexus to synapse with ganglion cells in the medulla
- cranial and facial structures (e.g. dilator pupillae, salivary glands) that accompany the carotid vessels; the larynx and pharynx are supplied by postganglionic fibres from the middle cervical ganglion which accompany the inferior thyroid artery.

The cervical sympathetic trunk and the stellate ganglion: see **ANATOMY**.

The thoracic sympathetic trunk comprises 11–13 ganglia and gives branches to all the corresponding spinal nerves; the first is usually fused with the lower cervical to form the stellate ganglion. Visceral branches pass from the upper six ganglia to the pulmonary and cardiac plexuses and three splanchnic nerves. The greater splanchnic nerve (T5–10) ends in the coeliac plexus, the lesser (T9 and 10 or T10 and 11) in the aortic plexus and the lowest in the renal plexus. The coeliac plexus lies around the origin of the coeliac artery and is formed from the greater splanchnic nerve and postganglionic fibres of L1. It is continuous with the network of sympathetic nerves on the aorta, the aortic plexus, the branches of which accompany the branches of the aorta.

The lumbar sympathetic trunk usually comprises four ganglia in each trunk. Its branches pass to the coeliac and hypogastric plexuses, and to each of the lumbar spinal nerves.

The hypogastric plexuses supply the pelvic viscera. The superior plexus receives branches from the coeliac plexus and the sympathetic trunks and its efferent fibres mainly travel in two hypogastric nerves descending on each side of the rectum supplying the rectum, bladder and genitalia. The plexus receives autonomic sensory fibres of pain and bladder and rectaldistension, from the pelvic viscera. The inferior plexus also receive parasympathetic branches from the nervi erigentes (S2–4).

Parasympathetic system
The parasympathetic system is much smaller and comprises a cranial and sacral component on each side. Its actions contrast with those of the sympathetic system – constriction of the pupils, decrease in the rate and conduction of the heart, broncho-constriction, an increase in peristalsis, sphincter relaxation and an increase in glandular secretion. Its pelvic component inhibits the bladder's internal sphincter and it is stimulatory to the bladder's detrusor muscle. Its medulated preganglionic fibres are much longer than those of the sympathetic system and synapse with postganglionic cells close to or in the walls of the viscera they supply. The cranial outflow is conveyed in the oculomotor, facial, glossopharyngeal and vagus nerves (Figure 2). The latter is the largest component and most widely distributed. The parasympathetic nerves of the oculomotor, facial and glossopharyngeal nerves are transmitted via four ganglia through which also pass sympathetic and somatic fibres.

- The ciliary, lateral to the optic nerve, from which passes postganglionic fibres to sphincter pupillae and ciliary muscles.
- The sphenopalatine in the pterygopalatine fossa is supplied by fibres from the greater petrosal branch of the facial nerve; postganglionic fibres supply the lacrimal gland, nasal and pharyngeal glands.
- The submandibular ganglion receives fibres from the facial nerve through the chorda tympani branch and via the lingual nerve which lies on the hyoglossus muscle. Preganglionic fibres pass in the lingual nerve to supply the submandibular and sublingual salivary glands, and oral and pharyngeal glands.
- The otic ganglion receives fibres from the glossopharyngeal nerve via the tympanic plexus and the lesser petrosal nerve; postganglionic fibres pass in the auriculotemporal nerve to the parotid gland.

The parasympathetic supply of the abdomen and pelvis is derived from the vagi and the pelvic splanchnics. The anterior and posterior vagal trunks are distributed through the coeliac plexus along the branches of the aorta to the alimentary tract and its derivatives as far as the splenic flexure. The pelvic splanchnic nerves (S2,3,4) pass to the hypogastric and pelvic plexuses. From the former, branches pass along the inferior mesenteric artery to supply the gut distal to the splenic flexure; from the latter are supplied the pelvic viscera. Their action helps in micturition and defecation by producing relaxation of bladder and bowel sphincters.

The Axilla

John Craven

John Craven was formerly Consultant Surgeon at York District Hospital, York, UK. He trained in Manchester, Uganda and Cardiff. He is past chairman of the primary examiners of the Royal College of Surgeons of England.

The axilla is a fat-filled space, the shape of a truncated cone, lying between the lateral thoracic wall and the arm. At its apex it is bound by the upper border of the scapula, the outer border of the first rib and the middle third of the clavicle and it is through this that structures pass from the posterior triangle of the neck to the upper limb. The base of the axilla is formed by skin and subcutaneous tissue. It is bounded anteriorly by the pectoralis major and, deep to that, pectoralis minor. The posterior wall extends lower than the anterior wall and is formed, from above downwards by subscapularis, latissimus dorsi and teres major muscles. The axilla is limited medially by the upper ribs and intercostal spaces, which are here covered by slips of the serratus anterior muscle. The lateral wall is thin and is represented by the narrow intertubercular groove of the humerus, into the lips of which the muscles of the anterior and posterior walls are inserted. It contains the axillary artery and vein, cords and branches of the brachial plexus, coracobrachialis and biceps, axillary lymph nodes and vessels, and fat.

The axillary artery begins as the continuation of the subclavian artery at the outer border of the first rib below the middle of the clavicle. It passes through the axilla to become the brachial artery as it leaves at the lower border of teres major. Throughout its course it lies on the muscles of the posterior wall of the axilla and is surrounded by the cords and branches of the brachial plexus. The axillary vein lies medial to this neurovascular bundle; coracobrachialis and the short head of biceps are lateral. Anteriorly, the vessels and nerves are crossed by the pectoralis minor. It supplies branches to the upper thoracic wall, the muscles of the axilla and the shoulder joint. Its largest branch, the subscapular artery, gives an important contribution to the scapular anastomosis, which provides a collateral circulation to the upper limb in the event of obstruction of the axillary artery by virtue of its communication with branches of the thyrocervical trunk, which arises from the subclavian artery.

The axillary vein is a continuation of the brachial vein and ascends through the axilla, medial to its artery, before leaving it to become the subclavian vein at the outer border of the first rib. Its branches correspond to those of the artery, apart from the cephalic vein which drains the superficial tissues of the upper limb. It ascends in the groove between pectoralis major and deltoid muscles before piercing the deep fascia just below the clavicle. Obstruction of the axillary vein by a thrombus, though not as common as that of the leg veins, occasionally occurs after prolonged infusion of hyperosmotic fluids and/or intravenous nutrition. It results in acute swelling of the arm and the possibility of pulmonary embolus.

The brachial plexus is described elsewhere. The three cords of the plexus (lateral, medial, posterior) are named according to their position around the axillary artery.

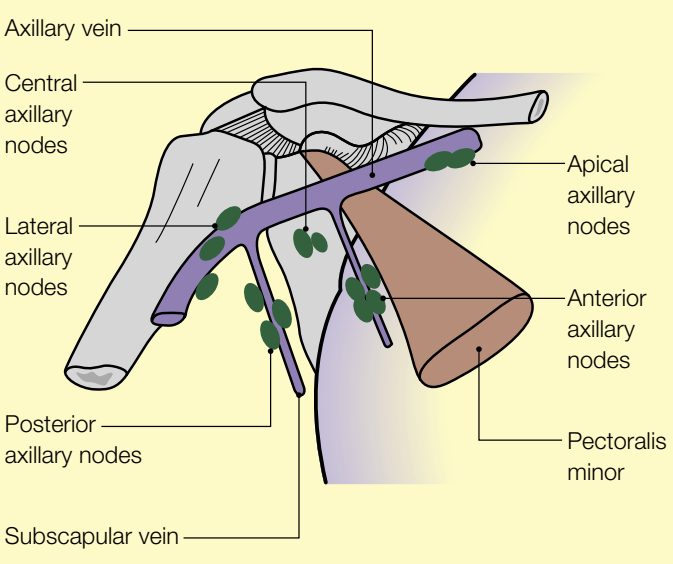
Lymph system

Lymph vessels are superficial or deep. The superficial group drains the skin; medially the vessels accompany the basilic vein and terminate in the axillary nodes; laterally the vessels accompany the cephalic vein and drain via infraclavicular nodes into the axillary nodes.

The axillary lymph nodes are of considerable clinical importance because they drain the arm, the upper abdominal wall and the pectoral region and also receive most of the lymphatic drainage of the breast. They are arranged in five groups (Figure 1).

- The anterior group lie deep to pectoralis major draining the lateral and anterior chest wall, the breast and the upper abdominal wall.
- The lateral group lie on the lateral wall of the axilla and receive the efferent vessels from the upper limb.
- The central group are arranged around the axillary vessels in the axillary fat.
- The posterior group lie to the lateral edge of the subscapularis muscle on the posterior wall of the axilla.
- The apical group lies at the apex of the axilla immediately behind the clavicle; they are continuous with the inferior deep cervical nodes and receive drainage from all the preceding groups.

Lymph nodes of the axilla



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A subclavian lymph trunk conveys the lymph from the apical group to the right jugular trunk or the thoracic duct. Lymphoedema, an excessive accumulation of tissue fluid, occurs when the lymph trunk becomes disrupted or obstructed. In the developed world, the most common cause of this occurring in the arm is a combination of radiotherapy and surgical excision of the axillary lymph nodes in the treatment of advanced breast cancer. ◆

Central Nervous System

John S P Lumley

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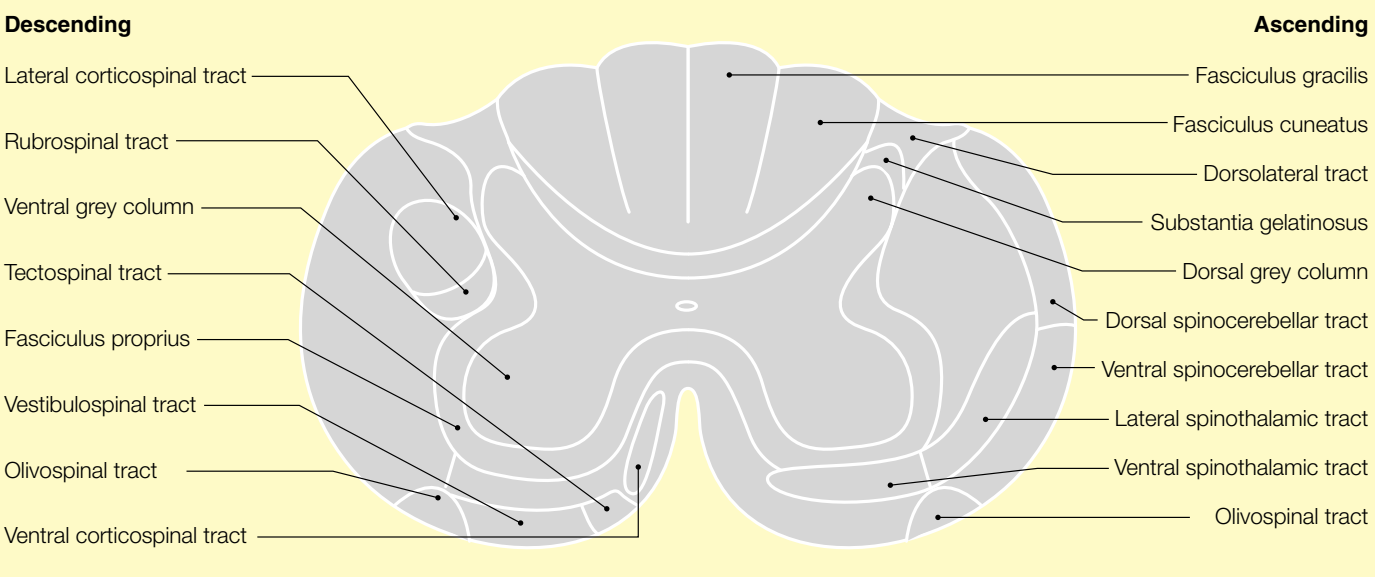
The brain and spinal cord develop from a longitudinal dorsal tube of neural plate ectoderm. The walls of the tube become greatly expanded by the cell bodies, dendrites and axons of the developing neurons, and peripheral neural extensions from the paired 12 cranial and 31 spinal (8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal) nerves making up the peripheral nervous system. The spinal nerves carry somatic sensory fibres and innervate skeletal muscle. In addition, the cranial nerves carry special sensory fibres from the head and neck and supply branchial arch musculature.

The autonomic nervous system overlaps the central and peripheral nervous systems. It innervates smooth and cardiac muscle, and glands, and carries visceral sensory fibres. The complementary sympathetic and parasympathetic parts of the autonomic system are carried, respectively, in the thoracolumbar (T1–L2) and craniosacral (cranial nerves 3, 7, 9, 10 and S2, 3, 4) outflow.

Spinal cord

The spinal cord retains its longitudinal cylindrical form. Its fine central canal is surrounded by cellular grey matter. The dorsal horns have a predominantly sensory function and the ventral horns contain motor neurons. The fibres in the peripherally placed white matter are organized into tracts (Figure 1).

Principal descending and ascending pathways of spinal cord



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Brain stem

The brain stem is made up of the medulla and pons of the hindbrain, and the midbrain. It is in continuity with the spinal cord below and the diencephalon of the forebrain above. Posteriorly the cerebellum is united to it by three paired cerebellar peduncles. The brain stem and cerebellum lie within the posterior cranial fossa, the midbrain passing through the anterior midline opening of the dural roof of the fossa – the tentorium cerebelli. The brain stem gives attachment to, and contains the nuclei of, the 3–12 cranial nerves. It gives passage to the ascending and descending fibres from forebrain to the spinal cord, and the afferent and efferent fibres to the cerebellum.

The crossed and uncrossed corticospinal pathways form the prominent pyramids of the anterior medulla. These bundles are broken up in their passage through the pons but form part of the cerebral peduncles in the midbrain. The olivary nuclei produce anterolateral oval longitudinal swellings in the upper medulla before forming the ipsilateral inferior cerebellar peduncles. The pons forms the prominent anterior convexity between the medulla and midbrain, and is formed of transversely running fibres passing posterolaterally to become the middle cerebellar peduncle.

The midbrain is formed anteriorly by the cerebral peduncles, containing frontoparietal and frontotemporal, as well as pyramidal fibres. Posteriorly are the paired inferior and superior colliculi concerned with the integration of auditory and visual sensation, respectively. The intervening tegmentum contains the prominent decussation of the superior cerebellar peduncles, passing to the red nuclei.

The cerebellum is attached by the inferior, middle and superior cerebellar peduncles, respectively, to the medulla, pons and midbrain. It comprises a central, midline vermis and a hemisphere on each side. A deep primary transverse fissure divides anterior and posterior lobes and the posterolateral fissure, across the caudal surface of the cerebellum, separates the posterior and flocculonodular lobes. The ridges (folia) of the greatly convoluted surface represent only one-sixth of this area, the remainder lining the deep sulci.

Most afferent fibres to the cerebellar cortex end in the middle granular and outer molecular layers, where a profuse dendritic network of flask-shaped, Purkinje fibres is situated. The complex circuitry of the cortical neuronal units and the profuse connections of the cerebellum uniting all major motor regions throughout the CNS, provide an integrative control of motor function, not only in locomotion but also in posture, tone and equilibrium.

The reticular formation is an extensive collection of nuclear masses in the brain stem, partly organized into median, medial and lateral columns. It forms an isodendritic core traversing the entire brain stem. The reticular formation has extensive connections, both crossed and uncrossed, with input and back projection to and from all parts of the CNS, including the spinal cord, diencephalon, limbic system and the neocortex. It influences somatic and visceral neural activity. Investigation has shown a complex facilitatory and inhibitory synaptic transmission. The diffuse nonspecific activity is linked with arousal, levels of consciousness, sleep patterns and biorhythms, together with providing an ascending sensory gating mechanism that influences all forms of behaviour.

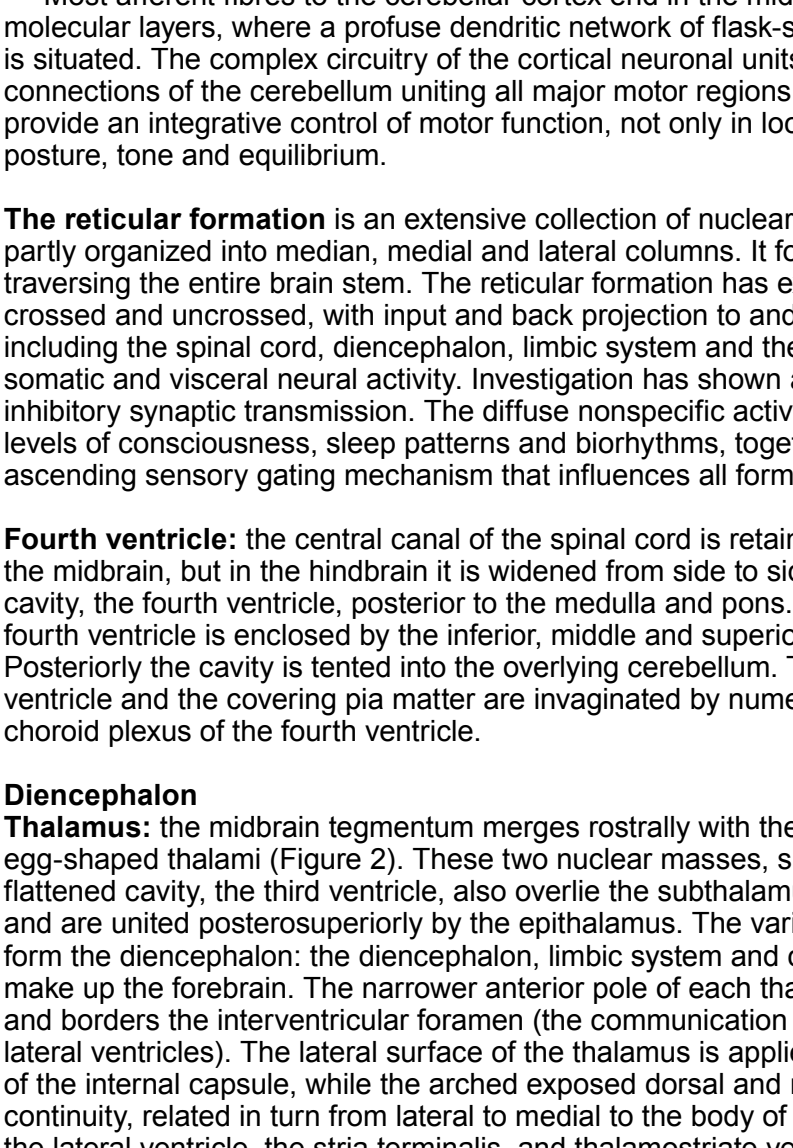
Fourth ventricle: the central canal of the spinal cord is retained as the aqueduct in the midbrain, but in the hindbrain it is widened from side to side into a diamond-shaped cavity, the fourth ventricle, posterior to the medulla and pons. On either side, the fourth ventricle is enclosed by the inferior, middle and superior cerebellar peduncles. Posteriorly the cavity is tented into the overlying cerebellum. The ependyma lining of the ventricle and the covering pia matter are invaginated by numerous vessels to form the choroid plexus of the fourth ventricle.

Diencephalon

Thalamus: the midbrain tegmentum merges rostrally with the inferior surface of the egg-shaped thalami (Figure 2). These two nuclear masses, sitting on either side of a flattened cavity, the third ventricle, also overlie the subthalamus and the hypothalamus, and are united posterosuperiorly by the epithalamus. The various thalamic structures form the diencephalon: the diencephalon, limbic system and cerebral hemispheres make up the forebrain. The narrower anterior pole of each thalamus is near the midline and borders the interventricular foramen (the communication between the third and lateral ventricles). The lateral surface of the thalamus is applied to the posterior limb of the internal capsule, while the arched exposed dorsal and medial surfaces are in continuity, related in turn from lateral to medial to the body of the caudate nucleus, the lateral ventricle, the stria terminalis, and thalamostriate vein, the stria medularis and the third ventricle.

Pain reaches consciousness at the thalamic level, though it is poorly localized, while thalamic injury alters the discrimination of all sensation. The thalamus serves to integrate somatic and visceral function. This has a powerful influence on emotional and endocrine activity, and profound effects on the arousal reaction.

Coronal section through the brain showing relations of thalamus and striatum



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Subthalamus is that part of the diencephalon merging inferiorly with the red nucleus and substantia nigra of the midbrain; superiorly with the lateral thalamic nuclei; and anteriorly it lies adjacent to the hypothalamus. Anterolateral to the subthalamus the cerebral peduncles of the midbrain become the posterior limbs of the internal capsule. The area contains the discrete subthalamic nucleus on each side and a grey lamina, the zonar inserrata, passes rostrally in front of the thalamus.

The subthalamus is the site of integration of motor centres, particularly the midbrain tegmentum, the corpus striatum and dorsal thalamic nuclei. Prominent bands of fibres, the funiculus and ansa lenticularis, traverse the internal capsule, uniting the corpus striatum and dorsal thalamic regions. Lesions of the subthalamus produce hemibalismus, with disabling and violent uncontrolled choreiform movements, predominantly of the limbs, suggesting loss of corpus striatal control over the motor cortex.

Hypothalamus lies in the midline in the floor of the third ventricle anterior to the subthalamus and below the two thalami. Anteroinferior to the hypothalamus is the optic chiasm, and behind this an elevation (the tuber cinereum) gives rise to the stalk (infundibulum) of the pituitary. Two small elevations (the mamillary bodies) lie behind the tuber cinereum, and separate it from the posterior perforated substance and the cerebral peduncles of the midbrain.

The medial parts of the hypothalamus have a number of named nuclear masses, the more obvious being the preoptic, supraoptic, paraventricular, dorsomedial, ventral, ventro-medial, infundibular and posterior. Afferent fibres pass to the hypothalamus from the orbital surface of the frontal cortex, the septal nuclei, the hippocampus (through the fornix) and the amygdaloid nucleus (through the stria terminalis). Afferent fibres pass in the median forebrain bundle and dorsal longitudinal bundle to the midbrain reticular nuclei. Fibres from the mamillary bodies pass to the anterior nucleus of the thalamus (mamillothalamic tracts) and the midbrain (mamillotegmental tracts).

The hypothalamus has powerful influences on anterior and posterior lobe hormone production of the pituitary, but the associated behavioural changes, particularly those of an emotional nature, are closely linked to its connections with the limbic system. The area is concerned with temperature regulation and control of circadian rhythms. A rigid hypothalamic division of the autonomic regulation of the parasympathetic and sympathetic nervous systems is no longer supported, but the region has profound influence on the cardiovascular, respiratory and alimentary systems.

Epithalamus: the midline epithalamus is situated in the posterior wall of the third ventricle between the posterior ends of the thalami. It comprises the habenular nuclei and commissure, the posterior commissure and the pineal body. The habenular nuclei receive the stria medullaris, a narrow bundle of fibres passing backwards over the thalamus from the septal nuclei. Its efferents pass through the habenular commissure to the interpeduncular nucleus of the subthalamus. The habenular nuclei and connections contain a large number of neuromed-iators and these influence, particularly through hypothalamic connections, gastrointestinal function, metabolism and thermal regulation. The posterior commissure unites the two superior colliculi and the medial longitudinal bundles of the two sides. It is a focus of interaction of olfactory, visual and somatic afferent pathways.

The pineal body develops as an outgrowth from the third ventricle. It is an oval mass lying between the superior colliculi. It has a powerful inhibitory effect on the hypothalamus, releasing factors influencing thyroid, adrenal and gonadal hormone secretion. Serotonin secretion and melanin production are reduced by photic stimulation and the organ probably influences circadian rhythmicity.

Cerebral hemispheres
The dorsolateral aspect of each side of the primitive forebrain undergoes extensive expansion, at first backwards and then anteroinferiorly to form the hemisphere. The two limbs of this expanded hemisphere overlap a submerged area of cortex known as the insula. The line of contact is termed the lateral fissure. The areas of the hemisphere are named after the bones that overlie them. The anterior and posterior extremities are respectively the frontal and occipital poles of the frontal and occipital lobes, with the parietal lobe in between. The anteroinferior extension of the hemisphere is the temporal lobe, housed within the middle cranial fossa, its apex being the temporal pole.

The rostral end of the primitive forebrain persists as a thin glial sheet, the lamina terminalis, passing from the optic chiasm to the anterior commissure and corpus callosum. The adjacent area on the inferior surface of each hemisphere houses the olfactory bulb, tract and medial and lateral olfactory striae.

The surface of the hemisphere is convoluted, the exposed gyri being only one-third of the surface area, the rest being hidden from view in the sulci. The sulci and gyri have characteristic patterns (Figure 3). The central and calcarine sulci provide the anterior and posterior limits of the parietal lobe. The surface is covered by a cellular outer layer of grey matter – the cortex, or pallium. The human neocortex is a highly organized neuronal hemispheric covering with a great deal of functional localization. Conflicting literature on these subjects is partly a result of the evidence being predominantly derived from non-human studies. For example, Brodmann's mapping of 52 cortical areas in 1909, while providing a useful reference grid, was based on comparative studies of simian brains and did not include the human cortex.

Left hemisphere functional localization

3

Cortical cells are predominantly of two types: pyramidal (agranular) and stellate (granular). Pyramidal cells vary from small (10 μ) to very large (70 μ), the latter including the Betz cells characteristic of the human motor cortex. They have a large apical dendrite and each forms the core of a columnar unit extending through the cortex, having numerous horizontal communications, and many inter-hemispheric and projection fibres. This unit has enormous potential for intercommunication and interconnections, each column having more than a thousand interconnecting neurons. Stellate cells are 6–8 μ in diameter with a short axon and an extensive dendritic field: they are of various shapes (e.g. the basket cell). Different workers have used the dispersion of these cell types to identify major cortical areas. The most favoured system identifies six cortical layers: Brodmann's mapping was based on this template.

In spite of the variable phylogical patterns throughout the pallium, with the exception of the striate cortex, there is remarkable homogenicity of cellular numbers and ratios of the two prime cell types: independent of the thickness (1.5–4.5 mm). Two-thirds of neurons in any area are pyramidal and one-third stellate. The striate cortex, while representing only 3% of the surface, contains 10% of cortical neurons.

Anatomical localization based on single projections to an area is oversimplistic, because all areas of the pallium receive and project extensively by association and commissural fibres, to the dorsal and reticular thalamic nuclei, the corpus striatum and pons, and other areas throughout the CNS.

Initial focal pathology and anatomical localization of cortical somatomotor and sensory pathways were supported in humans by operative recording and stimulation, by Penfield and Rasmussen in the 1950s. However, stimulation of the motor cortex never produced a co-ordinated movement, emphasizing that functional localization is linked to association and efferent pathways, being more a mosaic than a clear body image. The trend has thus been to label the first or leading area (e.g. Brodmann 4 as MsI) and adjacent associated areas as secondary or tertiary fields (Brodmann 6, 8 as MsII, III). Secondary areas in motor and sensory localization are involved with coordination and discriminative interpretation, and generally linked with behavioural activity.

Asymmetrical localization was recognized by early workers undertaking cortical mapping, but Broca's classical studies linked speech with the left hemisphere. It became fashionable to attribute speech and linguistic comprehension to a 'dominant' hemisphere and although this was supported by pathological studies, other functions such as spatial comprehension and musicology can be attributed to the 'non-dominant' counterpart. In the intact brain, the complementary nature of the two hemispheres ensures appropriate concise complex bilateral responses to multifactorial stimuli.

Hemisphere white matter is organized into commissural fibres, uniting the two hemispheres across the midline; association fibres joining adjacent or widely separated gyri of the same hemisphere: and projection fibres to or from lower-lying parts of the CNS.

The largest commissural band is the corpus callosum in which 200 million fibres unite corresponding areas on the two sides. The callosum develops with the enlarging hemispheres extending in hook-like fashion from the lamina terminalis, at first forwards and then horizontally backwards over the diencephalon, the space between them being the transverse fissure. The point of continuation with the lamina terminalis is termed the rostrum, the anterior bend the genu, and the main bulk the body. The posterior thickest portion of the corpus callosum, overhanging the posterior thalami, epithalamus and midbrain colliculi, is termed the splenium. Despite this extensive point-to-point communication, the rare congenital absence of the structure in the human may go unnoticed.

Cortical projection fibres pass predominantly in the internal capsule, a broad V-shaped band lying between the caudate nucleus and thalamus medially, and the lentiform nucleus laterally. It fans out within the hemisphere as the corona radiata, interdigitating with the transverse fibres of the corpus callosum. The anterior limb of the capsule lies between the head of the caudate nucleus and globus pallidus, and is crossed by extensive intercommunicating pathways between these structures. It contains frontopontine fibres, from the frontal lobe to the nuclei of the pons, and thalamic and hypothalamic cortical pathways.

The genu, between the anterior and posterior limbs of the internal capsule, contains the corticonuclear fibres passing to the cranial nerve nuclei, while the adjacent part of the posterior limb carries corticospinal fibres from the motor cortex.

Corpus striatum is a group of large nuclear masses situated in the substance of the cerebral hemispheres adjacent to the internal capsule. The caudate nucleus has an expanded head bulging into the anteral horn of the lateral ventricle. It then tapers into a body and tail, curving around the lateral aspect of the thalamus in the wall of the lateral ventricle, at first in the lateral wall and then in the roof of its inferior horn.

The corpus striatum receives fibres from all areas of the neocortex, and also from the thalamus and brain stem. It has dense reciprocal connections with the subthalamus and substantia nigra. Its principal outflow is to the thalamus, particularly the ventral nuclei, the motor and pre-motor cortex, and to the reticular nuclei and thence to the reticulospinal and rubrospinal tracts.

It is involved in motor coordination and damage to the structure increases tone, producing resistance to stretch or rigidity. There is also loss of associated movement and sometimes accessory, choreiform, athetoid and ballistic movements and tremor, these being purposeless and uncontrolled. Ablation of the striatum produces poverty of movement and manipulative skills. It has also been used to reduce the tremor and rhythmicity of Parkinsonian movements, although the link with dopamine transmission is unconfirmed.

Limbic system: the median area of anterior fusion of the two hemispheres, together with their medial aspect, are drawn with the developing hemisphere into a C-shape round the thalamus and are developed into a number of distinct nuclear tracts (Figure 4). This region was originally termed the olfactory brain or rhinencephalon. However, the development of this area in the human renders this term meaningless, and the functional name of limbic system is more appropriate.

The system encompasses the bulb, tract, and medial and lateral olfactory striae, the anterior perforated substance between the striae, the adjacent inferior frontal (pre-piriform) cortex on each side, and the anterior commissure linking these structures. Three nuclear masses – the hippocampus, amygdala and septal nuclei, and their projections and commissural fibres, also contribute to the system.

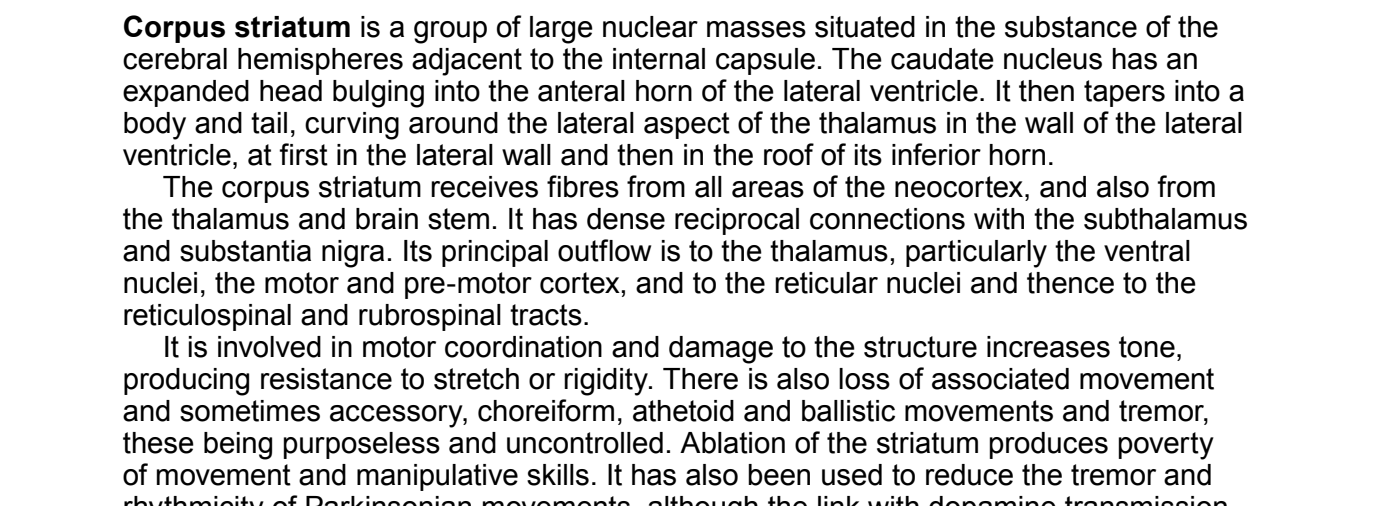
The hippocampus lies in the floor of the inferior horn of the lateral ventricle, three grooves in its distal enlargement giving it a paw-like shape and the name pes hippocampus. Its afferent fibres are from adjacent cortical areas but the sole efferent channel forms on its surface as the alveus, and passes backwards as the fimbria: the two fimbria meet in the midline to form the body of the fornix which projects to the anterior thalamic nuclei.

The amygdala is a composite nuclear mass situated in the roof of the inferior limit of the inferior horn of the lateral ventricle. It connects with its fellow on the opposite side via the anterior commissure and its main efferent pathway is the stria terminalis. This follows the curve of the caudate nucleus and passes anterior to the interventricular foramen and thence to the hypothalamus and septal nuclei. Some fibres then pass backwards within the striae medullaris to the epithalamus. Other fibres pass to the dorsal thalamus.

The septal nuclei are most prominent in humans and lie adjacent to the lamina terminalis. The anterior commissure is embedded within the lamina and carries fibres from the stria terminalis and commissural linkages between the medial olfactory tracts, the anterior perforated substance, the pre-piriform cortex and the amygdala. There are also extensive temporal neocortical connections of ill-defined function.

The complex network of nuclei, fibres and cortical areas in the limbic system is concerned with the interaction of olfactory, visceral and somatic information and is particularly concerned with emotional behaviour.

Limbic system



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The third and lateral ventricles: the cavity of the forebrain is made up of the midline third ventricle, communicating through two interventricular foramina with the lateral ventricle on each side. The third ventricle lies between the two thalami. Posteroinferiorly, it communicates with the aqueduct of the midbrain and above this is related to the epithalamus, the cavity being recessed into the base of the pineal body. Anteriorly, the third ventricle is limited by the midline lamina terminalis, the original anterior limit of the primitive forebrain.

The lateral ventricle comprises a body and anterior, posterior and inferior horns. The cavity extends backwards from the interventricular foramen over the thalamus and then downwards in a C-shaped curve within the medial aspect of the hemisphere. It is limited laterally by the reciprocally curved body and tail of the caudate nucleus. The ventricle is overlain superiorly by the corpus callosum, as it curves into the temporal lobe; the inferior horn has the hippocampus and overlying fimbria in its floor and is overlain by the amygdala.

The body of the lateral ventricle is completed medially by the fused pial and ependymal layers, the tela choroidea, passing from the undersurface of the fornix to the upper border of the thalamus. In the third and lateral ventricles, the tela choroidea is greatly expanded and infolded into the ventricles to form the choroid plexus which has an extensive capillary network within it. It produces CSF, partly by filtration and partly by secretion from the blood stream. The fluid passes through the midbrain aqueduct into the fourth ventricle, and is added to by the choroid plexus invaginating the roof of the fourth ventricle. It then circulates into the subarachnoid space through pores in the tela choroidea of the fourth ventricle, known as the median foramen of Magendi and lateral foramina of Luschka, between the superior and inferior cerebellar peduncles on each side. The subarachnoid CSF is reabsorbed into the blood stream through venous sinuses and spinal veins, through areas termed arachnoid granulations.

Cervical and Brachial Plexuses

John Craven

John Craven was formerly Consultant Surgeon at York District Hospital, York, UK. He trained in Manchester, Uganda and Cardiff. He is past chairman of the primary examiners of the Royal College of Surgeons of England. His particular interest is gastric cancer.

There are two plexuses of nerves in the neck:
• the cervical plexus supplies the diaphragm and the skin and muscles of the neck
• the brachial plexus supplies the upper limb.
Each lies on scalenus medius and is formed by the anterior divisions of spinal nerves.

The cervical plexus

The cervical plexus is formed by the upper four cervical nerves, which each receive *rami communicantes* from the superior cervical ganglion. Its most important cutaneous branches are the lesser occipital nerve (C2) and the great auricular nerve (C2, 3). They emerge from the middle of the posterior border of the sternocleidomastoid muscle to supply the neck and scalp posterior to the ear. The muscular branches of the cervical plexus supply the rhomboids, neighbouring prevertebral muscles and the diaphragm via the phrenic nerve (C4 with contributions from C3 and C5). The phrenic nerves contain motor, sensory and sympathetic fibres, which provide the sole motor supply to the diaphragm and sensation to its central portion and the mediastinal pleura. They travel down the neck behind the jugular vein on scalenus anterior and pass anterior to the root of the lung under the mediastinal pleura to reach the diaphragm

The brachial plexus

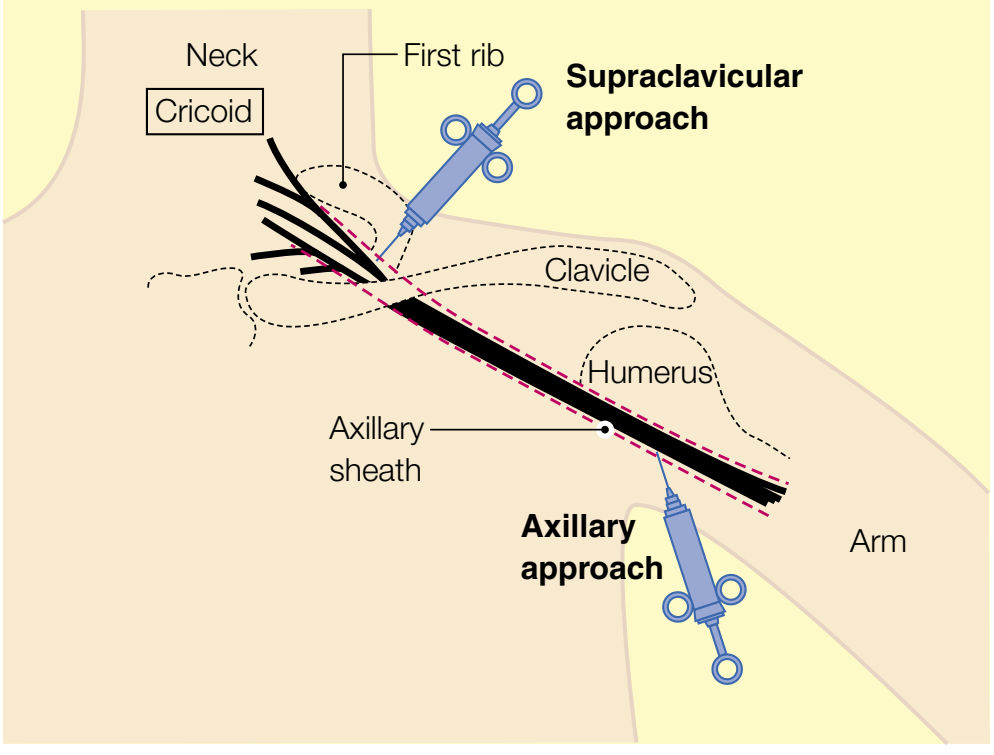
The brachial plexus lies in the posterior triangle of the neck along a line from the middle of the posterior border of the sternocleidomastoid to the middle of the clavicle (Figure 1). Knowledge of the anatomy of the brachial plexus and its branches is of great practical importance to the anaesthetist who may use it to induce regional anaesthesia in the upper limb.

The brachial plexus is formed from the anterior primary rami of the lower four cervical and the first thoracic nerves. These five roots of the plexus emerge between the middle and anterior scalene muscles and unite to form three trunks. The upper two roots (C5, 6) form the upper trunk, the middle root (C7) the middle trunk and the lower two roots (C8, T1) the lower trunk.

Behind the middle of the clavicle, at the apex of the axilla, each trunk divides into anterior and posterior divisions. The three posterior divisions join to form the posterior cord, the anterior divisions of the upper and middle trunks form the lateral cord and the anterior division of the lower trunk continues as the medial cord. The cords lie around the axillary artery related to it as their names imply (Figure 2) and are enclosed with the artery in a neurovascular sheath – the axillary sheath. The posterior cord and its branches supply structures on the dorsal surface of the limb and end by dividing into axillary and radial nerves.

The medial and lateral cords and their branches supply structures on the flexor surface of the limb; the lateral cord ends by dividing into the musculocutaneous nerve and the lateral head of the median nerve, the medial cord ends as the ulnar nerve and the medial head of the median nerve (Figure 3).

Surface anatomy of the brachial plexus emphasizing the approaches for brachial plexus block



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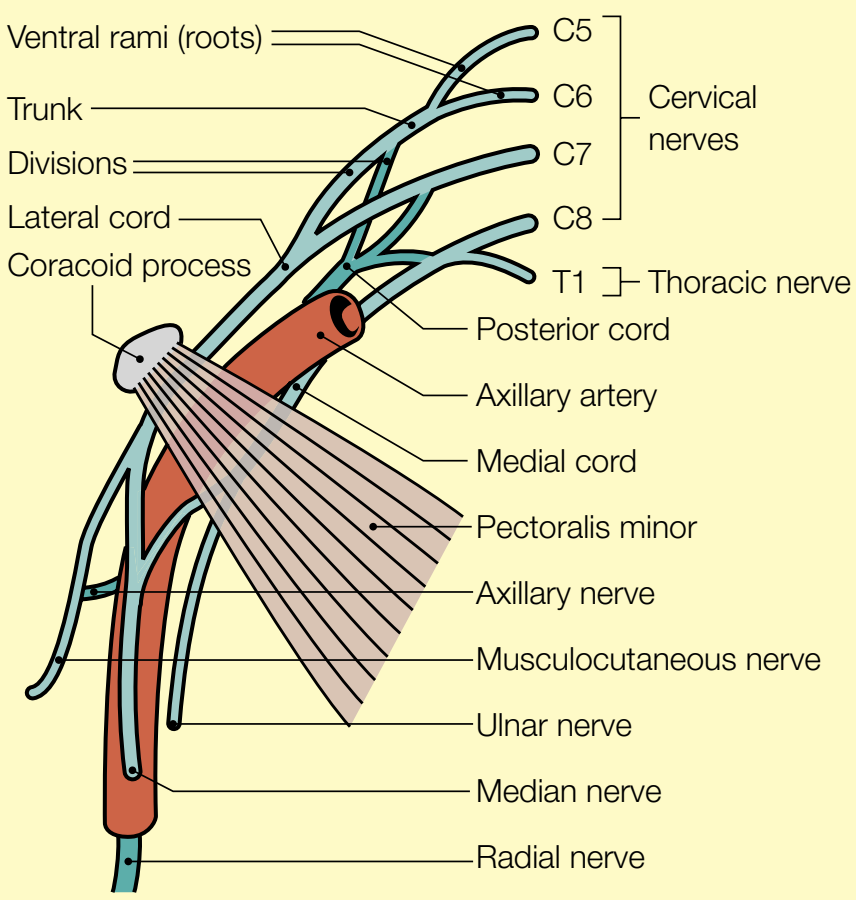
Relationship of the brachial plexus to the axillary artery



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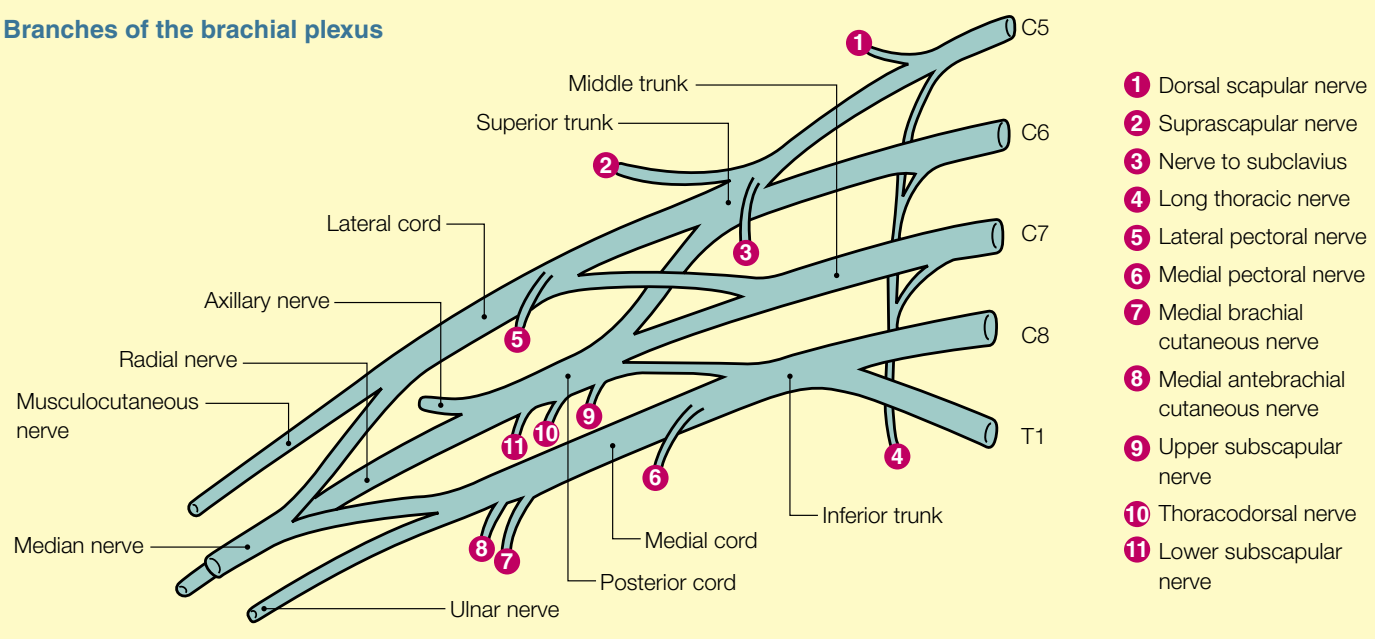
Branches of the brachial plexus



3

Branches of the plexus
From the roots: there are small branches to the back muscles, C5 contributes to the phrenic nerve, the long thoracic nerve passes posteriorly to the medial wall of the axilla to supply serratus anterior.

From the trunks: from the upper trunk arises the suprascapular nerve, which crosses the root of the neck to supply supraspinatus and infraspinatus.

From the lateral cord branches the lateral pectoral nerve, which supplies pectoralis major, the musculocutaneous nerve, which supplies coracobrachialis, biceps and brachialis, before becoming the lateral cutaneous nerve of the arm, and the lateral head of median nerve.

From the medial cord: the medial pectoral nerve supplies pectoralis major and minor, the ulnar nerve supplies flexor muscles in the forearm, small muscles in the hand and the skin of the medial side of the hand. Also branching from the medial cord are the medial head of the median nerve, the medial cutaneous nerves of the arm which supply skin on the medial side of the arm, and the medial cutaneous nerve of the forearm which supplies the skin of the medial side of the forearm.

From the posterior cord the subscapular nerves descend the posterior axillary wall to supply subscapularis and teres major. The thoracodorsal nerve supplies latissimus dorsi by entering its upper border. The axillary nerve descends on subscapularis and turns posteriorly around the surgical neck of the humerus supplying deltoid, teres minor and the shoulder joint before ending as the upper lateral cutaneous nerve of the arm, which supplies a small patch of skin over the insertion of deltoid muscle. The radial nerve is a terminal branch of the posterior cord and descends through the posterior compartment of the arm supplying triceps, brachioradialis and extensor carpi radialis longus and brevis and sensory branches to the skin on the posterior and medial sides of the limb and the posterior surface of the lateral three and a half fingers.

Brachial plexus block
The two techniques most commonly used are described here (Figure 1).

Axillary approach: the patient lies supine, arm abducted to a right angle with the humerus externally rotated. A weal of local anaesthetic is raised over the palpable axillary artery and the needle advanced until the neurovascular sheath is felt to be entered. Anaesthetic solution can then be injected. Finger pressure over the artery distal to the point of injection will prevent the downward spread of the analgesic. There are few complications following this technique and the anatomical landmark is easy to find, but the shoulder joint, supplied by the suprascapular nerve is not anaesthetized.

Supraclavicular approach: the patient lies supine, head rotated away from the side of injection. A weal is raised 1 cm above the midpoint of the clavicle just lateral to the palpable pulsation of the subclavian artery. The needle is advanced downwards, inwards and backwards towards the spine of T4 until a motor jerk or sensation indicates that the needle has pierced the neurovascular sheath. The local anaesthetic solution can then be injected. A cough would suggest that the pleura has been touched or pierced by the needle. This is a more difficult approach to perform safely. Pneumothorax and haematomas due to vessel trauma are well-recognized complications.

Cervical, Thoracic and Lumbar Vertebrae

John Craven

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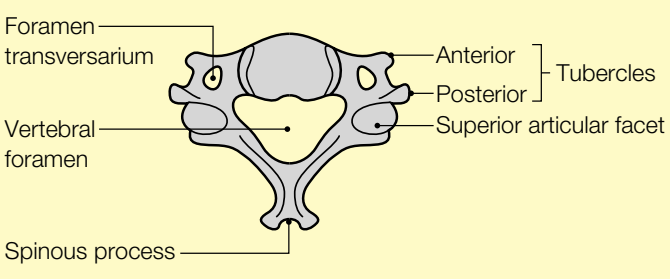
The 33 vertebrae of the vertebral column have a basic form though they show regional differences. They each have a body, neural arch and a vertebral canal. The body is short and cylindrical, with flat upper and lower articular surfaces. The neural arch is made up of paired pedicles that arise from the posterior surface of the body and paired flattened laminae that fuse in the midline posteriorly to form a spinous process. Each arch bears lateral paired transverse processes that arise close to the junction of the laminae and the pedicles, and paired upper and lower articular processes. Each pedicle is notched superiorly and inferiorly and these, with those of their neighbour, form a intervertebral foramen which transmits a spinal nerve. Cervical, thoracic and lumbar vertebrae are recognizable by characteristics that are most marked in their central members, while those at either end of the group tend to resemble in part those of the adjacent group.

A typical cervical vertebra (Figure 1) has an oval small body. Its superior articular surface has lateral lips that articulate by synovial joints with the articular surface of the vertebra above. The vertebral foramen is large. The short wide transverse processes enclose a foramen transversarium, containing the vertebral vessels, and end laterally in anterior and posterior tubercles. The articular processes on the junction of the lamina and the transverse process are large, the superior faces backwards and upwards and the inferior in the opposite direction. The spine is bifid and gives attachment to the neck extensor muscles. The 1st, 2nd and 7th cervical vertebrae vary from this pattern.

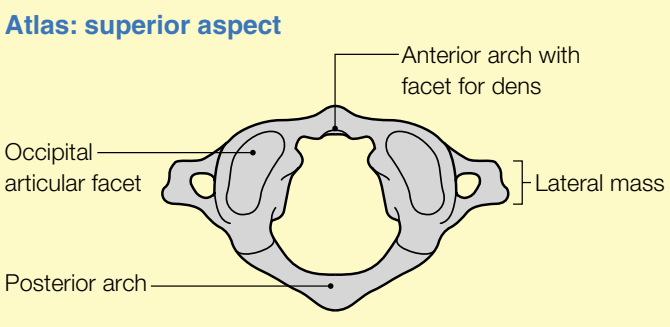
A typical cervical vertebra: superior aspect



1

The 1st cervical vertebra, the atlas, allows free movement of the head and is modified to comprise a ring of bone with neither body nor spine (Figure 2). Two bulky articular lateral masses are united by a short anterior and a longer posterior arch. The superior articular facets are large and oval and articulate with the occiput, the lower facets are smaller. The posterior surface of the anterior arch has a small midline facet for articulation with the dens of the axis, and lateral to this there are two tubercles on the medial surface of the lateral mass for attachment of the transverse ligament of the atlas. The superior surface of the posterior arch is grooved laterally on each side by the vertebral artery. The transverse processes are long and wide and the tip of each is palpable behind the angle of the mandible.

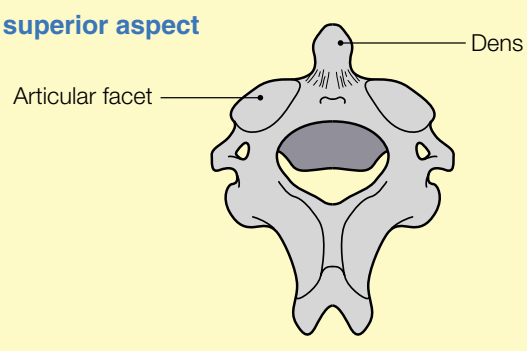
Atlas: superior aspect



2

The 2nd cervical vertebra (Figure 3), the axis, bears a conical projection, the dens on its upper surface which articulates with the anterior arch of the atlas and is held in position by the transverse ligament of the atlas. Lateral to the dens are two large circular upward-facing articular facets.

Axis: superior aspect

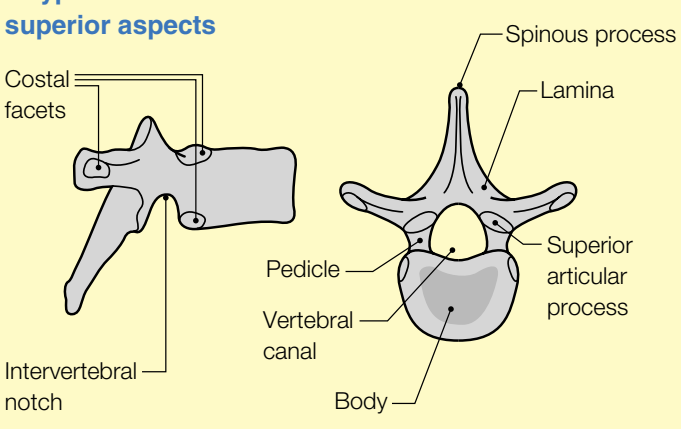


3

The 7th cervical vertebra is also known as the vertebra prominens because it has a long spine, easily palpable on the back of the neck at the lower end of the nuchal furrow.

A typical thoracic vertebra (Figure 4) has a wedge-shaped body that is shallower anteriorly. Each side of each body articulates with a rib at superior and inferior costal facets towards the back of its upper and lower borders. The transverse processes point backwards and laterally, and bear articular facets for articulation with the tubercle of the corresponding rib. The broad laminae and the downward-projecting spines overlap with those of the vertebra below. The bodies of the upper thoracic vertebrae are smaller and narrower; the spines of the lower vertebrae are more horizontal. The transverse processes of the lower two thoracic vertebrae do not bear costal facets. The costal facets on the bodies of the 10th, 11th and 12th vertebrae are normally single and complete.

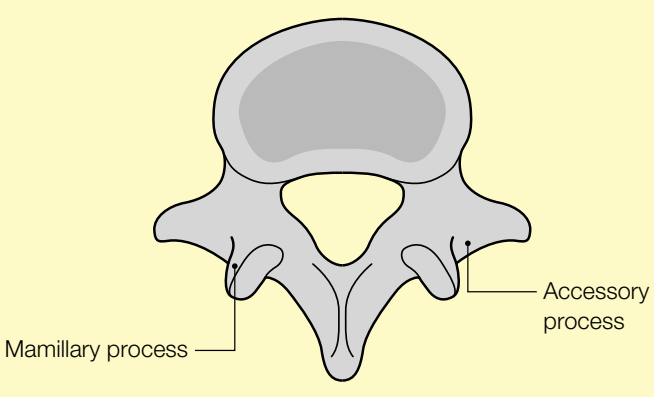
A typical thoracic vertebra: lateral and superior aspects



4

A typical lumbar vertebra (Figure 5) has a larger kidney-shaped body that is wider from side to side. The transverse processes are bulky and project directly laterally. The superior articular facets face backwards and medially, and each spinous process is broad and projects horizontally backwards. The 5th lumbar vertebra is untypical – its body is wedge-shaped, being thicker anteriorly and its transverse process is small and conical.

A typical lumbar vertebra: superior aspect



5

Joints and ligaments

Hyaline cartilage covers the articular surfaces of the vertebral bodies, which are united by a thick fibrocartilaginous inter-vertebral disc. The peripheral fibrous part, the anulus fibrosus surrounds a gelatinous centre, the nucleus pulposus. The discs are, in part, shock absorbers and contribute about 25% of the length of the vertebral column. They are thicker in the cervical and lumbar regions. The vertebral bodies are united by anterior and posterior longitudinal ligaments, which are also attached to each intervertebral disc and extend the length of the vertebral column. The ligamenta flava are formed of elastic tissue and play a part in maintaining the shape of the spine. They unite adjacent laminae. There are also supraspinous, interspinous and intertransverse joints.

Adjacent vertebrae also articulate by plane synovial joints between the paired articular processes. The atlanto-occipital joints are synovial joints with only weak capsular ligaments and the accessory anterior and posterior atlanto-occipital membranes. There are three atlanto-axial joints; two lateral synovial joints between the lateral masses of the two vertebrae and a median joint between the dens of the axis and the ring formed by the transverse ligament of the atlas and its anterior arch. ◆

Cranial Nerves: Part I

John S P Lumley

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The twelve pairs of cranial nerves originate from the forebrain (I–II), midbrain (III–IV) and hindbrain (V–XII), and leave the skull through foramina in the anterior (I), middle (II–VI) and posterior cranial fossae (VII–XII). Collectively, the cranial nerves carry general somatic motor and sensory fibres; general visceral motor and sensory fibres; special somatic sensory fibres; and special visceral motor and sensory fibres. The general somatic motor fibres, passing to somatic mesoderm, are carried in the IIIrd, IVth, XIth and XIIth cranial nerves. The general somatic sensory fibres passing to the skin of the face are carried by the Vth cranial nerve. The general visceral motor and sensory fibres making up the cranial component of the parasympathetic (craniosacral outflow) nervous system, are carried in the IIIrd, VIIth, IXth and Xth cranial nerves. The special somatic sensory fibres comprise the organs of vision (II), and hearing and balance (VIII). The special visceral motor fibres innervate mesoderm derived from the branchial arches, and are carried in the Vth, VIIth, IXth and Xth cranial nerves. The special visceral sensory fibres carry smell (I) and taste (VII and IX).

Damage to cranial nerves may be the first indication of an intracranial lesion and nerve damage is characteristic of various types of head injuries. The identification of cranial nerve lesions and a knowledge of their anatomy are thus an essential part of clinical practice. Cranial nerves I–VI are described in this article, the other cranial nerves will be described in *Anaesthesia and Intensive Care Medicine* **3:5**.

Olfactory nerve (I)

The olfactory mucosa is situated on the upper nasal septum, the roof and the superior concha on the lateral wall of the nose. The 15–20 olfactory nerves innervating this area on each side pass through the sieve-like cribiform plates of the ethmoid bone to the olfactory bulbs. The nerves may be sheared off in anteroposterior impact head injuries, and this may be accompanied by a CSF leak through the nerve channels or through an associated fracture of the cribiform plate.

Optic nerve (II)

The optic nerve passes from the back of the eyeball through the orbit and enters the middle cranial fossa through the optic canal. In the middle cranial fossa the nerves from each side meet in the midline and their medial (nasal) halves decussate at the optic chiasm, before reforming as the right and left optic tracts that pass to, and synapse in, the lateral geniculate body. Each lateral geniculate body projects ipsilaterally through the optic radiation to the visual cortex. (Other fibres from the lateral geniculate body pass to the adjacent ipsilateral superior colliculus of the midbrain; these are concerned with optic reflexes.)

The optic nerve is purely sensory. Its cell bodies form the ganglion layer of the retina and its fibres converge posteriorly at the optic disc. The disc is sited medial to the axis of the eyeball and has no retinal rods or cones; it thus produces the blind spot on visual field mapping. The nerve pierces the sclera to lie within a meningeal sheath that extends from the middle cranial fossa through the optic canal to the back of the eyeball. The sheath is embedded in orbital fat and lies within the cone of extraocular muscles. The ciliary ganglion and the ophthalmic artery lie on its lateral side, the artery is also a lateral relation within the optic canal. Its retinal branch pierces the meningeal sheath about 1 cm behind the globe and for a short distance lies within the CSF, before entering the nerve to become the central artery of the retina.

The optic chiasm lies in the floor of the third ventricle above the hypophysis cerebri and anterior to its stalk. The chiasm lies medial to the termination of the internal carotid artery above the cavernous sinuses. The optic radiation passes distally in the posterior limb of the internal capsule, grooving the floor of the posterior horn of the lateral ventricle. The fibres converge on to the superior and inferior margins of the calcarine sulcus along the medial aspect of the occipital lobe.

Spatial orientation is preserved through the length of the visual pathways. Fibres from the nasal half of each retina (receiving light from the temporal field) cross in the optic chiasm;thus the optic tract, lateral geniculate body, optic radiation and visual cortex of each side receive visual information from the contralateral side. Fibres from the lower retina pass through the temporal lobe to the inferior margin of the calcarine sulcus. Upper quadrant fibres pass through the parietal aspect of the optic radiation and to the upper margin of the calcarine sulcus. The macula is the most sensitive part of the retina, and makes up about 25% of the visual cortex.

Assessment

Assessment of vision is carried out by history, and tests of acuity, visual fields and ophthalmoscopy. The history in-corporates questions on near and distant vision, visual loss, visual phenomena (e.g. blurring, flashes, double vision), ocular pain and headache. Tests of visual acuity and of the visual fields are undertaken in each eye separately (the other eye being covered with a hand or card) and then together. Abnormalities of acuity are predominantly refractory, and patients are assessed with and without their spectacles. Near vision is assessed with varying sized text, distant vision with Snellen charts, and colour with Ishihara cards. Further tests of acuity are carried out by an optician using an appropriate series of lenses.

Clinical assessment of the visual fields is by confrontation of the examiner and subject, each covering in turn an opposing eye, the examiner's other hand is brought in from each quadrant. A red-topped hatpin is used to identify the blind spot and any central defect (scotoma). Both the examiner's hands are used to determine visual preference or suppression of an image on one side. Normal pupils react to light and accommodation.

Ophthalmoscopy is used to examine the anterior aspect of the eye, the cornea, the anterior chamber, iris and lens, and then the posterior chamber and retina.

Abnormalities of vision

Vision is affected by abnormalities of the eye and the neural pathways: these may co-exist. The former include abnormalities of the lens (e.g. refractory errors, cataract) or retina (e.g. detachment, ischaemia, hypertension, diabetic eye disorders); macular degeneration; inflammation; or trauma to the globe. Lesions of the various parts of the visual pathway produce characteristic visual field defects (Figure 1).

Visual defects

1 Tunnel vision with damage to peripheral visual field with night blindness: glaucoma, papillitis, chorioretinitis, retinitis pigmentosa, papilloedema, migraine, hysteria, syphilis

2 Enlargement of blind spot; enlargement of optic head, papillitis, papilloedema

3 Central scotoma with spectrum from enlarged blind spot, patchy scotoma and arcuate lesions to blindness: advanced papilloedema, optic nerve damage or tumours, demyelination, toxic (e.g. methyl alcohol) symmetrical, nutritional, vascular

4 Unilateral blindness: damage to optic nerve, tumours, vascular malformation, severe trauma. In blindness, the visual light reflexes are lost, but the consensual pupillary responses are retained

5 Bitemporal hemianopia: midline pituitary tumours and suprasellar meningiomas

6 Ipsilateral nasal field loss: aneurysms of the internal carotid artery and its proximal divisions, tumours

7, 8, 9 Homonomous hemianopia: tumours, trauma and vascular damage of the optic tract, lateral geniculate body or optic radiation, producing incongruous defects (i.e. unequal involvement of the two half fields)

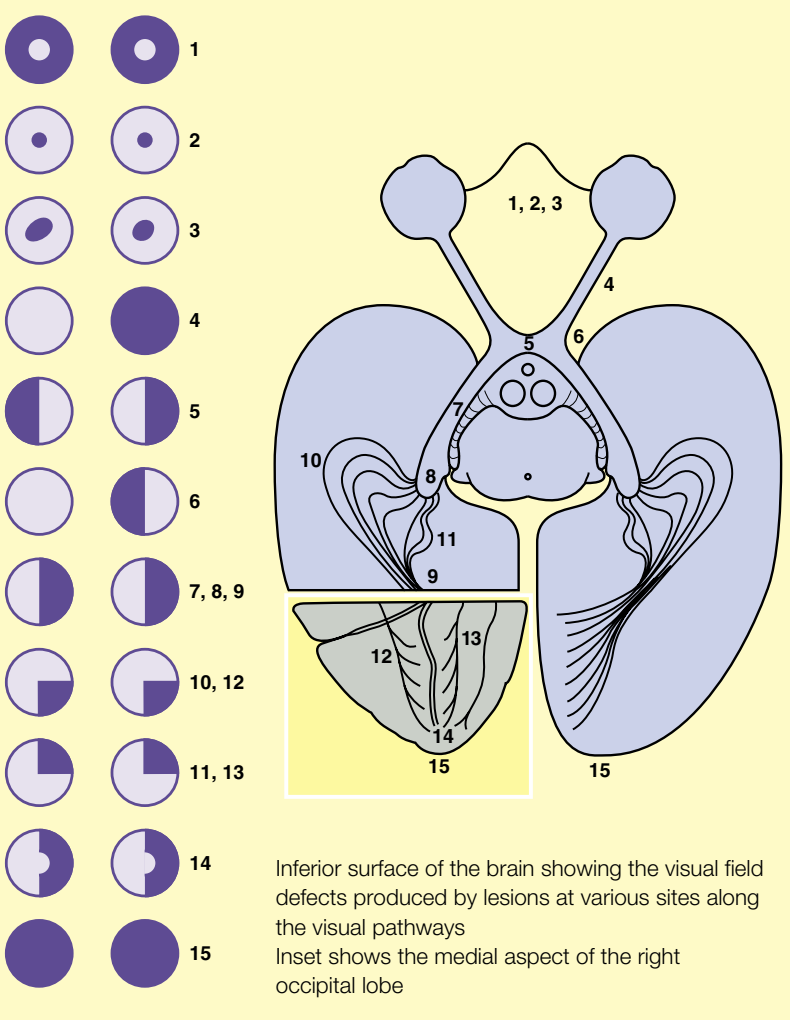
10 Lower quadrantic hemianopia, with incongruous defects, and suppression or loss of image with simultaneous delivery from each side, parietal lobe tumours, particularly with lesions of the non-dominant hemisphere

11 Upper quadrantic hemianopia: temporal lobe lesions, due to occlusion of the middle cerebral or the thalamogenicular branch of the posterior cerebral artery

12, 13 Lower and upper quadrantic hemianopia: respectively from lesions above and below the calcarine fissure.

14 Homonomous hemianopia, congruous defects with macular sparing due to the large cortical representation of the macula: reading is preserved: posterior cerebral artery occlusion

15 Cortical blindness: degenerative arterial disease with bilateral ischaemic infarction of the occipital lobes, near drowning, basilar artery spasm in severe migraine



Inferior surface of the brain showing the visual field defects produced by lesions at various sites along the visual pathways
Inset shows the medial aspect of the right occipital lobe

Oculomotor (III), trochlear (IV) and abducent (VI) nerves

The oculomotor, trochlear and abducent nerves carry somatic motor fibres to the extraocular muscles. In addition, the oculomotor nerve carries parasympathetic fibres that synapse in the ciliary ganglion and supply the pupillary and ciliary muscles. The nuclei of the three nerves are in the periaqueductal grey matter of the upper (III) and lower (IV) midbrain, and in the lower pons (VI).

The oculomotor nerve passes anteriorly through the midbrain, and emerges between the cerebral peduncles; it passes through the posterior and middle cranial fossae to divide into superficial and inferior branches near the supraorbital fissure. In the posterior cranial fossa the nerve passes near the edge of the tentorium cerebelli. In the middle cranial fossa the nerve pierces the cerebral layer of dura to pass forwards on the lateral wall of the cavernous sinus. The superior division passes through the superior orbital fissure and supplies the superior rectus and levator palpebrae superioris. The inferior division supplies the medial and inferior recti, and inferior oblique muscles. The nerve to inferior oblique gives the parasympathetic branch to the ciliary ganglion.

The trochlear nerve is the thinnest cranial nerve. It passes posteriorly and undergoes a dorsal decussation with its fellow of the opposite side caudal to the inferior colliculus. The nerve then passes through the posterior and middle cranial fossae and enters the orbit through the superior orbital fissure to supply the superior oblique muscle. In the posterior cranial fossa, the nerve passes forward around the midbrain. In the middle cranial fossa, it pierces the cerebral layer of dura, and lies between the oculomotor and ophthalmic nerves in the lateral wall of the cavernous sinus. It passes through the superior orbital fissure outside the tendinous ring and passes medially between levator palpebrae superioris and the roof of the orbit, to reach and supply the superior oblique muscle.

The abducent nerve leaves the inferior border of the pons near the midline, passing forwards through the posterior and middle cranial fossae, the cavernous sinus and the orbit to reach and supply the lateral rectus muscle. In the posterior cranial fossa the nerve lies between the pons and the basilar part of the occipital bone and passes over the apex of the petrous temporal bone, through the cavernous sinus lateral to the internal carotid artery. It enters the orbit through the superior orbital fissure within the tendinous ring.

Assessment

When examining the IIIrd, IVth and VIth cranial nerves, first check the extraocular movements (LR_6, SO_4 provides a way of remembering the muscles supplied by the IVth and VIth nerves). In addition, the IIIrd nerve is responsible for the pupillary responses to light and accommodation, and eyelid elevation by the levator palpebrae superioris (PERLA – pupils react to light and accommodation). Note any squint or nystagmus.

Horizontal movements are brought about specifically by the lateral and medial recti muscles, but other movements are more complex: upward and downward gaze should be assessed in extremes of abduction and adduction (i.e. in H fashion). The eyes are examined together but when abnormalities of conjugate gaze are present, or the patient complains of diplopia, the eyes are examined independently.

With abnormalities of the IIIrd nerve, there is:
- weakness of elevation and adduction (i.e. a divergent strabismus is present, the eye looking downwards and outwards on forward gaze)
- ptosis – the patient is unable to elevate the eyelid (compared with retention of voluntary lid-raising in Horner's syndrome)
- a dilated pupil non-reactive to light or accommodation, though the consensual light reflex is retained
- proptosis, as a result of muscular relaxation
- diplopia.

In IVth nerve paralysis, there is torsion of the globe on downward gaze. The head may be tilted to the opposite shoulder, so the patient can achieve binocular vision. Although the superior oblique muscle directs the eye downwards and outwards, adduction is also produced by the inferior rectus and the prime defect is that of intorsion (i.e. the patient cannot look at the tip of their nose). Damage to the VIth nerve produces a convergent strabismus, the patient is unable to abduct the eye and diplopia is a prominent feature.

The three nerves can be damaged by tumours within the orbit and the nasopharynx. In lesions of the superior orbital fissure (Tolosa-Hunt syndrome) there is additional damage to the ophthalmic division of the trigeminal nerve, producing pain. In the middle cranial fossa, caroticocavernous fistulae and aneurysms of the internal carotid artery may produce nerve damage, and in the posterior fossa, aneurysms, particularly of the posterior communicating artery. The three nerves commonly provide important signs in head injuries; in tentorial coning, the IIIrd nerve is first stimulated and then progressively paralysed, the pupil becoming fixed and dilated. The IVth nerve is damaged in reversed coning from expanding lesions in the posterior fossa. The effect can be the result of direct nerve pressure on the lateral edge of the tentorium, or posterior shift of the brainstem with pressure of the tentorium on the third and fourth nerve nuclei in the midbrain. The VIth nerve can produce false localizing signs owing to its long intracranial course.

Trigeminal nerve (V)

The trigeminal nerve is the largest cranial nerve. It emerges from the cerebellopontine angle as a large sensory (general somatic) and a smaller motor (special visceral) root. The roots pass over the apex of the petrous temporal bone to the trigeminal ganglion, pushing a pouch of dura (Meckel's cave) into the middle cranial fossa. The semilunar (Gasserian) ganglion lies lateral to the cavernous sinus in the middle cranial fossa. The ophthalmic, maxillary and mandibular divisions arise from the anteroinferior aspect of the ganglion. The motor root, passing medial to the ganglion, joins the mandibular division.

The ophthalmic division is the smallest. It lies in the lateral wall of the cavernous sinus below the oculomotor and trochlear nerves. Near the superior orbital fissure, it divides into lacrimal, frontal and nasociliary branches that pass through the fissure into the orbit. The lacrimal nerve supplies the lacrimal gland (conveying parasympathetic fibres from the zygomaticotemporal branch of the pterygopalatine ganglion), the upper eyelid and the lateral conjunctiva. The frontal nerve divides into supraorbital and supratrochlear branches, supplying the upper eyelid, medial forehead and the scalp as far as the vertex. Only the nasociliary branch passes through the tendinous ring. It divides into anterior ethmoidal and infratrochlear nerves, supplying the ethmoidal and sphenoidal air sinuses, the upper eyelid and the adjacent nose. Long ciliary branches carry sympathetic dilator pupillae fibres that pass through the ciliary ganglion.

The maxillary division passes forward, lateral to the cavernous sinus in the middle cranial fossa to the pterygopalatine fossa to enter the inferior orbital fissure and become the infraorbital nerve. The pterygopalatine ganglion is suspended from it in the pterygopalatine fossa where it is also related to the terminal branches of the maxillary artery. Through the ganglion, the maxillary nerve supplies sensory fibres to the lateral nose and nasopharynx. The zygomatic nerves supply skin over the cheek and temple. Posterior superior alveolar nerves supply the maxilla, and upper molar and premolar teeth. The infraorbital nerve emerges through the infraorbital foramen on the face to supply the lower eyelid and conjunctival side of the nose and upper lip. Its middle and anterior superior alveolar branches, given off in the infraorbital canal, supply the premolar, canine and incisor teeth, and the lateral wall of the nose and maxillary air sinus.

The mandibular division leaves the middle cranial fossa through the foramen ovale to lie between tensor palati and the lateral pterygoid muscles, with the otic ganglion on its medial side. The surface marking of this opening is 4 cm medial and just anterior to the neck of the mandible, the nerve may be anaesthetized using these relationships. The motor branches supply the muscles of mastication, tensor tympani and tensor palati.

The sensory branches have a wide distribution to the meninges of the middle cranial fossa, the skin and mucous membrane in the cheek, through the buccal nerve, the temporal region of the scalp, tympanic membrane, external auditory meatus and the anterior auricle through the auriculotemporal nerve. This nerve also carries parasympathetic fibres from the otic ganglion, and sympathetic fibres from the plexus around the middle meningeal artery, to the parotid gland. The inferior alveolar branch of the mandibular nerve enters the mandibular foramen and passes along the mandibular canal to supply the gums and teeth. The mental nerve emerges through the mental foramen, and supplies the skin and mucous membrane of the lower lip, and gum. The inferior alveolar nerve also carries motor fibres, that pass to the mylohyoid and anterior belly of the digastric muscles, before the nerve enters the mandibular canal.

The largest branch of the mandibular nerve is the lingual, which is formed between the tensor palati and lateral pterygoid muscles. It passes forward between the medial pterygoid and ramus of the mandible, and under the mucous membrane, over the root of the third lower molar tooth (an important relation for dental anaesthesia) and then between hyoglossus and mylohyoid. On the hyoglossus, the lingual nerve is overlapped by the submandibular gland and has the submandibular ganglion suspended from it. The nerve supplies sensory branches to the anterior two-thirds of the tongue, the floor of the mouth and the lingual gums. 3 cm below the base of the skull, the nerve is joined by the chorda tympani branch of the facial nerve, carrying parasympathetic fibres; these synapse in the submandibular ganglion and pass to the submandibular and sublingual salivary glands, and taste fibres for the anterior two-thirds of the tongue.

Assessment

Examination of the three divisions is by assessment of sensation over the forehead, cheek and lower jaw, together with the corneal reflex. Motor fibres are assessed by palpation of the masseter and temporalis, on jaw-clenching, protrusion of the jaw by the pterygoid muscles and the jaw jerk. The proximal divisions may be damaged by caroticocavernous fistulas and aneurysms in the middle cranial fossa, and by fractures, aneurysms, meningiomas, acoustic neuromas and other intracranial tumours in the middle and posterior cranial fossa. Brainstem lesions such as vascular, tumours and syringobulbia produce a bulbar palsy, and bilateral cortical lesions produce a pseudobulbar palsy, affecting the motor component, and the nerve is subject to trigeminal neuralgia. ◆

Cranial Nerves: Part II

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This article describes cranial nerves VII–XII. Cranial nerves I–VI are described in *Anaesthesia and Intensive Care Medicine* **3:3:** 116.

Facial nerve (VII)

The facial nerve carries special visceral, and autonomic, motor and sensory fibres. The special visceral motor fibres supply the muscles of the second pharyngeal arch mesoderm, which are primarily those of facial expression, while the special visceral sensory fibres carry taste from the anterior two-thirds of the tongue to the tractus solitarius, they pass through the chorda tympani branch to the lingual nerve. Parasympathetic fibres are secretomotor to the submandibular, sublingual and lacrimal glands, and glands of the mucous membrane of the nose, pharynx and mouth, branches passing via the pterygopalatine and submandibular ganglia.

Sensory (nervus intermedius) and motor roots leave the lower lateral surface of the pons and enter the internal auditory meatus, passing to the geniculate (facial) ganglia. The nervus intermedius also carries the parasympathetic fibres. The nerve turns sharply posteriorly through a bony canal medial to the middle ear and then downwards, related to the posterior aspect of the middle ear, through the temporal bone to emerge at the stylomastoid foramen. The nerve then turns forwards into the parotid gland where it divides into temporal, zygomatic, buccal, mandibular and cervical motor branches, to supply facial muscles, buccinator and platysma.

The greater petrosal branch

The greater petrosal branch leaves the geniculate ganglion to pass through the petrous temporal bone and middle cranial fossa to join the deep petrosal nerve (sympathetic branches from the internal carotid plexus) and pass through the pterygoid canal to the pterygopalatine ganglion.

The chorda tympani branch

The chorda tympani branch arises from the nerve in the temporal bone, just above the stylomastoid foramen, and passes forward through the middle ear between the tympanic membrane and the handle of the maleus. It passes forward through the temporal bone to emerge from the petrotympanic fissure, to join the lingual nerve 3 cm below the base of the skull.

Assessment

Motor function is assessed by facial symmetry (forehead wrinkles, nasolabial fold, corner of mouth) and expression, and power of eye closure, whistling and blowing out the cheeks actively and against resistance. Lower motor neuron damage produces paralysis of the ipsilateral face, whereas in upper neuron damage, only the contralateral lower face is paralysed, sparing the muscles of the forehead and eyebrow, which are bilaterally innervated. Sensory examination is of taste over the anterior two-thirds of the tongue.

The most common lower motor neuron lesion is Bell’s palsy, but the nerve may be damaged by lesions and surgery of the parotid gland, basal skull fractures, Hunt's syndrome, otitis media and tumours of the posterior cranial fossa, particularly acoustic neuromas. Nuclear lesions include vascular, tumours, syringobulbia and multiple sclerosis. Supranuclear lesions are primarily vascular or tumours. Bilateral facial weakness may be part of a pseudobulbar palsy of vascular origin, Guillain-Barré syndrome, bilateral parotid disease and skull fractures. The onset following a skull fracture may be delayed owing to oedema, this has a better prognosis than primary nerve damage. Isolated loss of taste is unusual, but may be related to middle ear infection, damaging the chorda tympani.

Vestibulocochlear nerve (VIII)

This special somatic sensory nerve consists of vestibular fibres, concerned with balance, and cochlear fibres, concerned with hearing. The latter originate in the organ of Corti and pass in the bipolar cells of the spiral ganglia within the modiolus. Vestibular fibres pass from the semicircular ducts, saccule and utricle to the bipolar cells in the vestibular ganglion in the internal auditory meatus. The two components of the nerve unite in the internal auditory meatus and pass medially to enter the cerebellomedullary angle of the brainstem, to reach the nuclei in the floor of the fourth ventricle.

Assessment

Assessment of hearing includes examination of the external auditory meatus to identify disease of the canal or eardrum, and the appreciation of soft noises, such as a watch tick or a whisper. Rinne’s test assesses whether air conduction of the sound of a clinical 512 Hz tuning fork is better than bony conduction of the base of the fork placed over the mastoid process (the normal pattern). In Weber’s test sound transmission from the base of the tuning fork placed in the centre of the forehead is transmitted equally to the two ears (normal).

Deafness may be related to:

- wax
- infective and other diseases of the external auditory meatus, tympanic membrane and middle ear
- tumours, particularly acoustic neuromas and those of the skull base
- toxicity (e.g. streptomycin and alcohol) and degenerative disease such as excess environmental exposure
- otosclerosis and bony abnormality (e.g. Paget’s disease).

Abnormalities of balance are usually detected by the patient’s history and they may be associated with nystagmus and vertigo. They may be caused by acute labyrinthitis, Menière’s disease, drug toxicity and motion sickness, as well as trauma, and lesions of the skull base and brainstem.

Glossopharyngeal nerve (IX)

General visceral sensory fibres arise from the pharynx, posterior third of the tongue, the carotid sinus and carotid body, taste from the posterior third of the tongue and parasympathetic fibres synapsing in the otic ganglia supplying the parotid and pharyngeal glands.

The glossopharyngeal nerve carries special visceral motor fibres to the tylopharyngeus muscle. The nerve rootlets leave the medulla lateral to the olive and the nerve passes through the jugular foramen medial to the vagus and accessory nerves, descending between the internal and external carotid arteries to enter the pharyngeal wall, between the superior and middle constrictor muscles.

The tympanic branch of the nerve passes through the petrotympanic fissure to the tympanic plexus in the middle ear, from whence lesser petrosal nerve fibres pass to the otic ganglion, carrying parasympathetic fibres to the parotid gland. The sinus nerve descends between the internal and external carotid arteries to supply the carotid body and carotid sinus.

Isolated nerve damage is uncommon, but produces loss of sensation over the anterior pillar of the fauces (gag reflex) and loss of taste from the posterior third of the tongue, including the circumvalate papillae, and impairment of carotid sinus and carotid body reflexes. The gag reflex is reduced with age. Lesions resemble those of the Xth nerve, to which it is closely related intracerebrally.

Vagus nerve (X)

The vagus nerve has a more extensive distribution than any other cranial nerve. It carries:

- visceral motor fibres to the striatal muscle of the palate, pharynx and larynx
- parasympathetic visceral motor and sensory fibres to the mucosa of the palate, pharynx and larynx and to the heart, lungs and alimentary tract as far as the splenic flexure
- somatic sensory fibres to the posterior aspect of the external auditory meatus and tympanic membrane, via its auricular branch
- a few taste fibres.

The nerve is formed from a number of rootlets emerging lateral to the olive and leaves the posterior cranial fossa through the internal jugular foramen, between the IXth nerve medially and the XIth laterally. It has swellings within and just below the jugular foramen; these ganglia are somatic and visceral sensory in nature. It lies posteriorly in the carotid sheath as it descends through the neck and in the thorax, the two vagal nerves pass posteriorly to each bronchus to form the pulmonary plexus and then converge on the oesophagus to form the oesophageal plexus, and thence the anterior and posterior vagal nerves (the left and right vagal trunks, respectively) for distribution to the alimentary tract.

The various branches include pharyngeal, cardiac and pulmonary, together with two constant branches to the larynx. The superior laryngeal nerve descends between the pharynx medially and the internal carotid artery laterally. It divides below the hyoid bone into the internal laryngeal nerve that pierces the hyoid membrane to supply the mucous membrane of the larynx above the vocal folds, and the external laryngeal nerve, that descends on the larynx to supply the cricothyroid muscle. The recurrent laryngeal nerves hook round the subclavian on the right and the aortic arch on the left, to ascend in the groove between the trachea and oesophagus, closely related to the thyroid gland, entering the larynx deep to the inferior constrictor muscle to supply the mucous membrane below the vocal folds and all the intrinsic muscles except the cricothyroid.

Assessment

The muscles of the palate are assessed by watching:

- the uvula and palate rise when saying ‘aah’
- the pharynx for evidence of regurgitation when swallowing a cup of water
- the larynx by coughing and saying a high ‘ee’.

Clinically demonstrably abnormal signs are limited to the pharynx and larynx. Pareses produces lateral displacement of the uvula, coughing and spluttering on swallowing, implying fluid regurgitating into the larynx rather than passing down the oesophagus, and a bovine cough because the vocal cords are not fully approximated. Bilateral recurrent laryngeal nerve injuries may produce stridor and respiration obstruction.

The vagal nuclei lie on the medulla and are the dorsal motor and sensory (parasympathetic) and the nucleus ambiguous (special visceral motor), taste fibres pass to the nucleus of the tractus solitarius.

Lower motor neuron lesions are produced by tumours of the posterior fossa and around the skull base, aneurysms, chronic meningitis and Guillain-Barré syndrome. Nuclear abnormalities are produced by tumours, syringobulbia and motor neuron disease. The bilateral pyramidal innervation requires bilateral lesions to produce a pseudobulbar palsy, this is usually secondary to cerebrovascular disease.

Accessory nerve (XI)

This somatic motor nerve supplies sternomastoid and trapezius muscles, the fibres having their nuclei in the upper five cervical segments of the cervical cord. The fibres ascend through the foramen magnum to the posterior fossa, and the nerve leaves the fossa through the jugular foramen, lateral to the IXth and Xth nerves. It then passes laterally, anterior to the internal jugular vein and the transverse process of the atlas into the substance of the sternomastoid, crossing the posterior triangle of the neck, over levator scapulae, to reach the deep surface of the trapezius. Inside the posterior fossa, the cranial root of the accessory nerve, carrying fibres from the nucleus ambiguus, joins the accessory, but those fibres ultimately return to the vagus.

Examination of the nerve is by assessing the bulk of the trapezius and sternomastoid muscles, asking the subject to turn the head to the opposite side against resistance, and watching shoulder shrugging.

Lesions occur through trauma of the base of the skull, tumours of the posterior cranial fossa and skull base, poliomyelitis, syringomyelia, motor neuron disease and Guillain-Barré syndrome. The nerve may be damaged by trauma or surgery in the neck. These muscles may also be involved in muscular dystrophies.

Hypoglossal nerve (XII)

The hypoglossal nerve provides the somatic motor supply to all the intrinsic and extrinsic muscles of the tongue except palatoglossus. Its nucleus is situated in the medulla in the floor of the fourth ventricle. The nerve emerges from the medulla between the pyramid and the olive and leaves the posterior cranial fossa through the hypoglossal canal, above the occipital condyle. It descends behind the carotid sheath, then passes forwards round the pharynx between the internal carotid artery and the internal jugular vein to cross in turn the internal and external carotid arteries, the loop of the lingual artery on the middle constrictor, and the hyoglossus muscle. It is covered laterally by the posterior belly of the digastric, the submandibular gland and the mylohyoid muscle. The hypoglossal nerve also receives branches from the first cervical nerve near the base of the skull and conveys these fibres to the geniohyoid and thyrohyoid muscles, they then form the descendens hypoglossi nerve which supplies the infrahyoid muscles through the ansa hypoglossi.

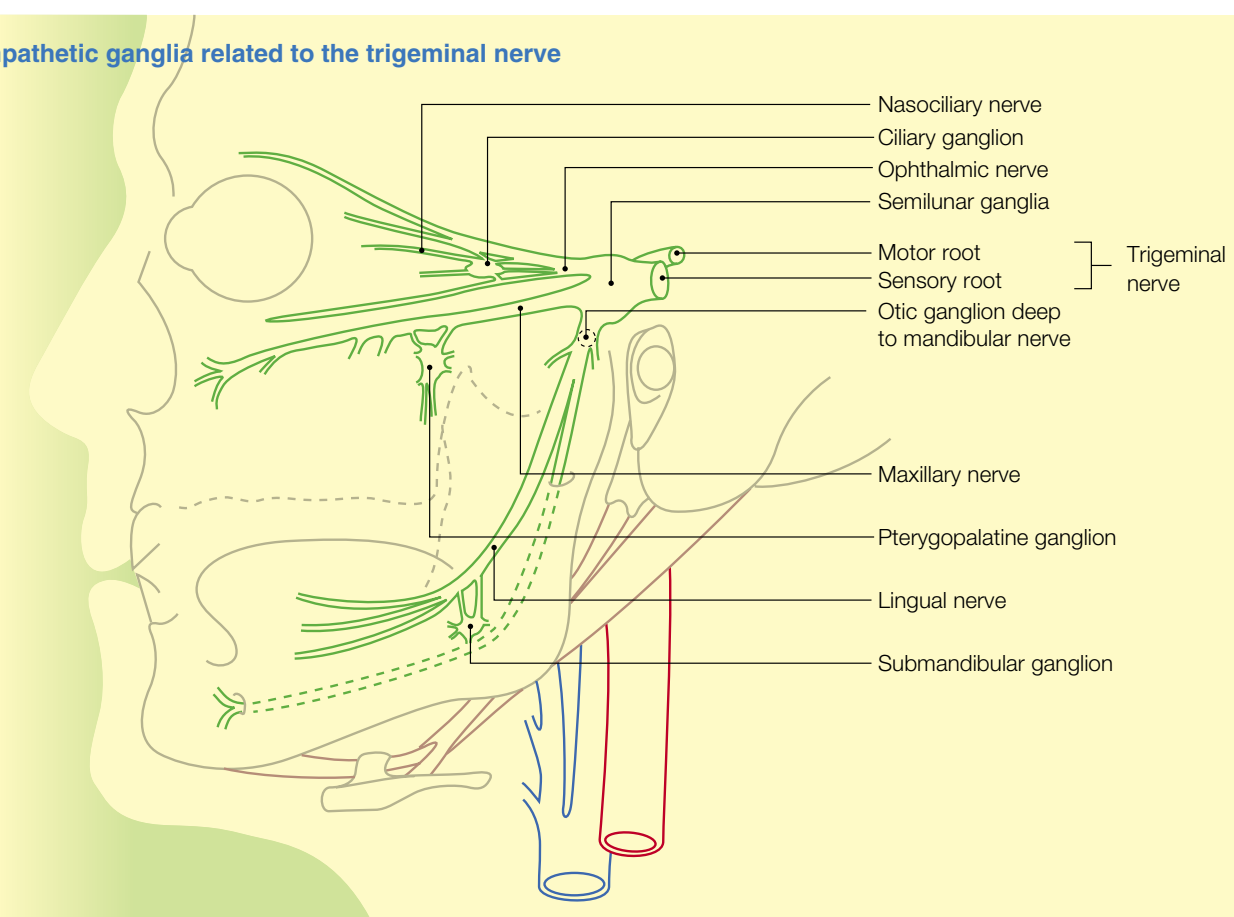
In lower motor neuron lesions, the tongue is observed for wasting, weakness, and fasciculation and dysarthria: the tongue is protruded towards the side of a lesion.

Upper motor neuron defects are unusual in view of the bilateral innervation, but may occur in vascular diseases. Nuclear lesions are seen in motor neuron disease, tumours, thrombosis of the vertebral artery, syringobulbia and lower motor neuron lesions due to tumours and aneurysms of the posterior cranial fossa, trauma, chronic meningitis, Arnold-Chiari malformation, poliomyelitis and the Guillain-Barré syndrome.

Parasympathetic cranial ganglia

Whereas the sympathetic nerve fibres relay in a proximally placed series of ganglia in the sympathetic chain (T1–L2), the ganglia of the parasympathetic system (craniosacral) are sited near the organs they innervate. There are four well-defined cranial ganglia: the ciliary, pterygopalatine, submandibular and otic (Figure 1).

Parasympathetic ganglia related to the trigeminal nerve



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Ciliary ganglion

The ciliary ganglion is the smallest and the size of a pin head; it is situated between the optic sheath and the lateral rectus muscle, near the apex of the orbital cavity. It is usually lateral to the ophthalmic artery.

The parasympathetic fibres arise in the Edinger–Westphal nucleus in the midbrain and are carried by the short ciliary nerves to the back of the eyeball to supply the sphincter pupillae and ciliary muscles.

Sympathetic fibres from the superior cervical ganglion reach the ciliary ganglia via the plexus on the ophthalmic artery and pass without synapse to the blood vessels and smooth muscle of the eyeball.

Sensory fibres pass without relay through the ganglia to the eyeball, reaching the ciliary ganglion through the long ciliary branches of the nasociliary nerve.

Pterygopalatine (sphenopalatine) ganglion

The pterygopalatine (sphenopalatine) ganglion is the largest of the peripheral parasympathetic ganglia. It is situated in the pterygopalatine fossa suspended from the maxillary nerve receiving afferent and efferent branches from it.

Parasympathetic fibres originate in the VIIth nerve nuclei, leaving the nerve in the temporal bone as the greater petrosal nerve. This receives sympathetic fibres from around the internal carotid artery as the deep petrosal nerve, to form the nerve of the pterygoid canal that passes to the ganglion. The numerous branches of the ganglion, including nasal, nasopalatine and pharyngeal, are primarily derived from the maxillary nerve but carry postsynaptic secretomotor fibres to the palate, pharynx and nasal glands, and also via the connection to the zygomatic frontal nerve to the lacrimal gland.

Sympathetic fibres are similarly distributed to the smooth muscle of the blood vessels of the palate, pharynx and nose.

Submandibular ganglion

The submandibular ganglion lies on the hyoglossus muscle, suspended from the lingual nerve by afferent and efferent branches, and above the deep part of the submandibular gland. Its parasympathetic fibres originate in the seventh nerve, and pass with the taste fibres via the chorda tympani nerve. Parasympathetic fibres originate in the superior salivary nucleus in the midbrain and the taste fibres in the tractus solitarius. Postsynaptic parasympathetic fibres pass via the lingual nerve and direct branches to the submandibular, sublingual and other oral glands, accompanied by sympathetic fibres derived from the superior cervical ganglion and reaching the submandibular ganglion via the facial artery.

Otic ganglion

The otic ganglion lies between the tensor palati muscle laterally and the auditory tube medially, with the middle meningeal artery posteriorly. It is closely related to the nerve to the medial pterygoid muscle.

Parasympathetic fibres are derived from the inferior salivary nucleus of the IXth nerve, passing through the foramen ovale to the otic ganglion. Efferent fibres pass via the auriculotemporal nerve to the parotid gland.

Sympathetic fibres derived from the superior cervical ganglion pass via the plexus on the middle meningeal artery and through the otic ganglion without synapse, to be distributed to the blood vessels of the parotid gland. ◆

The Cubital Fossa

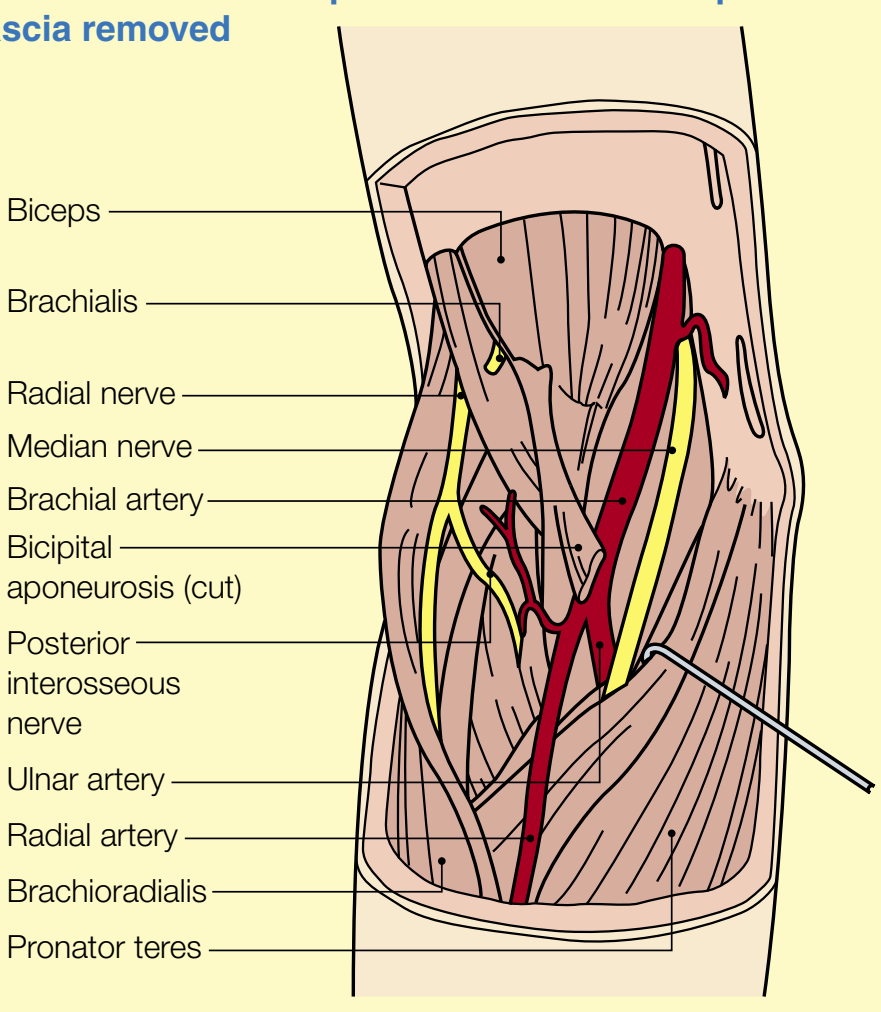
John Craven

John Craven was formerly Consultant Surgeon at York District Hospital, York, UK. He trained in Manchester, Uganda and Cardiff. He is past chairman of the primary examiners of the Royal College of Surgeons of England. His particular interest is gastric cancer.

The cubital fossa is a triangular hollow area that lies in front of the elbow joint. It is bounded (Figure 1):

- superiorly by an imaginary line connecting the medial and lateral epicondyles
- medially by the pronator teres muscle
- laterally by the brachioradialis muscle.

Cubital fossa with superficial veins and deep fascia removed



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Its floor is formed of the brachialis and supinator muscles overlying the capsule of the elbow joint. The deep fascia of the forearm forms its roof, which is strengthened by fibres of the bicipital aponeurosis. Lying on the roof in the superficial fascia are the anterior branches of the medial and lateral cutaneous nerves of the forearm and the median cubital vein which joins the cephalic and basilic veins.

The cephalic, basilic and median cubital veins are usually easily seen and palpated in the roof of the fossa, and this is therefore a common site for venepuncture. It is worth noting that variations in venous anatomy at this site are common (Figure 2). The use of the cubital fossa for intravenous fluid therapy is not recommended because movement of the elbow joint disturbs the cannula and irritates the vein wall with the consequence that thrombosis of the vein quickly occurs.

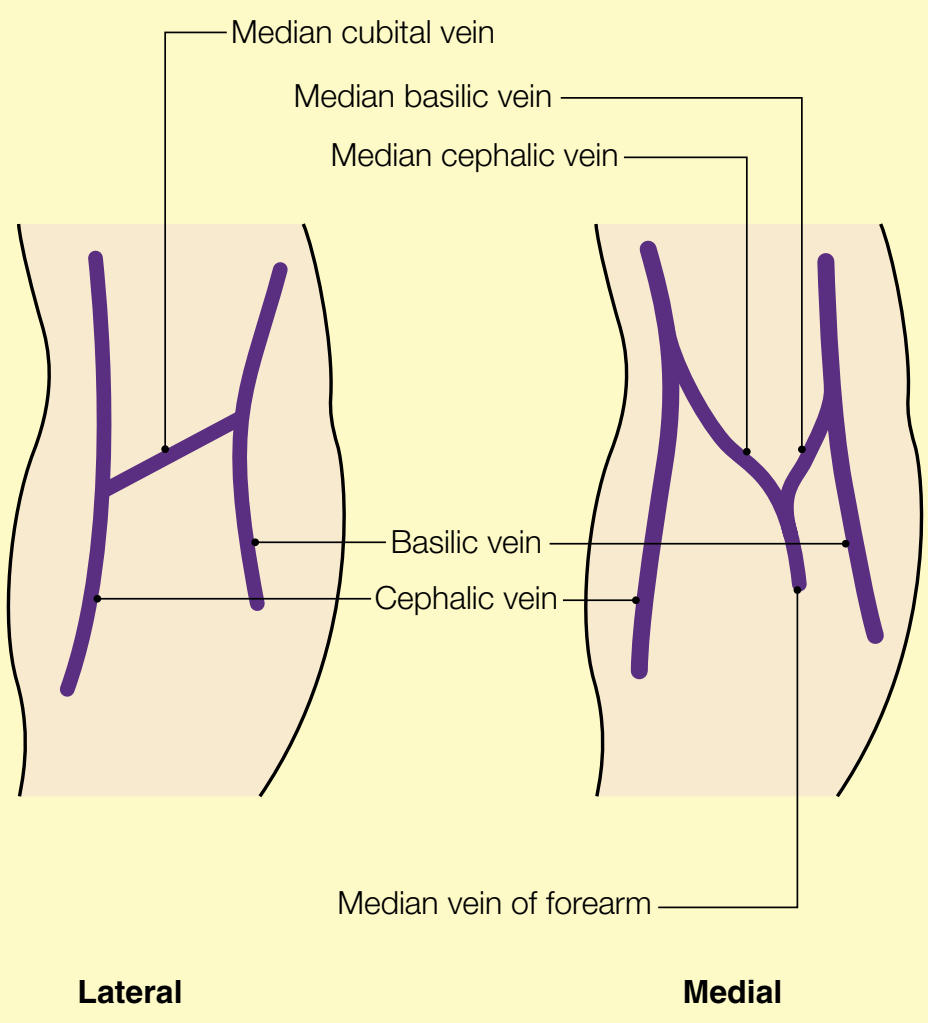
The contents of the fossa from medial to lateral are:

- median nerve
- brachial artery and its terminal branches, the radial and ulnar arteries
- biceps tendon and bicipital aponeurosis (which separates the median cubital vein from the brachial artery)
- radial and posterior interosseous nerves, which are often overlapped by the fibres of brachioradialis.

The brachial artery is palpated here when the arterial pressure is being taken by a sphygmomanometer but, because of the bicipital aponeurosis, the elbow should be fully extended so that the artery is pressed back on to the elbow joint, which renders palpation a little easier. The brachial artery is in close relation to the medial nerve, which lies on its medial side. Awareness of this relationship should minimize the incidence of nerve trauma during arterial puncture for blood sampling or the insertion of arterial catheters for cardiac or other investigations. Rarely, the cubital fossa is used for distal nerve blocks.

The median nerve can be anaesthetized by injecting 5 ml of local anaesthetic solution through a weal raised midway between the outer side of the tendon of biceps and the medial epicondyle. This anaesthetizes the lateral half of the palm and fingers.

Common arrangements of veins in the cubital fossa



2

The Diaphragm, its Action and Innervation

John Craven

John Craven was formerly Consultant Surgeon at York District Hospital, York, UK. He trained in Manchester, Uganda and Cardiff. He is past chairman of the primary examiners of the Royal College of Surgeons of England. His particular interest is gastric cancer.

The diaphragm is a musculotendinous septum that separates the abdominal and thoracic cavities. It has a peripheral muscular portion, which attaches to its central tendon. It is attached peripherally to:

- the sternum − by two muscular slips from the back of the xiphoid process
- the ribs − from the inner surfaces of the lower six ribs and costal cartilage where its fibres interdigitate with fibres of transversus abdominis
- the upper lumbar vertebrae.

It is attached to the sides of the upper lumbar vertebrae by two crura and from the medial and lateral arcuate ligaments on each side. The right crus attaches to the first three vertebral bodies and the left crus to the first two. The right crus is the larger and passes forwards and to the left, surrounding the oesophageal opening.

The medial arcuate ligament, the thickened upper edge of the psoas fascia extends in front of the psoas from the body of the first lumbar vertebra to its transverse process. The lateral arcuate ligament lies anterior to the quadratus lumborum attached between the transverse process of the first lumbar vertebra and the 12th rib. The central attachment of the diaphragm is to the margins of a trilobed central tendon.

Nerve supply

The right and left phrenic nerves (C3,4,5) supply the corresponding halves of the diaphragm.

- The right phrenic nerve descends on the lateral wall of the right brachiocephalic vein then on the pericardium over the superior vena cava, the right atrium and the inferior vena cava before passing through the caval opening of the diaphragm. It is covered throughout its course by the mediastinal pleura.
- The left phrenic nerve enters the thorax between the left subclavian artery and the left brachiocephalic vein and descends to cross the aortic arch and the pericardium over the left ventricle. It too is covered laterally by the mediastinal pleura.

Both nerves also supply sensory fibres to the central part of the diaphragm, the mediastinal and diaphragmatic pleura, the pericardium and the diaphragmatic peritoneum. The peripheral part of the diaphragm receives sensory fibres from the lower intercostal nerves.

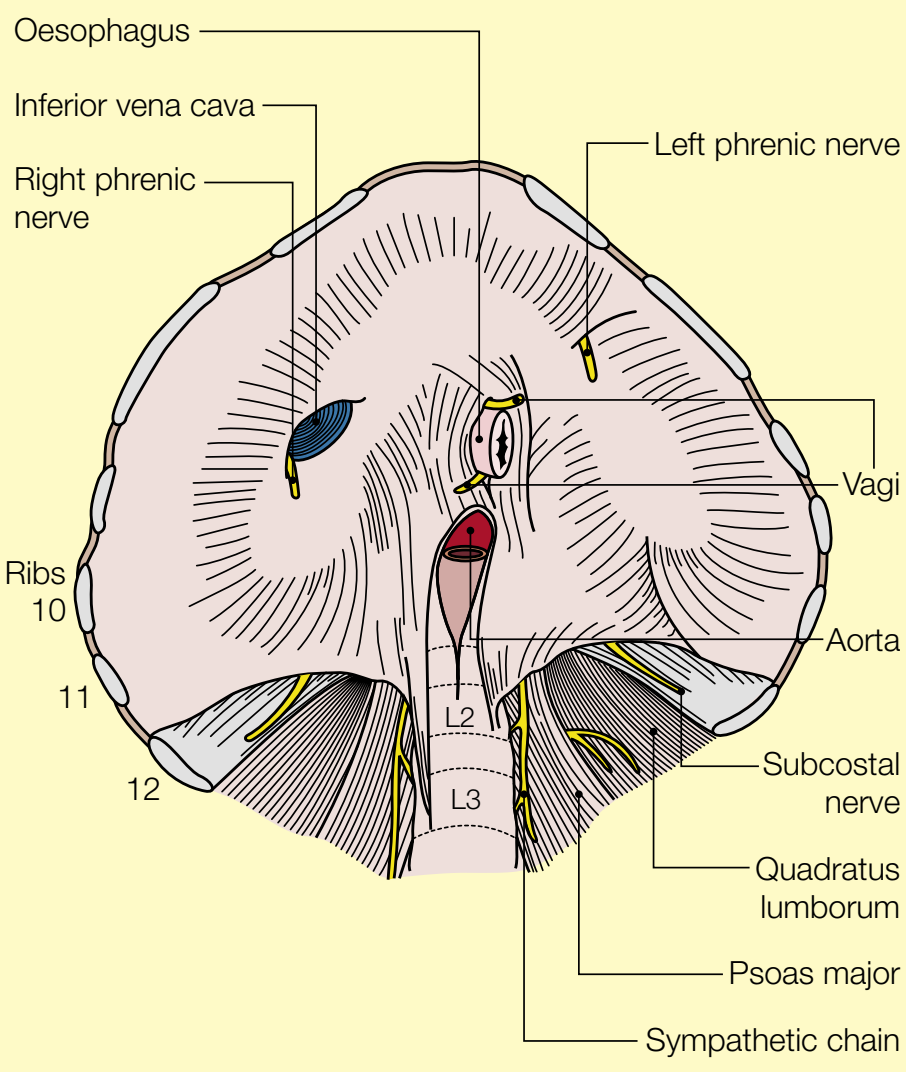
Pain from inflammation of the diaphragmatic pleura or peritoneum may be referred to the ipsilateral shoulder tip, the cutaneous area which is innervated by the supraclavicular nerves, mainly originating like the phrenic nerve, from the C4 segment of the spinal cord.

Openings in the diaphragm

There are three openings in the diaphragm (Figures 1 and 2). From the posterior, they are for the aorta, oesophagus and inferior vena cava.

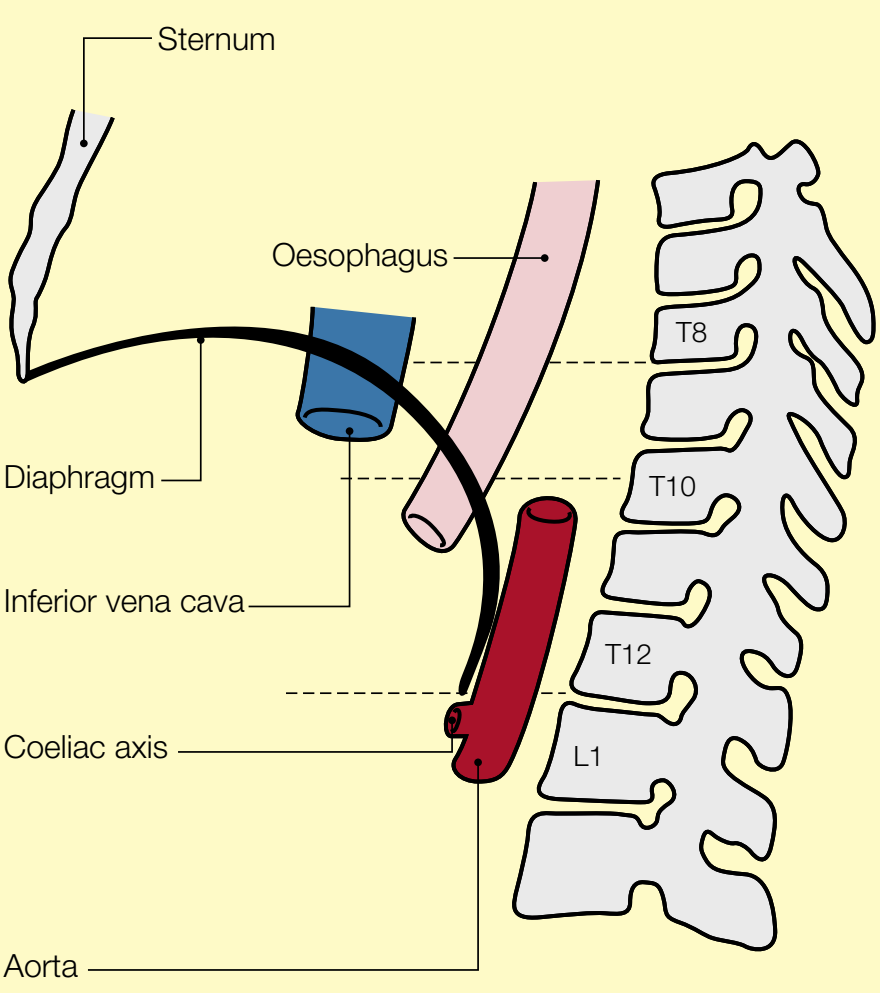
- The opening for the aorta lies between the crura of the diaphragm in front of the 12th thoracic vertebra, which also transmits the thoracic duct and the azygos vein.
- The opening for the oesophagus lies within the right crus at the level of the 10th thoracic vertebra, which also transmits the anterior and posterior gastric branches of the vagus nerves and the oesophageal branches of the left gastric vessels.
- The opening for the inferior vena cava lies to the right of the midline within the central tendon, which also transmits the right phrenic nerve.

Inferior view of the diaphragm



1

Level of the diaphragmatic openings



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Relationships

The heart and lungs lie within the pericardial and pleural sacs, respectively, on the upper surface of the diaphragm. The pericardium is adherent to the central tendon. Below the diaphragm on the right side are the liver, the right kidney and suprarenal gland and, on the left, the fundus of the stomach, spleen, left kidney and suprarenal gland.

Respiration

Inspiration and expiration are produced by increasing or decreasing the volume of the thoracic cavity. Quiet respiration is produced by diaphragmatic action alone.

Inspiration
The diaphragm contracts and descends, the first rib is fixed by the scalene muscles and the external intercostals elevate and evert the succeeding ribs which increases the anteroposterior diameter of the upper chest and, by elevating the costal margin, increases the transverse diameter of the lower chest. Forced inspiration is achieved by fixing the shoulder girdle, which allows serratus anterior and the pectoral muscles to raise the ribs.

Expiration
Expiration is produced mainly by recoil of the lung tissue and the costal cartilages but simultaneous contraction of the abdominal wall muscles forces the diaphragm upwards, an action that is exaggerated in forced expiration.

Eye and Orbit

Hari Jayaram

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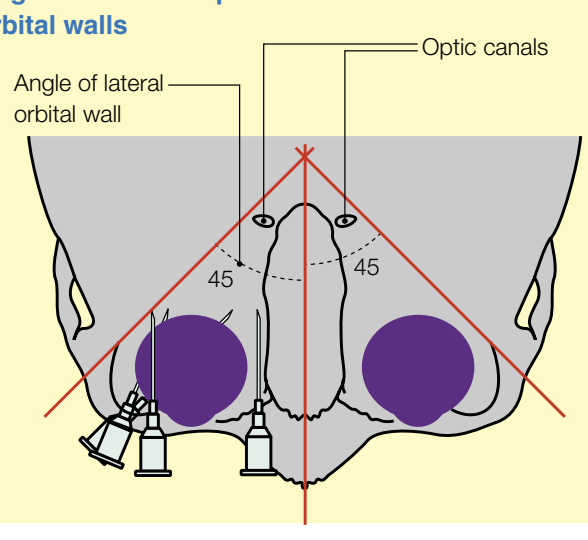
Anatomy
Orbit: each orbit is pyramidal in shape with its base anteriorly and its apex posteromedially directed towards the optic canal. The average dimensions are 40 mm wide, 35 mm high and 25 mm deep. The angle between both lateral walls is 90° and between lateral and medial walls of the same side is 45° (Figure 1). The medial walls are almost parallel to the sagittal plane. Needles introduced in this plane travel a greater distance towards the orbital apex and can potentially cause more damage, compared with those inserted laterally along the orbital wall.

Angular relationships of medial and lateral orbital walls

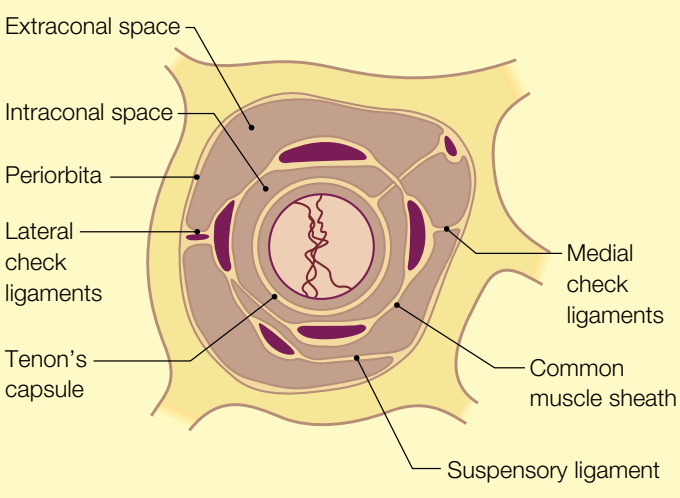


1

Globe: the globe is located anteriorly within the orbit in a superolateral position; its dimensions vary. Myopic eyes are longer with thin sclera, and are at greater risk of needle perforation. An axial length over 26 mm should hazard caution. A 'socket' is formed by Tenon's capsule, which extends from the optic nerve meninges posteriorly to within millimetres of the corneoscleral limbus anteriorly. This layer is pierced by the extraocular muscle tendons, which pass to insert into the sclera. The globe itself has three layers. The outermost fibrous sclera which envelops the globe except the anterior transparent cornea, the vascular pigmented layer (choroid, iris and ciliary body) and the innermost sensory retina. The conjunctival mucosa lines the inner surface of the eyelids and the anterior aspect of the eyeball.

Orbital apex: the four recti muscles arise from a common tendinous ring formed from periosteum at the orbital apex, which lies medial to the globe. This ring encloses the optic canal and the medial portion of the superior orbital fissure. The cone formed by the recti muscles passing towards the globe, helps define an incomplete extraconal (peribulbar) and intraconal (retrobulbar) space (Figure 2). The relationship of the important anatomical structures to this muscular cone is shown in Figure 3.

Conal space and fibrous septa



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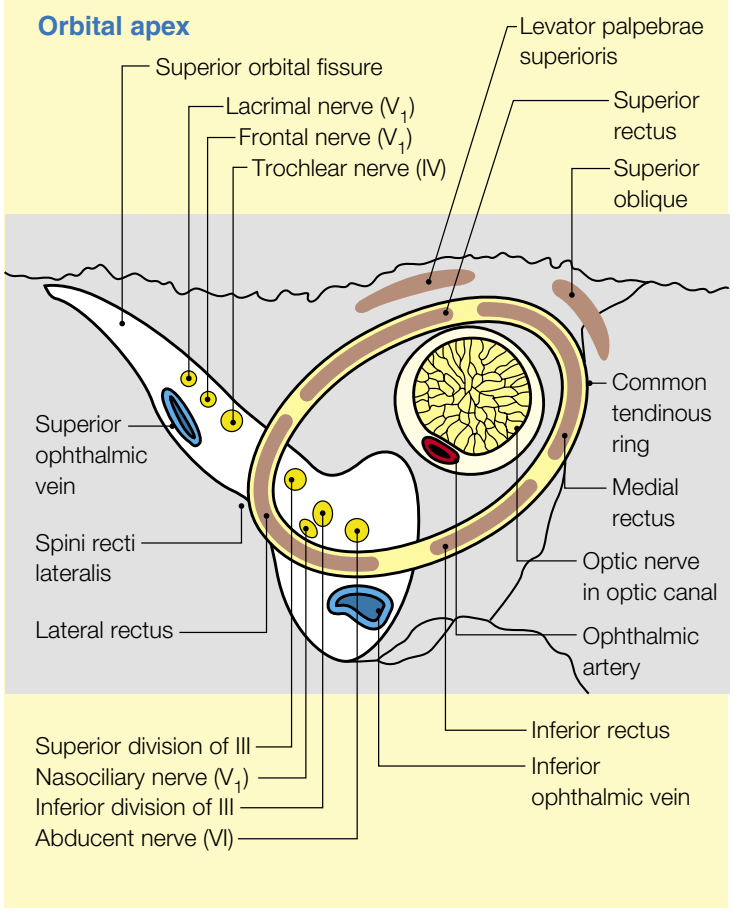
Orbital apex



3

Fibrous septa: there is no strict anatomical separation of the extraconal and intraconal spaces. A matrix of connective tissue gives support, allows dynamic function and controls the spread of injectate within fibro-adipose compartments (Figure 2).

Blood vessels: the main supply is from the ophthalmic artery. This is a branch of the internal carotid after it emerges from the cavernous sinus. It initially lies within the subarachnoid space, but pierces the optic nerve sheath meninges after leaving the optic canal. It first runs inferiolateral to the nerve, but then moves above and towards the superomedial orbit with a tortuous course. Behind the medial upper lid, the facial and supraorbital veins pass posterolaterally as the superior ophthalmic vein. The venous plexus on the anterior orbital floor contributes to the inferior ophthalmic vein.

Nerves: the abducent nerve supplies lateral rectus, trochlear nerve supplies superior oblique and the other muscles are supplied by the oculomotor nerve, which also gives a branch to the upper lid levator. The skin and conjunctiva of the upper lid are supplied by the lacrimal and frontal branches of V_1 (extraconal), and those of the lower lid by the infraorbital nerve (terminal branch of V_2). The nasociliary division of V_1 gives branches to the ciliary ganglion, medial aspect of eyelid skin and conjunctiva, ciliary body and cornea.

Lacrimal gland is located in the superolateral orbit. Drainage is via superior and inferior puncta near the medial lid margins. Each punctum leads to the respective canaliculus, which passes medially to the lacrimal sac. This drains via the nasolacrimal duct to the inferior meatus of the nose. Injection between the caruncle and canthal fold will avoid these structures, and anaesthetize the medial aspect of the eyelids and cornea.

Anaesthesia
Injection into avascular regions such as the medial or preferably inferolateral compartment, can provide adequate regional anaesthesia while minimizing complications. The superomedial compartment must be avoided, because of the risk of damaging the vasculature, muscles and optic nerve at the orbital apex. Current guidelines suggest the use of fine, short needles (25 mm or less), though the issue of blunt versus sharp is still being debated. ◆

FURTHER READING

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The Great Vessels of the Thorax, Abdomen and Neck

John Craven

John Craven was formerly Consultant Surgeon at York District Hospital, York, UK. He trained in Manchester, Uganda and Cardiff. He is past chairman of the primary examiners of the Royal College of Surgeons of England. His particular interest is gastric cancer.

Aorta

The aorta arises from the left ventricle and ascends for a short distance before arching backwards to descend through the thorax and abdomen.

The ascending aorta ascends to the right from the aortic orifice to the sternal angle. It is about 5 cm long and lies within the fibrous pericardium in a sheath of serous pericardium directly behind the sternum. Above each of the semilunar valvules of the aortic valve is an aortic sinus – the right and left coronary arteries arise from the anterior and left posterior sinuses.

The arch of the aorta ascends from the sternal angle and arches backwards and leftwards over the root of the left lung before descending to the left side of the fourth lumbar vertebra. On its left side lie the phrenic and left vagus nerves under the mediastinal pleura and on its right side, from front to back lie the superior vena cava, right phrenic nerve, trachea, oesophagus, thoracic duct and the body of the fourth thoracic vertebra. It has the following branches.

- The brachiocephalic artery ascends to behind the sternoclavicular joint to divide into the right subclavian artery and right carotid artery.
- The left common carotid artery ascends the neck to divide into the internal and external carotid arteries at the upper border of the thyroid cartilage.
- The left subclavian artery ascends to the neck, lateral to the oesophagus and trachea and medial to the left pleura.

The descending aorta descends in the posterior mediastinum inclining medially from the left side of the fourth thoracic vertebra behind the root of the left lung to the front of the twelfth thoracic vertebra where it passes through the diaphragm. It is in contact with the left pleura throughout its course. It has the following branches:

- third to eleventh posterior intercostal arteries and the subcostal artery
- small bronchial branches
- small oesophageal branches.

Severe deceleration trauma, for example, in a car crash, can cause injury to the aorta. The arch of the aorta is relatively fixed by its branches but the more mobile descending part continues to travel forwards during severe deceleration, producing a shearing force and tearing at the junction. If the adventitia remains intact, a false aneurysm is caused, resulting in mediastinal widening which is visible on radiography. Urgent surgical attention must be sought.

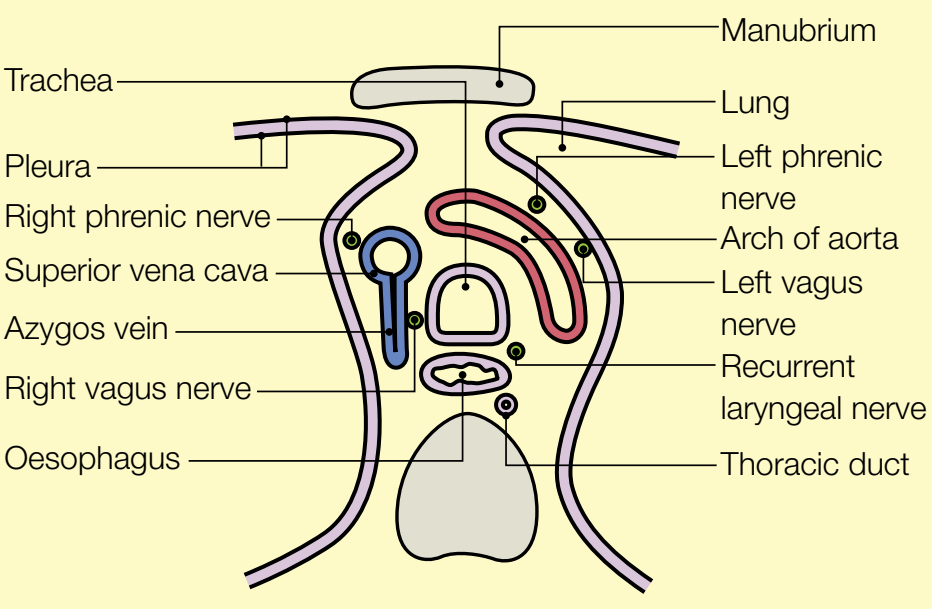
The abdominal aorta enters the abdomen between the two crura of the diaphragm in front of the twelfth thoracic vertebra and descends on the posterior abdominal wall slightly to the left of the midline. On its left side is the inferior vena cava. It is surrounded by networks of autonomic nerves and ganglia, lymph vessels and nodes. Anteriorly it is covered by the lesser sac, pancreas, duodenum and small intestine. It ends on the body of the fourth lumbar vertebra by dividing into two common iliac arteries. It has the following branches.

- The coeliac trunk arises above the pancreas. Its three branches (the left gastric, common hepatic and right gastric arteries) supply the lower oesophagus, stomach, duodenum, liver, pancreas and gallbladder.
- Superior mesenteric.
- Inferior mesenteric.
- Paired branches: the suprarenal, renal and gonadal arteries supply their respective organs.
- Parietal branches: the four pairs of lumbar arteries supply the posterior abdominal wall and spinal cord.
- Terminal branches: the two common iliac arteries each descend without branches away from the midline to divide into internal and external iliac arteries anterior to the sacroiliac joint. The external iliac artery continues to descend and passes below the midpoint of the inguinal ligament to form the femoral artery. The internal iliac artery passes backwards, anterior to the internal iliac vein, to provide branches to the pelvic viscera, perineum and buttock.

Vena cava

The superior vena cava is a wide vessel about 7 cm long formed by the union of the two brachiocephalic veins at the right border of the manubrium. It descends behind the sternum to enter the right atrium at the level of the third right costal cartilage. It has no valves. Its lower half is covered by fibrous and serous pericardium and on its lateral side lies the right pleura and phrenic nerve. The azygos vein is its only tributary, entering it posteriorly (Figure 1).

Structures seen in a cross-section of the mediastinum at the level of the fourth thoracic vertebra



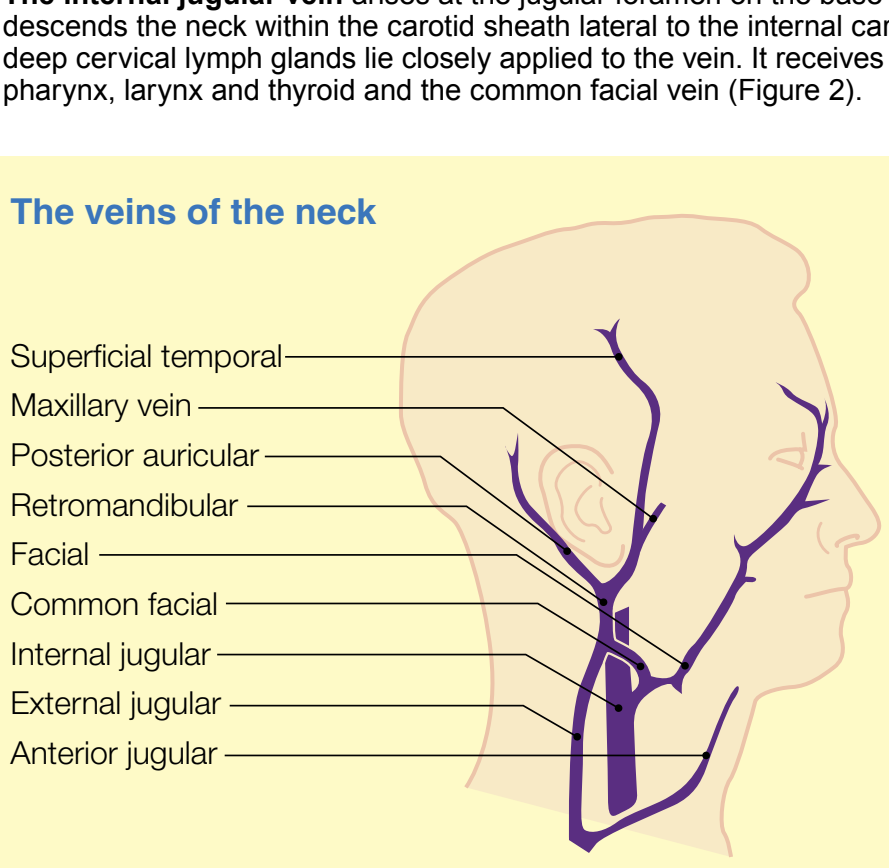
1

The brachiocephalic veins are formed behind the sternoclavicular joints by the union of the corresponding internal jugular and subclavian veins. The right brachiocephalic vein is 3 cm long and descends behind the right border of the manubrium. The right phrenic nerve lies on its lateral surface. The left brachiocephalic vein, about 6 cm long, descends obliquely behind the manubrium above the arch of the aorta and anterior to its branches.

Tributaries from the neck muscles, the thyroid and the anterior chest wall enter both veins and the thoracic duct enters the origin of the left brachiocephalic vein.

The internal jugular vein arises at the jugular foramen on the base of the skull and descends the neck within the carotid sheath lateral to the internal carotid artery. The deep cervical lymph glands lie closely applied to the vein. It receives tributaries from the pharynx, larynx and thyroid and the common facial vein (Figure 2).

The veins of the neck



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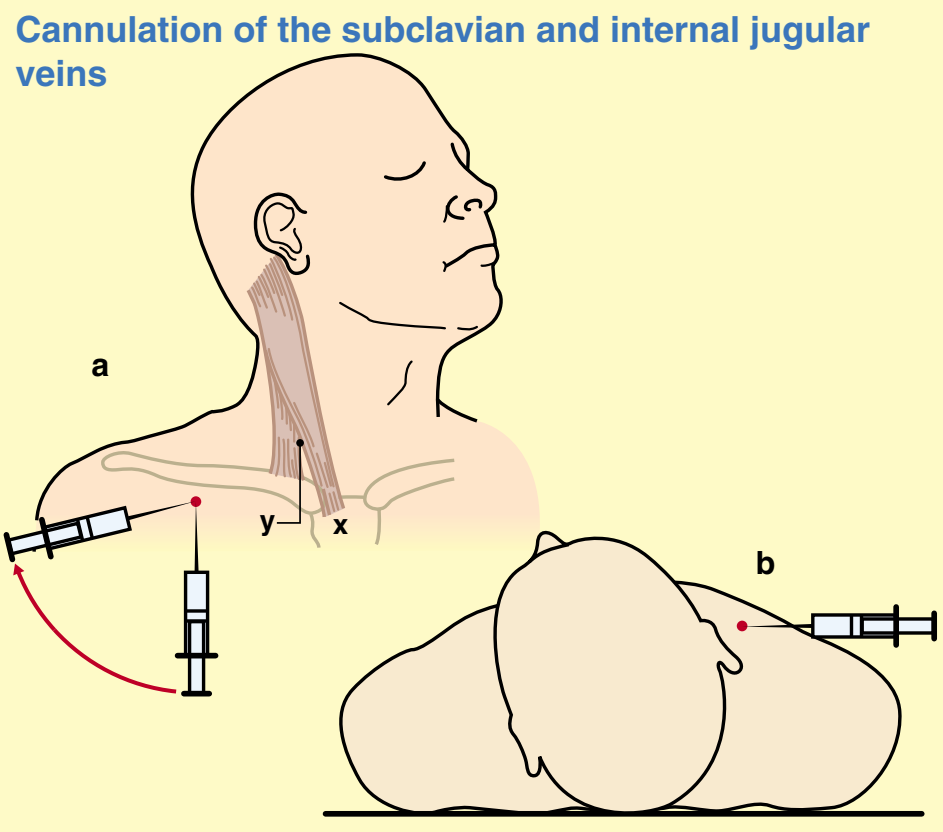
The subclavian vein is the continuation of the axillary vein, beginning at the outer border of the first rib. It joins the internal jugular vein behind the sternoclavicular joint. Central venous catheterization is an important clinical technique widely used to measure central venous pressure, to administer rapid fluid replacement and for long-term administration of chemotherapy and intravenous feeding (Figure 3).

Cannulation of the subclavian and internal jugular veins



Cannulation of the subclavian vein is best achieved by an infraclavicular approach. **a** The needle is inserted below the midpoint of the clavicle and aimed toward the sternal notch (**x**). **b** The danger of pneumothorax is minimized by keeping the needle horizontal as it is being advanced. Cannulation of the internal jugular is achieved on a supine patient by insertion of the needle at the apex of the triangle formed by the clavicular and sternal heads of sternomastoid (**y**) and guiding it towards the posterior aspect of the sternal notch

3

The inferior vena cava formed in front of the body of the fifth lumbar vertebra by the union of the two common iliac veins ascends the posterior abdominal wall, to the right of the midline through the caval opening of the diaphragm. It has a short intrathoracic course before it opens into the right atrium. The right sympathetic trunk lies behind it. Anteriorly it is covered by the parietal peritoneum below and is crossed by the pancreas and duodenum. Superiorly it lies behind the right lobe of the liver in which it is embedded. The aorta is in contact with its left side.

Right and left common iliac veins are formed anterior to the sacroiliac joints by the union of the internal and external iliac veins. They each ascend obliquely to join their fellow to the right of the body of the fifth lumbar vertebra.

The internal iliac vein is formed by tributaries draining the venous plexuses which drain the pelvic viscera. Both veins lie behind their arteries.

The external iliac vein is the proximal continuation of the common femoral vein which enters the abdomen under the inguinal ligament medial to its artery.

In the case of total occlusion of the inferior vena cava by thrombus or tumour, extensive oedema of the lower body follows. A collateral circulation develops between tributaries of the inferior vena cava which include the superficial and inferior epigastric veins. These convey the blood to the thoraco-epigastric and superior epigastric veins and thence to the superior vena cava. This collateral flow is evident as tense and tortuous veins visible over the trunk

Great vessels of the neck

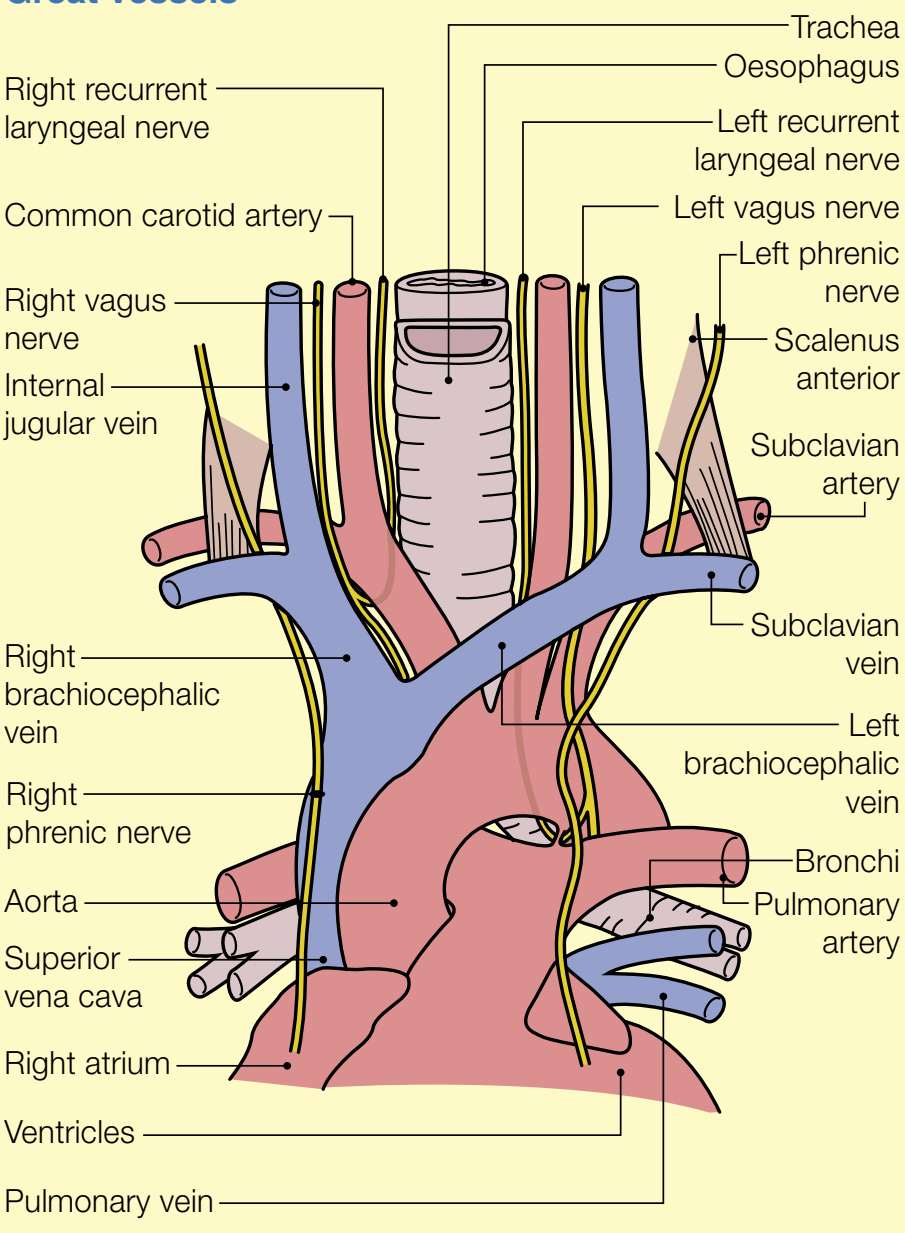
Arterial blood supply
The head, neck and upper limbs are supplied by the three large branches of the aortic arch: the innominate, and the left carotid and subclavian arteries (Figure 4). The innominate artery divides into the right common carotid and right subclavian arteries: the common carotid arterial supply to the head and neck is supplemented by the vertebral branch of each subclavian artery, arising as this vessel passes over the apex of the lung.

Each common carotid artery ascends through the neck from behind the sternoclavicular joint and divides into its terminal (and only) branches, the internal and external carotid arteries, lateral to the upper border of the thyroid cartilage (fourth cervical vertebra). The artery lies within the fascial carotid sheath, accompanied by and medial to the internal jugular vein, with the vagus lying between and posterior to both.

The left common carotid artery in the thorax lies between the innominate, anteromedially, and the left subclavian artery, posterolaterally; the trachea, oesophagus and recurrent laryngeal nerve lie posteromedially. Anterolaterally, the common carotid is covered by the pleura, the left lung and the thymic remnant. The left phrenic and left vagus nerves descend anterior to the artery, and the vessel is crossed by the left brachiocephalic vein.

Each common carotid artery in the neck lies on the transverse processes of the fourth to the sixth cervical vertebrae, separated by the prevertebral muscles and the sympathetic chain. Medially are the trachea and larynx and behind this, the oesophagus and pharynx, with the recurrent laryngeal nerve descending in the groove between these structures. The lateral lobe of the thyroid gland overlaps the proximal common carotid artery in the neck. The artery is overlain by the sternomastoid muscle with its deep fascial coverings: the platysma and skin become direct relations of the distal common carotid above the medial border of the sternomastoid. The common carotid artery is crossed anteriorly by the superior belly or the intermediate tendon of the omohyoid muscle, and the inferior thyroid and common facial veins.

Great vessels



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The internal carotid artery of each side continues distally from the carotid bifurcation to the base of the skull. It passes through the latter within the carotid canal of the petrous temporal bone and within the dural coverings of the cavernous sinus, before piercing the dural roof and dividing into its middle and anterior cerebral terminal branches. It gives off the ophthalmic artery in its intracavernous portion.

In the neck, the posterior relations are similar to those of the common carotid artery with the transverse process of the upper three cervical vertebrae, the prevertebral muscles and the sympathetic chain posteriorly, the internal jugular vein laterally, with the vagus posteriorly between them, and the pharynx medially. The proximal internal carotid artery is covered with deep investing fascia, platysma muscle and skin, but it is crossed by the hypoglossal nerve and then the posterior belly of the digastric, with the occipital artery below and the posterior auricular artery above the muscle.

As the internal carotid artery approaches the skull base, the styloid process and the attached muscles lie anterolaterally. The stylopharyngeus, accompanied by the glossopharyngeal nerve, pass between the internal and external carotid arteries.

The external carotid artery is at first medial to the internal, but then becomes anterior and lateral, and also crossed by the hypoglossal nerve, the posterior belly of the digastric muscle and adjacent arteries. As it ascends laterally it reaches and passes through the carotid sheath and thence through the substance of the parotid gland, anterior to the facial nerve, dividing within the gland into terminal, superficial, temporal and maxillary branches, respectively passing to the scalp and pterygoid regions. Other branches are the superior thyroid, passing to the superior pole of the lateral lobe of the thyroid gland, an inconstant ascending pharyngeal, a lingual branch to the tongue, a facial branch and the occipital.

The distal end of the common carotid artery is expanded to form the carotid sinus and this may also include the origin of the internal carotid artery. The adventitia of the sinus contains stretch receptors, and these pressure-sensitive baroreceptors provide a rapid mechanism for responding to changes in blood pressure. They are innervated by the carotid sinus branch of the glossopharyngeal nerve descending medial to the internal carotid artery. The nerve also supplies to the carotid body, a vascular chemoreceptor situated posterior to the distal common carotid or external carotid artery. The receptor is stimulated by hypoxia, hypercapnia or increased hydrogen ion concentration, producing reflex increase in the rate and volume of ventilation.

The vertebral artery arises from the superoposterior aspect of the first part of the subclavian artery, as it arches over the apex of the pleura, lung and suprapleural membrane. It passes between the prevertebral muscles to enter the transverse process of the sixth cervical vertebra and ascends through the canal in the proximal six transverse processes, accompanied by its vein. It turns medially over the posterior arch of the atlas to pierce the cervical dura and enter the posterior fossa, joining its fellow on the opposite side to form the basilar artery.

The internal jugular vein
The main venous drainage of the head and neck is through the internal jugular vein. Additional superficial contributions come from the anterior jugular vein over the anterior aspect of the neck (passing laterally deep to the sternomastoid to enter the internal jugular) and the external jugular vein passing from the angle of the jaw superficially over the sternomastoid muscle to pierce the deep fascia and enter the subclavian vein behind the midpoint of the clavicle.

The internal jugular vein is the continuation of the sigmoid sinus, commencing at the jugular foramen in the occipital bone, and descending vertically in the neck to terminate behind the medial end of the clavicle, joining the subclavian vein to form the right or left innominate vein. A slight dilatation near its termination contains a pair of valves.

The relations of the internal jugular vein in the neck are similar to those of the common and internal carotid arteries. It lies lateral to them within the carotid sheath, with the vagus nerve between and posterior to both.

The internal jugular vein is related posteriorly to the tips of the transverse processes of the first to sixth cervical vertebrae and the attached muscles, their covering prevertebral fascia and the cervical sympathetic chain. Posteromedially are the rectus capitus and prevertebral muscles, while posterolaterally are the attachments of levator scapulae and the scalenus anterior muscles. The latter overlies the scalenus medius with the roots of the cervical and brachial plexuses between. The phrenic nerve passes on to the anterior surface of scalenus anterior and descends across the muscle deep to the internal jugular vein. It is at this site it is approached surgically, and may be damaged in approaches to the subclavian and common carotid arteries, or the sympathetic chain.

Inferiorly, the internal jugular vein passes anterior to the first part of the subclavian artery and its thyrocervical trunk, together with the vertebral vein, and either the right mediastinal lymph trunk or the thoracic duct.

The internal jugular vein lies lateral to the internal and common carotid arteries, and at the skull base is related to the last four cranial nerves. The twelfth passes medially, anterior to the internal carotid artery, the eleventh passes laterally anterior to the internal jugular vein, the tenth descends in the carotid sheath posterior to those vessels, and the ninth passes medially between the internal and external carotid arteries.

The sternomastoid muscle overlies the anterior and lateral surfaces of the internal jugular vein with the superior belly of the omohyoid muscle and the anterior jugular vein passing between them. The descendens hypoglossi descends over the anterior aspect of the interior jugular vein before turning laterally to become the ansa hypoglossi. The deep cervical lymph nodes are grouped around the vessel, the cranial nodes lying more medially and termed the retropharyngeal nodes, and in the lower neck a more laterally placed group is termed the supraclavicular nodes.

The tributaries of the internal jugular vein are the inferior petrosal sinus, and the facial, laryngeal, pharyngeal, and superior and middle thyroid veins, together with the right mediastinal lymph trunk or, on the left side, the thoracic duct.

The common carotid artery and internal jugular vein provide important sites of vascular access. The common carotid artery runs distally from behind the sternoclavicular joint towards the angle of the jaw, and can be palpated or compressed on the transverse processes of the fourth and sixth cervical vertebrae. This is either through, or above, the sternomastoid muscle.

The internal jugular vein, lying lateral to the common and internal arteries, runs over the tips of the transverse processes, the transverse mass of the atlas being palpated deeply between the angle of the jaw and the mastoid process. If the artery is not palpable the surface marking of the internal jugular vein is from the earlobe to the medial end of the clavicle. A constant and useful site of access to the lower internal jugular vein is between the sternal and clavicular heads of the sternomastoid muscle.

The jugular venous pressure can be observed within the internal jugular vein by rotating the head to the opposite side and appropriate positioning of the trunk. The level can be modified by deep breathing and a Valsalva manoeuvre.

Anatomy of the Heart

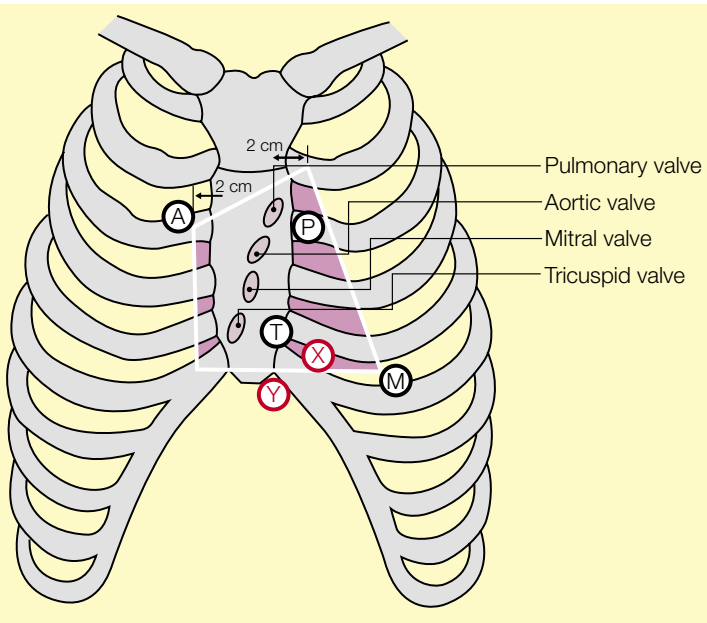
Anatomy of the Heart

John Craven was formerly Consultant Surgeon at York District Hospital, York, UK. He trained in Manchester, Uganda and Cardiff. He is past chairman of the primary examiners of the Royal College of Surgeons of England. His particular interest is gastric cancer.

The heart is a cone-shaped organ that lies obliquely in the mediastinum within the pericardial sac, suspended by the large vessels (Figure 1). Its four chambers, the left and right atria, and the left and right ventricles are demarcated on its surface by coronary and interventricular sulci. Its square base lies posteriorly and is formed largely of the left atrium, which receives the four pulmonary veins at each corner. The inferior vena cava enters the right atrium at its right postero-inferior angle, which rests on the central tendon of the diaphragm; the superior vena cava enters the upper part of the atrium.

Position of the heart

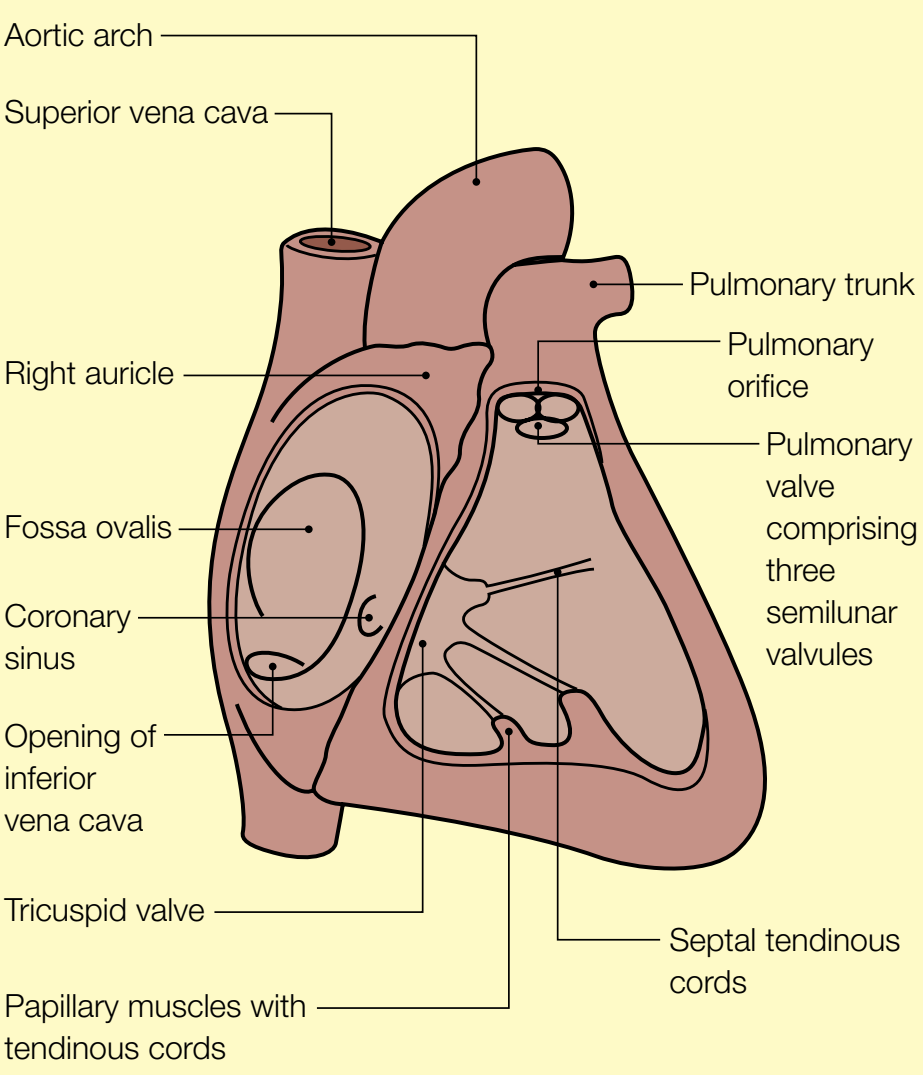
The right border lies 2 cm from the sternal edge between the 3rd and 6th right costal cartilages; the inferior border lies between the latter point and the 5th left interspace in the midclavicular line. A line from this point to the 2nd left costal cartilage, 2 cm from the sternal edge, defines the left border. The valves (pulmonary, aortic, mitral and tricuspid) lie obliquely behind the sternum. However, their sounds are best heard at the auscultatory areas over the chamber or vessel into which blood is pumped (P, A, M, T, respectively). An intracardiac injection can be made through the medial aspect of the 5th intercostal space (X). Pericardial aspiration, in cases of effusion or tamponade, can be achieved by a needle inserted alongside the xiphisternum (Y), which is directed deep to the sternum towards the left shoulder



1

The right atrium is a thin-walled chamber. It forms the right border of the heart and has a small projection, the right auricle, overlapping the origin of the ascending aorta (Figure 2). Its posterior wall behind the caval openings is smooth and marked by a shallow depression, the fossa ovalis, which is the remnant of the fetal opening.

Interior of the right atrium and right ventricle



2

The right ventricle is a thick-walled chamber that projects to the left of the right atrium forming part of the heart's anterior and inferior surfaces. The interventricular septum separates the right from the left ventricle and bulges into the right cavity, making it crescentic in cross-section. The atrioventricular (AV) orifice lies postero-inferiorly guarded by the tricuspid valve, comprising three cusps each consisting of thin fibrous tissue covered on both sides by endocardium. The atrial surfaces of the cusps are smooth and the ventricular surfaces are rough and anchored to the ventricular walls by tendinous cords arising directly from the septum or from two papillary muscles. The muscles tighten the cords during ventricular contraction and thereby prevent eversion of the cusps into the atrial cavity. The pulmonary orifice is a fibrous ring lying at the upper end of the ventricle, the infundibulum. A valve, comprising three semilunar valvules lies at the entrance to the orifice.

The left atrium is a thin-walled chamber that lies behind the right ventricle and forms most of the base of the heart. Superiorly, the left auricle, a small projection, overlies the origin of the pulmonary trunk. The four pulmonary veins enter each corner of the posterior wall. Their orifices possess no valves. The left AV orifice lies in the anterior wall. The posterior wall of the left atrium is separated from the oesophagus and the left bronchus by the pericardial sac.

The left ventricle extends forwards and to the left from the left atrium, and lies mainly behind the right ventricle. It forms the apex, the left border and surface, and part of the anterior and inferior surfaces of the heart. Its walls are thick and surround a conical cavity with two orifices, the left AV orifice posteriorly and the aortic orifice superiorly. The left AV orifice is guarded by the mitral (bicuspid) valve, the two cusps of which are attached to a fibrous ring surrounding the orifice. The free margins of the cusp are anchored to papillary muscles on the ventricular wall by tendinous cords. The aortic orifice is a fibrous ring guarded by a valve of three semilunar valvules similar to the pulmonary valve. The thick interventricular septum is marked on the surface by anterior and posterior interventricular sulci; the right ventricle lies anterior to the left ventricle.

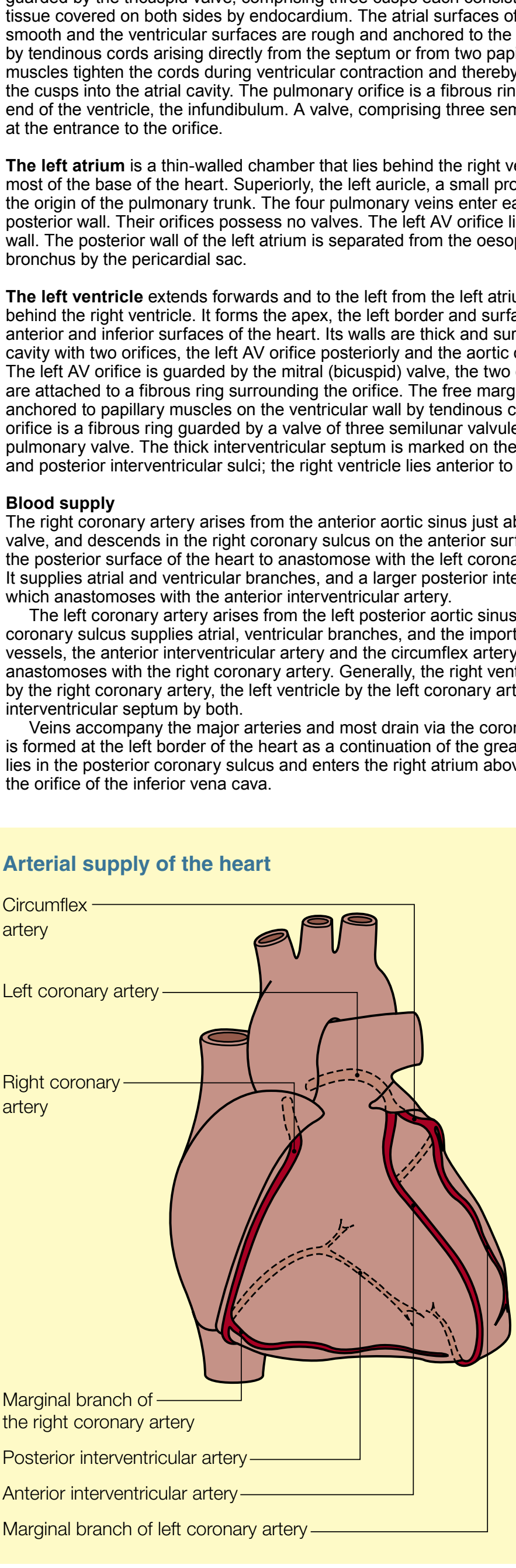
Blood supply

The right coronary artery arises from the anterior aortic sinus just above the aortic valve, and descends in the right coronary sulcus on the anterior surface and crosses the posterior surface of the heart to anastomose with the left coronary artery (Figure 3). It supplies atrial and ventricular branches, and a larger posterior interventricular artery, which anastomoses with the anterior interventricular artery.

The left coronary artery arises from the left posterior aortic sinus and, in the left coronary sulcus supplies atrial, ventricular branches, and the important anastomotic vessels, the anterior interventricular artery and the circumflex artery. The latter anastomoses with the right coronary artery. Generally, the right ventricle is supplied by the right coronary artery, the left ventricle by the left coronary artery and the interventricular septum by both.

Veins accompany the major arteries and most drain via the coronary sinus, which is formed at the left border of the heart as a continuation of the great cardiac vein. It lies in the posterior coronary sulcus and enters the right atrium above and posterior to the orifice of the inferior vena cava.

Arterial supply of the heart



3

Nerve supply

The nerve supply is by vagus and sympathetic fibres through the cardiac plexus. The fibres are distributed with the coronary vessels. Parasympathetic ganglion cells are found in the heart walls. Sensory fibres subserving reflex activity pass in the vagus and pain fibres in the spinal nerves (T1–3).

The conducting system of the heart is formed of specialized heart muscle cells. It comprises the sinoatrial node, the AV node, the AV bundle (of His), its right and left branches, and a terminal subendocardial plexus of Purkinje fibres. The conducting system initiates the muscle contractions of the cardiac cycle and controls its regularity.

The sinoatrial node (pacemaker) is a small vascular area of conducting tissue in the anterior wall of the right atrium to the right of the superior vena caval opening. Impulses are conducted from it through the atrial wall to the AV node, a similar nodule in the septal wall of the right atrium above the coronary sinus opening. The AV bundle arises from the node, descends in the interventricular septum, and divides into right and left branches to supply their respective ventricles. If the AV bundle is damaged, as it may be following infarction, total heart block occurs and the ventricles contract slowly at their own rate, independent of the atria, which continue to contract at the rate determined by the sinoatrial node.

FURTHER READING

McMinn R M H, Hutchings R T, Pegington J, Abrahams P A. *Colour Atlas of Human Anatomy.* 3rd ed. London: Wolfe, 1993: 160–176.

Large Veins of the Neck

John Craven

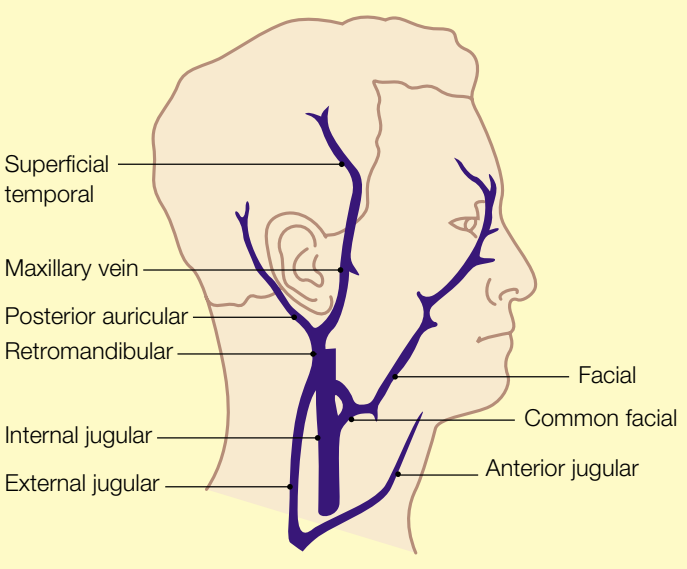
John Craven was formerly Consultant Surgeon at York District Hospital, York, UK. He trained in Manchester, Uganda and Cardiff. He is past chairman of the primary examiners of the Royal College of Surgeons of England.

The internal jugular vein drains blood from the intracranial region and the head and neck. It arises at the jugular foramen on the base of the skull as a continuation of the sigmoid venous sinus, passes downwards through the neck and, behind the medial end of the clavicle, is joined by the subclavian vein to form the brachiocephalic vein. The vein has a dilatation at each end, the superior and inferior jugular venous bulbs and a fairly constant pair of valves just above the lower bulb.

The vein lies within the carotid sheath with the vagus nerve behind and the internal or common carotid arteries medially. The deep cervical lymph nodes lie around it. At the base of the skull it lies lateral to the last four cranial nerves. Posteriorly it lies on the sympathetic chain, prevertebral fascia and muscles, the phrenic nerve and, inferiorly, the subclavian artery. It is crossed laterally by the accessory nerve passing downwards and laterally, then by the posterior belly of digastric and the omohyoid muscles.

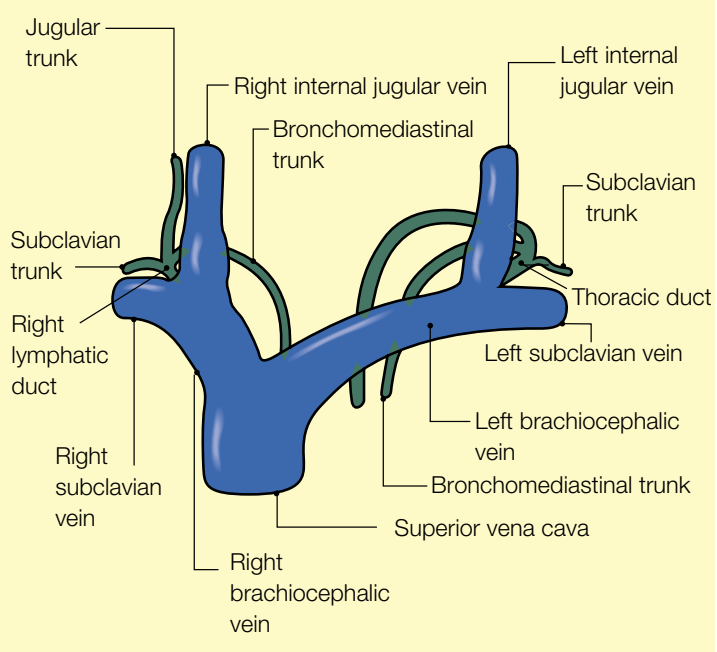
Further laterally, from above downwards, are the styloid process and its muscles, the sternocleidomastoid muscle and the medial end of the clavicle. Its tributaries are the pharyngeal plexus, facial vein, lingual vein and the superior and inferior thyroid veins. On the left side, the thoracic duct may enter the vein and on the right the right lymph duct (Figures 1 and 2).

Veins of the neck



1

Termination of the thoracic and right lymphatic ducts



2

Most techniques for cannulating the internal jugular vein depend on identifying the sternal and clavicular heads of sternocleidomastoid muscle. One preferred technique is to insert the needle in the triangular gap between the clavicular and sternal heads of sternomastoid just above the clavicular. The needle is inserted at the apex of the triangle at an angle of 40° and advanced caudally and slightly medially behind the clavicle along the posterior border of the sternocleidomastoid cephalic to the point where the external jugular vein can be seen crossing the posterior border. The needle is directed towards the sternal notch and aimed about 10◦ above the coronal plane.

The maxillary vein and superficial temporal vein join below the ear to form the retromandibular vein in the substance of the parotid gland.

The external jugular vein, a superficial vein, is formed behind the angle of the mandible by the union of the posterior auricular and a branch of the retromandibular vein. It descends in the subcutaneous tissues over sternocleidomastoid and pierces the cervical fascia above the midpoint of the clavicle to enter the subclavian vein.

The anterior jugular vein begins below the hyoid bone near the midline and passes downwards and laterally, crossing the thyroid isthmus deep to the sternomastoid to enter the external jugular vein behind the clavicle. ◆

CROSS REFERENCE

Anaesthesia and Intensive Care Medicine **2:4:** 163.

The Larynx

Lynn M Carragher
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The larynx started life among the lungfish as a simple circular collar of muscle fibres, which could tighten and prevent water entering the lung buds while the fish was submerged. In modern humans, the larynx is still needed to protect the air passages, but has evolved into a complex sphincter with sophisticated control, which is needed for breathing, coughing, lifting and speaking.

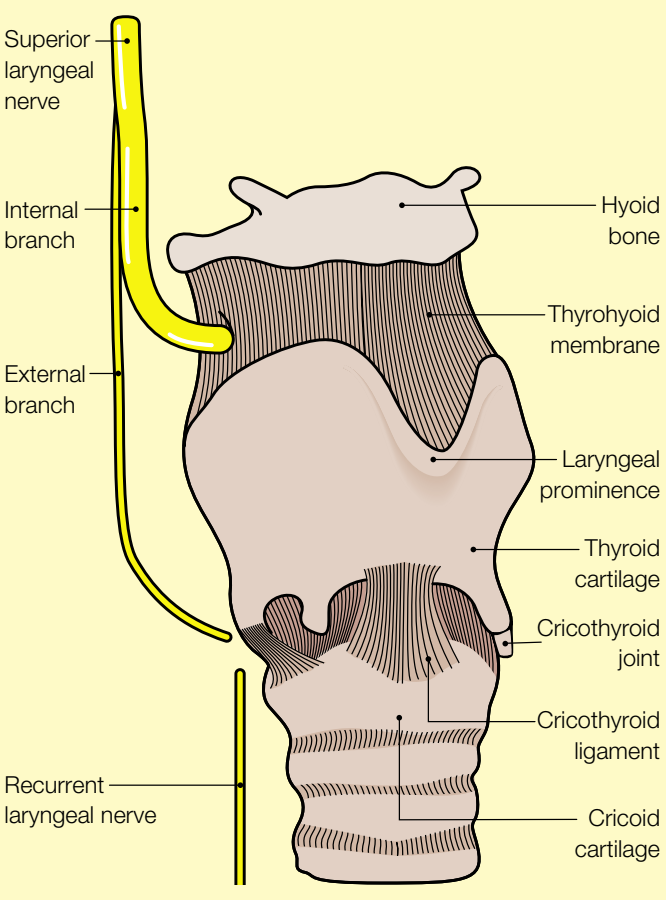
Anaesthetists and Intensive Care Specialists require a thorough knowledge of the anatomy of the larynx for direct laryngoscopy, tracheal intubation, regional anaesthesia for awake intubation, cricothyroid puncture for retrograde intubation and cricothyroidotomy in the 'can't intubate can't ventilate' situation.

Skeleton of the larynx

The larynx lies level with the third to sixth cervical vertebrae in adult men. In women and children, it is slightly higher.

The laryngeal skeleton (Figure 1) is part of the primitive skeleton of the pharynx derived from the pharyngeal arches. It is composed of the hyoid bone and nine cartilages (three single and three paired). The hyoid bone is U-shaped and best felt gently from the sides. The thyroid cartilage, shaped like the prow of a ship, projects forward at the laryngeal prominence and is well marked in men, while the cricoid cartilage is like a signet ring, with the narrower arch in front. It forms most of the posterior wall of the larynx and the lower part of the anterior and lateral walls. It is the only complete skeletal ring of the airway and is of relevance in the application of cricoid pressure during rapid sequence inductions.

Anterolateral view of the larynx with a scheme of the laryngeal nerves



1

The epiglottis (Figure 2) is visible from inside the pharynx. It is a large elastic cartilage, classically leaf-shaped and projecting obliquely up behind the tongue and the hyoid bone. The paired arytenoid cartilages, pyramidal in shape and sited superolaterally on the cricoid lamina, are best seen from the back of the larynx. The corniculate cartilages, over the apices of the arytenoid cartilages and the cuneiform cartilages, complete the skeleton of the larynx.

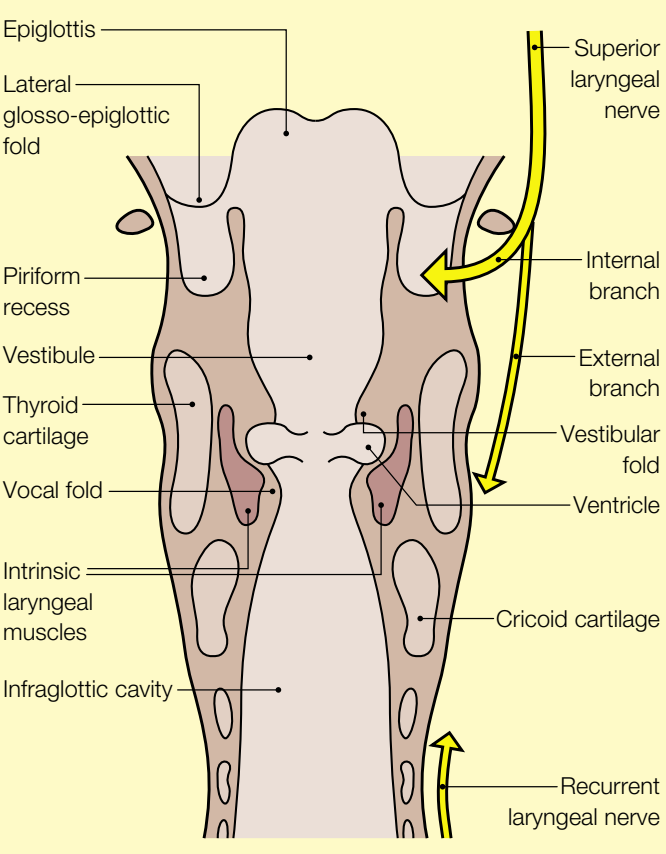
The cartilages articulate with each other at tiny synovial joints and are connected by fibroelastic membranes. The thyrohyoid membrane lies above the thyroid cartilage and the cricothyroid ligament below. The position of each can be felt with the tips of the fingers. Knowledge of the relationship of the internal branch of the superior laryngeal nerve to the thyrohyoid membrane and hyoid bone is important because the nerve can be blocked at this site. The cricothyroid ligament is the membrane punctured in cricothyroidotomy and in the infiltration of local anaesthetic, if required, for awake intubation and bronchoscopy.

Muscles and interior of the larynx

The laryngeal muscles are divided into extrinsic and intrinsic groups. The extrinsic muscles are attached to the outside of the cartilages and the hyoid bone, whereas the intrinsic muscles are confined to laryngeal attachments.

The cavity of the larynx extends from the laryngeal inlet to the lower border of the cricoid cartilage (Figure 2). Mucosa, extending from the tongue to the anterior surface of the epiglottis, forms the midline-raised fold called the median glosso-epiglottic fold and on either side, the lateral glosso-epiglottic folds. The depression formed between the folds is the vallecula, into which the standard Macintosh blade is inserted for laryngoscopy.

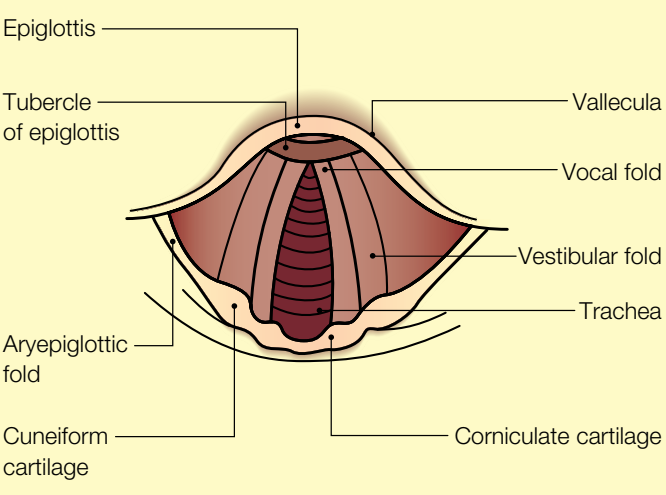
Coronal section of the larynx looking forwards to the anterior comissure



2

From the epiglottis, the mucosa sweeps down in the aryepiglottic folds to the vestibular folds (false cords) and then to the vocal folds (true cords) below. This forms a three-tier sphincter, bounding a series of compartments – the vestibule, the ventricle and the infraglottic cavity. These structures can be seen, typically foreshortened, at direct laryngoscopy (Figure 3).

View of the larynx as seen on direct laryngoscopy



3

The upper sphincter is the laryngeal inlet, with the epiglottis in front and the aryepiglottic folds at the side, almost in a vertical plane. The vocal folds form the lower sphincter, surrounding the glottis or rima glottidis. The vocal folds are wedge-shaped and contain the vocalis muscle. The mucosa is covered by stratified squamous, non-keratinized epithelium, which, firmly bound to the underlying ligament, gives the typical pale appearance. In the adult, this is the narrowest part of the larynx. In children, less than 8–10 years of age, the cricoid ring is the narrowest part. With the exception of the vocal folds, the whole interior of the larynx is covered with pseudostratified ciliated respiratory epithelium.

During quiet respiration the folds swing outwards and inwards with the tidal flow of air. The folds adduct completely and close off the glottis in speech and in cough, as well as in effort. The arytenoids probably rock inwards and downwards to close the glottis.

The intrinsic muscles of the larynx, apart from the crico-thyroid, lie between the mucosa and the laryngeal skeleton. It is easiest to think of a ring of muscles that close the sphincters (the lateral cricoarytenoids and the transverse and oblique arytenoids) and a pair of dilator muscles that open them (the posterior cricoarytenoids). Much of the opening and closing of the sphincters may be biomechanical and depend on longitudinal compression of the larynx, causing the folds to buckle inwards like the pleated folds of a jack-in-the-box.

Nerve supply

The larynx develops from the pharyngeal arches and this relationship can be seen in the nerve supply, which comes from the superior laryngeal nerve, the nerve of the fourth arch and the recurrent laryngeal nerve, the nerve of the sixth arch. Both are derived from the vagus nerve.

The superior laryngeal nerve arises below the inferior vagal ganglion and divides, usually within the carotid sheath, into an internal branch (sensory and autonomic) and an external branch (motor). The larger internal branch pierces the thyrohyoid membrane with the superior laryngeal artery and supplies sensory fibres to the laryngeal mucosa, above the vocal cords (Figure 1). Two methods of nerve blockade of the internal branch for awake intubation are infiltration of local anaesthetic where the nerve pierces the thyrohyoid membrane or direct application of cotton pledgets soaked in local anaesthetic into the piriform recesses, using Krause's forceps. The external branch runs downwards to reach the cricothyroid and the inferior pharyngeal constrictor muscles.

The recurrent laryngeal nerve loops around the aortic arch on the left and the subclavian artery on the right. It ascends on the trachea and passes behind the cricothyroid joint in the wall of the larynx. It supplies all the intrinsic laryngeal muscles except the cricothyroid and sensation to all the mucosa below the vocal folds. It is an important nerve on the afferent limb of the cough reflex. Various reviews and case reports suggest that there may be some overlap between the different territories of supply, even across the midline. ◆

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Joints and Ligaments of the Vertebral Column

John Craven

John Craven was formerly Consultant Surgeon at York District Hospital, York, UK. He trained in Manchester, Uganda and Cardiff. He is past chairman of the primary examiners of the Royal College of Surgeons of England.

The articular surfaces of the bodies of adjacent vertebrae are covered by hyaline cartilage and united by a thick fibrocartilaginous intervertebral disc. The disc centre (nucleus pulposus) is gelatinous and surrounded by a fibrous part, the annulus fibrosus. The disc is a shock absorber. Occasionally the semisolid nucleus protrudes through a defect in the annulus; it may press on the spinal cord or a spinal nerve to produce symptoms and signs of nerve compression. Adjacent vertebrae articulate by two synovial joints between the paired articular processes. The vertebral bodies are united by anterior and posterior longitudinal ligaments.

The anterior ligament extends from the occiput to the sacrum and is attached to each vertebra. Its deep fibres blend with the intervertebral discs.

The posterior ligament extends from the occipital bone to the sacrum and is attached to each vertebral body and disc. Its superior part, from the body of C2 to the occiput is known as the tectorial membrane.

The ligamenta flava unite the adjacent laminae. They contain a large amount of yellow elastic tissue and are strong. Because of their elasticity they remain taught during flexion and extension of the spine, maintaining the curvature of the spinal column and supporting it when it is flexed. The ligaments have no sensory supply and can be pierced painlessly when a lumbar puncture is performed.

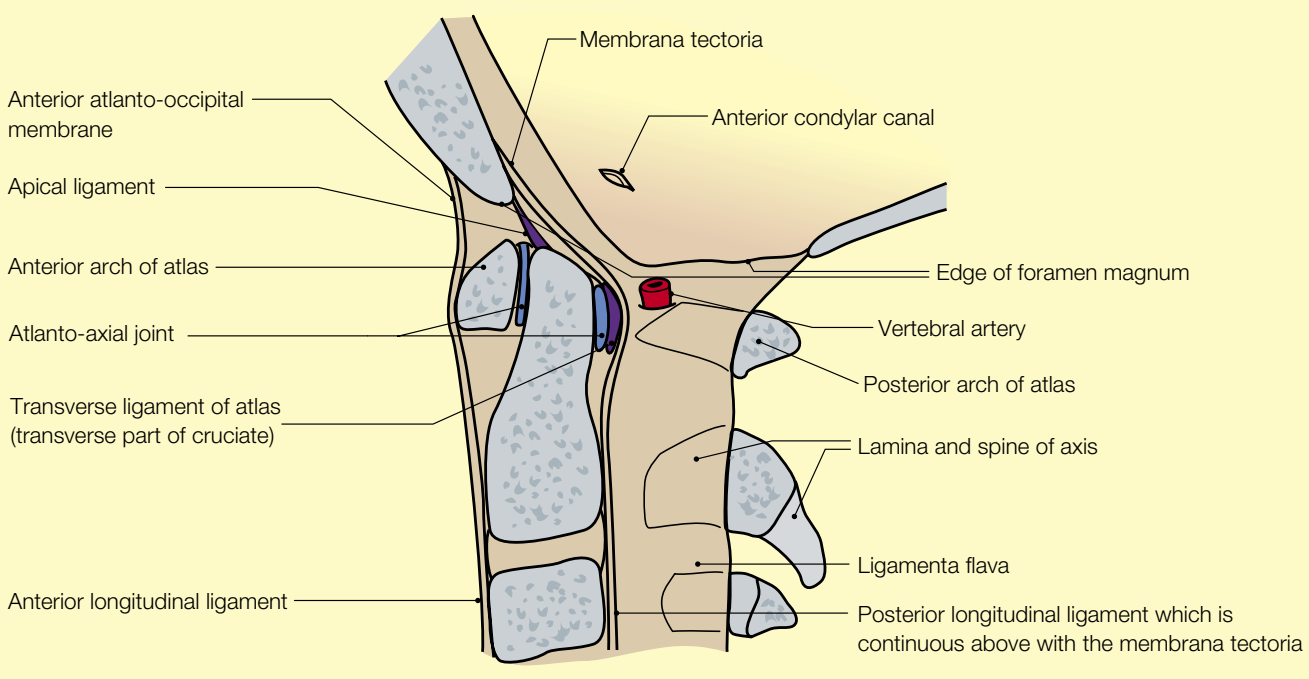
The supraspinous, interspinous and intertransverse ligaments help to unite adjacent vertebrae. The supraspinous is a strong ligament connecting the tips of the spinous processes from C7 to the sacrum. Above C7 it forms the ligamentum nuchae which attaches to the occipital protuberance and provides attachment to neck muscles. The intertransverse ligaments are weak but best developed in the lumbar region.

The articular ligaments around the joints of the articular facets provide additional support.

All these ligaments contribute to supporting the spinal column when it is in the flexed position.

The occipito-atlanto-axial articulation: the atlanto-occipital and atlanto-axial joints (Figure 1) are modified to allow free movement of the head. Radiographs taken through the wide open mouth are used to demonstrate these joints.

Median section to show ligaments of axis, atlas and occiput



1

The atlanto-occipital joints are condyloid synovial joints between the convex occipital condyles and the concave upper articular surfaces of the atlas. Flexion and extension occur at these joints. The joints are supported by the posterior longitudinal ligament, here known as the membrana tectoria, and the anterior atlanto-occipital membrane, which connects the anterior margin of the foramen magnum with the anterior atlas.

The atlanto-axial joints comprise two lateral synovial plane joints between the lateral masses of the two vertebrae and a midline synovial pivot between the dens or odontoid process, a stout pillar projecting vertically from the body of the vertebra in the midline, and a ring formed by the anterior arch and the transverse ligament of the atlas. Rotation occurs at this joint. The joint is strengthened by accessory ligaments; the apical ligament attaches the apex of the odontoid process to the foramen magnum, laterally there are two alar ligaments attaching the odontoid process to the margin of the foramen magnum, the membrana tectoria covers the entire joint and connects the back of the axis, the occiput and the adjacent cruciate ligament.

Functional aspects

Curvature and mobility – in fetal life the vertebral column is flexed – its primary curvature. After birth, two secondary curvatures develop: extension of the cervical region by the muscles raising the head; and extension of the lumbar region after adoption of the erect posture. The primary curvature is retained in the thoracic and sacral regions. These curvatures and the intervertebral discs give some resilience to the column.

Muscles – the extensor muscles of the back and neck extend the head and vertebral column. They form a large composite mass lying deep to trapezius and girdle muscles and extend from the sacrum to the occiput. The largest and most powerful are the erector spinae muscles but these are supported by shorter muscles attached to adjacent vertebrae and to nearby ribs. These muscles play a large part in maintaining posture and are in constant action when standing at rest for the centre of gravity lies anterior to the vertebral column. The muscles attached to the skull produce extension, lateral flexion and rotation of the head.

Movements – only limited movements are possible between adjacent vertebrae but because these can augment each other it is possible to produce extensive movement of the whole vertebral column. Flexion is most marked in the cervical region, rotation in the thoracic, and extension and lateral flexion in the lumbar region (Figure 2).

Muscles causing movement of the vertebral column

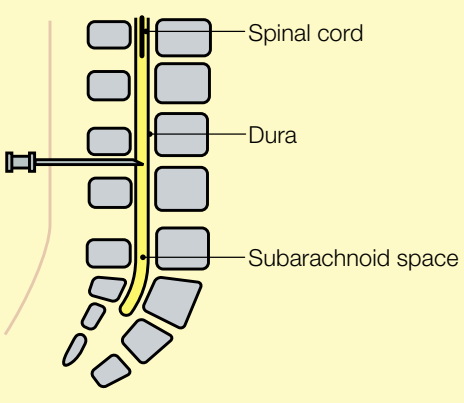
Movement	Muscles
Trunk	
Flexion	Rectus abdominis and prevertebral muscles
Lateral flexion	The oblique abdominal muscles and quadratus lumborum
Neck	
Rotation	Sternocleidomastoid, trapezius
Flexion	Longus capitis and the muscles depressing the fixed mandible
Extension	Postvertebral muscles
Lateral flexion	Sternocleidomastoid and trapezius

2

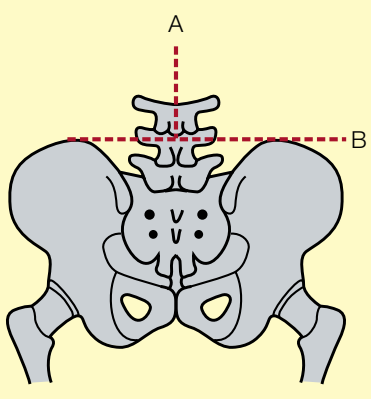
Stability depends almost entirely on the pre- and post-vertebral muscles helped by the ligamenta flava; neither the bones nor ligaments alone could withstand the large forces occasionally acting on the column. Most vertebral functions do not produce instability of the vertebral column for the intervertebral ligaments are not easily torn. If, however, the ligamenta flava and interspinous ligaments are ruptured, the vertebral column is unstable and subsequent displacement may produce compression of the spinal cord and irreversible nerve damage. Fracture of the odontoid process allows the forward displacement of the arch of the atlas together with the skull and fractured part of the odontoid process; a similar forward displacement follows a rupture of the transverse ligament of the atlas. Only 15% of such injuries are followed by neurological damage because the spinal canal is wide at this level.

Vertebral canal – a bony ligamentous structure that extends from the foramen magnum to the sacral hiatus. The spinal cord ends at L2, the dural sac at S2, the supracristal plane, which lies between the highest points of the iliac crests, crosses the spine of L4 (Figure 3).

Site of lumbar puncture



a The site of choice for lumbar puncture is between L3 and L4. The spinal cord is out of danger. Cauda equina not shown.



b The usual site for lumbar puncture is shown as the intersection of the midline (A) with the intercristal plane (B).

3

Lumbar puncture – a needle inserted just above the spine of L4 passes through the interspinous ligament and ligamentum flavum entering the epidural space and then the dura to enter the spinal canal, from which cerebrospinal fluid can be drawn off for examination. Local anaesthetic solution can be injected into the extradural (epidural anaesthesia) or into the spinal (spinal anaesthesia) canal. The dural sac, with its contents, the spinal cord, the spinal nerves and the cerebrospinal fluid, is separated from the walls of the spinal canal by the extradural space, in which lie the emerging spinal nerves and vertebral venous plexus. ◆

Lumbar, Sacral and Coccygeal Plexuses

John Craven

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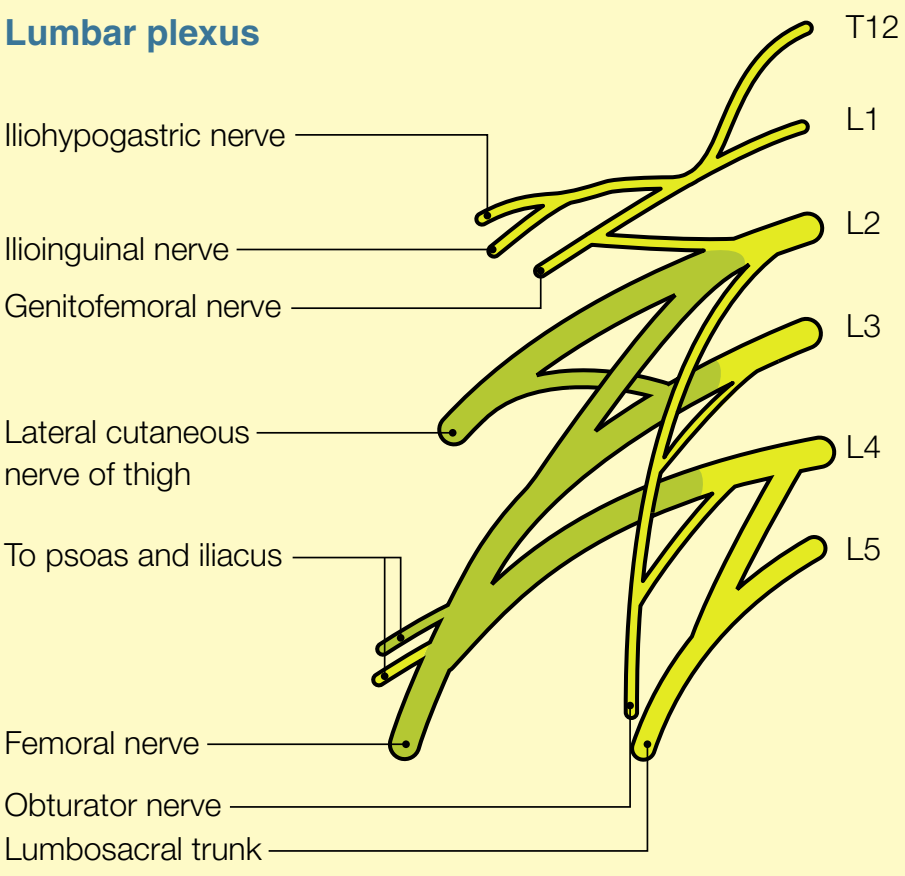
Lumbar plexus
The lumbar plexus (Figure 1), is formed by the anterior primary rami of L1–L4 nerves. It lies within psoas major on the posterior abdominal wall. All nerves receive grey rami communicantes from the sympathetic trunk. From the plexus emerge:

- the obturator nerve (L2–4) supplying the thigh adductors
- the femoral nerve (L2–4) supplying iliacus and the knee extensors
- the lumbosacral trunk (L4–5), which descends over the sacrum to contribute to the sacral plexus
- the ilioinguinal (L1), and the iliohypogastric (L1) nerves, which obliquely traverse the abdominal wall muscles, supplying them and the inguinal and suprapubic skin
- the lateral femoral cutaneous nerve (L2–3) entering the thigh just medial to the anterior superior iliac spine to supply the skin of the anterolateral surface of the thigh
- the genitofemoral nerve, (L1–2) supplying the skin of the genitalia and the femoral triangle.

Lumbar plexus



The yellow branches are derived from the anterior and the green branches from the posterior divisions of the anterior primary rami of the lumbar nerves

1

Sacral plexus
The sacral plexus is formed by the lumbosacral trunk, a conjunction of the anterior divisions of the L4 and L5 nerves and the upper four sacral nerves (S1–S4). It lies in front of the sacrum on piriformis deep to the pelvic fascia (Figure 2). Its branches can be divided into pelvic branches and those leaving the pelvis.

In the pelvis there are muscular branches to the piriformis, levator ani, coccygeus and the external anal sphincter. Pelvic splanchnic nerves arise from the anterior primary rami of S2–4 to supply the pelvic viscera. These have a vasodilator function when acting on the erectile tissue (nervi erigentes), an inhibitor action on the internal anal and vesical sphincters and a motor function on the smooth muscle of the rectum and bladder.

Leaving the pelvis – most of these branches pass through the greater sciatic foramen, above or below piriformis.

Above piriformis – the superior gluteal nerve supplies gluteus medius and minimus.

Below piriformis

- The sciatic nerve (L4–5, S1–3) descends in the posterior compartment of the thigh to end by dividing into the tibial and peroneal nerves just above the popliteal fossa. It supplies the hip and knee joints and the hamstrings, semimembranosus, semitendinosus and biceps. The sciatic nerve lies midway between the ischial tuberosity and the greater trochanter and may be injured by a carelessly placed intramuscular injection. The only safe area in which to place injections is the upper, outer quadrant.
- The pudendal nerve, S2–3 enters the perineum via the lesser sciatic foramen and runs forward in the pudendal canal on the medial surface of obturator internus. It supplies levator ani, the perineal muscles, including the external anal sphincter, and the perianal and perineal skin. It carries parasympathetic fibres to the corpora of the penis or clitoris. A pudendal nerve block can be achieved by inserting a finger into the vagina, to guide the needle to the ischial spine and injecting local anaesthetic there. An effective nerve block results in relaxation of levator ani, anaesthesia over the vulva and loss of the anal reflex.
- Muscular branches supply gluteus maximus, obturator internus and quadratus femoris.
- Cutaneous branches supply the back of the thigh and the gluteal region.

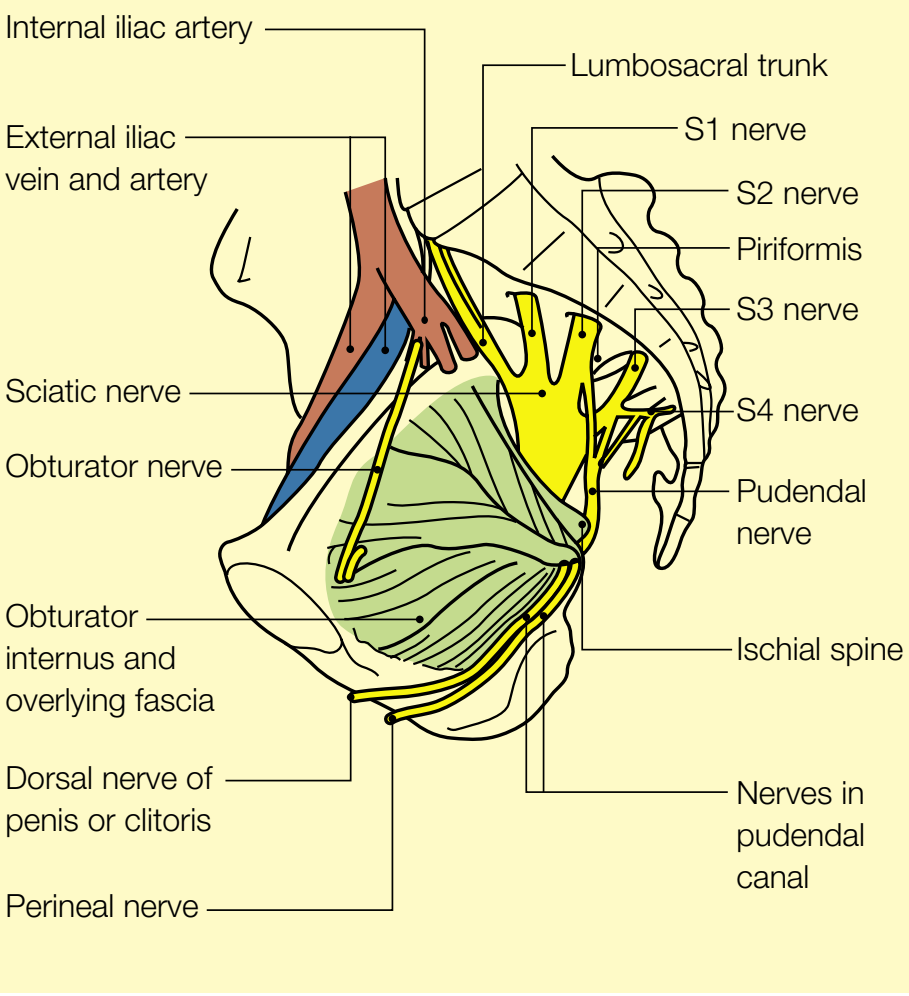
Major nerves of the leg – the sciatic nerve branches at or above the popliteal fossa into the tibial and common peroneal nerves. The tibial nerve descends vertically in the popliteal fossa through the flexor compartment of the leg to reach the back of the medial malleolus where it divides into medial and lateral popliteal nerves. Its branches are:

- the sural nerve, which descends on gastrocnemius then passes behind the lateral malleolus, to supply the skin of the back of the leg and lateral surface of the heel and foot
- muscular branches to gastrocnemius, soleus, tibialis posterior, flexor hallucis longus and flexor digitorum longus.

The common peroneal nerve descends laterally through the popliteal fossa and divides in peroneus longus into:

- the superficial peroneal nerve, which descends between peroneus longus and brevis, supplying them, and ends by dividing into cutaneous branches, which supply the skin of the lower lateral part of the leg and the dorsal surface of the foot and lateral four toes
- the deep peroneal nerve, which lies subcutaneously and winds round the neck of the fibula, and descends in the extensor compartment of the leg supplying the long extensor muscles before passing in front of the ankle to divide into medial and lateral terminal branches to supply the ankle joint, extensor digitorum brevis and the skin of the first interdigital cleft.

Lateral wall of pelvis showing sacral plexus



2

Nerve blocks
Lower and upper limb nerve blocks are discussed elsewhere.

The Lungs and their Relations

John Craven

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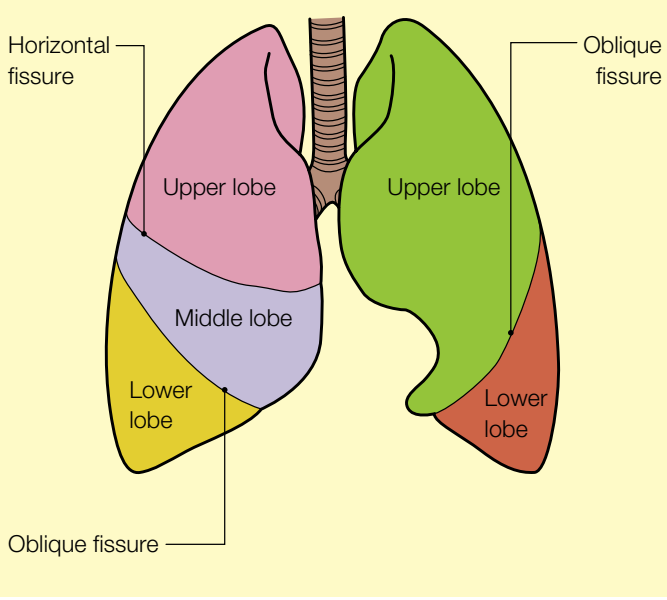
Each lung lies in a pleural sac (see page 315) attached by the pulmonary vessels to the mediastinum. Each is cone-shaped to conform to the contours of the thoracic cavity and is spongy and elastic in texture. The right lung is slightly larger (620 g) than the left (560 g). Each lung has an apex in the root of the neck and a base resting on the diaphragm. The base is separated by a sharp inferior border from a lateral convex surface and a medial concave mediastinal surface. In the centre of the mediastinal surface the structures forming the root of the lung are surrounded by a collar of reflected pleura. The medial surface of the left lung is concave to accommodate the left ventricle of the heart and the anterior border of the left lung is indented by the heart to form the cardiac notch. In both lungs the posterior border is rounded and lies in the paravertebral sulcus.

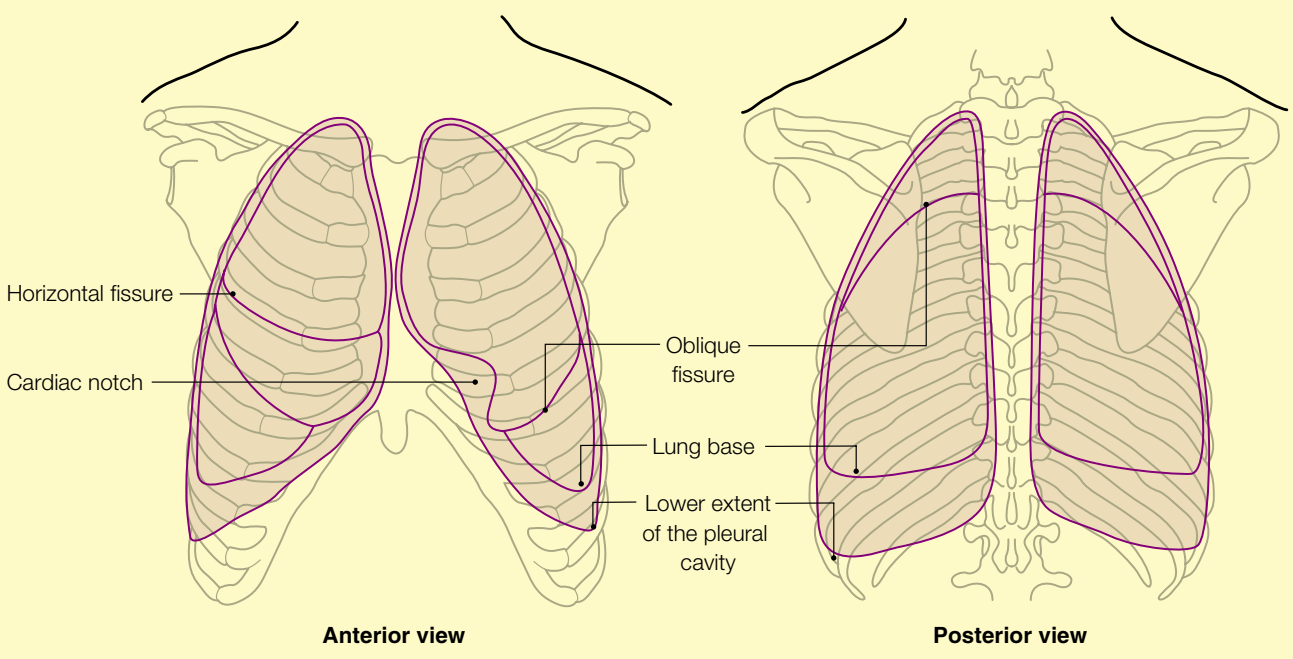
Each lung is divided into lobes by fissures that extend deeply into their substance (see *Anaesthesia and Intensive Care Medicine* **3:5:** 191). An oblique fissure divides the left lung into an upper and a lower lobe. In the right lung, oblique and horizontal fissures divide the right lung into upper, middle and lower lobes (Figure 1). In both lungs the surface marking of the oblique fissure is a line extending round the chest wall from the spine of the third thoracic vertebra to the sixth costochondral junction. The horizontal fissure is marked on the surface by a horizontal line passing laterally to the oblique fissure from the fourth right costochondral junction (Figure 2).

Lobes and fissures of the lungs



1

Surface anatomy of pleurae and lungs



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The lower lobes of both lungs lie below and behind the oblique fissure and comprise most of the posterior and inferior borders and parts of the medial and costal surfaces.

The upper lobe of the left lung lies above and in front of the oblique fissure and comprises the apex, large parts of the mediastinal and costal surfaces and the whole of the anterior border. The equivalent part of the right lung is divided by the horizontal fissure into a large upper lobe and a smaller, wedge-shaped, anteriorly placed middle lobe. Some variation exists in this lobar pattern. Fissures may be missing or incomplete.

The hilus of each lung contains a main bronchus, pul-monary artery, two pulmonary veins, the pulmonary nerve plexus and lymph nodes. It is surrounded by the collar of pleura reflected from the lung onto the mediastinum, the narrow inferior extension of which is known as the pulmonary ligament.

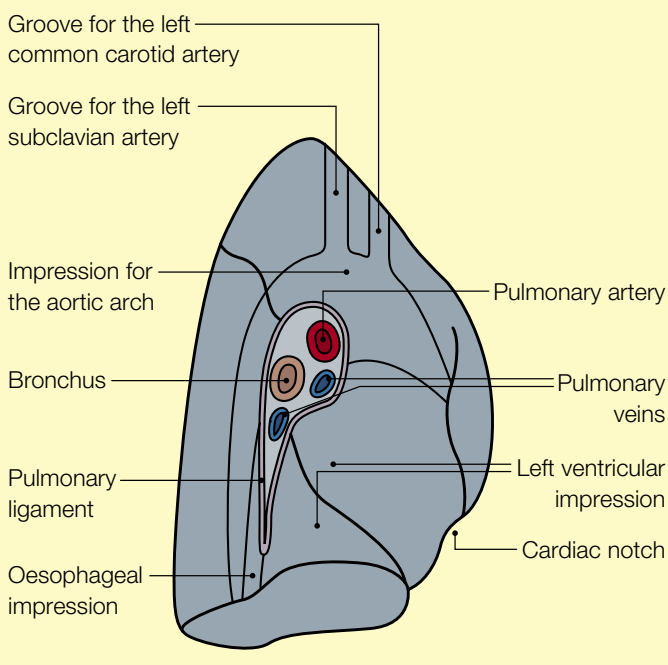
Parietal relations
The borders of the lungs closely follow the lines of pleural reflection on the chest wall except where the inferior border of the lung lies about two intercostal spaces above the inferior limit of the pleura and in front on the left side where the cardiac notch lies about 3 cm lateral to the pleural refection (Figure 2). The costal surface is related to the thoracic wall. The base is separated by the diaphragm, on the right side from the right lobe of the liver, and on the left side from the left lobe of the liver, the stomach and the spleen. The apex is covered by the dome of the pleura and the suprapleural membrane and above them arch the subclavian vessels.

Posteriorly the apex is separated from the neck of the first rib by the anterior primary ramus of the first thoracic nerve, the superior intercostal artery, the sympathetic trunk and the pleura.

Medial relations
The medial relations of the two lungs differ (Figures 3 and 4). On the left lung there is a concavity antero-inferiorly for the left ventricle, which is continuous superiorly with a groove for the aortic arch passing in front of and above the hilum. Above this groove the surface is in contact with the left brachiocephalic vein, left common carotid and left subclavian arteries and the oesophagus.

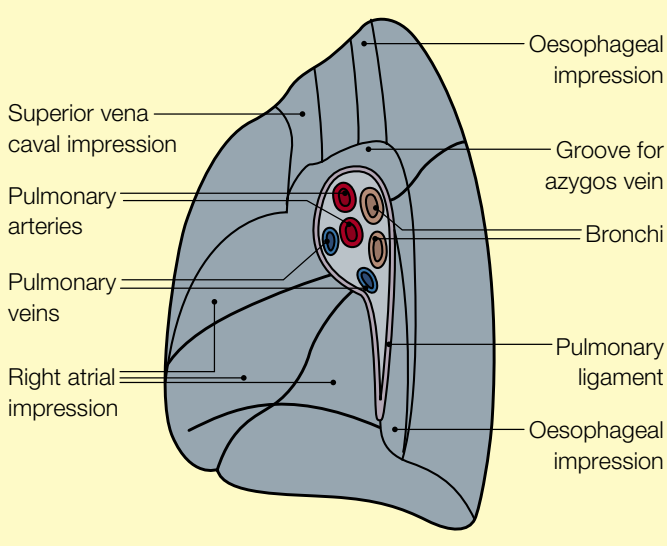
Medial surface of the left lung

The hilus is surrounded by the cut edges of the pleura and pulmonary ligament (inferiorly)



3

Medial surface of the right lung



4

On the right lung there is a shallow concavity in front of the hilum for the right atrium which is continuous above and below with shallow grooves for the superior and inferior vena cavae. Above the superior groove the surface is in contact with the left brachiocephalic vein, the left common carotid and subclavian arteries and the oesophagus.

Blood supply
The heart returns mixed venous blood to the lungs by the pulmonary trunk. After respiratory exchange the blood is then returned by the pulmonary veins.

The pulmonary trunk is a wide vessel, about 5 cm long. It begins at the pulmonary valve, ascends posteriorly to the left of the aorta and bifurcates under the concavity of the aortic arch into right and left pulmonary arteries.

The right pulmonary artery passes horizontally to the hilus of the right lung behind the ascending aorta and in front of the oesophagus and right main bronchus before dividing into branches that follow the segmental bronchi, ending in a capillary network within the alveolar walls.

The left pulmonary artery passes to the left lung hilus in front of the left bronchus and the descending aorta (see *Anaesthesia and Intensive Care Medicine* **3:2**: 76, Figure 1). It is connected by the ligamentum arteriosum, normally fibrosed shortly after birth, to the lower surface of the aortic arch. It also divides within the substance of the lung, its branches following the segmental bronchi.

Bronchial arteries: lung tissue is supplied, not by the pulmonary arteries, but by the bronchial arteries, which are small branches of the descending thoracic aorta. The corresponding bronchial veins drain into the azygos or hemiazygos veins. Some of the bronchial arterial blood drains back to the heart in the pulmonary veins.

The pulmonary veins are short, wide vessels that pass directly horizontally into the left atrium. There are usually two (upper and lower) from each lung. In the lung hilus they lie below the pulmonary artery; on the right they lie behind the superior vena cava and the right atrium and on the left behind the left atrium and in front of the aorta. The pulmonary veins are formed by the union of smaller veins that drain oxygenated blood from the capillary bed in the alveolar walls.

Lymphatic drainage
Lymphatic drainage of the lungs is via a superficial subpleural lymph plexus and a deep plexus of lymph vessels accompany-ing the bronchi. Both groups drain through hilar or broncho-pulmonary nodes to tracheobronchial nodes and thence to mediastinal lymph trunks.

The tracheobronchial nodes lie alongside the trachea and bronchi and receive afferents from the lungs, bronchi, trachea and heart. Their efferents drain to the bronchomediastinal lymph trunks which ascend alongside the trachea to end in the right lymph duct and, on the left, the thoracic duct.

Nerve supply
Innervation of the lung is by the pulmonary plexus which conveys both the sympathetic (bronchodilator) fibres from the upper four thoracic sympathetic ganglia and parasympathetic (bronchoconstrictor) fibres from the vagus. Sensory fibres pass largely in the vagus nerves. ◆

FURTHER READING

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Anatomy of the Nose, Mouth and Pharynx

N Woodall
John Shaw-Dunn

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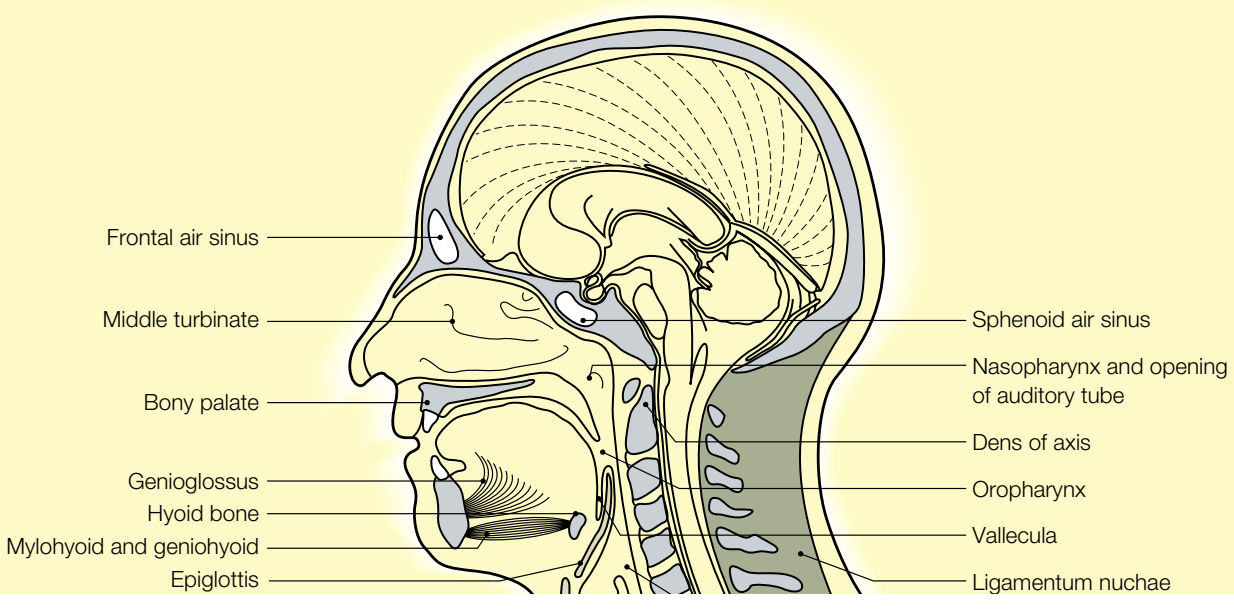
The nose: within the external nose the hair-lined vestibules act as a nasal valve, causing turbulence to improve air conditioning. Each nasal cavity is about 10–14 cm long in the adult.

The floor of the nasal cavity is the bony palate (Figure 1). The arched roof includes the delicate cribriform plate of the ethmoid bone, which separates the nasal cavity from the anterior cranial fossa. The septum contains cartilage anteriorly and the vomer more posteriorly. The septum is seldom midline, perhaps because of microtrauma during labour. Three delicate turbinates project from the lateral wall of each cavity. Air sinuses open on to the lateral wall as do the nasolacrimal ducts. The nasal cavity and sinuses have a thick mucosa with cilia which warms, moistens and cleans incoming air, an action lost during intubation.

Sagittal section of mouth, nose and pharynx



1

Sensation to most of the nasal cavity is provided by branches of the sphenopalatine ganglion, which is accessible to topical anaesthesia behind the middle turbinate.

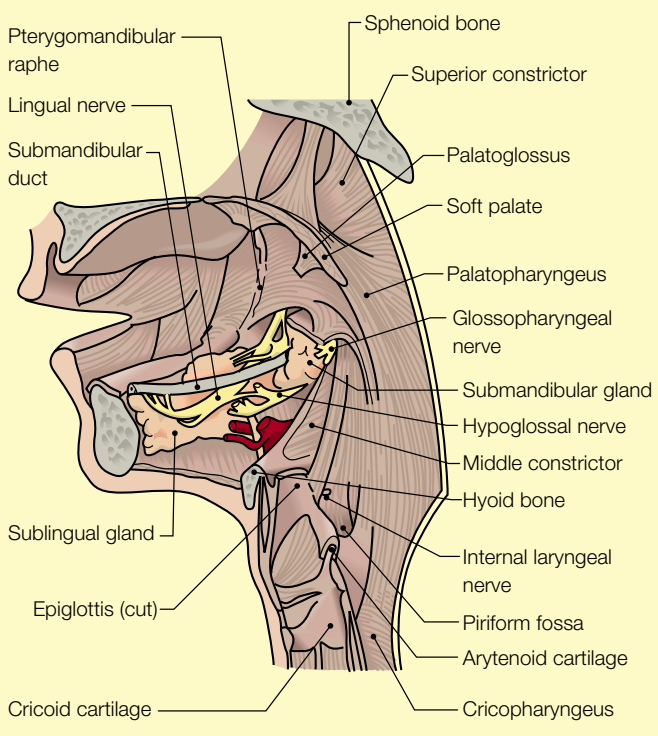
The mouth: the lips and cheeks contain the orbicularis oris and buccinator muscles and form the outer wall of the vestibule. The mouth cavity is limited posteriorly by the fauceal isthmus.

The tongue: the buccal surface of the tongue is separated from the posterior pharyngeal portion by a V-shaped groove behind a row of large vallate papillae with taste buds. The pharyngeal portion has multiple lymphoid nodules, which produce an irregular pebble-like appearance. The intrinsic muscles of the tongue modify its shape and the extrinsic group alter its position. Genioglossus, which forms the bulk of the tongue mass, protrudes the tongue. It originates from the mid-line mental spine on the inner surface of the mandible. During sleep and anaesthesia, reduced muscle tone may allow the tongue to fall backwards and obstruct the airway. This can sometimes be relieved by extending the neck with the mouth closed, stretching the extrinsic muscles like a washing line.

Floor of mouth: the mylohyoid creates a muscular floor for the mouth. On the outside it is covered by deep fascia, platysma and skin. Infection, swelling or bleeding into the deep layers may elevate the tongue, or spread backwards into the pharynx leading to problems with direct laryngoscopy or obstruction of the pharynx.

Salivary glands: the parotid ducts open into the vestibule at the level of the second upper molar crown. Each submandibular gland duct (Figure 2) opens at the sublingual papilla lateral to the frenulum linguae, which connects the underside of the tongue to the floor of mouth. Multiple sublingual glands drain directly into the sublingual folds.

Dissection of constrictor muscles and nerves of the pharynx from the medial side



Redrawn from Romanes G J. Cunningham's *Manual of Practical Anatomy*. Oxford: Oxford University Press, 1986, by kind permission of the publishers.

2

Teeth: the 24 deciduous teeth are replaced by up to 32 permanent teeth. Permanent teeth are recorded numerically in each quadrant. 1 and 2 correspond to the central and lateral incisors anteriorly, 3 the canines, 4 and 5 the premolars and 6, 7, and 8, the molars, posteriorly. Deciduous teeth are recorded alphabetically in the same way.

Nerve supply: the anterior and posterior superior alveolar nerves supply the upper jaw, while the lower is innervated by the inferior alveolar nerve. Lateral to the pterygomandibular raphe a needle can be inserted through the buccinator into the pterygomandibular space to block the inferior alveolar nerve. The anterior two-thirds of the tongue are supplied by the lingual nerve, though fibres conveying taste pass via the chorda tympani to the facial nerve. Extrinsic and intrinsic muscles of the tongue are innervated by the hypoglossal nerve except the palatoglossus muscle, supplied by the vagus.

The pharynx is a muscular tube lined by mucosa extending from the base of the skull to the lower border of the cricoid cartilage at the level of C6.

The nasopharynx lies behind the nasal cavity. The lateral wall bears the opening of the Eustachian tube. This cartilaginous structure, with attachment to the salpingopharyngeus muscle, produces the tubal elevation that is often visible during fibre-optic endoscopy. Behind it lies the blind pharyngeal recess. High on the superior pharyngeal constrictor are the pharyngeal tonsils, which when enlarged become the adenoids. Deep to the pharyngeal muscle layer are the arch of the atlas, the axis and the cervical vertebrae. During nasotracheal intubation, contact with the posterior wall forces the tube tip downwards. Insertion may be impeded by a prominent vertebral arch, tubercles or osteophytes.

The oropharynx is entered through the nasopharyngeal isthmus, formed by the soft palate, uvula and the superior pharyngeal constrictor. Anteriorly, the oropharynx communicates with the mouth via the oropharyngeal or fauceal isthmus, bounded by palato-
glossus and palatopharyngeus between which lie the tonsils.

The laryngopharynx commences at the upper level of the epiglottis and extends to the lower level of the cricoid cartilage. The base of the tongue is separated from the epiglottis by the vallecula, with the median glossoepiglottic fold in the midline. The larynx bulges posteriorly into the laryngopharynx producing a recess on either side, the piriform fossa. The internal laryngeal nerve which mainly provides sensation to the mucosa of the larynx pierces the thyrohyoid membrane and passes beneath the mucosa of the piriform fossa. At this point it may be anaesthetized, by the application of swabs soaked in local anaesthetic.

The pharyngeal wall is surprisingly thin and nerves and blood vessels are vulnerable to penetrating injury. The back and sides of the pharyngeal wall are reinforced by three flattened constrictor muscles, which overlap. They meet in a raphe, which extends from the pharyngeal tubercle on the sphenoid bone to merge with the oesophagus. During swallowing, the bolus is propelled downwards through the cricopharyngeal sphincter into the oesophagus by peristaltic waves in the constrictors. A pouch can develop between the sphincter and the thyropharyngeal portion of the inferior constrictor at Killian's dehiscence. Accumulation of undigested material here may be a potential source for aspiration.

Nerve supply: sensation to the pharynx is supplied by the glossopharyngeal nerve via the pharyngeal plexus. Sensation to the anterior surface of the epiglottis is therefore glossopharyngeal in origin but the inferior or posterior surface, which is anatomically part of the larynx, is supplied by the vagus. Transcranial electrical stimulation shows that one side of the brain is usually dominant in control of the pharynx, which may explain why cerebrovascular accidents on one side of the brain often cause dysphagia. ◆

FURTHER READING

Hiiemae K M, Palmer J B. Food Transport and Bolus Formation during Complete Feeding Sequences on Foods of Different Initial Consistency. *Dysphagia* 1999; **14**: 31–42.

The Pericardium

John Craven

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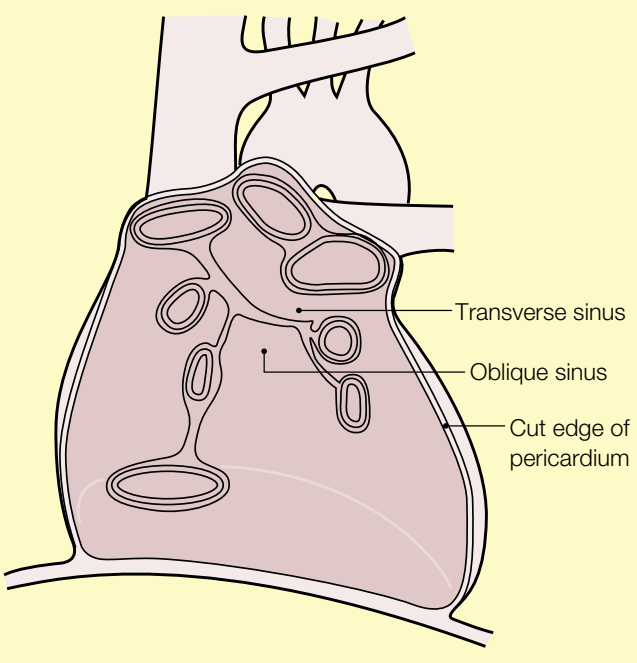
The pericardium is a fibroserous membrane investing the heart and the great vessels entering and leaving it. It is composed of two distinct layers, the outer fibrous pericardium and the inner serous pericardium.

The serous pericardium is a closed serous sac invaginated by the heart. It has visceral and parietal layers, which enclose a potential space, the pericardial cavity. The visceral pericardium covers the entire outer surface of the heart and is reflected to become continuous with the parietal pericardium, which lines the inner surface of the fibrous pericardium. These lines of reflection form:

- the oblique sinus behind the left atrium bounded by the four pulmonary veins and the inferior vena cava
- the transverse sinus below the reflection around the superior vena cava and also behind the left atrium (Figure 1).

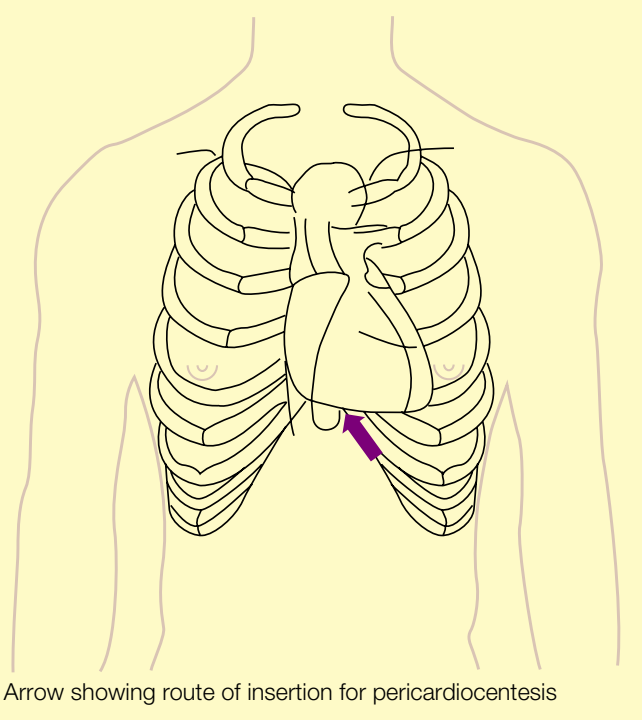
Interior of pericardium viewed after removal of heart and anterior part of pericardium



1

The fibrous pericardium forms a strong conical sac around the heart and the serous pericardium, blending inferiorly with the fibrous tissue of the central tendon of the diaphragm and the adventitia around the inferior vena cava. Superiorly, it blends with the adventitia around the aorta, pulmonary trunk and superior vena cava and posteriorly with that of the pulmonary veins. Anteriorly, the pericardium is closely related to the posterior surface of the body of the sternum, the 2nd to 6th costal cartilages and the thin anterior borders of both lungs (Figure 2). Posteriorly, it is related to the oesophagus, the descending aorta and the vertebral bodies T5–T8 and laterally to the mediastinal pleura. The entire thoracic part of the inferior vena cava, about 2 cm long, is within the pericardium.

Surface marking of pericardium



Arrow showing route of insertion for pericardiocentesis

2

The pericardial cavity in health contains no more than a thin film of fluid but a pericardial effusion may occur as the result of heart failure, generalized oedema and infection. If the effusion is extensive, the excess fluid in the pericardial cavity interferes with the action of the heart because the fibrous pericardium is inelastic. Similar cardiac embarrassment may occur as the result of blood accumulating within the pericardium after stab wounds to the heart. The condition is known as cardiac tamponade; the heart is compressed and its output falls. The veins of the neck and face become engorged because of constriction of the superior vena cava as it enters the pericardial sac. Pericardiocentesis, drainage of fluid from the pericardial sac, is readily achieved using a large-bore venous cannula inserted into the pericardial sac. It is inserted beneath the costal margin at its border with the xiphoid process and directed towards the left shoulder at an angle of 45° to the horizontal. ◆

The Pleura

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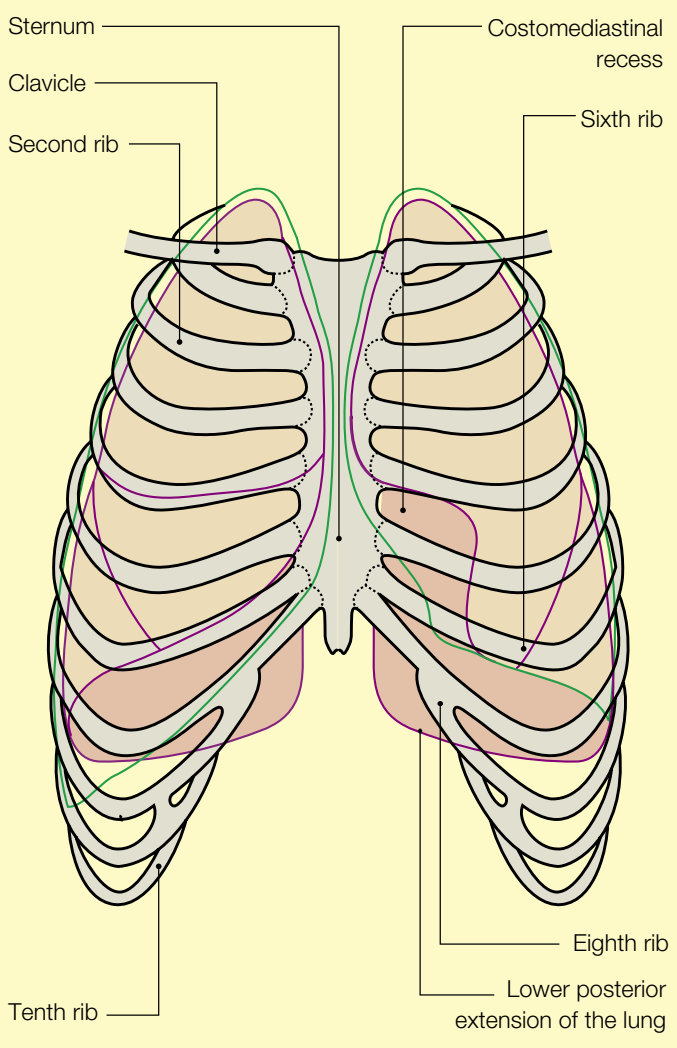
Each pleural cavity is a closed cavity of serous membrane invaginated by the lung. The visceral layer covers the lungs and the parietal layer covers the inner surface of the thoracic cavity. The layers are continuous around the root of the lung and separated by only a thin layer of serous fluid. Thus, the two layers glide easily over each other but are prevented from separating by the negative pressure within the thoracic cavity and the surface tension of the pleural fluid. This ensures that when the thoracic cage expands so does the lung and air is then drawn in from the trachea.

The pleura is a fibro-elastic membrane lined by squamous mesothelial cells; parietal pleura line the ribs, costal cartilages and intercostal muscles, the lateral surface of the mediastinum and the upper surface of the diaphragm. Superiorly it extends, above the thoracic inlet into the neck forming the cervical dome of the pleura. The apical pleura is covered by a fascia, the suprapleural membrane (Sibson's fascia) which is attached to the inner surface of the first rib and prevents the lung expanding too far into the neck on inspiration. At this point, the pleural cavity is at risk of being entered during surgery in the root of the neck or during subclavian cannulation. On the left side, anteriorly, in front of the heart the costal and mediastinal surfaces are in contact, forming the costomediastinal recess**.** The mediastinal pleura loosely invests the main bronchi and pulmonary vessels and continues on to the lung to form the pulmonary (visceral) pleura which covers the lung and extends into its interlobar fissures.

On both sides of the lung the cervical pleura extends about 3 cm above the middle of the clavicle (Figure 1). Anteriorly, on both sides, the lines of reflection (where the parietal pleura meets the visceral layer) descend behind the sternoclavicular joint to meet in the midline at the level of the second costal cartilage. They descend side by side to the fourth costal cartilage where the left pleural reflection deviates laterally, descending along the lateral border of the sternum to the sixth costal cartilage. The right pleural reflection, however, continues downwards near the midline to the same level. Thereafter the course of the reflection line is similar on both sides. Each passes laterally behind the costal margin, reaching the eighth rib in the midclavicular line, the tenth rib in the midaxillary line and the twelfth rib in the paravertebral line. The lower limit of the pleura medially is below the twelfth rib and thus at risk during renal or adrenal surgery. The posterior reflection line ascends, on each side, about 3 cm from the midline. A pneumothorax is best drained, with a catheter and underwater seal, by catheter insertion in the second intercostal space in the midclavicular line. A pleural effusion should usually be drained by insertion of the catheter in the sixth or seventh space in the midaxillary line.

Surface relationship of the lungs and pleural cavities



Only the anterior pleural markings are shown; posteriorly the pleural reflection reaches 1–2 intercostal spaces below the lung base.

1

The pleura gains its blood supply from adjacent tissues. Though the pulmonary pleura has no pain fibres the parietal pleura is richly supplied by the nerves in the subjacent tissues, the intercostal and the phrenic nerves. Therefore, pleurisy may produce pain referred to the upper abdomen from inflammation of the lower sixth intercostal nerves or referred to the root of the neck from the phrenic nerve. ◆

The Ribs and Intercostal Spaces

John Craven

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The thoracic contents are contained in an osteocartilaginous cage formed by the thoracic vertebrae behind, the sternum in front and between them the ribs and costal cartilage.

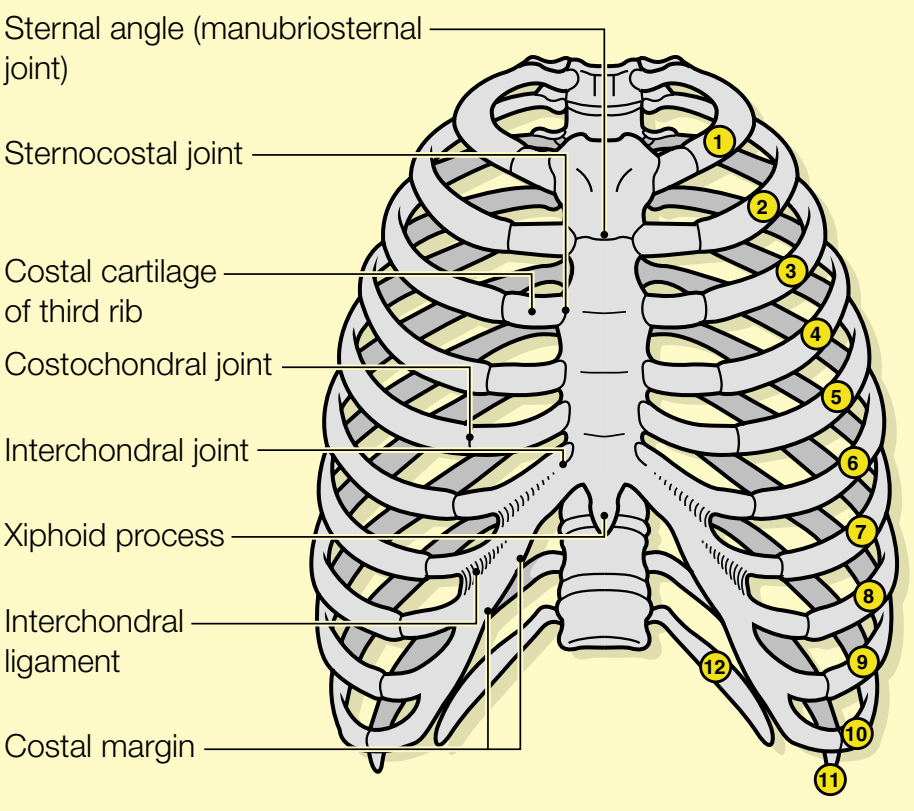
Ribs

The ribs (Figure 1) are narrow, curved flat bones. The first seven or eight pairs of ribs attach the vertebrae to the sternum through their costal cartilage. The eighth to tenth pairs are known as 'false ribs' because their cartilage articulates with the cartilage above them and not with the sternum. The eleventh and twelfth pairs of ribs are known as 'floating ribs' because their cartilage ends in the muscles of the posterior abdominal wall.

A typical rib (ribs 3–9) comprises a head bearing two facets. The lower facet articulates with its corresponding vertebra and the upper facet articulates with the vertebra above that. Lateral to the head (2–3 cm) is a tubercle that articulates with the transverse process of the corresponding vertebra (Figure 2). Close to this, the costotransverse ligament gains attachment. Beyond the tubercle, the shaft of the rib becomes flatter and wider and the inner surface of its lower border is grooved (costal groove) to accommodate the intercostal nerves and vessels.

The first rib is short, wide and flattened. On its upper surface the scalene tubercle separates an anterior groove for the subclavian vein and a posterior groove for the subclavian artery and brachial plexus. The heads of ribs 1 and 10–12 bear a single facet.

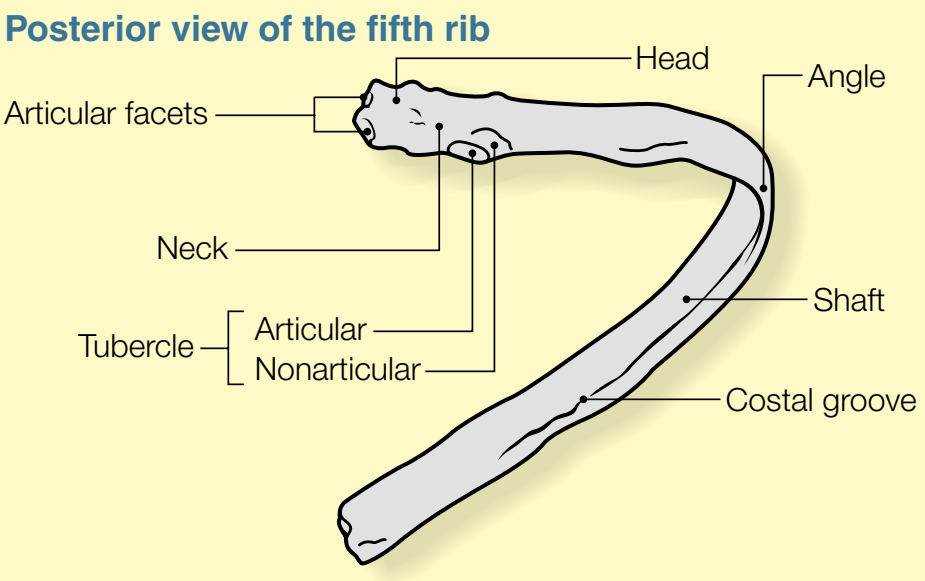
Anterior view of thoracic cage



The ribs are numbered 1 to 12.

1

Posterior view of the fifth rib



2

Intercostal spaces

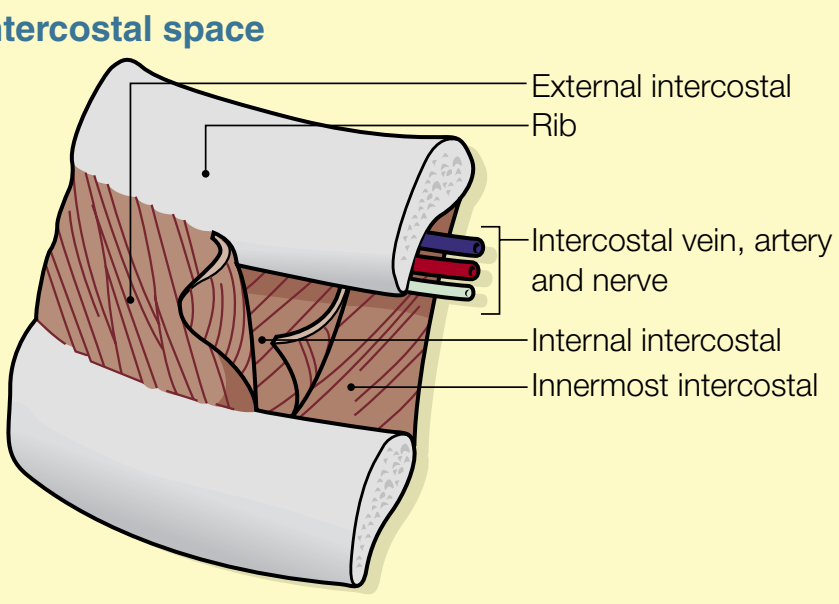
The intercostal spaces are bounded by adjacent ribs and costal cartilage and contain the intercostal muscles, vessels and nerves. Deep to them lies the pleura. The external intercostal muscle is the most superficial. Deep to it is the internal intercostal muscle and deepest of all is the incomplete sheet of the innermost intercostal muscle attached to the inner surfaces of the sternum, costal cartilage and ribs. The vessels and nerves lie together in the costal groove between the internal and innermost muscles. The artery lies between the vein superiorly and the nerve inferiorly in the neurovascular bundle (Figure 3).

Twelve pairs of thoracic spinal nerves supply the muscles and skin of the thoracic and abdominal wall. The cutaneous distribution of each nerve is striplike and is known as a dermatome (Figure 4). Though there is overlapping of the dermatomes, knowledge of their distribution allows the clinician to determine the extent of sensory deficiencies and the proximal extent of anaesthesia after, for instance, a spinal block.

The parietal pleura has a similar segmental 'dermatomal' distribution. Thus, inflammation of the pleura results in pain being referred to the cutaneous distribution of the nerve affected which, in the case of the lower pleura, is the anterior abdominal wall.

The intercostal arteries supply the chest wall and its overlying muscles and the breast. They anastomose with branches of the internal thoracic artery and its terminal branches.

Intercostal space



3

Cutaneous distribution of dermatomes

4

Procedures

Drainage

Fluid (e.g. blood, pus, inflammatory exudate) or air may be drained from the thorax for diagnostic or therapeutic reasons. This is done by inserting a narrow-bore or wide-bore needle through an intercostal space previously infiltrated with local anaesthetic. Radiography determines the level at which the fluid is best aspirated. The needle should be passed along the superior border of the rib to avoid the neurovascular bundle. There is a risk of penetrating the diaphragm if aspiration is attempted below the seventh intercostal space.

Anaesthesia

Local anaesthesia of intercostal nerves has an important role to play in managing the pain arising from fractured ribs or reducing the pain of a thoracotomy. The appropriate nerve and the two nerves above and below (because of the overlapping supply) are infiltrated at or around the rib angle. In each space, the needle is advanced until the rib is met, then withdrawn and guided under the inferior angle for 0.5 cm. If no blood is then aspirated, 1–4 ml of local anaesthetic solution is injected.

FURTHER READING

Rushman G B, Davies N J H, Cashman J N. *Lee's Synopsis of Anaesthesia.* Oxford: Butterworth-Heinemann, 1999: 626–34.

Sacrum and Sacral Hiatus

John Craven

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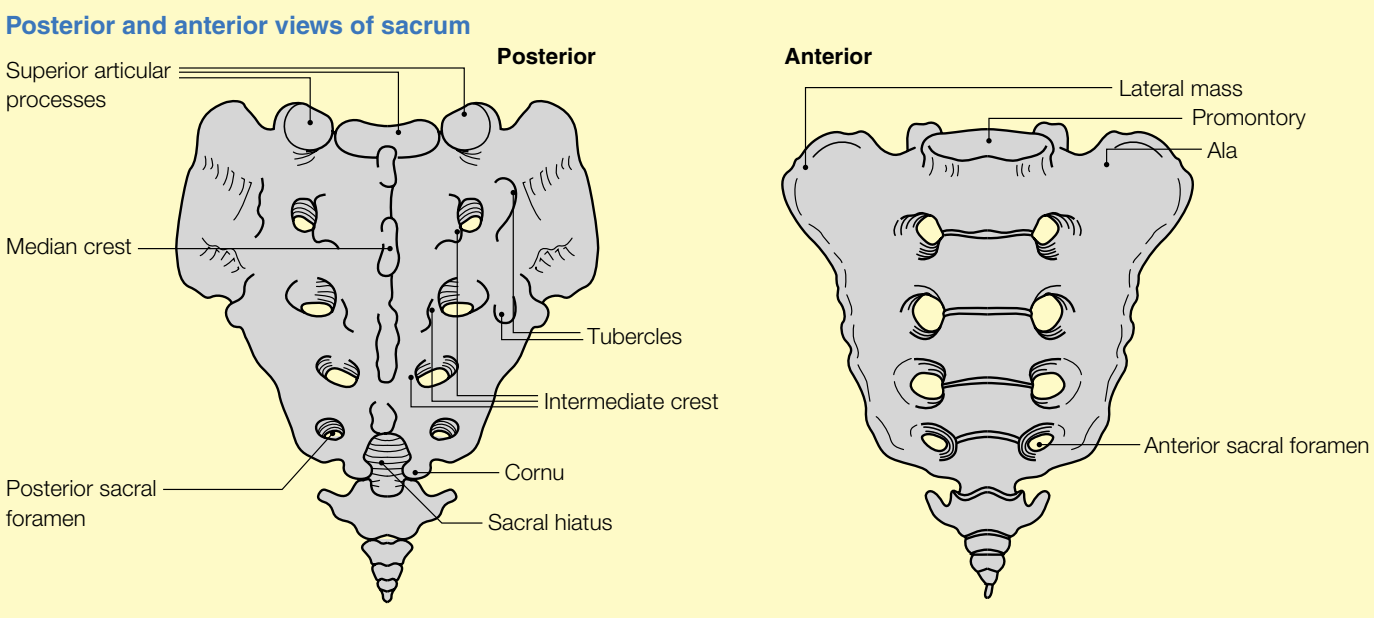
The sacrum is formed from the five fused sacral vertebrae (Figure 1). It is triangular and possesses a base superiorly, an apex inferiorly and dorsal (posterior), pelvic and lateral surfaces. Two rows of foramina on its dorsal and pelvic surfaces divide it into a median portion, the body, formed from the fused vertebral bodies, and two lateral masses formed from the fused transverse processes. The paired pelvic and dorsal sacral foramina communicate by intervertebral foramina with the central sacral canal and convey the ventral and dorsal rami of the sacral nerves. The base, directed upwards and forwards is formed from the upper surface of the first sacral vertebra and contains an oval concavity, the articular facet, for the disc that separates it from the 5th lumbar vertebra. Lateral to this the lateral masses of the sacrum are at their widest and form the prominent ala. The anteriorly protruding central part of the superior surface is known as the promontory. Behind the body, superiorly, is the upper opening of the sacral canal on each side of which project the superior articular processes for articulation with the 5th lumbar vertebra. The small apex articulates with the coccyx.

Posterior and anterior views of sacrum



1

The pelvic surface is concave and the smooth lateral masses give attachment to the piriformis muscle. Superiorly this surface is related to the peritoneum and inferiorly to the rectum. The posterior surface is convex and rough, and in the midline where it roofs the sacral canal it bears a median sacral crest, which is subcutaneous and palpable, and two less prominent intermediate sacral crests more laterally. Each row of dorsal sacral foramina lie lateral to the intermediate sacral crests. The posterior wall of the sacral canal is deficient posteriorly, forming the sacral hiatus which is covered by fibrous tissue. The hiatus is bounded on each side by the palpebral sacral cornua with which the coccyx articulates.

The sacral canal is triangular in transverse section and contains the cauda equina and CSF with the meninges. The dural sac ends at the 2nd sacral vertebra on a line joining the posterior superior iliac spines. Extradurally lie the spinal nerves and the internal vertebral venous plexus, the bulk of which lies anteriorly in the canal. The dorsal surface gives attachment to erector spinae, gluteus maximus and the thoracolumbar fascia.

The lateral surface is the roughened articular surface forming part of the sacroiliac joint. Strong interosseous ligaments connect the sacrum and ilium.

Spinal and caudal anaesthesia techniques are so commonly used that it is important to be aware of the anatomical abnormal-ities that may be encountered:

- the sacral hiatus may be displaced upwards or downwards
- the sacral canal may be narrowed or obliterated
- the fibrous sheet covering the hiatus may be ossified
- the dural sac may extend distally as far as S3 or, occasionally, S4. ◆

Segmental Bronchi and Structure of the Lung

John Craven

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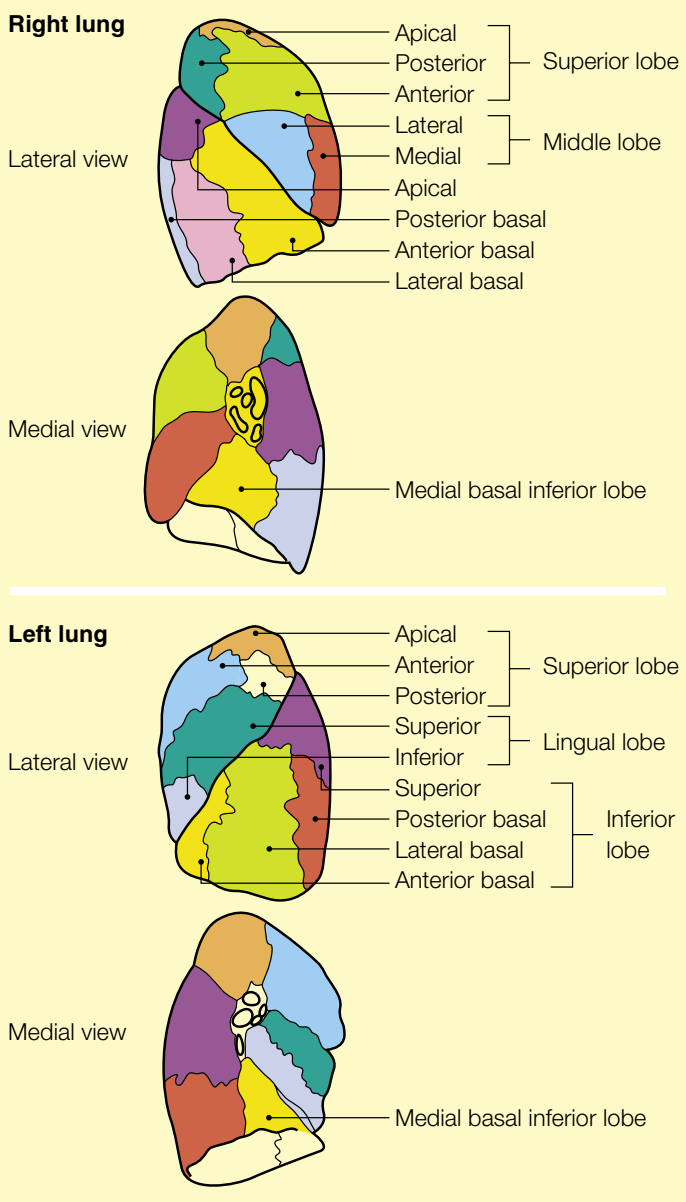
The segmental structure of the lungs is significant because infection and neoplastic processes are often localized to one or more adjacent segments. Knowledge of the anatomy of the intrapulmonary bronchial tree is important for:

- understanding lung radiology
- interpreting diagnostic bronchoscopy
- therapeutic application of bronchoscopy to sputum retention
- effective application of postural drainage for sputum retention
- the surgical resection of diseased segments of the lungs.

Although the lung appears to be a homogeneous entity, each lung consists of ten bronchopulmonary segments, which are in continuity. The parenchyma of each segment is distinct from that of its neighbours and there is little vascular anastomosis between them. Each segment has its own bronchus and is supplied by one or more pulmonary arteries and drained by its own veins. The arteries and bronchus have a central position in the segment, but the veins tend to lie peripherally along the intersegmental planes. Segmental resection along intersegmental lines is possible with little bleeding or leakage of air.

Each bronchopulmonary segment has a constant position, is wedge-shaped with its apex at the hilum, and its base extending on to the pleural surface of the lung (Figure 1). The differences in the anatomical arrangement of each side are slight; the arrangement on the two sides would be similar but for the fact that the lingular bronchus branches from the left upper lobe bronchus.

Bronchopulmonary segments



1

The right lung

The upper lobe – the three segments are anterior, posterior and apical (which forms the dome of the lung). The posterior segment of the right upper lobe is often the site of infective processes, especially aspiration pneumonitis. The most common lesion of the anterior segment of the upper lobes is neoplastic.

The middle lobe is divided vertically into a lateral and medial segment. The middle lobe bronchus is long and surrounded by hilar lymph nodes and therefore is subject to pressure and external compression by their enlargement. Thus, viral infections, bronchiectasis and tuberculosis may be the cause of middle lobe collapse.

The lower lobe is the largest. There is an apical or superior lobe and four basal lobes (medial, lateral, anterior, posterior) that are related to the diaphragm.

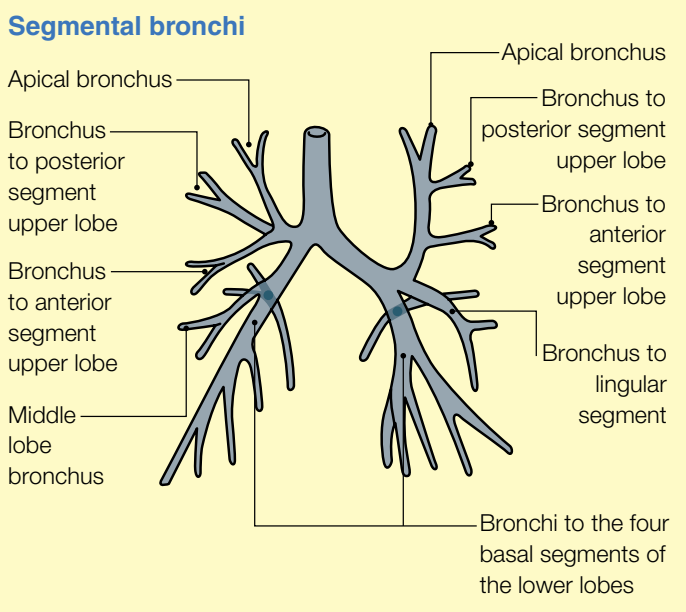
The left lung

The upper lobe consists of five segments. The lower two comprise the superior and inferior lingual segments. The remaining segments of the upper lobe are arranged in the same way as those on the right side – apical, anterior and posterior.

The bronchial tree (Figure 2)

The right main bronchus is wider, shorter and more vertical than the left and therefore more subject to accidentally inhaled foreign bodies. The upper lobe bronchus passes laterally for l cm before branching into its three divisions (apical, anterior, posterior). The pulmonary artery lies anteriorly to it and below this the middle lobe bronchus arises anteriorly to divide into medial and lateral branches. Beyond the origin of the middle lobe bronchus all other branches are destined for the segments of the lower lobe.

Segmental bronchi



2

The left main bronchus is longer than the right and about 5 cm from its origin it divides into a lateral branch (the left upper lobe stem bronchus) and the bronchus to the lower lobe. Just beyond the bifurcation, the upper lobe stem bronchus bifurcates into the bronchus to the lingular segment, which divides into two segmental branches, the anterior and posterior lingual branches. The stem bronchus to the upper lobe divides to give the anterior and then the apical and posterior branches. The left lower lobe bronchus usually gives off a posterior branch to the apical (superior) segment of the lower lobe and branches to the remaining segments arise distal to that.

The structure of the bronchi

The bronchi are strengthened by horseshoe-shaped rings of cartilage, similar to those of the trachea, and divide as they continue into the substance of the lungs into progressively smaller structures until they are reduced to a diameter of less than l mm when they lose their cartilaginous support. The bronchial tree is lined throughout by mucous, submucous and connective tissue coats that become progressively thinner in their distant ramifications. Plain muscle fibres bridge the intervals between the cartilaginous rings or plates and replace them in the bronchioles. The submucous coat contains mucous glands and the mucous coat consists of an elastic lamina on which lies the respiratory epithelium as far as the respiratory bronchioles where the abundant goblet cells and the cilia disappear. Each bronchiole ends in an alveolar sac. Fine elastic cells continue into the alveolar walls. The alveolar walls are invested in a dense capillary network.

Bronchial vessels

The bronchial vessels arise, one on each side, from the aorta or, sometimes from the intercostal vessels to supply the lung parenchyma. The bronchial and pulmonary vessels communicate freely on both the arterial and venous sides. These anastomoses are of significance in chronic inflammatory lung disease when the bronchial arterial system enlarges considerably. The bronchial circulation is an arteriovenous shunt; the artery arises from the systemic circulation, but the veins enter the pulmonary system.

Nerve supply

The pulmonary plexuses lie anterior to the hilum of the lung and derive fibres from both the vagi and the sympathetic trunk. Their efferent fibres pass to the bronchial musculature and they receive afferents from the mucous membranes of the alveoli and the bronchioles. ◆

Spinal Nerves and Dermatomes

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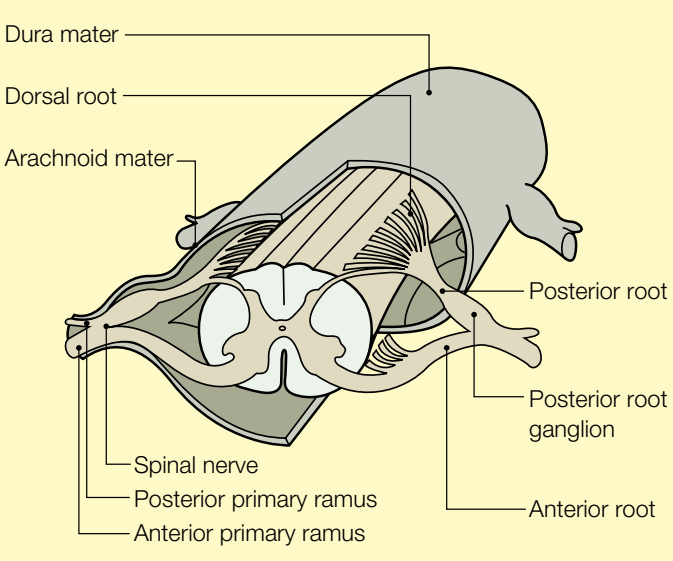
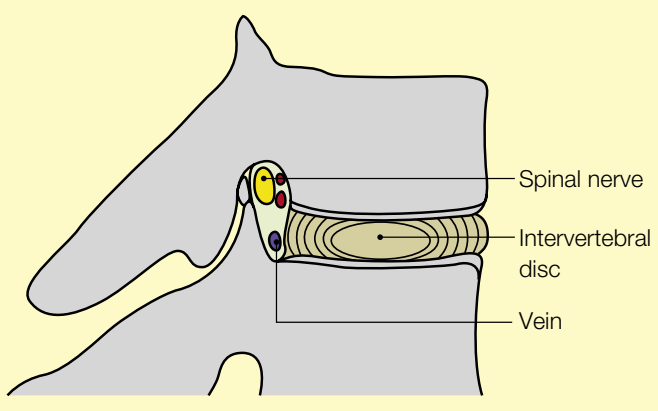
There are 31 pairs of spinal nerves, each attached to its appro-priate segment of the spinal cord, by anterior and posterior nerve roots which unite just beyond the posterior root ganglion (Figure 1). The nerves leave the vertebral column through the intervertebral foramina (Figure 2). They are numbered after their corresponding vertebra except the 8th cervical nerves, which pass out below the 7th cervical vertebrae, because there are only seven cervical vertebrae. The remaining spinal nerves take the name of the vertebra below which they emerge, there are 12 thoracic, five lumbar, five sacral and one coccygeal nerve. The segment of the spinal cord from which each pair of spinal nerves arises takes the same name and number as its nerves.

Spinal cord



1

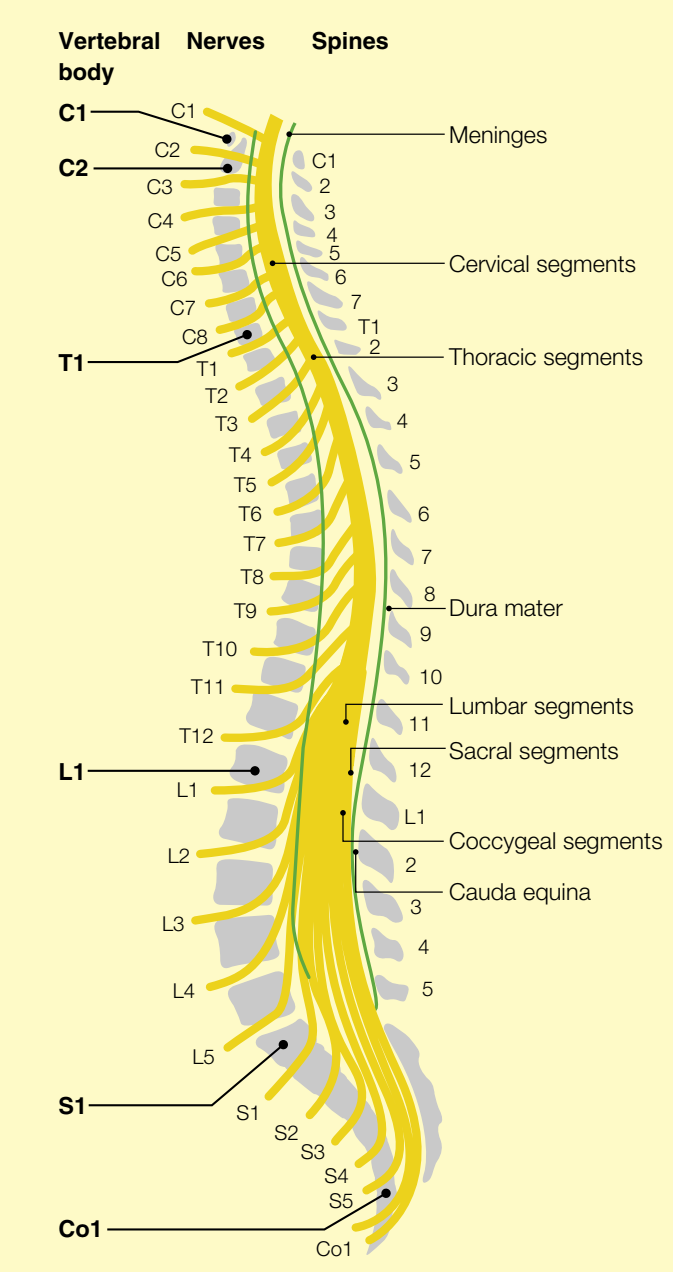
Intervertebral foramen and spinal nerve



2

The anterior and posterior nerve roots emerge separately through the cord's meninges. Each posterior root ganglion lies without the dural sac and, apart from the first two and the last two spinal nerves each lies in its intervertebral foramen. The adult spinal cord is shorter than the vertebral column and thus there is a progressive obliquity of the spinal nerve roots and the length of the nerve roots increases as the lower end of the vertebral column is approached (Figure 3). The lumbar and sacral nerve roots are the longest and most of these contribute to the bundle of nerve roots in the subarachnoid space caudal to the end of the spinal cord (the cauda equina).

Spinal cord in vertebral canal showing relationships of spinal cord segments, spinal nerves and dural sac to vertebral bodies and spines



3

The dorsal roots contain afferent or sensory fibres from the skin, subcutaneous and deeper tissues and often from viscera. The ventral roots contain efferent or motor fibres to skeletal muscles and most contain preganglionic autonomic fibres. The cell bodies of axons contributing to the ventral roots lie in the ventral grey horns of the spinal cord, but the cell bodies of axons contributing to the dorsal roots lie outside the cord in the dorsal root ganglion. Once the nerve lies outside the intervertebral foramen it is connected to the sympathetic nervous system by rami communicantes. The 12 thoracic and first two lumbar nerves each send a white ramus communicans to the sympathetic trunk and each receives back a grey ramus communicans, the fibres of which are then distributed with the branches of the spinal nerve. The spinal nerve then divides into anterior and posterior primary rami (Figure 1). The posterior primary rami supply the skin and the muscles of the back, the anterior primary rami supply the skin and muscles of the lateral and anterior parts of the trunks and both upper and lower limbs. It is the anterior primary rami that form the cervical, brachial and lumbosacral plexuses.

Dermatomes

The body skin is innervated in simple continuous strips, from behind forwards by branches of the posterior and anterior primary rami. Although there is great complexity of the several plexuses of the anterior roots, the nerve fibres of each spinal segment, irrespective of their differing courses, are distributed to one strip (dermatome) of skin. The dermatomes overlap each other so that on the trunk, for example, alternate dermatomes meet each other. Segments whose nerves are primarily concerned with limb innervation are absent or restricted from any innervation of the trunk. Muscles, which are derived from myotomes, are also segmentally innervated.

Clinical importance

The relationships of the nerves, nerve roots and spinal cord segments to the vertebral bodies and spines is of the greatest
clinical importance. Some useful surface markings include:

- the spine of C7 (vertebra prominens) is easily palpable
- the spine of T3 is opposite the medial portion of the spine of the scapula
- the spine of T7 is opposite the inferior angle of the scapula (with the arms to the sides)
- a line drawn between the summits of the iliac crests intersects L4 or the L4/5 interspace
- the dimples overlying the posterior superior iliac spines are on a line crossing the second posterior sacral foramen; the dural sac in the adult usually ends at this point.

Figure 3 summarizes the relationship of the spinal cord and the meninges to the vertebrae and their spines. ◆

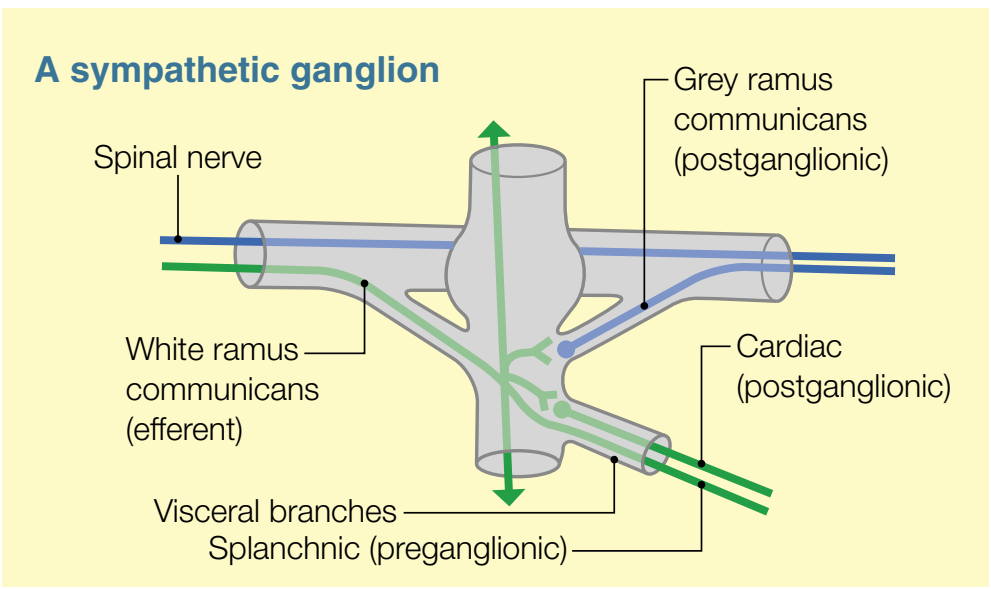
The Sympathetic Trunk and Stellate Ganglion

John Craven

John Craven was formerly Consultant Surgeon at York District Hospital, York, UK. He trained in Manchester, Uganda and Cardiff. He is past chairman of the primary examiners of the Royal College of Surgeons of England. His particular interest is in gastric cancer.

The sympathetic nervous system has motor and sensory functions. The important motor functions are the vasoconstriction of blood vessels and pilomotor and sudomotor control to the skin; they are conveyed by efferent fibres, which pass in the white (medullated) rami communicantes to synapse in a ganglion of the sympathetic trunk (Figure 1). The medullated, preganglionic fibres arise only from cells in the lateral horns of T1–L2 and are conveyed within their anterior primary rami to enter the sympathetic trunk. Within the trunk, fibres destined for the head and neck, arising from the uppermost thoracic segments, ascend to one of the three cervical ganglia (upper, middle or lower). In the ganglion, the fibres synapse with postganglionic, non-medullated nerves.

The afferent (sensory) fibres reach the sympathetic trunk travelling on blood vessels, within somatic nerves or within sympathetic nerves supplying sympathetic plexuses. They pass from the sympathetic ganglia in the white rami communicantes to the posterior root ganglion conveying visceral sensations such as colic or visceral pain. Each sympathetic ganglion has a somatic and a visceral branch; the somatic branches of the three cervical ganglia accompany the cervical nerves, the inferior cervical ganglion giving branches to C7 and C8. The three cervical ganglia each supply vascular branches, which allows wide distribution to the skin of the head and neck; each also has a cardiac branch passing to the cardiac plexus. Visceral branches of the superior cervical ganglion supply the dilator pupillae muscle and levator palpebrae superioris muscle. The paired sympathetic trunks are formed of ganglia connected by nerve fibres. They extend from the base of the occiput to the coccyx lying on the prevertebral fascia. Developmentally there are ganglia for each spinal nerve but their number has been reduced by fusion, producing three cervical, 11 thoracic, four lumbar and four sacral ganglia.



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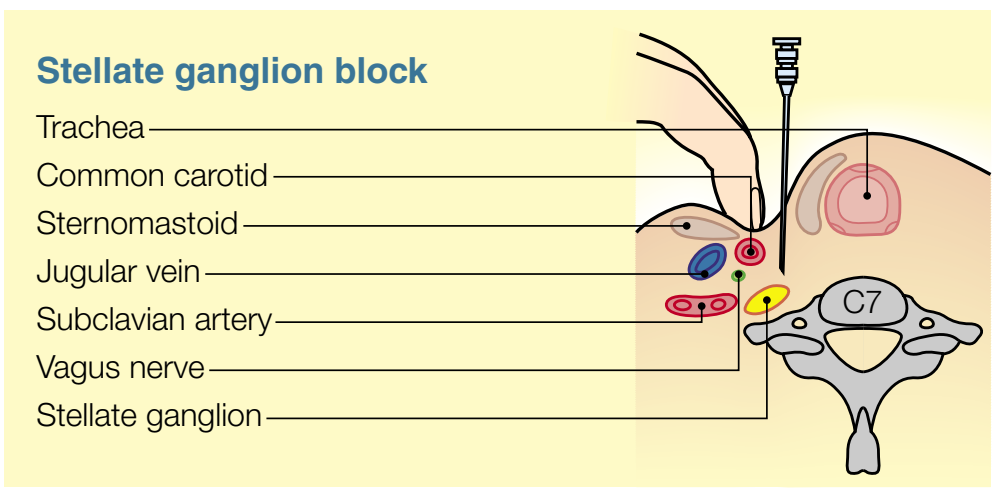
The stellate ganglion

In 80% of the population, the inferior cervical ganglion is fused with the first thoracic ganglion to form the large stellate ganglion, which lies on the neck of the first rib behind the cervical pleura. Its branches are conveyed by grey (non-medullated) rami communicantes to the C7, C8 and T1 spinal nerves and, via a plexus, to the subclavian artery and its branches, from where they are distributed to the upper limb. It is of clinical significance that the sympathetic nerve supply of the pupil and levator palpebrae superioris joins the sympathetic trunk from the grey rami of the first thoracic segment at the stellate ganglion.

Cervical sympathectomy: removal of the second and third thoracic ganglia is required occasionally to abolish the excessive sweating of hyperhidrosis, the vasospasm of Raynaud's disease and, more controversially, to relieve the pain of causalgia (complex regional pain syndrome type 2) after trauma to the upper limb. The aim of the operation is to obtain sympathetic denervation of the upper limb without dividing the oculopupillary fibres and thus producing the complications of ptosis, constriction of the pupil and loss of sweating on the affected side of the face (Horner's syndrome).

Sympathetic ganglion block with local anaesthetic solution (0.5% lidocaine (lignocaine)) can be attempted to establish whether benefit can be expected from sympathectomy (Figure 2). The patient lies supine, head and neck extended. A 6 cm needle is directed posteriorly, 1.5 cm superior and 1.5 cm lateral, to the suprasternal notch between the trachea and the carotid sheath alongside the body of the VIIth cervical vertebra until it strikes its transverse process. The needle is then withdrawn 0.5 cm, suction applied to ensure it is extravascular and 10 ml of anaesthetic is injected. A temporary Horner's syndrome results if the block is successful.



2

The Thoracic Inlet and First Rib

John Craven

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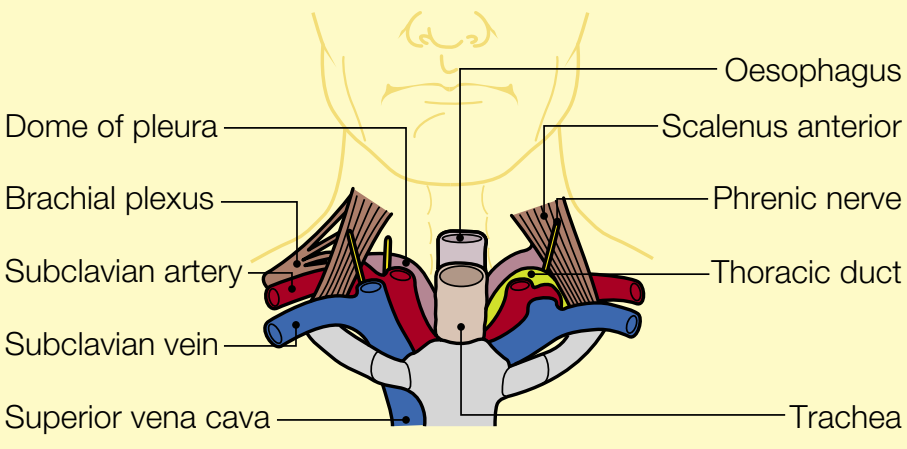
The thoracic inlet, small and kidney-shaped, is about 10 cm wide and 5 cm anteroposteriorly. It slopes forward and is bounded by the first thoracic vertebra posteriorly, the upper border of the manubrium anteriorly and the first rib and costal cartilage laterally. It transmits the oesophagus, the trachea, and the large vessels comprising the right and left subclavian arteries, and the right and left brachiocephalic veins, which unite behind the lower border of the right first costal cartilage to form the superior vena cava. Lying on the neck of the first rib posteriorly is the sympathetic trunk. On each side is the apex of the lung, some 3 cm above the medial third of the clavicle, covered by the dome of the pleura (Figure 1).

The subclavian arteries commence behind the sternoclavicular joint and curve laterally in front of the apex of the lung before passing on to the upper surface of the first rib. Both subclavian veins lie anterior to their respective arteries curving medially from the middle third of the clavicle to form the brachiocephalic vein by joining their internal jugular vein behind the sterno-clavicular joint.

The first rib (Figure 2) is short, wide, flattened and lies in an oblique plane, sloping forwards and downwards. It possesses a head that articulates with the body of the first thoracic vertebra, a rounded neck, a posterior tubercle and a body. The anterior end of the body bears the costal cartilage, which articulates with the manubrium. Its head bears a single facet for articulation with the first thoracic vertebra and posteriorly it bears a small tubercle posteriorly on its angle. The lower surface of the body is smooth and lies on the pleura. A small scalene tubercle on its medial border marks the attachment of the scalenus anterior muscle and this tubercle, on the upper surface of the body, separates an anterior groove for the subclavian vein from a posterior groove for the subclavian artery and the lower trunk of the brachial plexus which lies behind the artery. Scalenus medius is attached to the upper surface of the body behind the groove for the artery. Anterior to the neck of the rib and behind the pleura lie, from medial to lateral, the sympathetic trunk and the large branch of the first thoracic nerve to the brachial plexus.

The proximity to the surface and the constancy of their surface anatomy allows percutaneous access to the large veins in this region; the subclavian vein can be catheterized for intravenous feeding or monitoring central venous pressure. The infraclavicular approach is preferred because there is less chance of accidental puncture of the pleura by this route (Figure 3). The needle is inserted one finger's width below the midpoint of the clavicle and directed medially and as far anteriorly as possible (to ensure that neither the pleura nor the subclavian artery is pierced) towards the jugular notch of the manubrium. The subclavian vein should be entered as it curves over the body of the first rib.

The thoracic inlet



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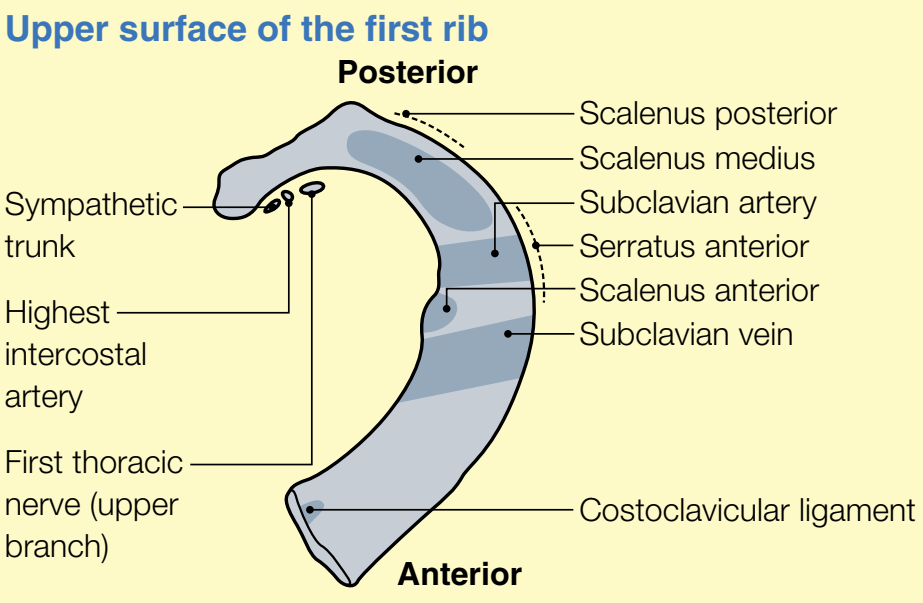
Upper surface of the first rib



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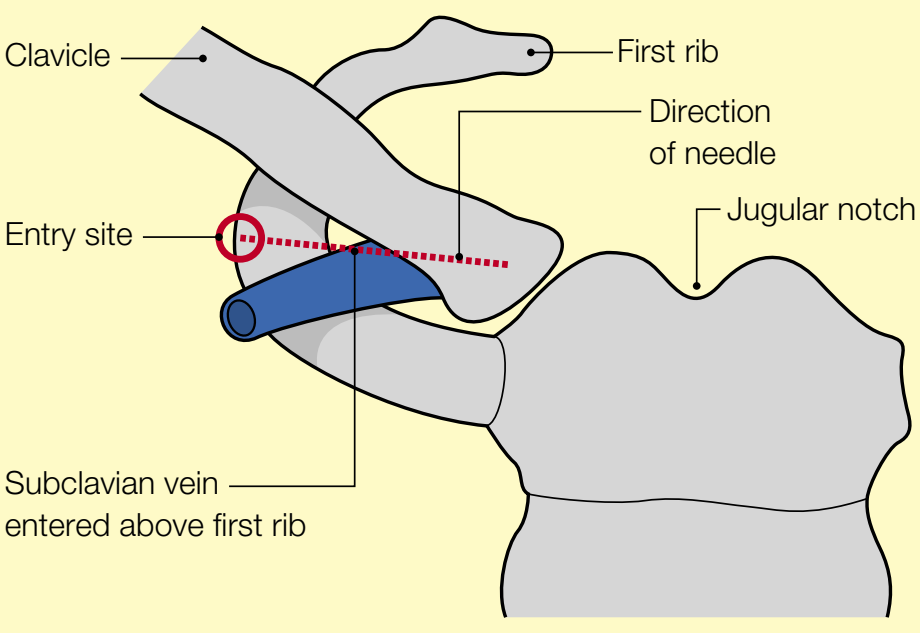
Infraclavicular access to the large veins



3

The Trachea and Extrapulmonary Bronchi

John Craven

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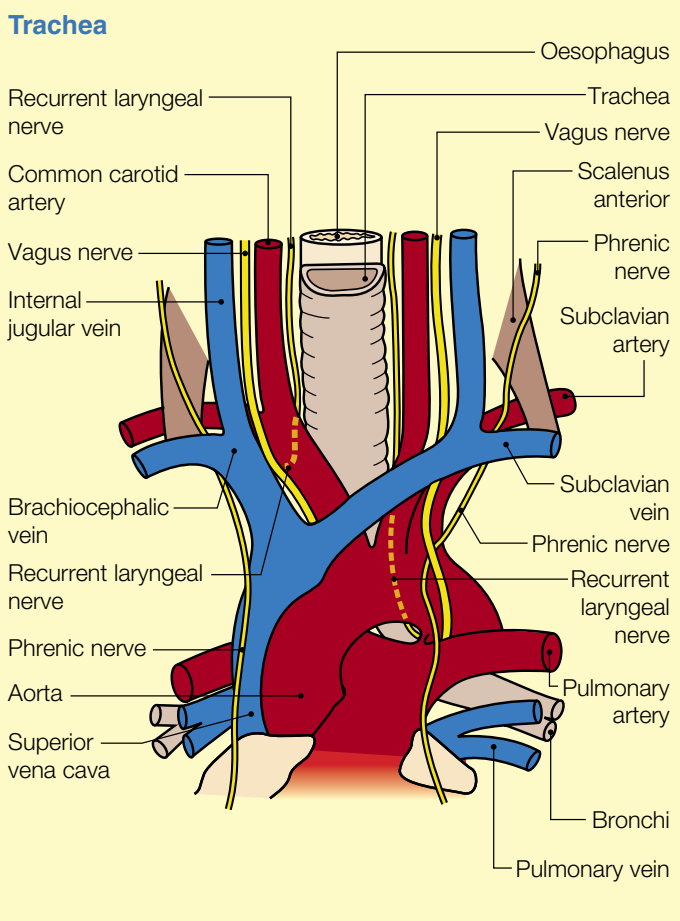
The trachea, beginning at the level of the 6th cervical vertebra, descends from the larynx through the neck and thorax to its bifurcation into the two bronchi at the sternal angle, at the level of the 4th thoracic vertebra. In the adult, it is about 10 cm long and 2 cm in diameter. It is covered by the pretracheal fascia, which is attached superiorly to the hyoid bone and the thyroid cartilage. The fascia splits to enclose the thyroid gland, below which it blends into the carotid sheaths (Figure 1).

Trachea



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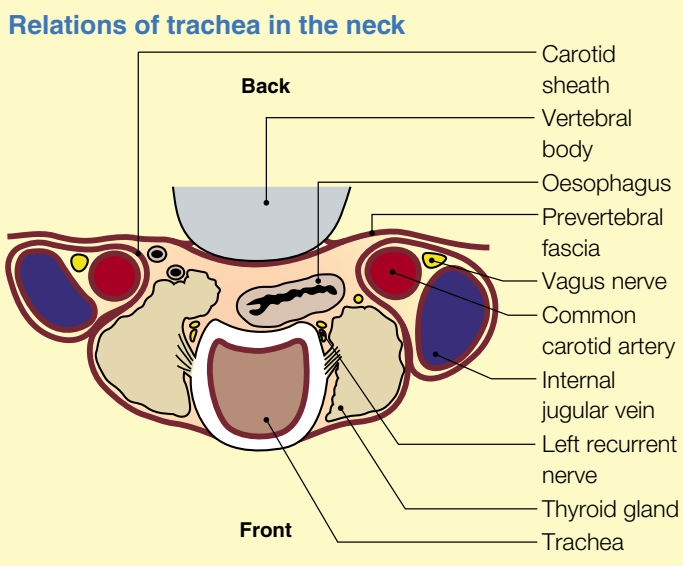
The wall of the trachea is formed of fibrous tissue reinforced by 15–20 cartilaginous rings. These are incomplete posteriorly where the trachea rests on the oesophagus and are there united by fibroelastic and smooth muscle tissue. The trachea is lined interiorly by respiratory epithelium. It lengthens and widens slightly during inspiration and recovers during expiration because of the elastic tissue within its walls.

Relations in the neck (Figure 2): the trachea lies anterior to the oesophagus with the recurrent laryngeal nerve lying laterally in the groove between them. Anteriorly it is covered by the cervical fascia and the infrahyoid muscles and is crossed by the isthmus of the thyroid gland and the left brachiocephalic vein. To its lateral aspect lies the lateral lobe of the thyroid gland, the inferior thyroid artery and the carotid sheath.

Relations of trachea in the neck



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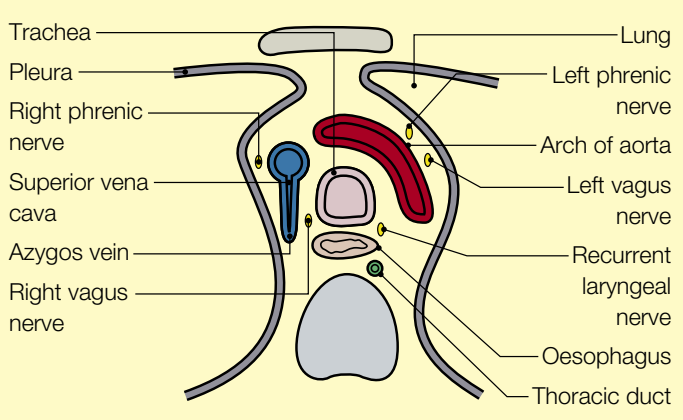
Relations in the thorax (Figure 3): the brachiocephalic artery and, below it, the arch of the aorta separate the trachea from the manubrium. The oesophagus descends behind the trachea. On its left lie the common carotid and subclavian arteries above and the aortic arch below, to the right lie the mediastinal pleura, the right vagus nerve and the azygos vein.

The tracheal bifurcation, the carina, lies anterior to the oesophagus and to its left lies the bifurcation of the pulmonary trunk. Tracheobronchial lymph nodes lie on either side.

Transverse section through the mediastinum at the level of the 4th thoracic vertebra



3

The extrapulmonary bronchi: each arises at the carina and descends laterally to enter the hilum of the lung where it divides to form the intrapulmonary bronchial tree. Their structure is similar to that of the trachea.

The right bronchus is about 3 cm long. It is wider and more vertical than the left bronchus, which is why inhaled foreign bodies tend to enter it more often. The right upper lobe bronchus arises from it just before it enters the hilum of the lung. Anteriorly, the right pulmonary artery separates it from the pericardium and the superior vena cava. The arch of the azygos vein is above it and the bronchial vessels lie posteriorly.

The left bronchus is about 5 cm long. Anteriorly, the left pulmonary artery separates it from the left atrium. The arch of the aorta is above it and posteriorly the bronchial vessels separate it from the oesophagus and the thoracic aorta. ◆

The Veins of the Lower Limb

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The veins of the lower limb are classified as superficial, deep or communicating (perforating) veins. Valves are present in all the larger vessels including the communicating veins.

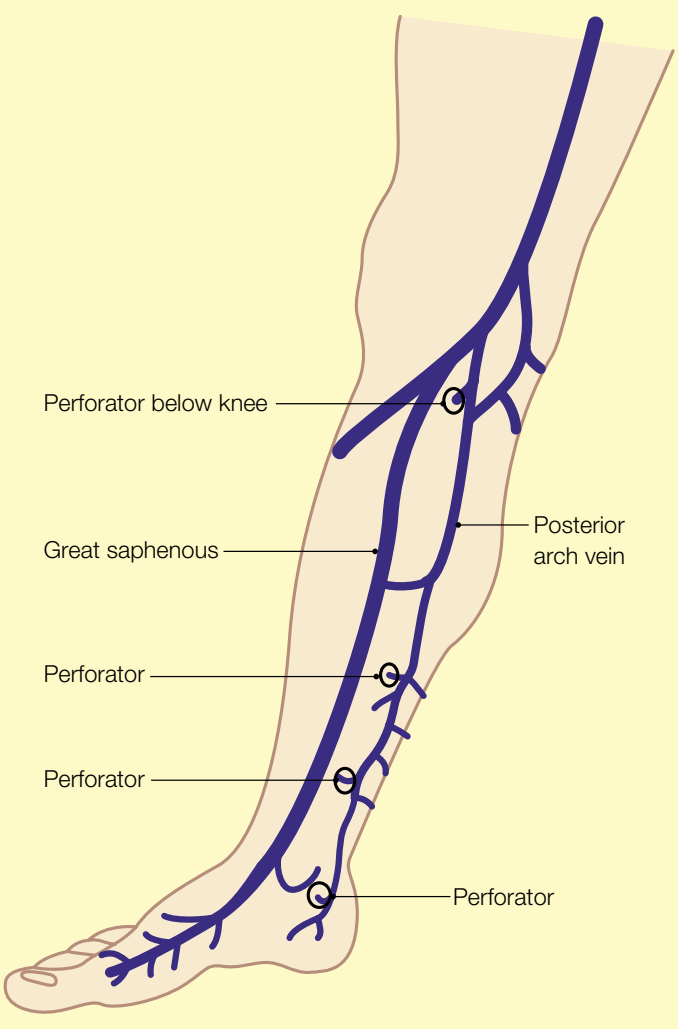
Superficial veins

The superficial veins drain the subcutaneous tissue and terminate in the two large longitudinal channels, the great and the small saphenous veins.

Great (or long) saphenous vein

The great (or long) saphenous vein originates from the medial side of the dorsal venous arch beginning just in front of the medial malleolus. It ascends the medial side of the calf and thigh (accompanied in the calf by the saphenous nerve) and passes through the saphenous opening of the deep fascia 1.5 cm below the inguinal ligament to enter the femoral vein. Its tributaries drain the leg, thigh, inguinal region and the pubic region but its most clinically important branches are the several communicating branches (or perforating veins) that drain from it into the deep veins of the calf and thigh, perforating the deep fascia generally on the medial side of the leg (Figure 1).

The long saphenous vein and calf perforators



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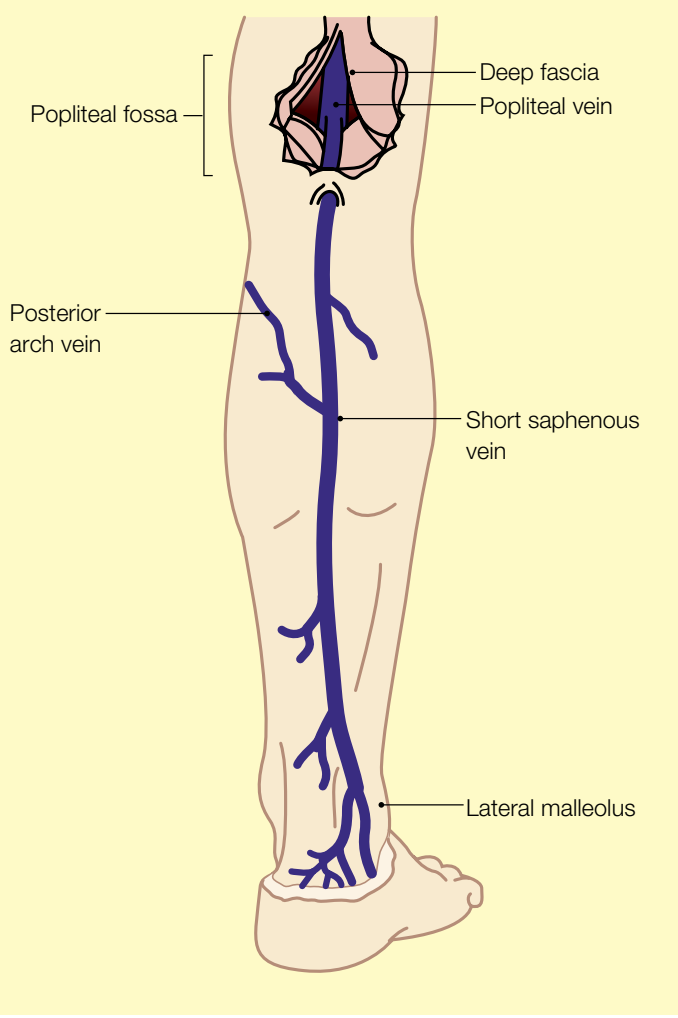
Small (or short) saphenous vein

The small (or short) saphenous vein originates from the lateral end of the dorsal venous arch. It ascends behind the lateral malleolus along the back of the calf to end by piercing the deep fascia a variable distance below the popliteal fossa to end in the popliteal vein. In its lower course it is accompanied by the sural nerve. It has tributaries communicating with the deep veins of the calf and one or more that join with the great saphenous nerve (Figure 2).

Short saphenous vein entering popliteal vein (deep fascia has been incised)



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Deep veins

The deep veins comprise the soleal plexus, the popliteal and the femoral veins. They communicate with the superficial veins by ‘perforators’, veins that perforate the deep fascia (Figure 1), the valves of which are arranged to allow blood to flow only towards the deep veins. The soleal plexus, which lies within the muscles of the calf, drains into the popliteal vein, which drains into the femoral vein and both accompany their corresponding artery deep to the deep fascia. The soleal plexus has a large volume and it is the pressure of the contracting calf muscles (the soleal pump) that is an important factor in ensuring venous return from the lower limb to the heart. The soleal pump is dependent for its efficiency on the competence of the valves in the communicating veins.

The soleal plexus is the most common site of origin of a deep vein thrombosis. Immobility as a result of bed rest or anaesthesia increases the stagnation of blood in the lower limb especially in the soleal plexus. The thrombus may extend from the soleal plexus to the popliteal and femoral veins, if so the risk of pulmonary embolism becomes significant. Thrombosis in the soleal plexus may also extend into the perforating veins; subsequently, after spontaneous recanalization, the protective valves in those vessels are destroyed, which allows venous blood to travel retrogradely, from the deep veins to the superficial resulting in obvious varicose veins. This results in venous hypertension in the superficial tissues of the leg as shown by soft tissue fibrosis, hyperpigmentation and, in severe cases, chronic skin ulceration. It is thought that the primary cause of varicose veins is the incompetence of the valves in the perforating veins and the retrograde flow that follows produces distension of the superficial veins. This distends the saphenous veins and renders their valves incompetent. ◆

Cardiac

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Anaesthesia for 'Off-pump' Coronary Artery Bypass Surgery

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Off-pump coronary artery bypass (OPCAB) surgery is performed on a beating heart without the use of cardiopulmonary bypass. The first work relating to coronary artery bypass graft on a beating heart was carried out in 1910 by Carrel, and the first successful surgery using cardiopulmonary bypass was performed in 1953 by Gibbon. The initial morbidity and mortality on cardiopulmonary bypass was high, allowing the development of coronary artery surgery without it. In 1967, Kolessov reported a series of six cases in which the internal mammary artery was anastomosed to the left anterior descending artery on the beating heart. With the development of bubble oxygenators and cardioplegia in the late 1960s, coronary artery surgery performed on cardiopulmonary bypass became the technique of choice, though cardiopulmonary bypass is still associated with deleterious effects.

In 1996, Calafiore introduced minimally invasive direct coronary artery surgery through a left anterior short thoracotomy incision or mini-sternotomy, which renewed interest in off-pump surgery. This technique was improved by the use of stabilizers designed to imobilise a target area of the heart. However, its main limitation was that access was limited to the left anterior descending and proximal right coronary arteries. The main potential benefit of minimally invasive direct coronary artery surgery was the avoidance of cardiopulmonary bypass. This has resulted in an increase in popularity of OPCAB through a median sternotomy, allowing access to multiple vessels, and the avoidance of one-lung ventilation (mandatory for minimally invasive direct coronary artery surgery) while retaining rapid access to cardiopulmonary bypass in difficult or failed procedures. OPCAB presents new challenges for the surgeon and anaesthetist.

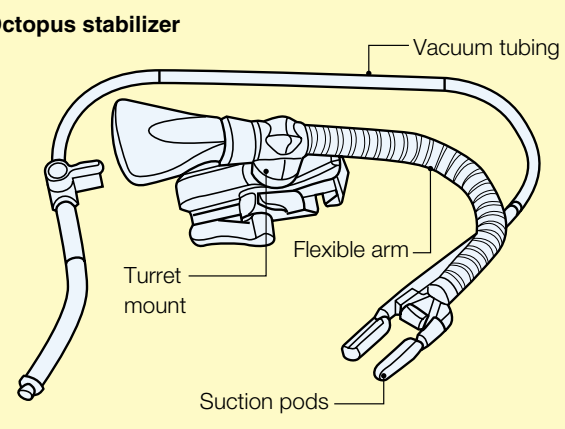
Exposure and stabilization of coronary arteries

Complete revascularization of the heart by accessing all coronary territories requires adequate exposure and stabilization of target coronary arteries. The left anterior descending and proximal right coronary arteries are exposed with minimal cardiac displacement and haemodynamic compromise using surgical packs. The circumflex, diagonal, posterior descending artery and distal right coronary artery are more difficult to expose. The application of slings, pericardial sutures and the placement of surgical packs help to displace and elevate the heart anteriorly providing adequate exposure. A Trendelenburg tilt with rotation of the operating table to the right and opening the right pleura reduces haemodynamic compromise due to compression of the heart against the right pleura, while performing anastomosis on the posterior and lateral walls. Exposure of the posterior descending artery may require a steep Trendelenburg tilt, such that the apex of the heart is almost pointing towards the ceiling! In order to prevent bleeding from the open coronary artery during anastomosis, the target vessel is occluded with slings or microvascular clamps. A humidified carbon dioxide blower is used to prevent blood obscuring the arteriotomy site. Intracoronary shunts may be used to maintain perfusion, display the suture line and reduce back-bleeding.

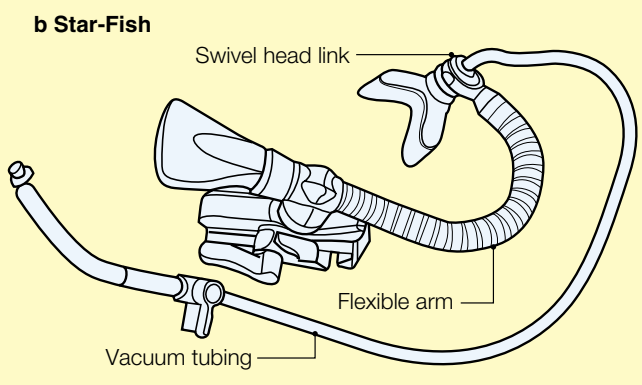
Mechanical stabilizers have greatly contributed to the feasibility of beating heart surgery, allowing good quality anastomotic suturing. Stabilization of the target site is accomplished by using stabilizers such as the Octopus Systems (Medtronic) (Figure 1a), which offer secure, stable access to all coronary arteries. Using gentle suction, the Star-Fish (Figure 1b) gently lifts, positions and holds the beating heart. Stabilization of the tissue at the grafting site is achieved by the smaller, more flexible arm and turret-mounted design of the Octopus device. The malleable suction pods assure easy application, such that the site is lifted and not depressed, thus avoiding impairment of ventricular filling.

Mechanical anastomotic stabilizer

a Octopus stabilizer



b Star-Fish



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Anaesthetic technique

The most important anaesthetic considerations are the prevention of haemodynamic instability and ischaemia. The technique lends itself to early extubation and ambulation. Preoperative assessment should include a review of the angiogram and a discussion with the surgeon of the order of grafting. Adequate premedication is required and tachycardia avoided.

Operating room set up

Early extubation requires the maintenance of normothermia. The operating room is kept warm to avoid radiant heat loss. The head should be covered with drapes. A warming mattress and fluid warmer are used. A forced-air warming blanket is used over the lower half of the body once the saphenous vein has been harvested. The heart–lung machine and perfusionist should be available immediately, but it is usually unnecessary to have the machine primed. Facilities for defibrillation, cardiac pacing and intra-aortic balloon pump counterpulsation should also be available immediately. For multiple vessel OPCAB a cell saver reduces homologous blood transfusion.

Monitoring

Standard cardiac monitoring is used. The ECG may be distorted during cardiac displacement; in particular, the amplitude and ST segment changes may be reduced. ST segment trending is useful. Pulmonary artery pressure monitoring and transoesophageal echocardiography (TOE) may be used in high-risk patients with severe left ventricular dysfunction. TOE is useful in the detection of regional wall motion abnormalities and thus early ischaemic changes. During OPCAB, the heart is displaced or lifted and standard TOE views are lost. Furthermore, the stabilizers used may produce artefacts of regional wall motion abnormalities. However, a baseline TOE allows their assessment with particular attention to the areas supplied by the vessel to be grafted. A TOE examination following the completion of the anastomosis allows regional wall motion abnormalities to be re-checked. Continuous cardiac output monitoring is considered insensitive for routine use. The response time is too slow to detect sudden changes following manipulation and tilting of the heart; it is more useful as a trend monitor. Continuous monitoring of mixed venous oxygenation usefully detects abrupt changes in cardiac output.

Anaesthesia

Induction and maintenance of anaesthesia are determined by local extubation protocols. A balanced anaesthetic technique using limited doses of opioids, volatile agents and propofol is popular. A thoracic epidural technique provides cardiac sympathectomy, attenuates the stress response, reduces anaesthetic requirements and thus promotes early extubation and provides excellent postoperative analgesia. The risk of spinal haematoma formation can be reduced by siting the epidural catheter well before surgery. The advent of stabilizers has made the induction of pharmacological bradycardia, originally used to provide the surgeon with a relatively immobile area, less important, but tachycardia should be avoided. The serum potassium should be maintained at about 4.5 mmol/litre. Magnesium sulphate prevents and treats atrial and ventricular arrhythmias during OPCAB surgery and can be infused following induction of anaesthesia. Partial heparinization (1 mg/kg) maintaining an activated clotting time of 250–300 s and complete reversal with an appropriate dose of protamine is advocated. During proximal coronary anastomosis, arterial pressure should be reduced to 90 mm Hg to reduce the risk of aortic dissection on application of aortic side-biting clamps. Diuretics, in small doses, may be required to correct fluid balance.

Management of haemodynamic instability

The main causes of haemodynamic instability during OPCAB surgery are the impairment of venous return due to chamber compression and abnormal positioning, and pump failure due to direct ventricular compression or ischaemia during occlusion of the target arteries. Mitral valve distortion can contribute significantly to haemodynamic instability, and cardiac displacement increases the risk of intraoperative arrhythmia. The extent of the haemodynamic compromise depends on the coronary artery being anastomosed, the greatest being the circumflex artery and its branches on the posterior aspect of the heart, and the diagonal vessels on the lateral aspect. It may therefore be prudent to revascularize vessels on the anterior aspect of the heart, before any lifting or rotation occurs. Changes in arterial pressure and cardiac output may occur rapidly with cardiac manipulation and the anaesthetist must pre-empt these to maintain haemodynamic stability. The use of the Trendelenburg position, optimizing preload, the use of vasoconstrictors, inotropes, or repositioning of the heart may improve cardiac output. Occlusion of the target coronary arteries during anastomosis of grafts may result in ischaemia and arrhythmias, including ventricular fibrillation. Occlusion of the proximal right coronary artery may lead to ischaemia of the atrioventricular node and complete heart block. The application of pacing wires may be necessary before arterial occlusion. If adequate haemodynamic parameters cannot be maintained it may be necessary to convert to an on-pump technique. Good communication with the surgeon is mandatory.

Advantages and disadvantages of OPCAB

Advantages: off-pump surgery avoids the complexity and may avoid some of the deleterious effects of cardiopulmonary bypass. This includes derangements in coagulation, and multiple-organ dysfunction occurring through a combination of the systemic inflammatory response syndrome, flow abnormalities and emboli. The specific advantages of the technique are shown in Figure 2; the most important is the possible reduction of subtle neurological deficit and cognitive dysfunction. By avoiding cardio-pulmonary bypass the potential for emboli originating from the aorta and the bypass circuit is reduced, though the need for aortic manipulation is not eliminated. The renal impairment and respiratory dysfunction that may occur following cardiopulmonary bypass, have not been universally demonstrated to be reduced with an off-pump technique. The results of large randomized prospective trials are awaited.

Advantages of OPCAB

- Reduced systemic inflammatory response syndrome
- Reduced blood loss and transfusion requirements
- Short operating, intubation and ventilation times
- Possible reduced neurological and neuropsychological effects
- Shorter ICU and hospital stay
- Potential cost saving

2

Disadvantages: OPCAB surgery demands a high level of vigilance on the part of the anaesthetist and is technically demanding for the surgeon. Cardiovascular collapse or ventricular fibrillation may occur rapidly. The ability to respond quickly to such changes is essential, including conversion to an on-pump technique. Patients with severe left ventricular dysfunction requiring multiple grafts may be unsuitable for an off-pump technique as may patients with certain patterns of coronary artery disease. The long-term patency of grafts is unknown. ◆

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Anaesthesia for Patients with Cardiac Disease Undergoing Non-cardiac Surgery

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The number of patients with cardiac disease presenting for anaesthesia to facilitate non-cardiac surgery is increasing. They present some of the greatest anaesthetic challenges because their cardiac lesions will still exist after the operation, unlike patients undergoing cardiac surgery. Perioperative cardiac morbidity (myocardial ischaemia, infarction, arrhythmias) is the most common cause of death following anaesthesia and surgery. Despite improvements in anaesthetic technique, the mortality associated with a perioperative myocardial infarction is 40–70%. The prevalence of coronary artery disease increases with increasing age and it is estimated that about 33% of patients undergoing non-cardiac surgery are at risk of having cardiovascular disease. In many patients this will not have been diagnosed, therefore preoperative assessment is important to identify it and its attendant risks. Other forms of cardiac disease (valvular and congenital heart disease or heart transplant patients) should also be considered.

Preoperative assessment

Preoperative assessment is important to:

- assess the risk to the patient
- optimize the patient's condition
- form a plan for perioperative management to minimize the risk of an adverse outcome.

Assessment of risk

The best known scoring system for estimating the risk of surgery for patients with cardiac disease was developed by Goldman in 1977, and modified by Detsky in 1986. It is a multifactorial risk analysis that combines clinical and investigation parameters and allows patients to be grouped into four risk categories, for major complications or cardiac death. The most widely used index of perioperative risk remains the ASA (American Association of Anesthesiologists) physical status system even though it is somewhat subjective and lacks specificity.

In 1996, the American College of Cardiology and American Heart Association (ACC/AHA) produced guidelines for peri-operative evaluation for non-cardiac surgery; they were updated in 2002. These guidelines differentiate clinical predictors of increased perioperative cardiac risk into three categories (major, intermediate and minor; Figure 1). Recognition of these factors, the functional capacity and the type of surgery are then used to inform the anaesthetist as to the need for further cardiac investigation.

Clinical predictors for perioperative cardiac risk

Major risk factors

- Unstable coronary syndromes
  - Acute myocardial infarction (< 6 weeks)
  - Myocardial infarction > 6 weeks or < 6 months but with myocardium at risk
  - Unstable or severe angina (CCS Class III or IV)[1]
- Decompensated congestive heart failure
- Symptomatic arrhythmias
- Severe valvular disease
- Coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) ± stent < 6 weeks

Intermediate risk factors

- Stable angina (CCS Class I or II)
- Previous myocardial infarction by history or ECG
- Compensated or previous congestive heart failure
- Diabetes mellitus

Minor risk factors

- Age (physiological) > 70 years
- Abnormal ECG (left ventricular hypertrophy, left bundle branch block, ST abnormalities)
- Rhythm other than sinus (e.g. atrial fibrillation)
- Systemic hypertension
- History of stroke
- Hyperlipidaemia
- Low functional capacity
- Smoking
- Renal insufficiency

[1] CCS, Canadian Cardiovascular Society

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The history, physical examination, basic haematological tests, 12-lead ECG, and chest radiograph should be carried out to identify the:

- presence of heart disease
- severity, stability and previous treatment of the disease
- functional capacity of the patient
- presence of co-morbid conditions.

More detailed cardiac investigations may be appropriate in patients who are awaiting elective or, on occasions, urgent surgery. In the emergency situation, patients with cardiac risk factors and reduced functional capacity have a high perioperative risk, but delaying surgery for detailed investigation does not benefit the patient.

Patient risk factors

Previous coronary revascularization – patients who have undergone coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) with or without stent insertion in the previous 5 years and who have had no recurrence of symptoms with return to an active lifestyle do not need further testing. Those who have had a recent stent placement should have their surgery postponed for 6 (or preferably 12) weeks, if possible, because of the bleeding risks associated with the anti-platelet drugs (aspirin, clopidogrel) that they are obliged to take to prevent re-stenosis of the vessel and stent.

Previous coronary evaluation – those who have had cardiac evaluation in the previous 2 years should need no further investigation providing their symptoms have not changed and their activity levels have not deteriorated.

Myocardial infarction and ischaemia – advances in the treatment of myocardial infarction (thrombolysis, PTCA with or without stent) have meant that the traditional high-risk period following infarction of 6 months may be reduced, providing there is evidence that no further myocardium is at risk. This is assessed by stress testing (see later). The heart takes 4–6 weeks to remodel and heal following infarction, during which time it is more vulnerable to arrhythmias and myocardial stunning. The haemodynamic stresses and hypercoagulability associated with surgery may also lead to extension of the infarct. Patients who have unstable or severe angina (Canadian Cardiovascular Society (CCS) Class III or IV) also have a high probability of continuing plaque rupture and thrombosis. Although it is common practice to postpone truly elective surgery until 6 months after a myocardial infarction, patients who have had a myocardial infarction over 6 weeks previously and show no evidence that further myocardium is at risk can proceed with urgent surgery with perioperative cardiac risk reduction strategies. When at least 6 months have elapsed, those who have resumed normal daily activity and have no post-infarction angina should not need further testing, unless the risk of surgery or the functional capacity warrants it.

Arrhythmias – the cause should be identified and treatment instituted, especially for those that are symptomatic and cause hypotension. Indications for antiarrhythmic drugs and cardiac pacing are the same as in the nonsurgical patient.

Decompensated congestive heart failure – these patients should have their medical therapy optimized to minimize the risk of worsening their pulmonary oedema. If ischaemia is the cause, they are also at risk of developing a perioperative myocardial infarction.

Compensated congestive heart failure – patients with a left ventricular ejection fraction less than 35% are at particular risk for perioperative complications.

Diabetes mellitus – there is a high incidence of silent ischaemia associated with diabetic neuropathy, making the lack of angina with exercise a less reliable symptom. Dyspnoea, especially with minimal exertion, may be a more important symptom.

Hypertension – inclusion of hypertension as an intermediate or minor risk factor remains controversial. There is some evidence that if left ventricular hypertrophy is present and the blood pressure is not well controlled, the risk is more significant because the increase in left ventricular mass makes it more susceptible to changes in oxygen delivery and demand. Severe hypertension should be controlled before surgery if possible.

Minor risk factors – cerebrovascular disease and renal insufficiency are possibly not direct risk factors but markers of end organ damage from the same factors that cause coronary artery disease. The greater the number of minor and intermediate risk factors the greater the risk of the patient having coronary artery disease.

Functional capacity: exercise tolerance is assessed by history and is expressed as metabolic equivalents (1 MET = 3.5 ml O_2/kg/min) on a scale defined by the Duke Activity Status Index in order to estimate their maximal oxygen consumption capacity (Figure 2). Patients with moderate or excellent functional capacity and low clinical predictors of risk do not need further cardiac investigation. The functional capacity of some patients may be limited by other conditions (e.g. respiratory, peripheral vascular or joint disease). These patients and those with poor functional capacity should undergo detailed cardiac assessment.

Estimated energy requirements for various activities

Poor functional capacity (1–4 MET)

- Light housework
- Shower or dress without stopping
- Walk at 2.5 mph on level ground

Moderate functional capacity (5–7 MET)

- Climb a flight of stairs without stopping
- Walk briskly (> 4 mph) on flat
- Light gardening

Excellent functional capacity (> 7 MET)

- Digging in garden
- Carrying shopping upstairs
- More strenuous sports (e.g. cycling uphill, jogging)

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Surgical risk factors: the type of surgery and the resultant degree of haemodynamic stress influences the risk to the patient (Figure 3). Some procedures previously counted as high risk are now categorized as intermediate risk, owing to improved perioperative management. Account must also be taken of the risk of not performing the surgery, and the experience and skill of the surgeon and anaesthetist. Peripheral vascular surgery may also be counted as high risk because the extent of the cardiac disability can be masked by the limits imposed by intermittent claudication.

Further cardiac investigations: all cardiovascular tests have limitations and risks and should be carried out only if the results will change the patient's management.

Coronary angiography and revascularization – the indications for these are the same as for those not having surgery (e.g. unstable angina unresponsive to medical treatment, deteriorating severity of symptoms).

Ambulatory ECG monitoring has been used to assess silent ischaemia, but in a significant number of patients (up to 50%) resting ECG abnormalities make the interpretation difficult.

Stress tests (e.g. exercise ECG, dipyridamole-thallium scinti-graphy (DTS) or dobutamine stress echocardiography (DSE)) are dynamic investigations that elucidate the possibility of threatened myocardium and the maximal tolerated heart rate. DSE and DTS are the only non-invasive tests that improve preoperative risk stratification.

Echocardiography and technetium-99 scanning assess myocardial function but cannot predict ischaemic events. Echocardiography is also used to assess the nature and severity of valvular heart disease.

Surgical risk factors

High risk (complication rate > 5%)
- Emergency, intermediate and major procedures
- Aortic and major vascular procedures
- Prolonged procedures
- Procedures with large fluid shifts, blood loss or which produce haemodynamic instability

Intermediate risk (complication rate 1–5%)
- Minor vascular procedures (including carotid endarterectomy)
- Prostatic surgery
- Orthopaedic surgery
- Head and neck surgery
- Intraperitoneal surgery
- Intrathoracic surgery

Low risk (complication rate < 1%)
- Endoscopic procedures
- Superficial surgery
- Breast surgery
- Ophthalmic surgery
- Plastic and reconstructive surgery

Other systems (e.g. respiratory, renal, endocrine, skeletal, airway) need assessment and possible further investigation. The results may affect the anaesthetic plan.

Preoperative therapy

The patient's condition and medication should be optimized. Most cardiac medication should be continued peroperatively. There is evidence that continuation of ACE inhibitors may increase the incidence of hypotension and some physicians have recommended withholding them for 24 hours preoperatively.

Two specific strategies have been suggested to reduce postoperative morbidity and mortality.
- In goal-directed optimization, patients with high risk factors for major surgery are admitted preoperatively to a high dependency or intensive care unit for invasive monitoring (including pulmonary artery catheter) and manipulation of fluid and inotropic therapy in order to achieve the optimal cardiac index, oxygen delivery and consumption.
- In selected patients, β-blockade has reduced perioperative cardiac events and improved 6-month survival. The optimum time from surgery for commencing and discontinuing β-blockers is less clear and it seems that achieving a target heart rate is more important.

Other studies with α_2-agonists are not so convincing. There is insufficient evidence about the effects of preoperative and intraoperative nitroglycerine.

CABG and PTCA are appropriate only in patients who would require them even if they were not awaiting surgery. The combined risk of both procedures may be greater than that of non-cardiac surgery with perioperative risk-reduction strategies.

Premedication should be adequate to allay anxiety, and oxygen therapy preoperatively may be advantageous. Warfarin therapy should be replaced with heparin and antiplatelet drugs (aspirin, clopidogrel) should be stopped at the appropriate time. This depends on the severity of the coronary artery disease and the surgical procedure.

Intraoperative management

Principles: the oxygen supply:demand ratio must be maintained to avoid ischaemia (Figure 4). In coronary artery disease, the pressure gradient across the fixed stenoses is important because the coronary arteries cannot dilate in response to increased oxygen demand. Maintenance of arterial blood pressure and reduction of heart rate should reduce the risk of ischaemia. This is also important in patients with aortic stenosis. It has been suggested that in cardiac patients, a haemoglobin level of 10 g/dl or more is needed to optimize the oxygen supply.

Factors affecting myocardial oxygen supply and demand

Supply
- Coronary perfusion pressure (aortic diastolic perfusion – left ventricular end-diastolic pressure)
- Blood oxygen content
  - Partial pressure of oxygen in arterial blood (PaO_2)
  - Haemoglobin concentration
- Coronary vascular resistance
  - Coronary artery stenosis
  - Heart rate and left ventricular end-diastolic pressure
  - Autoregulation

Demand
- Heart rate
- Contractility
- Wall tension
  - Left ventricular end-diastolic pressure
  - Arterial pressure
  - Contractility

In the preoperative plan, it is important to decide which values of preload, heart rate, systemic vascular resistance, pulmonary vascular resistance and rhythm are acceptable and to anticipate the times when the maintenance of these values will be most difficult (e.g. induction, intubation, blood loss). Strategies to deal with these situations should be considered preoperatively.

Anaesthetic agents: the choice of anaesthetic agents and techniques does not significantly affect the risks of perioperative complications, providing hypertension, tachycardia and hypotension are avoided. It should be governed by the experience and skill of the anaesthetist and their familiarity with the techniques and drugs. Etomidate has the fewest cardiovascular effects but most people are more familiar with thiopental (thiopentone) or propofol, both of which should be titrated carefully to effect. Pretreatment with a dose of opioid reduces the required dose of induction agent and may attenuate the haemodynamic response to intubation. Remifentanil is a new, potent, ultra-short-acting opioid, which has great ability to produce haemodynamic stability and suppress the stress response. It is administered by infusion and transfer to other methods for postoperative analgesia needs careful consideration. Concerns were previously raised that isoflurane might cause a 'coronary steal' situation but these have subsided. It should be remembered that N_2O is also a myocardial depressant. The role of regional blockade is keenly debated. It has many advantages, not least in reduction of the stress response and in effective analgesia. Preservation of an adequate perfusion pressure is vital and the vasodilatation produced may be better avoided in some patients. However, incomplete anaesthesia can lead to increased stress response and myocardial ischaemia.

Monitoring: a 5-lead ECG gives better detection of myocardial ischaemia. Recent studies have shown that V5 is the most sensitive single lead. ST segments should be monitored in high-risk patients. Invasive monitoring by arterial and pulmonary artery catheters may be useful in those at high risk, especially if they have had a recent myocardial infarction with cardiac failure, providing the anaesthetist has the experience to insert them and interpret the data. The pulmonary artery catheter is most useful in monitoring volume status and cardiac performance, such as cardiac output/index, mixed venous oxygen saturation, systemic and pulmonary vascular resistances. Transoesophageal echocardiography may be used to assess volume status and valvular disease and is the best way to detect ischaemia early (segmental wall motion abnormalities), but requires expertise to interpret it. Information received from the monitors (e.g. hypotension, ischaemic changes, left ventricular dysfunction, arrhythmias) needs to be acted on urgently, especially in those with severe disease.

Temperature control: there is a higher incidence of cardiac morbidity in patients who become hypothermic, therefore active warming measures are often required.

Blood glucose control: it has been shown that tighter blood glucose control (4.4–6.1 mmol/litre) leads to reduced morbidity and mortality.

Postoperative management

The period after surgery is associated with increased levels of catecholamines and hypercoagulability. Most perioperative infarcts occur in the first 3 days, therefore the preoperative plan should include the most appropriate place for postoperative care and the same management goals should be adhered to in this period. All patients should receive humidified oxygen, for at least 72 hours after major surgery. Postoperative analgesia should be adequate. Anaemia should be treated and thromboprophylaxis continued. The patient's normal cardiac medication should be restarted as soon as possible.

Specific conditions

Valvular heart disease: stenotic lesions lead to a low, fixed cardiac output, which tolerates poorly any changes in rhythm, tachycardia and decrease in preload and vascular resistance. Replacement of the valve before non-cardiac surgery may need to be considered in severe symptomatic disease, especially aortic stenosis. Patients with regurgitant valves benefit from afterload reduction, faster heart rates and maintenance of preload. Antibiotic prophylaxis is necessary for all cases and should be governed by the type of surgery and local regimens.

Congenital heart disease: anaesthesia for these patients is discussed elsewhere. It is vital to understand the pathophysiology of the particular lesion.

Cardiac transplant: all electrical stimulation in the heart is initiated from the donor sino-atrial node. The resting heart rate is generally 90–120 beats/min and there is no response to carotid sinus massage, changes in body position, light anaes-thesia or hypotension. An adequate preload should be maintained. Cardiac drugs that act directly on the myocardium or peripheral vasculature are necessary because those acting on the autonomic system have no effect on the denervated heart. Invasive monitoring should be avoided where possible and strict asepsis used at all times. Antibiotic prophylaxis depends on the type of surgery and should include anti-staphylococcal cover. It is imperative that immunosuppressive therapy is continued. ◆

FURTHER READING

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Management of Cardiopulmonary Bypass

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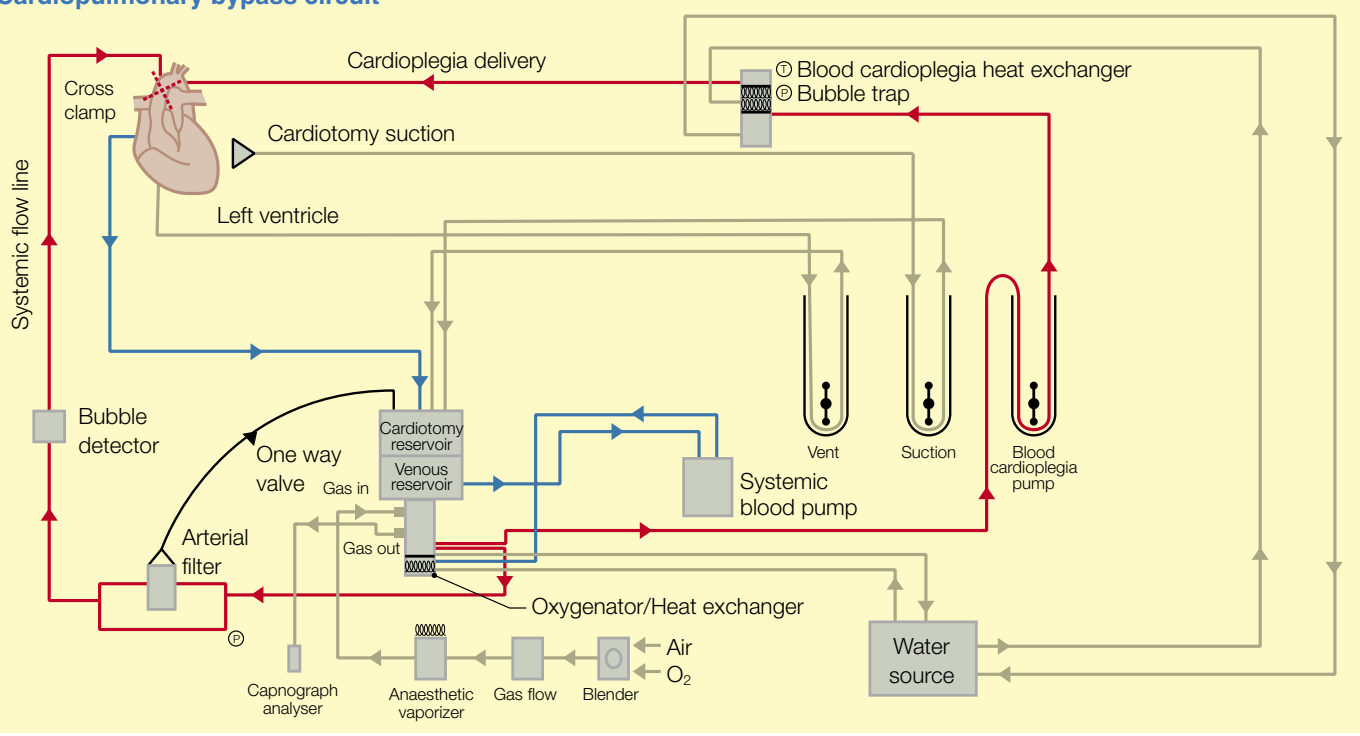
The driver for the development of cardiopulmonary bypass (CPB) was the desire to operate on a still heart in a blood-free surgical field. The concept was first applied in the animal laboratory by Gibbon in 1935. Research continued until the first clinical application of CPB by Dennis in 1951, in which the patient died due to surgical complications. In 1953, Gibbon successfully closed an atrial septal defect, using his design of heart–lung machine, and triggered the evolution of present day cardiac surgery.

The CPB circuit
The three basic functions of the CPB circuit are gas exchange, heat exchange and blood flow. The structural components of the circuit are outlined in Figure 1 and are connected with PVC tubing. The circuit requires a priming volume (usually a mixture of crystalloid and colloid) of 1.5–2 litres.

Cardiopulmonary bypass circuit



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Venous blood drains by gravity from a single cannula placed in the right atrium when the atria are not opened, for example in coronary artery bypass graft (CABG) and aortic valve replacements, or by direct cannulation of the inferior and superior vena cava in more complex procedures. Venous blood is collected in the venous reservoir, which can be separate from, or more commonly (as in Figure 1) integrated with the cardiotomy reservoir. The blood is pumped from the reservoir through the oxygenator by a roller or centrifugal pump. The pump flow rate, reflecting oxygen delivery requirements at rest, is 2.4 litres/min/m^2. The range is 1.6–3.0 litres/min/m^2, depending on body core temperature, mean arterial pressure and mixed venous saturation. For each 1°C decrease in temperature, the required cardiac output is 7% less, and the flow can be reduced by an equivalent factor. The prolonged use of high pump flow rates is associated with destruction of red cells. In prolonged procedures, even with reduced flows, haemolysis and haemoglobinuria are common.

The oxygenator system

The oxygenator system usually includes an integrated venous reservoir, heat exchanger and oxygenator. The heat exchanger regulates blood temperature by altering the water temperature flowing through its tubing. The heat exchanger is situated proximal to the oxygenator because alterations in the temperature of blood that is 100% saturated can cause nitrogen, in the form of gaseous microemboli, to be released. The oxygenator is a series of hollow fibres bundled together and encased in a polycarbonate shell. Venous blood flows around the fibres and the inlet gas (oxygen/air) passes though the centre. Gas exchange takes place by diffusion across the oxygenator membrane. The inlet fraction of oxygen in inspired air (FiO_2) controls the resultant partial pressure of oxygen in arterial blood (PaO_2) and the $PaCO_2$ is controlled by the sweep rate of the inlet gas. Carbon dioxide is exhausted to the atmosphere and can be monitored by a capnograph attached to the gas outlet to reflect membrane gas transfer function. An anaesthetic vaporizer can be placed in the circuit before the gas inlet to provide anaesthesia during CPB.

The oxygenated blood returns to the patient via an arterial cannula, usually placed in the ascending aorta. A 40 μm filter is placed distal to the oxygenator to remove any aggregated platelets, debris from the circuit materials or large microbubbles. This filter can be coated to remove leucocytes that are activated by the non-biological surfaces of the circuit.

Heparinized blood from the pericardium and intracardiac chambers is removed through the cardiotomy suckers and filtered before it is returned to the circulation.

Conduct of perfusion

In UK practice, the perfusionist is responsible to the surgeon for the provision of safe and effective CPB. The anaesthetist's position is less formally defined, in terms of accountability, but excellent communication between the three disciplines is vital. The training and professional conduct of perfusionists is regulated by the Society of Perfusionists of Great Britain and Ireland. Perfusionists have completed a structured 2-year postgraduate training period in perfusion. Perfusionists are licensed to administer heparin and the vasoactive agents, metaraminol and phentolamine. They regularly administer volatile anaesthetic agents via the CPB circuit, corticosteroids, mannitol and potassium supplementation.

Haemofiltration in association with CPB has become commonplace and is provided and regulated by the perfusionist. This is an efficient process, the combination of a large surface area filter and an extracorporeal pump allowing rapid manipulation of body water, control of haematocrit and correction of electrolyte and metabolic abnormalities. Perfusionists have also assumed responsibility for cell salvage technology, now routinely used for cardiac surgery in many centres and which results in a substantial reduction in the number of patients requiring homologous red cell transfusion.

Anticoagulation for CPB

Heparin is used almost universally as the anticoagulant for CPB. It potentiates the activity of antithrombin III, which inhibits the activity of thrombin and other clotting factors, thus inhibiting clot formation. The elimination kinetics of heparin are variable, dose-dependent and temperature-related. Near patient testing of anticoagulation in CPB is performed with the activated clotting time (ACT), which provides an indication of heparinization, but correlates poorly with measured heparin levels. ACT levels are usually maintained above 480 seconds with supplemental heparin doses.

Monitoring of anticoagulation may be much more difficult in complex, prolonged procedures and particularly if heparinization has been reversed and re-heparinization for a further period of CPB is required. In these circumstances, heparin level assays against residual factor Xa activity, can be provided with a laboratory turn-around time of 20 minutes. Heparin levels are usually over 3 units/ml for CPB.

The introduction of the antifibrinolytic agent, aprotinin, in cardiac surgery has complicated near patient testing. In the presence of aprotinin, celite-activated ACT tubes underestimate the ACT and should be maintained at over 700 seconds. Kaolin-activated ACT tubes are much less affected by aprotinin, and should display ACT over 480 seconds.

In adults, the initial heparin dose is usually 300–500 IU/kg (100 IU = 1 mg) with a pump priming dose of 5–10,000 IU. Supplemental doses of 5–10,000 IU are administered according to ACT values. The typical heparin dose has increased in the last 5–10 years with the recognition of higher thrombin and aggregate formation with lower heparin doses, and with more sophisticated measurements of clotting activation. Baseline levels of ACT should be checked before heparin administration and prolongation of ACT must be confirmed before institution of CPB.

Reversal of heparinization

Heparin is highly charged and is reversed by the administration of protamine, which binds ionically to form a stable precipitate. Various empirical reversal regimens are used, most commonly 1–1.5 mg per 100 IU heparin administered. Heparin management systems that employ dose-response curves usually indicate lower doses are required. Protamine, derived from salmon sperm, is associated with a range of adverse effects, including direct myocardial depression. Transient systemic hypotension is often observed due to release of nitric oxide and histamine in vascular endothelium. Pulmonary vascular resistance increases, and may be catastrophic in existing pulmonary hypertension. Anaphylactoid responses, mediated by IgG or complement activation, include bronchoconstriction and acute lung injury, and are in part associated with the heparin–protamine complex. True anaphylaxis (probably IgE mediated) seldom occurs, but the consequences are catastrophic. Patients at risk include those with fish allergy and diabetics exposed to protamine-containing insulin. Many of the adverse effects relate to the rate of infusion. Large bolus doses should be avoided; the dose is usually administered over 5–10 minutes, and over longer periods and preferably by controlled infusion to patients at risk of de-stabilization (e.g. poor ventricular function, pulmonary hypertension).

Control of parameters during CBP

The different approaches to the conduct of perfusion are influenced by the nature of the planned surgery, the individual surgeon's requirements and local practice. Arterial blood pressure is controlled by a combination of flow or vasopressors or vasodilators; the normal range is 60–80 mm Hg. Venous pressure should be low, often negative. High venous pressure often indicates poor venous return or venous obstruction. If SVC pressure is high and systemic pressure is low, cerebral perfusion is impaired. The temperature range is 15–37°C depending on the operation (32–35°C for coronary artery surgery). The acid–base balance should be maintained within normal limits throughout. The optimum haematocrit level is 20–25% owing to viscosity effects at low temperature; the transfusion trigger is usually a level of haemoglobin below 6 g/dl.

Patient characteristics also influence perfusion conduct. For example, it is usual to maintain a higher mean arterial pressure in elderly patients and those with known cerebrovascular disease.

Myocardial preservation

Effective myocardial preservation is one of the main determinants of outcome in cardiac surgery. There are various methods and delivery of protection.

Electrically induced ventricular fibrillation is used for short (15–20 minutes maximum) surgery. It is used mainly in CABG surgery for distal anastomosis and the heart is re-perfused during proximal anastomosis.

Cardioplegia: potassium causes electromechanical arrest and is the main ingredient of cardioplegic solutions (concentration of 20 mmol/litre), along with magnesium and procaine. Cardioplegia is delivered either anterograde through the aortic root or by direct cannulation of the coronary ostia, or retrograde via the coronary sinus.

Crystalloid cardioplegia uses ice-cold Ringer's solution plus cardioplegia solution, at a temperature of less than 4°C. It is commercially available in 1-litre bags.

Blood cardioplegia is a combined blood and crystalloid solution, usually administered via the CPB machine, at a volume ratio from 1:1 to 8:1. The potassium concentration in crystalloid solution is adjusted to maintain a delivered concentration of 20 mmol/litre. In some instances, substrates such as tham, glucose, glutamate and aspartate may be added. Blood cardioplegia reduces the amount of fluid given to the patient and delivers an oxygenated solution, which is theoretically attractive because although the heart is quiescent, oxygen utilization still occurs.

Monitoring on CPB

Standards of monitoring during CPB have been agreed by specialist societies. In addition to basic monitoring and invasive systemic arterial and venous pressures, continuous monitoring of CPB arterial and venous oxygen saturation (or PaO_2), the integrity of gas supply to the oxygenator and CPB arterial line pressure and blood temperature is mandatory.

Anaesthesia for CPB

During CPB, ventilation is usually discontinued to allow surgical access. If pulmonary blood flow persists, and is reflected by continuing left ventricular ejection, ventilation (albeit at low tidal volume and frequency) should be continued to prevent pulmonary blood flow through collapsed lungs contributing, as true shunt, to deoxygenation of arterial blood on CPB. Ventilation is not necessary when ejection on CPB is due to aortic regurgitation (i.e. ejected blood is fully oxygenated blood regurgitated through a leaking aortic valve).

Provision of anaesthesia on CPB relates strongly to the technique used before or after CPB and to the conduct of CPB. Anaesthetic requirements are reduced with hypothermia, but drug pharmacokinetics also alter owing to haemodilution and altered clearance. Supplemental doses of muscle relaxants and/or opiates are often administered at re-warming.

Several different approaches are used. Commonly in the UK, moderate dose opiates (usually fentanyl) are supplemented by volatile administration into the CPB inlet gas (typically 0.5–1% isoflurane). Although experience indicates that this is not strictly necessary, this technique is commonly supplemented by low dose propofol infusion (100–200 mg/hour), particularly during re-warming when the risk of awareness is thought to be higher. The efficiency of volatile transfer across the oxygenator membrane is inferior to native pulmonary function so steady-state blood levels of volatile achieved are lower, and wash-in and wash-out times are prolonged compared with transpulmonary transfer. An advantage of this approach is that delivery of anaesthetic agent can be confirmed by oxygenator exhaust gas analysis (i.e. connection of the capnograph tubing to exhaust port confirms isoflurane delivery).

Total intravenous techniques are also common, combining propofol infusions with incremental fentanyl, alfentil or remifentanil infusions. Benzodiazepines may be used with either technique to guarantee amnesia. A disadvantage of a total intravenous technique is that the effective delivery of anaesthetic agents by infusion is difficult to monitor, a problem recently highlighted by unreliable delivery from syringe pumps of propofol in defective pre-filled syringes.

Separation from CPB

The following general principles are applicable to most patients. Cardiac function should be judged acceptable, either by direct visualization or transoesophageal echocardiography (TOE) assessment and an acceptable re-perfusion time should be completed to allow recovery of ventricular function. In intracardiac procedures, effective de-airing must be ensured and can be facilitated by TOE. Arrhythmias should be controlled and epicardial pacing instituted for bradycardia, with sequential a–v pacing for nodal rhythm or heart block. Electrolytes and acid–base status should be within normal limits. Core temperature should approach normothermia, skin temperature (e.g. shoulder tip) should be warm and should reflect a core-peripheral temperature gradient not more than 5–7°C. Ensure the lungs have been fully re-inflated (the left lung may be difficult to see) and are ventilated effectively.

In coronary surgery, separation is often achieved with low filling pressures (RA or LA 2–5 mm Hg), to avoid ventricular distension and functional mitral regurgitation, hence low systolic arterial pressures (e.g. 60–70 mm Hg) may be accepted initially and the heart subsequently filled slowly to achieve more normal systemic pressures. In such patients, with good or moderate ventricular function, separation is commonly achieved without inotropic support or with low doses only (dopamine, 5–7 μg/kg/min, dobutamine, 5–10 μg/kg/min).

In patients with poor ventricular function or who have had prolonged or complex surgery, more potent inotropic regimens are generally required and are usually predetermined, somewhat empirically by surgeon and anaesthetist, before separation is performed. In such patients, adrenaline (epinephrine), usual range 0.1– 0.3 μg/kg/min, is commonly used and in recent years the phosphodiesterase inhibitors milrinone, 0.3–0.7 μg/kg/min, and enoximone, 5–12 μg/kg/min, have been used increasingly. These agents, particularly milrinone, have considerable vasodilator properties and are commonly combined with noradrenaline (norepinephrine), 0.08–0.15 μg/kg/min, which, in addition to modest direct cardiac effects, modulates the reduction in systemic vascular resistance. Much higher filling pressures may be required (LA 15–18 mm Hg) in these patients and a mild degree of mitral regurgitation may need to be tolerated. If haemodynamics remain unsatisfactory, a further period of support CPB may be beneficial and inotrope regimens should be further refined. Insertion of an intra-aortic balloon pump should be considered and temporary assistance with a ventricular assist device may be appropriate in a small number of patients. Mechanical support of the failing heart is considered elsewhere. ◆

Anaesthesia for Cardiothoracic Transplantation and Ventricular Assist Devices

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The International Society for Heart/Lung Transplantation (ISHLT) maintains a database of transplants carried out worldwide. The database includes information up to 2001 of 61,533 heart transplants, 2935 heart–lung transplants and 14,588 lung transplants. In 2000, in the UK, 286 cardiothoracic transplant procedures were carried out across eight centres.

Figure 1 shows the pathologies for which patients typically receive cardiothoracic transplantation. All these conditions have implications for the conduct of general anaesthesia.

Pathologies for which patients typically receive cardiothoracic transplantation

Transplant	Patients (%)
Heart transplants	
End-stage coronary artery disease	24
Cardiomyopathies	24
Congenital heart disease	48
Single lung transplants	
Emphysema	54
Idiopathic pulmonary fibrosis	24
α_1-antitrypsin deficiency	9
Sarcoidosis	3
Primary pulmonary hypertension	1
Double lung transplants	
Cystic fibrosis	35
Emphysema	24
Idiopathic pulmonary fibrosis	10
α_1-antitrypsin deficiency	10
Primary pulmonary hypertension	9
Bronchiectasis	5
Sarcoidosis	3

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The preoperative evaluation of transplant patients involves a variety of tests (Figure 2). Patients are evaluated for signs and symptoms of dysfunction of all major organ systems. Additional tests may be required depending on the patient and the type of transplantation proposed.

Routine tests before transplantation

- Height/weight
- Blood pressure
- Bacteriology status (swabs/samples)
- 24-hour urine collection
- Chest radiograph
- ECG and 24-hour Holter monitor
- Echocardiogram
- Full blood count, urea and electrolytes, liver function tests, thyroid function tests, viral screen, clotting profile, tissue typing, blood group
- HIV test
- Left and right heart catheter
- Lung function, VQ scan
- Arterial blood gas
- Exercise test

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Anaesthesia

Pre-induction: anaesthesia for cardiothoracic transplant patients is hazardous. All patients are ASA III or above. Monitoring is instituted before induction of anaesthesia and includes multi-lead ECG, oxygen saturation (SpO_2) and arterial blood pressure measurement. Large-bore venous access is mandatory for all transplant patients because haemorrhage can be significant and life threatening. Central venous access to allow intraoperative and postoperative infusion of drugs is usually sited via the internal jugular or subclavian veins. In cardiac transplant patients, this is usually via the left side, because this preserves the right internal jugular, which is required for endomyocardial biopsies following the transplant. It is not mandatory to site central venous access before induction but it is the policy in many institutions.

Additionally, external adhesive defibrillator pads are attached to those undergoing a re-do sternotomy because episodes of atrial fibrillation and VT/VF may occur before cardiopulmonary bypass. Also, defibrillation via internal pads may not be possible until the adhesed heart is fully dissected. Additional ECG electrodes are often attached before induction to allow synchronization of an intra-aortic balloon pump. Pulmonary artery flotation catheters are often used to determine cardiac output, left ventricular end-diastolic pressure and pulmonary artery pressure. The position of the catheter may have to be changed several times when re-anastomosis of the right heart or pulmonary artery occurs. Left atrial pressure lines can be sited intraoperatively to facilitate more accurate estimation of left ventricle end-diastolic pressure (filling pressure).

Pre-oxygenation of the patient before induction is mandatory, particularly if using moderate doses of opiates. Chest wall rigidity can interfere with bag/mask ventilation before the onset of muscle relaxation. Hypoxaemia, of even short duration, can lead to exacerbation of pre-existing pulmonary hypertension or myocardial ischaemia.

Induction: etomidate, ketamine, propofol and thiopental (thiopentone) have all been used successfully as induction agents in transplant patients. The choice of agent depends on the experience of the anaesthetist, but may be dictated by the pre-transplant condition of the patient. For example, in patients with severely impaired left ventricular function, etomidate may be preferred to propofol because of its increased cardiostability. Thiopental (thiopentone) is not a good choice for the severely emphysematous patient undergoing lung transplantation because of its histamine-releasing properties. In these patients, the exacerbation of pre-existing airway obstruction can cause ventilation problems. Air trapping during the early stages of ventilation can prove rapidly fatal.

Moderate doses of opiates (e.g. fentanyl, 5 μg/kg) are often used in transplantation because they can obtund the hypertensive response to intubation and are cardiostable. Intraoperatively they also decrease the sympathetic stimulation caused by painful procedures. Sufentanil is commonly used in cardiac anaesthesia in the USA, but is not licensed in the UK.

Muscle relaxation is commonly achieved by pancuronium. The tachycardia it produces can offset the loss of sympathetic tone at induction. Most muscle relaxants have been used in transplant patients, but those known to exacerbate bradycardia (vecuronium) may be hazardous in patients with severely impaired ventricular function. Tachycardia is a compensatory mechanism in heart failure and the increased ventricular filling time in bradycardia can allow overdistension of the failing myocardium and lead to catastrophic cardiovascular collapse.

Maintenance of anaesthesia can be achieved by a variety of techniques. A balance of inhalational agents and opiates is often used and total intravenous anaesthesia techniques are also suitable. Isoflurane and sevoflurane are both suitable volatile agents for maintenance of anaesthesia. Nitrous oxide is often avoided because of its sympathomimetic properties, which can exacerbate pre-existing pulmonary hypertension.

Thoracic epidural analgesia can be used in lung transplant patients to limit sympathetic stimulation intraoperatively, to provide postoperative analgesia, and to facilitate early extubation. Their use is controversial because of the theoretical risk of epidural haematoma following a bloody tap. In the literature, bloody taps and epidural haematomas are uncommon. In 6000 epidurals for routine cardiac surgery, no clinically apparent epidural haematomas occurred. The incidence of bloody tap is 1.5–4.5%.

Patient management

Patient positioning of the transplant patient requires care because procedures can be prolonged. Pressure areas should be well padded to avoid nerve compression.

Maintenance of normal body temperature in single lung transplantation, and following cardiopulmonary bypass in double lung, heart–lung or heart transplantation, makes early post-operative extubation feasible. Warming mattresses, forced-air blankets and blood warmers can be used.

Haemorrhage is often significant in transplant surgery and prior planning of transfusion requirements is mandatory. Patients who have had previous surgery and required blood transfusion may have developed antibodies to non-ABO red cell antigens. The routine use of cell salvage techniques is advised and the use of antifibrinolytic agents (e.g. aprotinin) can reduce the need for blood transfusion.

Inotropic support is usually instituted during re-warming, if it is not already in place. The choice of inotropes to facilitate weaning from cardiopulmonary bypass varies according to the anaesthetist's experience. Adrenaline (epinephrine), dobutamine and dopamine have all been used successfully. Phosphodiesterase type III inhibitors (milrinone, enoximone) may offer significant advantages over more conventional inotropic support because of their beneficial effects on the pulmonary circulation, reducing right ventricular afterload and helping to offset acute right ventricular failure.

Lung transplantation can be single or double. Both procedures can be carried out without the use of cardiopulmonary bypass if the patient is able to tolerate one lung ventilation. In single lung transplantation, conventional one lung ventilation allows the procedure to be carried out through a thoracotomy.

Donor lungs have no lymphatic drainage and following reperfusion injury, interstitial pulmonary oedema may develop. It is conventional to restrict the fluids given to lung transplant recipients in the perioperative period, and this may require the use of inotropic support to maintain the circulation.

Sequential double lung transplantation, is usually carried out through a clamshell incision. One lung ventilation can be used to allow the first lung to be transplanted, before switching ventilation to the new lung to allow the second lung to be transplanted. This can be a problem because the newly transplanted lung can manifest reperfusion injury and make one lung ventilation un-feasible. Many authorities recommend carrying out the second lung transplant on cardiopulmonary bypass to avoid exposing the newly transplanted lung to the whole cardiac output, and ex-acerbating reperfusion injury. It is now becoming commonplace to transplant both lungs on cardiopulmonary bypass, thus negating the need for one lung ventilation. The use of cardiopulmonary bypass is not thought to be associated with an adverse outcome compared with off-pump transplantation.

Emergence – true fast-track transplantation anaesthesia with extubation on the operating table has proved elusive or undesirable. Most patients require at least a short period of intensive care before weaning and extubation. Early postoperative problems such as bleeding, hypothermia and organ dysfunction requiring significant inotropic support are contraindications to rapid extubation. Patients requiring inhaled nitric oxide therapy for pulmonary hypertension or right ventricular dysfunction require continuing ventilation to control the undesirable effects of hypercarbia.

Following an uncomplicated transplantation, extubation may be feasible within 2 hours, particularly in lung transplant patients with functioning epidural analgesia.

Rejection indicates an immune response to the transplanted organ. All organ recipients experience episodes of rejection. Prompt diagnosis and treatment of rejection is crucial to ensure graft survival and patient longevity. Early fulminant rejection is rapidly fatal, and can occur in the first hours following transplantation. Accurate ABO typing can avoid this. Chronic rejection refers to the changes that take place in a transplanted organ over time.

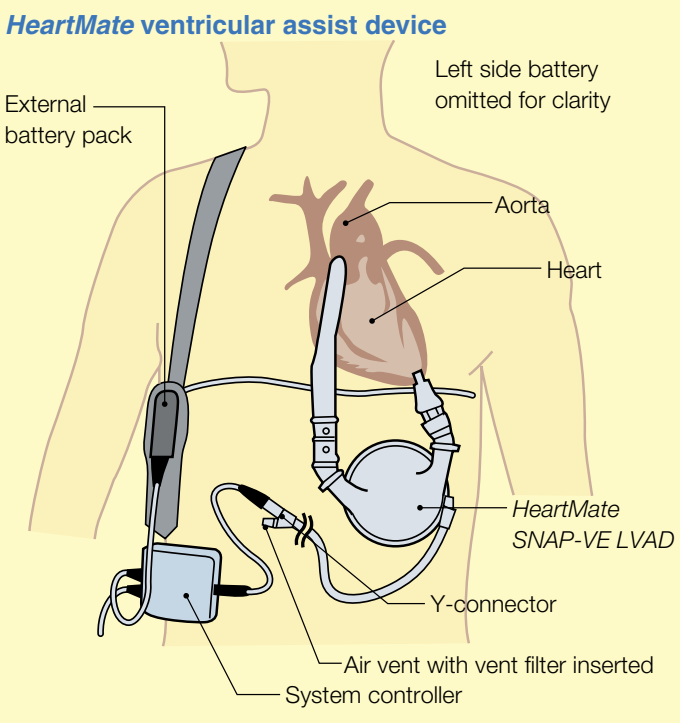
Ventricular assist devices

Ventricular assist devices (VADs) are becoming more widespread as newer devices, designed for long-term support, become available. They are used as 'bridge to recovery' support, in patients with acute cardiomyopathy (e.g. Coxsackie endocarditis), as a 'bridge to transplantation' in those with severe decompensating cardiac failure and as 'destination therapy' in those who are unsuitable for transplantation.

VADs are divided into extracorporeal and implantable types. External devices, such as the *Abiomed* VAD and the *Thoratec* pneumatic external VAD, are designed for relatively short-term support of a heart that has failed (e.g. owing to inadequate myocardial preservation during cardiopulmonary bypass). Both involve implanting pipes, to establish an extracorporeal circulation, and involve bulky machinery to drive the pumping mechanism. A portable drive apparatus for external devices is available to allow movement outside the hospital environment. Some devices (e.g. BiVAD) can support left and right hearts simultaneously.

Internal devices include the *Thoratec HeartMate* (Figure 3) and *HeartMate II*. Both are implanted under the skin but require a drive line that connects the device to its power source.

***HeartMate* ventricular assist device**



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Newer devices such as the *Thoratec HeartMate II* and the *Jarvik 2000* are implantable impeller devices. They are pumps connected between the apex of the left ventricle and the aorta. They are designed for longer term use, require less anticoagulation and have smaller drive units, making them more portable. The newest devices (e.g. *Arrow Lionheart LVAD, Thoratec HeartMate III LVAD*) are completely implanted into the body and power is provided by transcutaneous induction. The absence of drive lines or pipes penetrating the skin should lead to lower infection rates.

Anaesthesia for VAD implantation is technically challenging. Patients for elective VAD procedures are often in severe heart failure on maximal medical treatment; typically ASA IV. Careful induction, judicious fluid management and inotropic support are required until cardiopulmonary bypass is instituted, exactly as in transplant patients. Inotropic support is often required following the procedure, to support the parts of the heart not being supported by the VAD. The interplay between the native circulation and the VAD can be complicated.

Transoesophageal echocardiography (TOE) in VAD implantation: following implantation of the devices, TOE is a useful guide to the filling status of the heart. VADs require adequate inflow in order to function, and inadequate filling can lead to collapse of the left ventricle caused by the devices drawing too much blood. It may also be desirable to have the heart ejecting slightly, rather than all the circulation being provided by the VAD. For example, one device is implanted between the left ventricular apex and the descending aorta. The machine is programmed to decrease impeller speed, and hence flow through the VAD, for 10 seconds in every 60 seconds. The idea of this is to allow the native left ventricle to fill and eject through the aortic valve, in order to flush the arch of the aorta to discourage clot formation. When these devices are implanted as a bridge to recovery, weaning of the support provided by the VAD may require the institution, or modification, of inotropic therapy. The use of TOE allows real-time estimation and measurement of heart function.

Complications of VAD therapy

Haemorrhage at the time of VAD insertion can be catastrophic and blood conservation techniques are mandatory. Use of shed red cell salvage and the routine use of antifibrinolytic agents can help to avoid excessive transfusion.

Heart failure – sudden improvements in cardiac output following VAD implantation can compromise the unsupported ventricle. For example, following left VAD support, the increase in cardiac output can cause the right ventricle to become overloaded and to fail. Not infrequently, patients with left VAD require a period of right VAD support to allow the right heart to adapt to the improved cardiac output.

Anticoagulation – the newer VAD devices require less anticoagulation (*HeartMate II* patients require aspirin only), but thrombosis and embolization remain potential problems. This can cause failure of a device or systemic embolization to a limb or organ. Careful surveillance can avoid potentially fatal problems, especially with the older devices.

Mechanism failure can be fatal, but the reliability of these devices continues to improve. Off-loading the heart can achieve significant improvements in left ventricular function. If pump failure occurs, the native heart function may have improved sufficiently to allow the patient to get to hospital to remedy the situation. ◆

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Echocardiography in Cardiac Anaesthesia and Intensive Care

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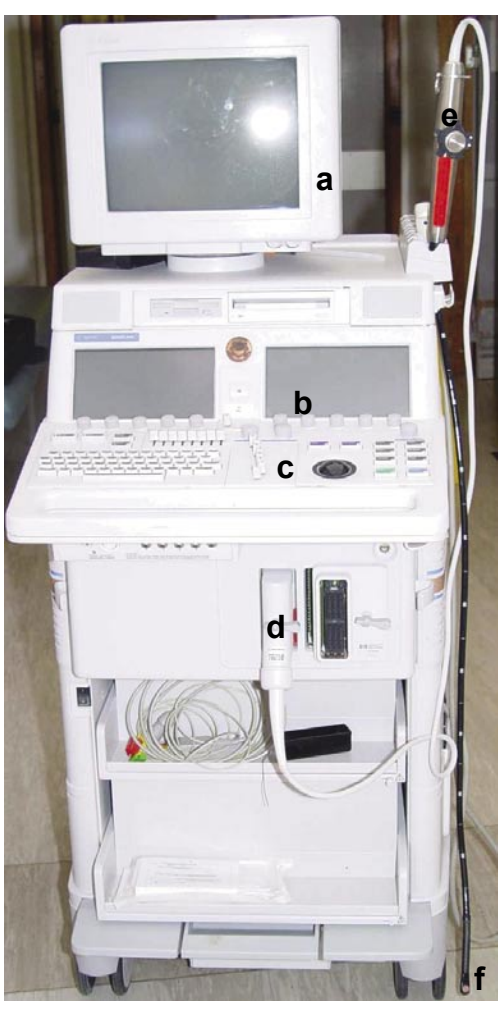
Echocardiography has become an essential part of cardiac anaesthesia and intensive care. The ability to perform echocardiography via the transoesophageal route allows accurate visualization of the heart, despite the presence of drains and positive-pressure ventilation, without interfering with the surgical procedure.

Basics of ultrasound

Figure 1 shows an echocardiography machine with a transoesophageal probe. Ultrasound (sound of frequencies above 20 kHz) represents a valuable and relatively safe tool for imaging soft tissues. The frequencies can travel through tissues, but when they meet interfaces of different echodensity they reflect (echo) as well as transmit through the tissue. This 'echo' is picked up by receiving transducers and translated into an image. Ultrasound transducers use a piezoelectric crystal to generate and to receive ultrasound waves. A piezoelectric crystal is a material (e.g. quartz or a titanate ceramic) that changes its size with electric current application. Conversely, when an ultrasound wave strikes the piezoelectric crystal, an electric current is generated. The transducer emits a brief burst of ultrasound and then switches to the 'receiver mode' to await the reflected ultrasound signals from the intracardiac acoustic interfaces. This cycle is repeated temporally and spatially to generate ultrasound images. Image formation is based on the time delay between ultrasound transmission and return of the reflected signal. Ultrasound information may be displayed in a number of ways to represent an image of the structures being examined. The most common representation is a two-dimensional image that represents a slice through the heart. The transducer emitting the ultrasound may be outside the thorax (transthoracic), directly on the surface of the heart during surgery (epicardial), or within the oesophagus (transoesophageal).



1 The echocardiography machine with a transoesophageal probe. **a** Echo display screen, **b** Touch screen control panel, **c** Data input track ball and control panel, **d** Transducer scan head, **e** Dial control for rotational probe, **f** Scan head.

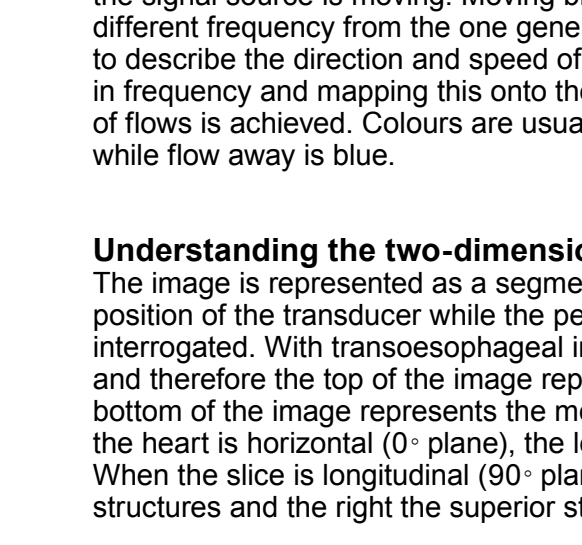
The Doppler principle is used to understand the movement of blood and tissues in the body. The Doppler effect is a change in observed frequency of a signal when the signal source is moving. Moving blood or tissue causes the transducer to 'hear' a different frequency from the one generated and the processor can use this information to describe the direction and speed of the tissue. By representing colours for changes in frequency and mapping this onto the two-dimensional image, intuitive representation of flows is achieved. Colours are usually adjusted so that flow towards the probe is red, while flow away is blue.

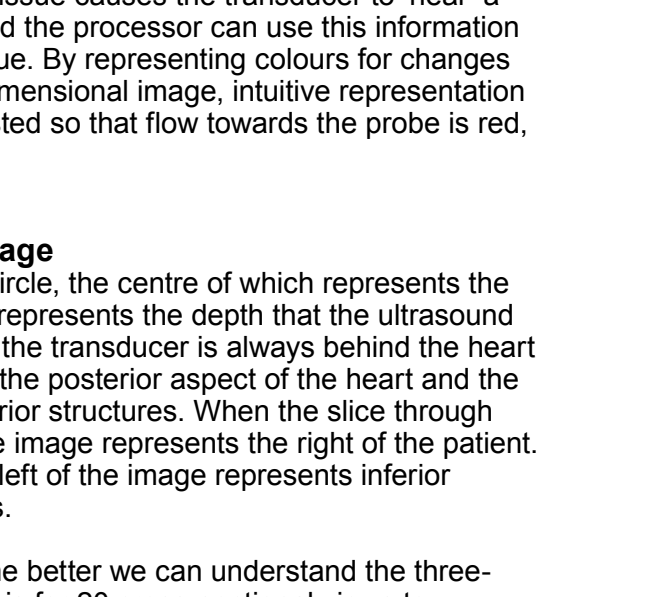
Understanding the two-dimensional image

The image is represented as a segment of a circle, the centre of which represents the position of the transducer while the periphery represents the depth that the ultrasound interrogated. With transoesophageal imaging, the transducer is always behind the heart and therefore the top of the image represents the posterior aspect of the heart and the bottom of the image represents the more anterior structures. When the slice through the heart is horizontal (0◦ plane), the left of the image represents the right of the patient. When the slice is longitudinal (90◦ plane), the left of the image represents inferior structures and the right the superior structures.

The more two-dimensional images we have the better we can understand the three-dimensional heart. A current recommendation is for 20 cross-sectional views to complete a routine examination. More recently, the two-dimensional images have been used to reconstruct a three-dimensional model. It is impossible to cover all the views in this article; we focus on three main cross-sectional views, to serve as an introduction to the main structural features of the heart, and then give examples to illustrate their utility.

The four-chamber view (Figure 2) is excellent for comparing the right and left sides of the heart. The interatrial and interventricular septa, and mitral and tricuspid valves are easily viewed and the left ventricle assessed. It is obtained by positioning the transducer in mid-oesophagus about 35 cm from the mouth. The probe is located posterior to the left atrium, so the left atrium is the structure closest to the transducer. The long axis of the left ventricle with the lateral wall, apex and inferior septum are seen in this tomographic plane. The mitral valve is well visualized, with the mitral annulus in its major dimension, the anterior mitral valve leaflet (located adjacent to the septum), and the posterior mitral valve leaflet (adjacent to the lateral wall), along with chordae and attachments to the anterolateral papillary muscle. The tricuspid annulus lies slightly closer to the apex than the mitral annulus. The septal and posterior tricuspid leaflets, which are thin and uniformly echogenic, are seen in this view with a wide diastolic opening.





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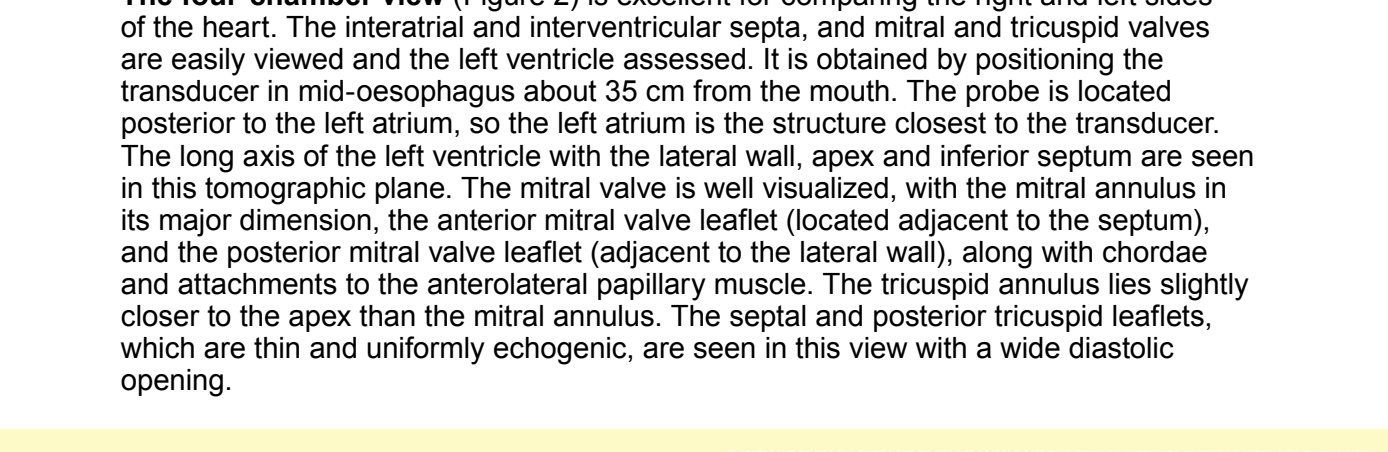
Long-axis view (mid-oesophageal view): (Figure 3) the angle of interrogation can be rotated electronically between 0◦ and 180◦ A long-axis view of the heart may be obtained by rotating to 130◦ from the four-chamber view. Different aspects of the heart can be seen by physically rotating the probe to the left and right. The aortic valve, left ventricular outflow tract, mitral valve, and part of the right ventricle outflow tract anterior to the aortic valve are seen in the long-axis view.



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The transgastric midpapillary short-axis view (Figure 4) is seen by passing the probe into the stomach with anterior flexion of the probe in the 0◦ plane. This classical 'doughnut' view of the left ventricle allows evaluation of global left ventricular systolic function, left ventricular dimensions, wall thickness and regional left ventricular function. This view is particularly valuable for intraoperative monitoring because all three major coronary arteries are represented. Regional wall motion abnormalities are a sensitive indicator of myocardial ischaemia. This view also allows a good assessment of the systolic function of the heart and the volume status of the patient.

Utility of echocardiography

In the assessment of the heart and cardiovascular status, basic physiological parameters should be considered (Figure 5). The ECG assesses heart rhythm, while central venous pressure or pulmonary pressures provide pressure measurements. Echocardiography provides volume assessment, structural assessment and diastolic function assessment.

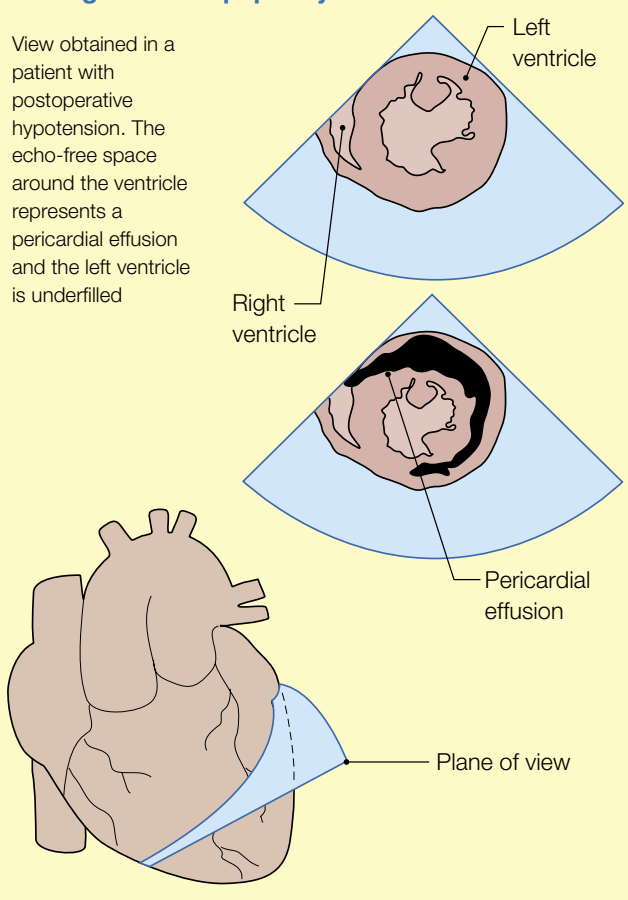
Intraoperative echocardiography is essential for mitral and aortic valve repair because of its ability to assess the results of surgery. In addition, new wall motion abnormalities can suggest areas of poor revascularization. A number of reports show the utility of echocardiography assessment for congenital heart surgery, ventricular assist device management and the management of ventricular dysfunction.

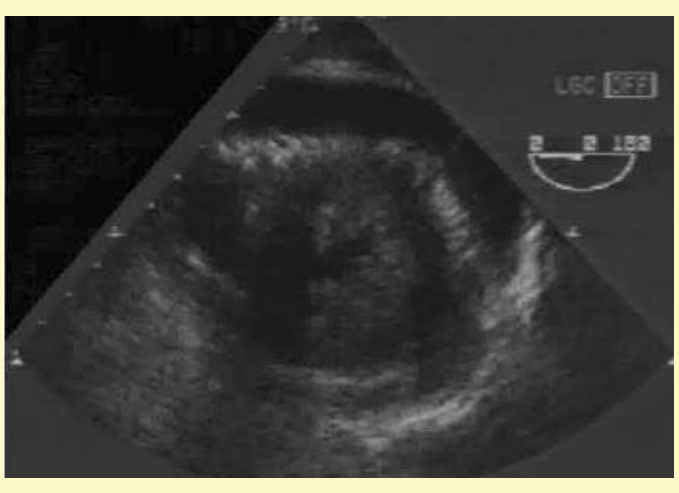
Diastolic function: there is increasing appreciation of the role of diastole in myocardial function. Diastole is not a passive process and requires energy for relaxation of the myocardial cells. Poor diastolic function of the left ventricle leads to higher left ventricular filling pressures to maintain end-diastolic volumes, with an accompanying propensity to shortness of breath and pulmonary oedema. An assessment of the compliance of the left ventricle may be made by measuring the thickness of the ventricle and comparing the peak mitral flow velocity of the early rapid filling wave (E) with the peak velocity of the late filling wave of atrial contraction (A) (the E:A ratio).

Pericardial disease: echocardiography is valuable for diagnosing pericardial effusions and cardiac tamponade and as an aid to pericardiocentesis. Two-dimensional echocardiography is especially accurate in estimating effusion size. Signs of tamponade include diastolic compression or collapse of the right atrium and right ventricle. Leftward displacement of the ventricular septum and an exaggerated increase in right ventricular size with a reciprocal decrease in left ventricular size during inspiration are also useful. Echocardiography also identifies the thick ventricle associated with aortic stenosis (Figure 6).

Transgastric midpapillary view

View obtained in a patient with postoperative hypotension. The echo-free space around the ventricle represents a pericardial effusion and the left ventricle is underfilled





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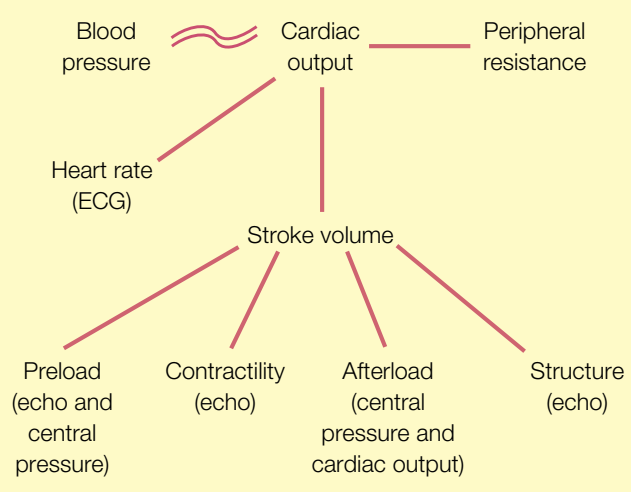
Assessment of hypotension



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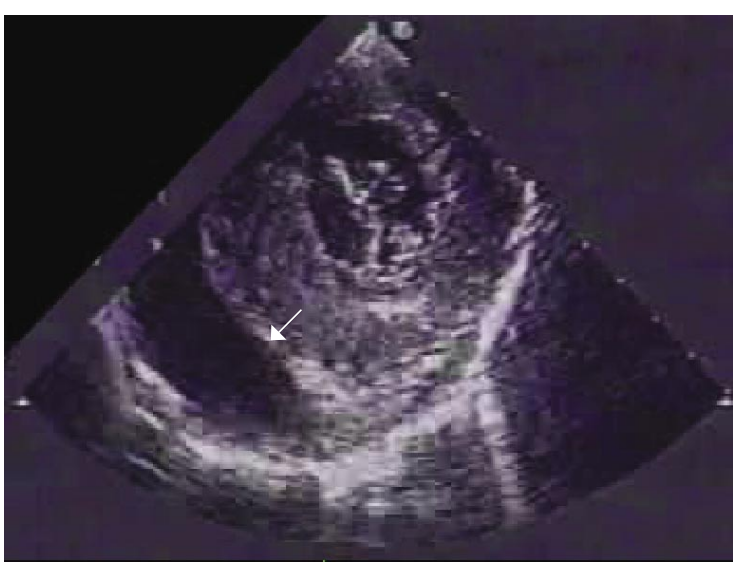
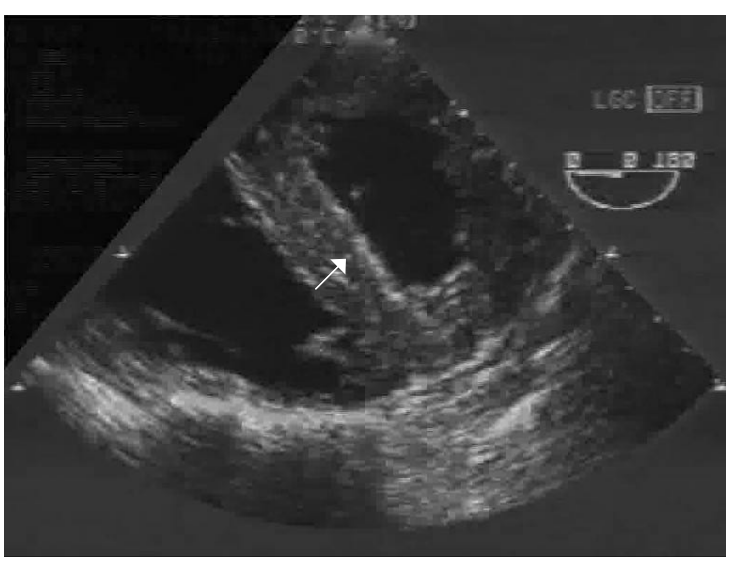


6 Thick ventricle (> 2 cm) (arrowed) associated with aortic stenosis, suggesting poor diastolic compliance.

Right ventricular failure is not easy to diagnose, particularly if it presents in a patient already in the ICU with organ dysfunction. Echocardiography helps to diagnose acute right ventricular failure (Figure 7), especially in an ischaemic setting, and to evaluate its severity and its response to implemented therapy. Echocardiography signs include volume and geometry of the right ventricle, the function of the free wall of the right ventricle and septum, the absence or presence of tricuspid insufficiency, and the distension and size of the inferior vena cava.

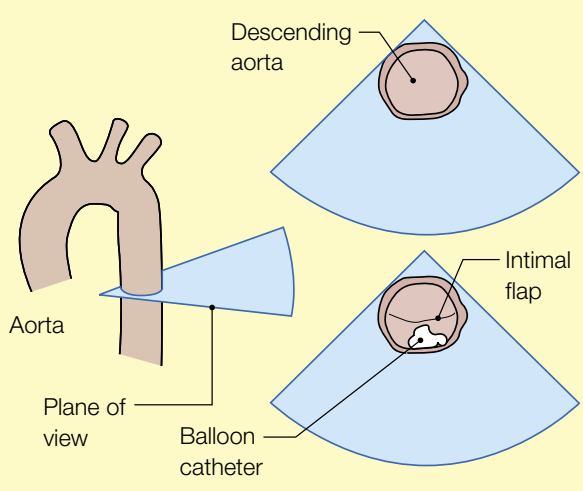


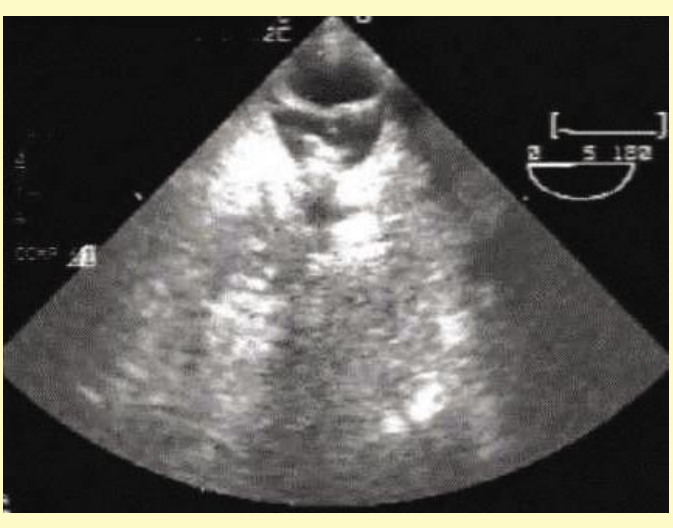
7 This transgastric image shows the normally circular left ventricle compressed on the right giving rise to a D-shaped ventricle (arrowed). This is the result of right ventricular pressures being greater than left ventricular pressures as a result of pulmonary hypertension or right ventricular failure. Hypotension management in this case may include the use of nitric oxide, phosphodiesterase inhibitors and would be different from management of left ventricular failure.

Other structures: rotating the probe to interrogate posteriorly can show the descending aorta (Figure 8). This can be useful for assessing the atheromatous state of the aorta, diagnosing dissection and confirming adequate placement of intra-aortic balloon catheters. With experience, a number of other structures can be seen, including pleural spaces, hepatic veins and renal arteries. Newer technology may allow better imaging (harmonics) or presentation in a new way (e.g. three-dimensional).

Short-axis view of the descending aorta

An intra-aortic balloon had been placed for hypotension following cardiopulmonary bypass. The catheter is seen to have created a false lumen with dissection of the aorta. The catheter was removed and the patient was eventually discharged having suffered nothing more than minor digital ischaemia





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Risks and benefits of echocardiography

There is risk associated with oesophageal intubation, but no risk has been ascribed to the use of ultrasound alone. Many studies have looked at the risk arising from routine use of intraoperative echocardiography. The largest series to date showed a complication rate of 0.14%. Although no deaths were reported in this series, others have reported deaths at a rate of 1/10,000, mainly secondary to oesophageal perforation.

The benefits of routine use have also been quantified in specific circumstances including coronary artery surgery, mitral valve surgery, aortic valve surgery and paediatric cardiac surgery. In general, a benefit in haemodynamic or other management decisions is expected in about 20% of patients, and a major benefit resulting in a change of surgical management or return to cardiopulmonary bypass of 5%. ◆

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Acknowledgement
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Intra-aortic Balloon Counterpulsation

Ruediger Stenz

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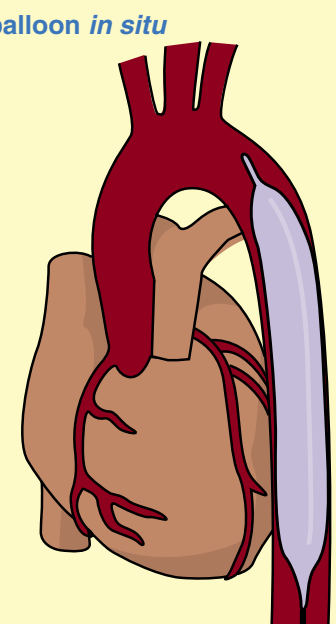
Intra-aortic balloon counterpulsation is a simple and affordable method of mechanical circulatory support using a balloon placed in the proximal descending aorta (Figure 1). This balloon (volume 30–50 ml) is inflated during cardiac relaxation and deflated during cardiac contraction. The intra-aortic balloon pump (IABP) was first used clinically in 1968, to support patients in cardiogenic shock after acute myocardial infarction. Initially, surgical exposure of the femoral artery and a vascular prosthesis were required for insertion but percutaneous insertion techniques have encouraged a wider use of the IABP, including postoperative support and aiding weaning from cardiopulmonary bypass. The IABP is now the most commonly used mechanical cardiac assist device and about 100,000 are inserted annually worldwide.

Intra-aortic balloon *in situ*



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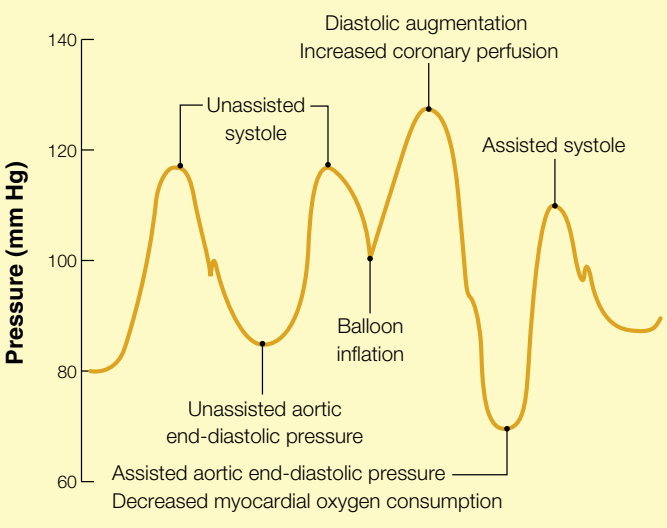
Theory and application

The IABP has two main effects (Figure 2):

- inflation during diastole increases coronary blood flow and thereby myocardial oxygen supply (and also generates a modest increase in aortic forward blood flow)
- deflation at the onset of systole decreases left ventricular workload and thus myocardial oxygen consumption via afterload reduction.

Aortic pressure variations during intra-aortic balloon pump therapy



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The clinical effects of IABP include improved ejection fraction and cardiac output in conjunction with a lower left ventricular end-diastolic pressure as well as alleviating myocardial ischaemia and reducing the frequency of atrial and ventricular arrhythmias. The increase in cardiac output can be as high as 25% depending on several factors, including patient and balloon size, aortic compliance, cardiac rhythm and balloon timing.

The IABP is connected to a mobile electropneumatic console, which controls its operation. The console provides an ECG, an arterial waveform transduced from the tip of the balloon and a numeric display of heart rate and aortic blood pressure. It allows manual adjustment of timing of balloon inflation and deflation and incorporates controls for trigger selection, balloon volume and ratio of support (generally between 1:1 and 1:4 augmented beats). The balloon gas delivery system (usually using the inert gas helium) and a battery back-up power supply are also integrated in the console. Portable models for patient transfer by ground or air are available.

Indications and contraindications

Indications for the use of the IABP have expanded rapidly (Figure 3) and there has been a shift from the treatment of haemodynamic decompensation to the control of myocardial ischaemia. IABP support can be used on its own, but is often instituted in conjunction with moderate doses of vasoactive drugs and/or mechanical ventilation. In routine use, the IABP remains *in situ* for a limited period (24–72 hours) but it has been used for several weeks in heart-transplant candidates. A system for permanent implantation has also been developed. Experience with IABP treatment in children is limited, but it appears to be most effective in older children with isolated left ventricular failure.

Indications and contraindications for the use of intra-aortic balloon pumps

Indications

- Unstable angina refractory to medical treatment
- Acute ischaemia associated with coronary angioplasty
- Perioperative low cardiac output
- Cardiogenic shock after myocardial infarction
- Congestive heart failure
- Ischaemic ventricular septal defect
- Acute mitral regurgitation
- Ischaemia-related ventricular arrhythmias
- Bridge to heart transplant

Contraindications

- Severe aortic regurgitation
- Aortic dissection
- Aortic aneurysm
- Severe calcific aorto-iliac or peripheral vascular disease

3

Insertion and removal

Most IABP are inserted percutaneously via the femoral artery using a Seldinger technique under aseptic conditions. This is often done outside the operating theatre in the catheter laboratory or in the intensive care or high dependency unit. If percutaneous access proves difficult, or in cases of known anatomical problems, surgical exploration should be considered early in order to minimize vascular damage. Sheathless insertion is possible if the diameter of the artery is expected to be small. The balloon is advanced into the proximal descending aorta until the tip of the balloon is positioned 2–5 cm below the left subclavian artery (Figure 1). Correct balloon positioning must be confirmed and documented by fluoroscopy, radiography or transoesophageal echocardiography. If the femoral artery is not available for balloon insertion (in about 5% of patients) alternative routes are the axillary and subclavian arteries or the transthoracic approach via the ascending aorta, in the operating theatre.

A surgically inserted IABP must also be removed surgically and embolectomy catheters may be used proximally and distally to clear any clot or atheromatous debris. After percutaneous insertion, closed or open removal can be performed. In the case of closed removal, the artery should be allowed to bleed for several seconds while the vessel is compressed distally in order to flush out any embolic material.

Timing and weaning

Accurate timing of balloon inflation and deflation in relation to the cardiac cycle is crucial to optimal function. Balloon inflation should occur immediately after closure of the aortic valve, represented in the arterial waveform by the dicrotic notch. Balloon deflation must happen just before the onset of systole. Late inflation and early deflation lead to suboptimal augmentation of coronary blood flow. Early inflation and late deflation obstruct anterograde blood flow in the aorta and increase afterload.

In order to synchronize balloon operation with cardiac contraction, the ECG or the arterial pressure waveform can be used to trigger the IABP. Although the IABP is most effective with a regular intrinsic rhythm, continuing progress in technology has made triggering from paced rhythms and compensation for irregular rhythms, such as atrial fibrillation, more reliable.

IABP support usually begins with a ratio of 1:1 (every cardiac contraction is followed by a balloon inflation/deflation), however, an initial short period of a 1:2 support ratio (every other contraction triggers the balloon) allows for a more accurate evaluation and adjustment of balloon timing. Also, in case of heart rates beyond 100/min an assistance ratio of 1:2 may be more effective. Balloon operation must be checked and adjusted regularly throughout the course of treatment.

IABP therapy should be gradually withdrawn rather than stopped abruptly. However, it is unclear whether reduction of the assistance ratio (most common approach) or decreasing the balloon volume is superior because both approaches have advantages and disadvantages. The indication for weaning of IABP support is mainly guided by the improvement in the patient's condition and protocols will help to establish appropriate criteria (i.e. cessation of ischaemia, adequate cardiac output or arterial blood pressure) for the weaning process.

Complications

Complications can be broadly divided into vascular injuries, balloon malfunction and infection. The overall reported incidence of all complications ranges from 11% to 42% with limb ischaemia being the most common adverse event. Consistent risk factors for vascular complications are female gender, history of peripheral vascular disease and diabetes. Most complications can be controlled by balloon removal or repositioning and antibiotic cover, although surgical intervention may become necessary. Potentially life-threatening complications of IABP insertion, such as aortic or iliac dissection or perforation, occur in about 1% of cases.

Trends and outlook

A clear trend towards the early commencement of IABP therapy and the superior outcomes in ischaemic patients have led to increased use in the perioperative period. There is little evidence or consensus regarding the optimum use of IABP in this setting, but data from smaller trials indicate a survival benefit and an advantage of preoperative over intra- and postoperative insertion. The substantial variation of practice between centres reflects the lack of widely accepted guidelines as well as differing resources and attitudes towards specific indications and patient selection. There is a trend toward prophylactic use to avoid, rather than treat, ischaemia and cardiogenic shock. The use of the IABP in high-risk angioplasty and off-pump cardiac surgery is likely to increase and smaller catheter sizes will help to reduce vascular complications. A beneficial effect on right ventricular failure, particularly in the transplant population, has been suggested. The role of the IABP in relation to other cardiac support strategies still needs to be better defined. ◆

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Rational Use of Inotropes

Peter Elliott

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Inotropes are pharmacological agents that affect the force or energy of ventricular muscle contraction, and which often have effects on other variables such as heart rate, preload and afterload, and peripheral vascular tone. The use of such agents is commonplace in the perioperative or critical care setting, and the indications for their use are multiple, and not confined to their inotropic actions. No inotrope exerts its effect purely by altering myocardial contractility, therefore the potentially useful effects on heart rate, systemic and pulmonary vascular tone and the side-effects of these agents must be taken into account when choosing an appropriate agent. The choice of inotrope is influenced by the therapeutic goal, which is seldom an elevation in systemic blood pressure alone. The purpose of manipulating a patient's haemodynamics in the acute situation is to ensure the adequate delivery of oxygen to vital tissues (to avoid or treat shock). The causes of inadequate oxygen delivery are:

- a cardiac output insufficient to meet the demands of the body or organ
- low perfusion pressure despite an adequate cardiac output.

Determinants of cardiac output

Cardiac output is determined by heart rate and stroke volume, the latter being influenced by preloading and ventricular function. Reduced preloading may be due to hypovolaemia (relative or absolute) or increased extracardiac pressure (e.g. raised intrathoracic pressure, or direct pressure on the cardiac chambers as in tamponade). Ventricular function depends on the interrelated factors of heart rate, preload, myocardial contractility and afterload, any of which can be manipulated pharmacologically. Ventricular dysfunction (systolic or diastolic, and left or right) may be caused by reduced coronary blood flow (coronary artery disease or severe systemic hypotension), myocardial infarction, drug effects, metabolic disturbances or post-cardiopulmonary bypass 'stunning'. These factors usually relate to the left ventricle, but apply to both ventricles, and there has been recent interest in the pathophysiology and treatment of right ventricular dysfunction. Left ventricular diastolic dysfunction is a separate pathophysiological entity caused by alterations in ventricular compliance and may be due to mechanical causes, left ventricular hypertrophy, ischaemia and hypertrophic cardiomyopathies. Drugs that have an effect on diastolic function (an active process) have lusitropic properties (enhanced active relaxation and improved filling characteristics in diastole resulting in a lower end-diastolic pressure for a given circulating volume). A decreased myocardial oxygen supply tends to cause systolic dysfunction, while increased demand tends to cause diastolic dysfunction.

In some instances, the cardiac output may be adequate, but the perfusion pressure, either globally (as measured by systemic blood pressure) or locally, to vital organs is low. Generally, organs attempt to maintain adequate blood flow in response to an inflammatory process by altering vasomotor tone, but at a particular minimum pressure, flow becomes proportional to perfusion pressure and the organ becomes at risk. Some organs (e.g. heart, brain) have few α-adrenergic receptors, and the flow to these organs is more closely related to the perfusion pressure. In some systemic diseases (e.g. septic shock) there may be a generalized low perfusion pressure and a normal or increased cardiac output, due to vasodilatation (mediated by nitric oxide). This type of hypotension is known as distributive shock.

Increasing the heart rate, within certain limits, increases myocardial contractility and cardiac output, although in patients with ischaemic heart disease it is important to control heart rate to minimize oxygen demand and maximize oxygen supply (longer diastole). However, in the presence of regurgitant valve lesions, ventricular overdistension (and therefore dysfunction) should be averted by avoiding bradycardia.

Afterload, determined by systemic vascular resistance for the left ventricle and pulmonary vascular resistance for the right ventricle is closely related to ventricular function. Raised systemic vascular resistance increases myocardial oxygen demand by increasing wall tension (Laplace's law) but may improve coronary artery perfusion and oxygen supply by raising the diastolic blood pressure. The right ventricle is exquisitely sensitive to variations in pulmonary vascular resistance, which has an inverse relationship with right ventricular output.

Management of impaired haemodynamics

Managing hypotension depends on diagnosing its cause and understanding the haemodynamic effects of the available drugs. To make informed decisions, adequate monitoring data should be available, including the standard measurement and analysis of the ECG and ST segments, invasive blood pressure and central venous pressure. Also useful are cardiac output and pulmonary artery pressure measurements with the derived parameters of systemic vascular resistance and pulmonary vascular resistance and, increasingly, transoesophageal echocardiography.

Often, combination therapy, using more than one inotrope, in addition to vasodilators, is indicated. Inotropes have many side-effects and Figure 1 shows the characteristics of an ideal agent.

Characteristics of an ideal inotrope

- Causes increased velocity and force of myofibril fibre shortening
- Lacks tolerance
- Does not cause vasoconstriction
- Does not cause changes in heart rate or rhythm
- Predictable and easily titratable
- Raises perfusion pressure by increasing cardiac output rather than systemic vascular resistance
- Redistributes blood flow to vital organs
- Direct acting (does not rely on release of endogenous amines)
- Compatible with other vasoactive substances
- Demonstrates lusitropy (see text)

1

Classification of inotropes

Inotropes may be classified according to Figure 2. Most of the inotropes in common use belong to Class I, but much research is being carried out into drugs of Classes II and III. Some drugs (e.g. vesnarinone, the α-adrenergic agonists) have multiple modes of action and belong to more than one class. The most commonly used drugs and drugs that are coming into routine clinical practice are described below (Figure 3). The general rules that apply to the use of inotropic agents are listed in Figure 4.

Classification of inotropes

Class I Drugs that increase intracellular calcium

- Calcium ion
- Calcium channel agonists (openers)
- Drugs that increase cardiac cAMP
  - β-agonists (adrenaline (epinephrine), noradrenaline (norepinephrine), dopamine, dobutamine, dopexamine, isoprenaline, ephedrine, xamoterol)
  - Phosphodiesterase inhibitors (milrinone, enoximone)
  - Glucagon
- Drugs that inhibit the Na-K pump (digitalis compounds)
- Drugs that prolong action potential duration (β-adrenergic agonists, vesnarinone)

Class II Drugs that increase sensitivity of actomyosin to calcium ions

- α–adrenergic agonists, vesnarinone, pimobendan, endothelin

Class III Drugs that act through metabolic or endocrine pathways

- Triiodothyronine, dichloroacetate

Adapted from Feldman (1993) and Merin (1995), see Further Reading.

2

Doses and effects of commonly used inotropes

Drug	Dose/range (μg/kg/min)	Predominant receptor	Effects[1]
Adrenaline (epinephrine)	0.01–0.02	β_2	Lowered SVR, BP
	0.03–0.2	β_1	Increased contractility, HR, CO
	0.2-0.3	α	Increased SVR, BP
Noradrenaline (norepinephrine)	0.01–0.4	α_1 α_2 β_2	Raised SVR, BP, possible reflex fall in HR, possible fall in CO
Dopamine	0.01–3	Dopaminergic	Renal and splanchnic vasodilatation
	3–7	β_1	Increased contractility, HR, CO
	> 7	α	Increased SVR, BP
Dobutamine	3–20	β_1 (plus some β_2, α)	Increased contractility, decreased SVR, increased CO, ?increased HR
Dopexamine	0.5–6	β_2 (plus some β_1, α, and dopaminergic)	Increased contractility, decreased SVR, increased CO, increased HR, increased renal and ?splanchnic blood flow at low dose
Isoprenaline	0.01–0.03	β_1, β_2	Decreased SVR, increased HR
Milrinone	Bolus 50 μg/kg		Increased cAMP
	0.35–0.75		Increased contractility, coronary blood flow Decreased SVR, PVR. Arrhythmias
Phenylephrine	0.1–1.0	α	α-agonist, prolongs action potential, increased sensitivity of actinomysin to Ca Increased SVR, inotropy

[1]Abbreviations: BP, blood pressure; CO, cardiac output; HR, heart rate; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Administration of inotropes

- Inotropic therapy should not be instituted until ventricular filling has been optimized – this may be difficult to assess and depends on the clinical circumstances
- Inotropic infusions must be administered through accurate infusion devices designed for the purpose
- Dedicated central line intravascular access must be used for infusions
- Accurate and continuous patient monitoring should be carried out by trained staff using appropriate monitoring equipment in an appropriate setting (high dependency unit or ICU)
- The effects of inotropic therapy should be regularly and frequently reviewed by appropriate staff
- Inotropic therapy should be used for short-term circulatory support

4

Calcium

The pathophysiology of heart failure includes decreased intracellular calcium, therefore it seems appropriate to treat it with calcium ions. However, there is little experimental evidence to support its routine use, and though it briefly causes a rise in arterial pressure, it does not raise cardiac output. Calcium is recommended as an inotrope in patients who have a low blood ionized calcium level, and may be of value in counteracting the effects of raised potassium (including potassium cardioplegia following cardiopulmonary bypass). It is usually administered as 10% $CaCl_2$ in a bolus dose of 5–10 mg/kg.

β-adrenoceptor agonists

Adrenaline (epinephrine) is an endogenous catecholamine that stimulates α- and β-receptors, with β_1 and β_2 effects being predominant at lower doses. Positive inotropy is the main effect and, like all inotropes, there is a possibility of myocardial ischaemia in patients with coronary artery disease as the oxygen demand increases. This is mainly a theoretical problem, and the secretion of endogenous adrenaline (epinephrine) is vital to maintaining contractility, vascular tone and modulating the stress response. Stroke volume and cardiac index increase in a dose-related manner at the lower end of the normal dose range, while α effects become significant as the dose increases. Adrenaline (epinephrine) may also cause pulmonary vasoconstriction. An increase in heart rate is apparent, but not usually clinically significant at lower doses, and adrenaline (epinephrine) causes less tachycardia than dopamine or dobutamine at equivalent inotropic doses. Side-effects include arrhythmias, but this is usually not a problem at lower infusion rates provided the patient is not hypercarbic or receiving other arrhythmogenic substances. Metabolic effects include glycolysis, causing lactic acidosis and hyperglycaemia. Most patients receiving adrenaline (epinephrine) infusions require strict control of blood sugars using insulin infusions.

The normal infusion rate is 0.02–0.3 μg/kg/min, but higher doses may be used for short periods. Its predictability, lack of serious side-effects and low cost make it a common and useful first-choice inotrope in the perioperative period and in the ICU, though chronic use (greater than 24 hours) may lead to down-regulation of the β-receptors.

Noradrenaline (norepinephrine) is an endogenous catecholamine. There has been a resurgence of interest in its use recently. It has powerful α-agonist activity, and β_1 activity similar to adrenaline (epinephrine) but with little β_2 activity. Low-dose infusions produce inotropy and an increase in heart rate, while higher doses cause vasoconstriction, a consequent rise in arterial pressure and a reflex decrease in heart rate. The increased afterload increases the myocardial oxygen demand (partially compensated for by a rise in aortic root pressure increasing coronary artery flow) and, in combination with the lowered heart rate, causes a fall in cardiac output. Mesenteric and renal arteries may be constricted, but renal blood flow may increase owing to the increased arterial pressure. It raises pulmonary vascular resistance.

Clinically, noradrenaline (norepinephrine) is used to raise the systemic vascular resistance in patients who have severe vasodilatation (e.g. in severe septicaemia, systemic inflammatory response syndrome, or following cardiac surgery). The dose, in the range 0.01–0.4 μg/kg/min is titrated in response to the desired effect; a rise in systemic vascular resistance with a concomitant rise in arterial pressure and a possible decrease in cardiac output.

Dopamine is an endogenous catecholamine, a precursor of adrenaline (epinephrine) and noradrenaline (norepinephrine), and its actions are mediated via α, β and specific postjunctional dopaminergic receptors in the renal, mesenteric and coronary arterial systems. Its effects on the circulation depend on the dose; low doses have a predominant effect on the dopaminergic receptors, intermediate doses on the myocardial β-receptors (inotropic effects) and higher doses on α-receptors (vasoconstrictor, noradrenaline-like effects). These dose-dependent effects are not highly specific and are altered by many factors including the regulation of adrenergic receptors (e.g. down-regulation in chronic congestive heart failure), the use of other inotropes or vasodilators and inter-patient and intra-patient variation in response. Dopaminergic effects may occur at higher doses, and vasoconstrictor effects at lower doses.

The pharmacodynamic effects of dopamine include inotropy, chronotropy, vasoconstriction and renal and splanchnic vasodilatation. At higher doses, arrhythmias may become a problem. Dopamine increases renal arterial blood flow by 20–40% by direct vasodilatation of the afferent arteries, and indirect vasoconstriction of the efferent arteries, which should (but has not been shown to) cause an increase in the glomerular filtration rate. There is also an inhibition of aldosterone activity.

These effects make dopamine the inotrope of choice in many situations but there are drawbacks. The renal effects have not been shown to cause a decrease in perioperative acute renal failure, length of hospital stay or mortality, though there is a possibility of converting a low output renal failure into a high output renal failure. The effect of increased inotropy and chronotropy increases myocardial oxygen demand and ischaemia may occur. The tachycardic effects may be more marked than with dobutamine or adrenaline (epinephrine) at equivalent inotropic doses. Other side-effects include an acute inhibition of prolactin secretion, with a possible detrimental effect on cell-mediated immune function. Dopamine may exaggerate the catabolic state found in critically ill patients by inhibiting growth hormone secretion and increasing basal metabolic rate at moderate doses. There may be down-regulation of the β-receptors and a consequent reduction in the effectiveness of the drug with prolonged administration or in patients with chronic heart failure.

Dobutamine is a synthetic catecholamine related to isoprenaline. It has predominantly β_1 effects with weak β_2 and α activity. It produces a dose-dependent increase in cardiac output with a reduction in filling pressures. In patients being treated with do-butamine for chronic heart failure, the heart rate has been shown to remain relatively unchanged, but in other settings it may cause a significant increase in heart rate, which is marked in some patients. It causes a reduction in the systemic vascular resistance and this effect, combined with the inotropic effect, causes a marked rise in the cardiac index, though the systemic blood pressure may not rise. It is particularly useful as an agent that increases oxygen transport, but may have to be given in combination with other agents to maintain an adequate haemodynamic response, particularly in patients with systemic sepsis. It has no specific effects on the renal vasculature, but may increase renal blood flow because of an increase in cardiac output.

Dopexamine is a relatively new synthetic catecholamine with very strong β_2 activity and less pronounced β_1, α and dopaminergic receptor activity. Its effects are positive inotropism (less than dobutamine) and peripheral and pulmonary vasodilatation, causing a marked increase in cardiac output. It causes a tachycardia, particularly at the higher end of the dose range, which may limit its use in patients with ischaemic heart disease. It also causes an increase in renal blood flow (dopaminergic effect), although, as with dopamine, its ability to prevent acute renal failure is not proven. There may be some gut-protective effect, either by increased splanchnic blood flow or by redistribution of gut blood flow to the mucosa (the main site of oxygen use in the gut). Its use in the treatment of patients with systemic sepsis is being investigated.

Isoprenaline is a potent synthetic catecholamine, with strong β_1 and β_2, but little or no α, activity. It dilates skeletal muscle, renal and mesenteric vascular beds and therefore decreases systolic and diastolic blood pressure. It is highly chronotropic, and this, in combination with the induced reduction in coronary perfusion pressure, limits its use in patients with ischaemic heart disease. Arrhythmias are common. It is a bronchodilator and may inhibit histamine liberation from mast cells. It is used mainly in the acute treatment of bradydysrhythmias associated with heart block by increasing automaticity and reducing refractoriness, in the treatment of pulmonary hypertension (and right ventricular dysfunction), and heart failure after some forms of congenital heart surgery.

Ephedrine is seldom used primarily for its positive inotropic effects. It has relatively weak α- and β-adrenergic activity and is valuable as a pressor agent, particularly in the treatment of hypotension caused by sympathetic blockade after regional anaesthesia. The weak inotropic effect may be an advantage in this situation. It is usually given as a bolus dose of 5–10 mg i.v. or i.m. repeated as necessary.

Phosphodiesterase inhibitors

The three available phosphodiesterase inhibitors are enoximone, amrinone and milrinone. Amrinone is not available in all countries and the use of enoximone has decreased with the introduction of milrinone. They do not depend on β-adrenergic receptor stimulation for their actions and therefore their effectiveness is not altered by previous β-blockade or by the down-regulation of β-receptors seen in patients with chronic heart failure or after prolonged use of catecholamines.

Phosphodiesterase inhibition in myocardium and vascular smooth muscle causes a secondary increase in cAMP, resulting in an alteration in intracellular calcium balance. There is positive inotropy and peripheral and pulmonary vasodilatation (the so-called inodilator action). When used in combination with β-agonists phosphodiesterase inhibitors have an additive effect, and they are usually administered as part of a combination therapy.

They were primarily used for the treatment of chronic heart failure and as a ‘bridge’ for patients awaiting heart transplantation. Recently, they have been used in a variety of clinical situations, such as acute left or right ventricular failure, and as part of a regimen for weaning patients from cardiopulmonary bypass.

Milrinone is a second-generation phosphodiesterase inhibitor. This bipyridine derivative was initially designed for prolonged use in patients with chronic congestive heart failure. However, in this clinical setting, its use was found to be associated with increased mortality. It is now used in the short term, in the management of heart failure and weaning from cardiopulmonary bypass. Unlike amrinone, there appears to be no thrombocytopenic effect, and it has a shorter half-life than enoximone.

Milrinone causes a rise in cardiac output without increasing myocardial oxygen consumption and this, in addition to the finding that it aids diastolic relaxation of the ventricles (lusitropy) and increases coronary artery blood flow, make it an appealing choice of inotrope in certain circumstances. It decreases systemic and pulmonary vascular resistances, thereby decreasing afterload and causing a decrease in mean systemic blood pressure and pulmonary artery pressure. Milrinone has an inotropy: vasodilatation ratio of 1:20 (compared with 1:4 for amrinone and 1:2 for enoximone). As a result, it is seldom administered alone but in combination with an appropriate inotrope or vasopressor. Despite the fact that the β-agonists and the phosphodiesterase inhibitors act through the same final pathway (increased cAMP) there is an additive effect. Milrinone is arrhythmogenic, which may limit its use in some patients.

Digoxin

Digoxin causes a rise in intracellular calcium and therefore inotropy by inhibiting the Na-K pump but it may also reduce the neuronal reuptake of catecholamines. It also reduces activation of the sympathetic nervous system, the renin–angiotensin system and the parasympathetic nervous system. Its use as an inotrope in patients with congestive heart failure is controversial and in the perioperative period other inotropes have taken precedence. Its main use is in the treatment of atrial fibrillation and flutter, and cardiac failure. Low dose digoxin increased the ejection fraction and the exercise tolerance of patients with congestive heart failure who were receiving concomitant therapy with either diuretics or ACE inhibitors.

Digoxin has a low therapeutic index, particularly in critically ill patients. The loading dose is 1 mg in divided doses over 12–24 hours given orally or intravenously, aiming for a plasma concentration of about 1.0 ng/ml. Digoxin toxicity is likely to occur with concentrations greater than 2 ng/ml, which, in the setting of the perioperative period, manifest in the form of arrhythmias and other ECG changes.

Class II drugs

Phenylephrine: the main action of the α-agonists is peripheral vasoconstriction mediated by adrenoceptors in peripheral vascular smooth muscle. They also have inotropic effects mediated by prolongation of the myocardial action potential (increasing intracellular calcium) and by increasing the sensitivity of the contractile proteins to calcium, two mechanisms that are unaffected by a down-regulation of the β-receptors. Phenylephrine may be used as an inotrope in patients in whom increasing doses of noradrenaline (norepinephrine) are required to achieve a desired effect. Under these circumstances it is best given as an infusion.

Vesnarinone is under investigation. It has effects on the action potential duration of cardiac muscle and on the sensitivity of actomyosin to calcium. Its inotropic action may be of value in the treatment of chronic congestive heart failure (the first drug to demonstrate this) but it has a narrow therapeutic ratio when used in this setting.

Triiodothyronine has been used for some time in high-risk cardiac surgical patients in whom it reduces ‘stunning’ after cardiopulmonary bypass. Its role in routine practice is not clear.

Other vasoactive agents

There are many other agents that are not inotropes, but which, by their actions, have a consequent effect on myocardial contractility and on haemodynamics. Such drugs include: nitric oxide, which, delivered through an adapted breathing system, causes pulmonary vasodilatation; prostacyclin, also a potent pulmonary vasodilator; and vasopressin, a potent systemic vasoconstrictor. Vasopressin has recently been used in the treatment of refractory ventricular fibrillation, in catecholamine-resistant hypotension caused by septicaemia, in haemodialysis-induced hypotension and after cardiopulmonary bypass. However, its use in these situations is still being investigated, and it may cause significant toxicity relating to splanchnic vasoconstriction and thrombocytopenia. ◆

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Postoperative Cardiac Intensive Care

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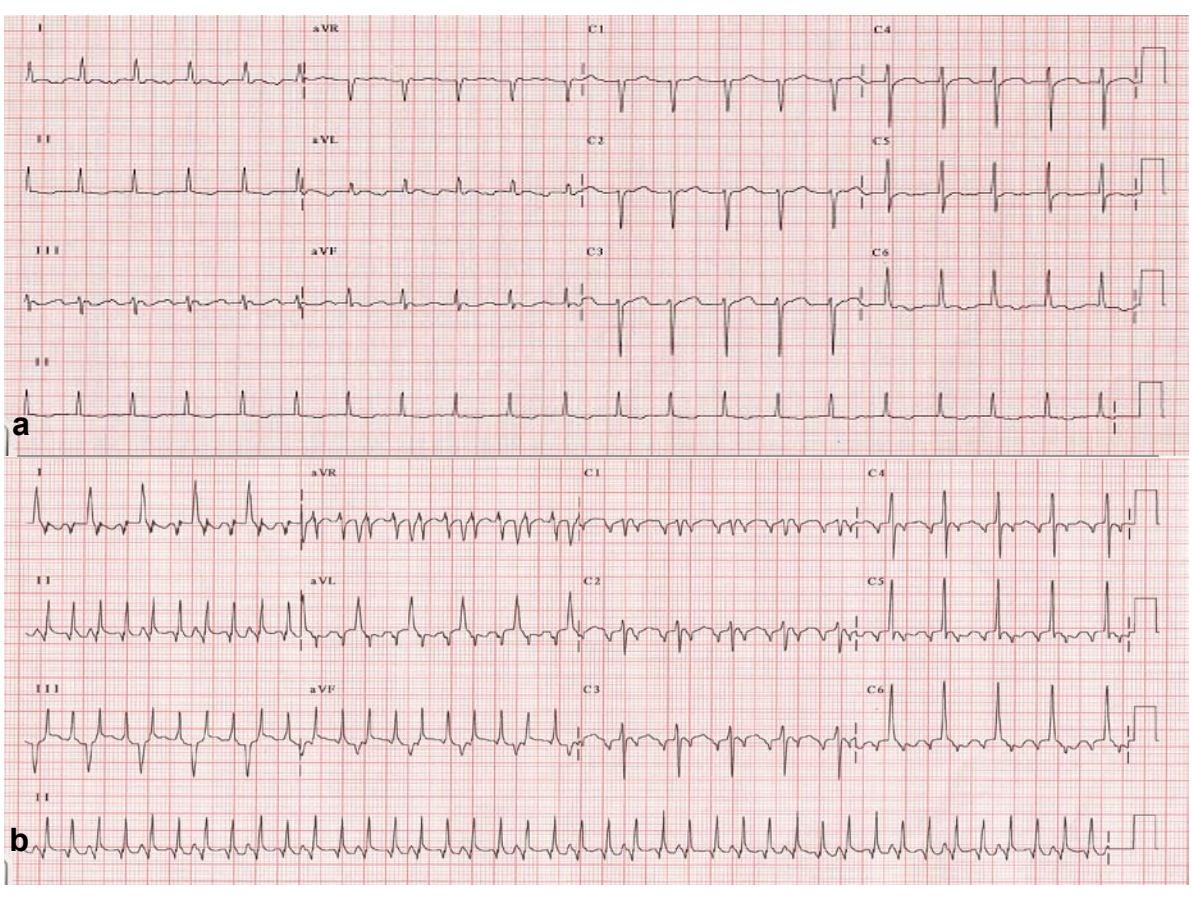
This article outlines some of the major considerations in the intensive care of patients after cardiac surgery.

Management of the cardiovascular system

Cardiac rhythm

Bradycardia and conduction block are common when the patient comes off cardiopulmonary bypass, particularly after aortic valve surgery, and may persist into the postoperative period. The usual treatment is pacing via epicardial wires, but atropine and isoprenaline infusion can be used as temporary measures. The diagnosis of supraventricular arrhythmias may be aided by the use of an 'atrial' electrocardiogram (ECG). This is performed by substituting atrial epicardial leads for the upper limb leads in a standard 12-lead ECG. The resulting ECG produces an exaggerated atrial depolarization trace making differentiation of atrial arrhythmias easier (Figure 1). Management should follow conventional lines, though causes such as electrolyte disturbances, hypoxia, hypercarbia, acidaemia, tamponade and ischaemia should be identified and corrected rapidly.



1a Surface standard 12-lead ECG demonstrating narrow complex tachycardia.
b Atrial ECG at same time showing atrial flutter with 2:1 block. The patient was subsequently cardioverted successfully.

Patients with poor left ventricular compliance benefit most from maintenance of atrioventricular synchrony and active measures should be taken to establish and maintain this. Atrial fibrillation is common in the first few postoperative days. Management includes potassium chloride (aiming for a serum potassium level of 4.5–5.0 mmol/litre) and magnesium sulphate replacement. Patients who are haemodynamically compromised should undergo DC cardioversion. Intravenous amiodarone is commonly administered to stable patients, but DC cardioversion should be carried out within 24 hours if pharmacological treatment is ineffective. Prolonged atrial fibrillation requires anticoagulation (increasing the risks of pericardial collection) and subsequent DC cardioversion preceded by transoesophageal echocardiography (TOE) to exclude intracardiac clot. Ventricular arrhythmias are uncommon after cardiac surgery and usually imply recent or continuing myocardial ischaemia.

Temporary pacing systems must be checked daily to ensure adequate pacing thresholds and to assess underlying rhythm. If the underlying rhythm remains inadequate after several days, insertion of a permanent pacemaker system is indicated. The use of two independent artificial pacing systems (usually a long-standing transvenous system and a temporary epicardial system) simultaneously is not to be recommended because of the risk of one system being inhibited by the output of the other, which may be failing to obtain mechanical capture.

Temporary pacing wires should be removed early in a normal working day in order to reduce the incidence of cardiac tamponade occurring out of hours.

Management of low cardiac output

Ideally, all patients would receive cardiac output monitoring in the perioperative and postoperative periods, but usually this is reserved for high-risk patients such as those with poor ventricular function or pulmonary hypertension. Oxygen transport related goal-directed therapy in cardiac surgical patients has been shown to decrease morbidity and length of hospital stay but has not been adopted widely. In some conditions (e.g. types of congenital heart disease, tricuspid regurgitation) the use of pulmonary artery flotation catheters is either contraindicated or would produce inaccurate cardiac output measurements. TOE is useful for guiding postoperative management in difficult cases.

Low cardiac output states (cardiac index less than 2.0–2.5 litre/min/m^2) may present insidiously postoperatively, and should be considered in patients with metabolic acidosis, core peripheral temperature gradient persistently more than 2°C, oliguria, tachycardia, obtundation or hypotension. Important causes to identify and treat rapidly are arrhythmias, decreased preload (hypovolaemia, tamponade, tension pneumothorax), pump failure (myocardial ischaemia, valve failure, myocardial stunning) and increased afterload (hypovolaemia, hypothermia and pain).

Although most hearts exhibit varying degrees of 'stunning' after cardiac surgery, inotropic support is usually weaned rapidly and any delay in weaning warrants investigation. Tamponade and left ventricular dysfunction may both be associated with hypotension and raised jugular or central venous pressure. Diagnosis may be aided by pulmonary artery catheterization and echocardiography, though transthoracic views are often inadequate in identifying posterior pericardial collections and TOE may be required. Tamponade cannot always be excluded by TOE and, if there is any doubt about the diagnosis in a patient with progressive deterioration, resternotomy should be performed urgently.

Optimization of preload is undertaken with serial fluid challenges. Patients with poor ventricular compliance may require high left atrial or pulmonary artery occlusion pressures to maintain an adequate stroke volume. There is continued uncertainty about the optimal haematocrit after cardiac surgery. For patients without cyanotic heart disease, the authors usually maintain the haemoglobin concentration above 8 g/dl.

Choice of inotropic support for impaired left ventricular function is a variable area of practice with little evidence base. For patients with mild-to-moderate ventricular impairment, dopamine, up to 5 μg/kg/min, is often used following cardiac surgery. In most patients, dopamine is weaned off within 24–48 hours. The immunomodulatory and pituitary effects of dopamine make it unsuitable for long-term use. Dopamine has no specific reno-protective effects and any improvement of glomerular filtration rate is related to increased cardiac output. However, because of its ease of use, dopamine remains a widely used inotropic agent. For patients with moderate-to-severe impairment of ventricular function a phosphodiesterase inhibitor (e.g. milrinone) is commonly used. The vasodilatory effects of milrinone usually necessitate concomitant administration of noradrenaline (norepinephrine) to maintain an adequate systemic arterial blood pressure. The half-life of milrinone is prolonged in patients with acute renal failure. Adrenaline (epinephrine) is also used for management of moderate-to-severe impairment of ventricular function. Undesirable effects include peripheral vasoconstriction and increased glucose and lactate concentrations.

Additional options for the management of impaired left ventricular function include the use of an intra-aortic balloon pump (IABP), insertion of a left ventricular assist device (LVAD) and cardiac transplantation.

Increased systemic vascular resistance is common in the postoperative period. Pain, hypothermia, hypercarbia, hypoxia and the rebound effects of discontinuing preoperative antihypertensive therapy should be considered and treated. The risks of untreated hypertension include myocardial ischaemia, and breakdown of suture lines and anastamoses. In the case of the latter (particularly aortic root replacement), strict upper limits for systolic blood pressures should be set and antihypertensive therapy commenced (e.g. sodium nitroprusside) if these limits are exceeded.

Specific problems

Right ventricular dysfunction is common in patients who have undergone cardiac surgery. Usually, it is minor and does not delay weaning from mechanical ventilation. However, some patients with elevated pulmonary vascular resistance (PVR) are at risk of acute right ventricular failure. Measures used to reduce PVR include hyperventilation, vasodilators and inhaled nitric oxide or nebulized prostacyclin. These patients should be weaned from mechanical ventilation slowly and may require tracheostomy. Endotracheal extubation should occur during daytime hours to ensure extra vigilance. Evidence of right ventricular failure (tachycardia, rising central venous pressure, oliguria, low cardiac output, respiratory distress) should prompt early re-sedation and endotracheal intubation. Severe right ventricular failure can be treated with a temporary right ventricular assist device.

Ventricular septal hypertrophy causing left ventricular outflow tract (LVOT) obstruction can be difficult to manage in the postoperative period. In addition to obstruction of ejection, because of the hypertrophied septum, the high velocity jet in the narrowed LVOT can cause systolic anterior motion of the anterior mitral valve leaflet, leading to further outflow tract obstruction. Diagnosis is made with echocardiography. Management includes maintenance of atrioventricular synchrony, controlling heart rate, ensuring optimal preload, β-blockade, and maintenance of systemic vascular resistance. Vasodilators and IABP increase ejection velocity in the LVOT and may exacerbate ventricular obstruction.

Patients with right-to-left intracardiac shunts are at risk of paradoxical veno-arterial embolization. Meticulous attention should be given to avoiding air and debris entering venous cannulae and the use of filters should be considered. Right-to-left shunt is increased if the ratio of pulmonary to systemic vascular resistances increases, resulting in increased hypoxaemia. Inhaled pulmonary vasodilators can be used to decrease PVR and vasopressors to maintain or increase systemic vascular resistance.

The systemic inflammatory response syndrome (SIRS) is common after cardiac surgery. Treatment is supportive and often includes fluid loading and maintenance of systemic vascular resistance with noradrenaline (norepinephrine). There is increasing evidence that 'relative' adrenal suppression may be important in critically ill patients. If rising doses of vasoconstrictors are required to maintain arterial blood pressure, adrenal dysfunction should be considered.

IABP are often used in the perioperative and postoperative periods. Their use is associated with a risk of limb and visceral ischaemia due to embolism, malposition and the inherent risks of anticoagulation. The management of IABP, ventricular assist devices, surgery for grown-up congenital heart disease (GUCH) and transplantation is beyond the scope of this article.

Postoperative haemorrhage

Bleeding from chest drains of more than 200 ml for 3 hours or more should prompt surgical re-exploration. However, bleeding is not always revealed and in patients with coagulopathy or in whom haemostasis was difficult, a high index of suspicion should be used with a low threshold for surgical intervention. Haemoglobin, platelet and coagulation levels should be monitored closely postoperatively. Medical management includes correction of coagulopathy with adequate heparin reversal, correction of hypocalcaemia, transfusion of platelets (platelet function may be abnormal postoperatively) and clotting products; the use of cell-saving devices to transfuse drained blood; positive end-expiratory pressure (PEEP); head-up tilt; and the administration of aprotinin and tranexamic acid. Surgical re-exploration in the ICU may be indicated.

Management of the respiratory system

Following cardiac surgery there is a decrease in vital capacity, functional residual capacity, total lung capacity, and lung and chest wall compliance. The work of breathing and the alveolar arterial gradient increase with a reduction in the ratio of partial pressure of oxygen in arterial blood to the fraction of oxygen in inspired air (PaO_2/FiO_2). Following valve surgery there may be an increase in lung compliance, due to reduction in lung water. The major determinant of prolonged postoperative ventilation is poor cardiac function emphasizing the importance of cardiac output in contributing to pulmonary dysfunction. Recent, less invasive, techniques of coronary artery bypass grafting (off-pump coronary artery bypass, OPCAB) have been used to promote early postoperative extubation and pulmonary rehabilitation, and several studies have shown no increase in mortality with significant cost savings. However, both on- and off-pump bypass surgery result in unfavourable changes to lung and chest wall mechanics and patients should be selected carefully before considering extubation in theatre.

Postoperative respiratory complications

Atelectasis and left lower lobe collapse are common, and occur more often following internal mammary artery grafting than with vein grafts alone. Treatment includes PEEP or continuous positive airway pressure, humidification of inspired gases and chest physiotherapy. Internal mammary artery grafting is also associated with a higher incidence of pleural collections, which may require drainage. The incidence of pneumonia following coronary artery bypass grafting (CABG) and valve surgery is 3–16% and 5–7%, respectively. Unless contraindicated, all intubated patients should be nursed with 30° head-up tilt to reduce the incidence of ventilator-associated pneumonia.

Phrenic nerve injury with clinically significant diaphragmatic dysfunction is more common if ice slush is used to cool the heart without a protective insulating pad.

The incidence of acute respiratory distress syndrome (ARDS) or ‘pump-lung’ following cardiopulmonary bypass has decreased with changes to techniques (e.g. the introduction of membrane oxygenators).

Ventilatory support

The incidence of prolonged postoperative mechanical ventilation is increased in patients with preoperatively decreased lung function, acute pulmonary or neurological dysfunction and those who require continued cardiovascular support. Mechanical ventilation decreases the work of breathing and reduces afterload owing to a decrease in transmural pressure gradient. However, prolonged mechanical ventilation is associated with an increased incidence of nosocomial pneumonia. In addition, positive intrathoracic pressure (especially PEEP) may increase pulmonary vascular resistance and exacerbate right ventricular failure.

Low-risk patients have similar ventilatory requirements to other postoperative patients and most are extubated within hours of arrival in ICU. Large tidal volumes (over 10 ml/kg) should be avoided in patients with internal mammary artery grafts. Standard ventilatory modes vary between units and need to be tailored according to individual patient needs. For example, patients with atelectasis may benefit from higher PEEP and mean airway pressures, but these manoeuvres can increase pulmonary vascular resistance. Weaning should follow the usual criteria. Extubation is indicated in an alert, cooperative patient who is able to protect their airway, with stable cardiovascular and respiratory function and without excessive bleeding.

Ventilatory management of patients with acute lung injury or ARDS following cardiac surgery should follow conventional lines with adjustments relevant to the individual patient’s cardiovascular physiology.

Temperature

Hypothermia is common after cardiac surgery for several reasons. Deliberately induced hypothermia is followed by core rewarming via the cardiopulmonary bypass circuit, however, on discontinuing bypass, heat redistributes to the colder fat layers. Significant heat is also lost through the surgical field. The resulting hypothermia results in shivering (with increased oxygen consumption), vasoconstriction (with increased systemic vascular resistance and hypertension), myocardial irritability and clotting abnormalities.

Rewarming should be active, using forced warm air blankets and warmed intravenous fluids, and passive by preventing further heat loss. Rapid rewarming should be avoided because it may result in sudden hypotension due to vasodilation. Hyperthermia should also be avoided because of the detrimental effects on neurological injury and the increase in oxygen consumption that may result. Shivering can be controlled with pethidine, sedation and occasionally neuromuscular blocking drugs.

Renal function and fluid balance

Acute renal dysfunction following cardiac surgery occurs in up to 10% of patients following CABG. Acute renal failure requiring mechanical renal support is less common (less than 2% of patients following CABG) but is associated with a greatly increased mortality. Risk factors for acute renal failure include increasing age, the presence of carotid artery bruit, congestive heart failure, diabetes mellitus, impaired renal function, higher body weight and duration of cardiopulmonary bypass.

Patients exposed to chronic or acute ischaemic states (e.g. renal artery stenosis, diabetes, hypovolaemia, radiocontrast agents), elderly patients and those exposed to nephrotoxic drugs are more likely to suffer acute renal failure after subsequent exposure to a surgical insult. Many patients undergoing cardiac surgery have these risk factors.

The most important factors that decrease the incidence of acute renal failure are reducing exposure to nephrotoxic agents and maintaining adequate renal perfusion by careful monitoring and management of cardiac output and systemic arterial blood pressure. No drug has been demonstrated in large randomized studies to be specifically reno-protective in the peri- or postoperative cardiac surgical patient.

There are theoretical benefits from using OPCAB instead of cardiopulmonary bypass techniques with respect to reducing renal dysfunction. However, given that postoperative renal failure is uncommon in patients without preoperative risk factors, many studies have been underpowered to show any difference and others have shown conflicting results.

Continuous veno-venous haemofiltration or haemodiafiltration is the renal replacement technique of choice in a haemodynamically unstable patient.

Sedation and neurological problems

Various mixtures of drugs provide postoperative sedation, but generally propofol/opiate combinations are used for short-term sedation and benzodiazepine/opiate combinations for long-term sedation. There is evidence that long-term sedation should be stopped daily to allow a degree of neurological recovery and to prevent the side-effects of over-sedation.

Pain management is extremely important to allow early mobilization, physiotherapy and respiratory rehabilitation. Patient-controlled analgesia is the most commonly used, with regular oral or nasogastric analgesia being used when enteral feeding begins. The use of thoracic epidural analgesia in patients undergoing procedures with full anticoagulation is controversial because of the risk of epidural haematoma formation.

The ICU is often the first place that postoperative neurological problems are diagnosed. The rate of neurological complications after cardiac surgery depends on a number of factors. Surgical risk factors include operations involving calcified valves or an atherosclerotic ascending aorta, the use of cardiopulmonary bypass, prolonged surgery, low cardiac output states and gas or debris entering the systemic circulation. Patient risk factors include previous cerebrovascular accidents or disease, diabetes and advanced age. The periods of highest risk are during aortic cannulation, onset and weaning of cardiopulmonary bypass, and removal of calcified valves.

Many complications, including postoperative confusion, associated with cardiopulmonary bypass are transient, however, some may be prolonged or permanent. CT is the most common investigation used for diagnosis, though MRI may be required. Peripheral nerve injuries can occur, as with any prolonged general anaesthetic.

Management of gastrointestinal problems

The incidence of gastrointestinal problems is about 1% after cardiac surgery. Gastrointestinal bleeding accounts for almost half of these complications, followed by hepatic dysfunction, intestinal ischaemia, acute cholecystitis and ischaemic pancreatitis. The clinical manifestations of these conditions may be atypical and may be masked by postoperative analgesia or sedation. Routine investigations should include liver function tests, serum lactate, arterial blood gas analysis and serum amylase with unexpected metabolic acidosis prompting further investigations to exclude an abdominal cause. Preservation of adequate cardiac output, routine stress ulcer prophylaxis in patients without full enteral nutrition, and early postoperative enteral feeding can reduce the risk of these complications. Treatment follows conventional lines.

Other considerations

The metabolic changes that occur after cardiac surgery are complex and multifactorial. Surgical trauma, cardiopulmonary bypass, hypothermia, drug treatments and the transfusion of blood products all contribute. The most significant changes relevant postoperatively to ICU patients are activation of the inflammatory and coagulation pathways, and increased gluconeogenesis resulting in hyperglycaemia. Systemic inflammatory and coagulation activation are multifactorial and their aetiologies and treatments are beyond the scope of this article. Altered coagulation may be deliberate (through pharmacotherapy) or pathological, but is significant because of the risk of bleeding. A fine balance exists between the commencement of anticoagulant therapy and the immediate postoperative risk of bleeding. Anticoagulation is often required after prosthetic mechanical valve insertion, treatment of intravascular or intracardiac thrombus and thromboembolic prophylaxis (particularly if there are areas of low or turbulent flow). In each case, the therapeutic range and timing of anticoagulation varies, weighing up the benefits against the risk of bleeding. For example, aortic valve prostheses pose a low risk of clot formation in the absence of anticoagulation when compared with mitral valve prostheses, owing to the high pressures associated with the former. Of note, pericardial effusions may increase in size on commencement of therapeutic anticoagulation. Should coagulopathy develop, its aetiology should be sought and treatment commenced as appropriate. Prophylaxis against thromboembolic disease should be considered in all patients. Heparin-induced thrombocytopenia should be considered if the platelet count is falling.

There is compelling evidence supporting tight glycaemic control following cardiac surgery, though the exact limits with in which blood glucose should be maintained in order to have a benefit on morbidity and mortality have yet to be established. ◆

Preoperative Assessment for Cardiac Surgery

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The assessment of the patient presenting for cardiac surgery allows the anaesthetist to:
- take a history and examine the patient with particular reference to the cardiovascular disease
- plan the anaesthetic approach
- educate the patient about the anaesthesia (e.g. tracheal intubation, invasive monitoring, postoperative intensive care, and the use of intraoperative transoesophageal echocardiography or regional analgesia)
- discuss specific anaesthetic risks including damage to teeth and the potential need for transfusion of blood and blood products.

History and examination

Most patients presenting for adult cardiac surgery undergo cardiac revascularization. History taking should be directed towards assessing evidence of previous myocardial infarction, continuing cardiac ischaemia on exercise or at rest, and pulmonary oedema. The Canadian Cardiovascular Society Classification of Effort Angina is a widely accepted method of scoring the severity of anginal symptoms (Figure 1).

The Canadian Cardiovascular Society Classification of Effort Angina

- **Class 1**
Ordinary physical activity does not cause angina. Angina occurs with strenuous or rapid or prolonged exertion either at work or recreation

- **Class 2**
Slight limitation of ordinary activity. Angina occurs with walking or climbing stairs rapidly, walking up hill, walking or stair climbing after meals, or in the cold, or wind, or under emotional stress, or only during the few hours after awakening. Angina occurs when walking more than two blocks on the level or climbing more than one flight of stairs at a normal pace and in normal conditions

- **Class 3**
Marked limitation of ordinary physical activity. Angina occurs with walking one to two blocks on the level and climbing one flight of stairs in normal conditions at a normal pace

- **Class 4**
Inability to carry on any physical activity without discomfort. Angina may be present at rest

Patients presenting for valvular heart surgery range from those who are seriously ill (e.g. with infective endocarditis) to those who are relatively asymptomatic, because the decision to undergo surgery is now often based on changing ventricular dimensions rather than increasing severity of symptoms. Severe valvular heart disease may typically present with dyspnoea, syncope or angina. The New York Heart Association Functional Classification is a widely accepted system for grading dyspnoea secondary to cardiac disease (Figure 2).

New York Heart Association Functional Classification

- **Class 1**
Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnoea or angina

- **Class 2**
Patients with cardiac disease resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnoea or angina

- **Class 3**
Patients with cardiac disease resulting in marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, dyspnoea or angina

- **Class 4**
Patients with cardiac disease resulting in an inability to carry out any physical activity without discomfort. Fatigue, palpitations, dyspnoea or angina may be present at rest. If any physical activity is undertaken the symptoms of cardiac insufficiency are increased

Many patients undergoing cardiac surgery have concomitant disease, including diabetes mellitus, pulmonary disease, hypertension and peripheral vascular disease (e.g. ascending aortic and carotid atheroma). The presence and severity of associated disease should be fully evaluated preoperatively because it may have a substantial impact on the perioperative anaesthetic management, and ultimately the on outcome.

Medication

As a general principle, drugs taken to control hypertension or cardiac disease (e.g. β-blockers, calcium channel antagonists or anti-anginals) must not be stopped immediately before surgery. A possible exception to this rule is the angiotensin-converting enzyme inhibitors (e.g. lisinopril) because they may be associated with profound hypotension during cardiopulmonary bypass. They are often discontinued 24–48 hours before surgery.

Aspirin and clopidogrel both irreversibly inhibit ADP-induced platelet aggregation and should be stopped 7–10 days before surgery to allow a new population of normally functioning platelets to enter the circulation and decrease the risk of excessive postoperative bleeding. Many patients presenting for valvular surgery may be taking warfarin preoperatively which should be stopped 2–3 days before surgery to allow the international normalized ratio (INR) to fall below 2.0. If anticoagulation is essential (e.g. in the presence of a prosthetic valve) warfarin may be replaced by heparin until the time of surgery.

Risk stratification

The UK Cardiac Surgical Register data show that in 2000 the national average mortality for isolated coronary artery bypass grafting was 2.2% and for isolated valve surgery was 5.5%. The risk is not the same for all patients, so scoring systems have been developed to attempt to stratify patients according to their individual risk. These range from simple additive scores such as the Parsonnet Score, to highly complex statistical algorithms.

The Parsonnet score has been widely used for many years by cardiac surgeons attempting to predict morbidity and mortality. However, it is heavily weighted towards factors such as advan-cing age and re-do surgery, the impact of which on mortality has declined over the last decade, thus diminishing its relevance.

More recently, the Euro Score has become popular. This is a simple additive score with different weighting and risk factors, which takes into account recent advances in surgical practice. The score achieved is approximately numerically equivalent to the percentage risk of death (Figure 3).

Euro Score for Cardiac Operative Risk

Factor	Definition	Score
• Age	Per 5 years of age or part thereof from 60 years	1
• Gender	Female	1
• Chronic lung disease	Long-term use of bronchodilators or corticosteroids for lung disease	1
• Extracardiac arteriopathy	One or more of the following: claudication, carotid occlusion or > 50% stenosis, previous or planned surgery on the abdominal aorta, limb arteries or carotids	2
• Neurological dysfunction	Disease severely affecting ambulation or day-to-day functioning	2
• Previous cardiac surgery	Involving opening of the pericardium	3
• Serum creatinine	> 200 mmol/litre preoperatively	2
• Active endocarditis	Still on antibiotic treatment for endocarditis at the time of surgery	3
• Critical preoperative state	Preoperative intermittent positive-pressure ventilation, inotropic support, intra-aortic balloon pump or preoperative acute renal failure	3
• Unstable angina	Requiring intravenous nitrates until arrival in the anaesthetic room	2
• Left ventricular dysfunction	Moderate ejection fraction (30–50%)	1
	Poor ejection fraction (< 30%)	3
• Recent myocardial infarction	< 90 days	2
• Pulmonary hypertension	Systolic pulmonary artery pressure > 60 mm Hg	2
• Emergency surgery	Carried out before next available list	2
• Cardiac surgery other than isolated coronary artery bypass grafting	Cardiac surgery other than or in addition to coronary artery bypass grafting	2
• Thoracic aortic surgery	Ascending, arch or descending	4
• Postinfarction septal rupture		4

The most commonly used anaesthetic scoring systems include the American Society of Anesthesiologists (ASA) grading system and more recently the Cardiac Anaesthesia Risk Evaluation (CARE) score, which attempts to evaluate the anaesthetic risk specifically for patients undergoing cardiac surgery. It is a simple risk classification based on co-morbid disease (controlled or uncontrolled) and the complexity and urgency of the surgery (Figure 4). The anaesthetic risks must be discussed sympathetically with the patient, in the context of the need for surgery. Although it is uncommon to cancel cardiac surgery on medical grounds or on the basis of a high risk score, it may be appropriate to delay surgery to allow optimization of the patient's medical condition.

Cardiac Anaesthesia Risk Evaluation (CARE) Score

Score	Description	Predicted mortality (%)
1	Patient with stable cardiac disease and no other medical problem. Non-complex cardiac surgery planned	0.5
2	Patient with stable cardiac disease and one or more controlled medical problems (e.g. hypertension). Non-complex cardiac surgery planned	1.1
3	Patient with any non-controlled medical problem (e.g. unstable angina) or patient in whom complex cardiac surgery under-taken	2.2
3E	As 3 but with emergency surgery	4.5
4	Patient with any uncontrolled medical problem and in whom complex cardiac surgery undertaken	8.8
4E	As 4 but with emergency surgery	16.7
5	Patient with chronic or advanced cardiac disease for whom cardiac surgery is undertaken as a last resort or to save life	29.3
5E	As 5 but with emergency surgery	46.2

Investigations

In addition to routine haematological and biochemical investigations before cardiac surgery, all patients undergo an ECG and chest radiograph. Many UK centres also screen for hepatitis and multi-resistant *Staphylococcus aureus*. Patients presenting for cardiac surgery will have undergone certain specialized investigations, and it is important that the anaesthetist has an understanding of the principles behind them.

Exercise tolerance test is a non-invasive diagnostic test often used in patients with suspected ischaemic heart disease. Many different exercise-testing protocols exist, but the Bruce and modified Bruce protocols are commonly used. The modified Bruce protocol starts at a lower workload and is used in patients who have had a myocardial infarct, those whose history suggests symptoms at a low workload, or those who are elderly or sedentary. The test is conducted in 3-minute stages through which the patient's workload is progressively increased by increasing the speed and incline of the treadmill. The protocol is continued until one of several end points is reached: a true positive or negative test, hypo- or hypertension, fatigue, dyspnoea, ventricular arrhythmias or difficulty in ambulation. The test is described as positive if typical chest pain or diagnostic ST depression (at least 1 mm at 0.08 s after the end of the QRS complex) occurs. The test is negative if the patient reaches a specified heart rate (dependent on age) without chest pain or ST segment changes.

An exercise test is considered strongly positive for triple vessel or left main stem disease if the systolic blood pressure drops by 10 mm Hg or more, more than five leads show ST segment changes, and the ischaemic changes occur within 3 minutes of starting the test and take more than 9 minutes to resolve.

Perfusion imaging – patients who are unable to exercise may undergo a thallium stress test. A common protocol is to infuse dobutamine, 10–40 μg/kg/min, in conjunction with intravenous thallium-201. The dobutamine simulates exercise causing maximal dilatation of the coronary arteries. The patient is scanned with a gamma camera at peak stress and if there is a fixed coronary stenosis, the artery is unable to dilate and the blood and thallium are distributed away from the area. Hypoperfused areas appear on the scan as image defects. The patient is re-scanned 2–4 hours later, by which time the thallium will have reached the hypoperfused areas but will demonstrate very slow clearance, resulting in thallium detection in the areas of the scan where there was previously a perfusion defect. A persistent hypoperfused area indicates non-viable myocardium.

The gamma camera is also used in multiple gated acquisition (MUGA) scanning in which radiolabelled technetium-99 is injected intravenously. The image produced as it passes through the cardiac chambers can be used to quantify right and left ventricular stroke volume and therefore function. It is also useful in the assessment of intracardiac shunts and valvular regurgitation.

CT may be used to provide detailed information about the great vessels (e.g. in aortic dissection). It is particularly useful in defining cardiac anatomy in patients presenting for re-do surgery (e.g. the position of the heart in relation to the sternum).

MRI is increasingly valuable as a technique for imaging the heart and great vessels because the flowing blood produces a unique signal obviating the need for contrast media or radiographs. It is the procedure of choice in the evaluation of pericardial disease, intracardiac masses and the assessment of many forms of congenital heart disease, and is becoming increasingly recognized as a valuable tool in the preoperative and postoperative evaluation of ischaemic heart disease.

Cardiac catheterization remains the gold standard in the diagnosis of cardiac pathology, in particular coronary artery disease. A catheter is placed in turn in each of the two coronary ostia, and dye injected. A 50% reduction in vessel diameter is equivalent to a 75% reduction in cross-sectional area and represents a significant stenosis.

Left ventricular ejection fraction, cardiac output, pulmonary vascular resistance and end-diastolic pressures may be measured during cardiac catheterization. In valvular lesions, the pressure gradient or alternatively the regurgitant fraction across the valve can also be estimated.

Echocardiography and stress echocardiography – echo-cardiography (transthoracic, transoesophageal and three-dimensional) has become invaluable in the diagnosis and pre-operative assessment of many cardiac abnormalities, in particular valvular disease, allowing the measurement of gradients and the calculation of valvular areas. Echocardiography is also used to assess systolic and diastolic ventricular function and to define regional wall motion abnormalities.

Stress echocardiography, using an infusion of dobutamine incrementally increasing to 20 μg/kg/min, is also useful to identify viable myocardium in the presence of coronary artery disease and to differentiate ischaemic from non-ischaemic myocardial dysfunction. In the presence of coronary artery disease, low-dose dobutamine may be expected to increase myocardial blood flow and improve regional wall motion abnormalities. Conversely, high-dose dobutamine leads to an oxygen metabolic mismatch in areas at ischaemic risk and results in worsening regional wall motion. Thus, there is classically a biphasic response to dobutamine stress in ischaemic heart disease. Segments of the ventricle that remain akinetic or dyskinetic despite dobutamine infusion are non-viable and represent scar tissue.

Premedication

A common approach to premedication is to prescribe a short-acting benzodiazepine (e.g. temazepam) 2 hours before surgery. In most cases, this achieves anxiolysis without significant cardiac or respiratory depression, and may be supplemented if necessary in the anaesthetic room with intravenous midazolam. In addition, if the patient is to undergo beating-heart surgery, it may be appropriate to prescribe a β-blocker such as atenolol, 50 mg orally, at the time of premedication, in order to contribute to the stability of the surgical field. ◆

FURTHER READING

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Principles of Cardiac Anaesthesia

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There are a number of accepted anaesthetic techniques for cardiac surgery. New drugs continue to be introduced into clinical practice and there are differences of opinion about the optimal anaesthetic for a particular cardiac procedure. However, there is evidence that it is not the initial choice of a particular anaesthetic technique or group of drugs that is crucial to outcome but rather the manner in which they are applied in different clinical circumstances. A discussion of all anaesthetic agents and their cardiovascular effects is beyond the scope of this article but a knowledge of these agents is essential. The principles of cardiac anaesthesia are outlined below, but the anaesthetist is also involved in many other aspects of patient care during cardiac surgery, including the management of anticoagulation and clotting defects, cardiopulmonary bypass, fluid and electrolyte balance, gas exchange and acid–base status, inotropic support, pacing techniques and mechanical support of the heart.

Monitoring

The monitoring modalities used for cardiac anaesthesia are listed in Figure 1. Routine invasive monitoring for all cardiac patients includes arterial cannulation and central venous access. Pulmonary artery catheters are used routinely in many North American centres, but in the UK they are used mainly for high-risk cases. Transoesophageal echocardiography is a rapidly expanding field, which is likely to dominate perioperative monitoring in the next decade.

Monitoring for cardiac anaesthesia

Essential
ECG (5 lead)
Invasive arterial pressure
Central venous pressure
Core temperature
Urine output
Anaesthetic agent analysis
Ventilation
- Tidal volume/respiratory rate
- Airway pressure
- End-tidal carbon dioxide

Oxygenation
- Inspired/expired oxygen
- Pulse oximetry

Optional
Pulmonary artery catheter
Transoesophageal echo
Cardiac output
- As above
- Oesophageal Doppler
- Pulse contour analysis
- Lithium dilution

Cerebral function monitors

1

Arterial cannulation

Cardiac surgery is often associated with sudden changes in blood pressure, and a safe, reliable, method of measuring these acute changes is required. For this purpose, a cannula (20 or 22 G) is usually inserted percutaneously into the radial artery of the non-dominant hand. If the radial artery is to be harvested for use as a conduit during coronary artery bypass grafting, it is taken from the non-dominant arm, providing there is adequate collateral flow via the ulnar artery, and the radial artery cannula is placed in the dominant arm.

In high-risk cases, such as aortic stenosis, left main stem coronary disease and patients with poor ventricular function, it is advisable to place the arterial line under local anaesthetic before induction of anaesthesia.

The right radial artery may be preferred if aortic surgery (e.g. repair of coarctation) is to be undertaken or if an intra-aortic balloon pump (IABP) is likely to be used. This is because the right subclavian artery is unlikely to be involved in aortic surgery and in the case of an IABP it will not be occluded by the balloon and is thought to give the optimal arterial trace for timing balloon inflation. Other arteries (e.g. brachial, femoral, axillary, dorsalis pedis) can be used to measure systemic arterial pressure. Damage to the brachial artery can, rarely, result in limb ischaemia because of the poor collateral circulation at this point, and the femoral artery may be required for insertion of an intra-aortic balloon or for institution of cardiopulmonary bypass in re-do surgery.

Central venous access

Peripheral venous access will have been established before induction and a large-bore cannula can be sited in the arm for volume replacement during surgery. Central venous access is primarily required to measure the filling pressure of the right heart and for the administration of vasoactive drugs. Additional access may be required to allow the flotation of a pulmonary artery catheter. The right internal jugular vein is commonly used because:

- it can usually be ballotted in the anaesthetized patient and is easy to cannulate
- it can usually be easily located, with ultrasound if necessary
- there is a low incidence of complications
- pressure recordings are not affected if the innominate vein is stretched on opening the chest, a manoeuvre that can lead to erroneously high readings with left-sided lines
- multiple catheters can be placed in the same vessel.

A higher anatomical approach to the internal jugular vein is preferable because pneumothorax and damage to vascular structures within the chest are less likely. The Seldinger technique is safe and widely practised, though complications relating to over-zealous use of the dilator have been described. Puncture of the carotid artery with a small needle is not usually serious, but if this is undetected and a large sheath is passed into the vessel, surgical repair may be necessary. The subclavian vein is an alternative site, but is more hazardous.

The National Institute of Clinical Excellence (NICE) has recommended that ultrasound devices are made available and more widely used to aid central venous cannulation.

Pulmonary artery catheterization and cardiac output measurement

Thermodilution remains the 'gold standard' for clinical determination of cardiac output but the routine use of pulmonary artery catheters remains a subject of debate. In certain patients, such as those with poor ventricular function or valve disease, pulmonary artery catheters facilitate haemodynamic management, including choice of inotropic drugs. They may also be useful in the management of patients with significant pulmonary hypertension. The authors' practice is to insert a pulmonary artery catheter introducer sheath following induction of anaesthesia in most patients. A pulmonary artery catheter can then be introduced easily, if required, at the termination of cardiopulmonary bypass or once the patient reaches the ICU.

Pulmonary artery catheterization allows measurement of pulmonary artery pressure, pulmonary capillary wedge pressure, thermodilution cardiac output and mixed venous oxygen saturation. More sophisticated catheters can measure continuous cardiac output and/or mixed venous oxygen saturations and some have a pacing facility. A variety of haemodynamic indices can be calculated from this data (most usefully systemic and pulmonary vascular resistance) when combined with measurements of systolic/diastolic arterial pressure and central venous pressure. In difficult cases, this information may help if separation from cardiopulmonary bypass is not straightforward. Left-sided filling pressures can be measured directly with a left atrial line inserted under direct vision at surgery.

Insertion of pulmonary artery catheters is associated with the production of arrhythmias, pulmonary artery rupture, infection, catheter knotting and thromboembolism as well as complications related to central venous cannulation.

Less invasive methods of monitoring haemodynamic function and cardiac output during cardiac surgery include oesophageal Doppler, pulse contour analysis (lithium dilution) and transoesophageal echocardiography.

Transoesophageal echocardiography (TOE)

The use of intraoperative echocardiography is well established. TOE is now regarded as an essential monitor (Figure 2) during valve repair surgery and during correction of some congenital defects. It is also useful to demonstrate adequate de-airing of the heart and to monitor ventricular function when weaning a patient from cardiopulmonary bypass. Complications include dental injury, damage to the airway or oesophagus, bacteraemia and (most importantly) distraction of the operator from patient care.

Indications for transoesophageal echocardiography

Haemodynamic instability
- Evaluation of left and right ventricular disease
  - Global and regional
  - Systolic and diastolic
  - Valvular function
- Assessment of haemodynamic function
- Detection of hypovolaemia
- Cardiac tamponade
- Acute pulmonary embolism
- Dynamic left ventricular outflow tract obstruction

Cardiac surgery
- Cardiac valve reconstruction and replacement
- Myocardial revascularization (especially poor function)
- Surgical correction of congenital heart disease
- Aortic dissection
- Minimally invasive cardiac surgery
- Minimal access heart surgery
- Pulmonary embolectomy
- Resection intracardiac tumours/thrombi
- Aneurysmectomy
- Myotomy for hypertrophic cardiomyopathy
- Heart transplantation

2

Induction of anaesthesia

After appropriate monitoring has been established and pre-oxygenation completed, induction of anaesthesia is commenced, most commonly via the intravenous route in adults. The drugs used for induction (Figure 3) vary with the intended technique, but a common approach is to administer a moderate dose of opioid (e.g. fentanyl, 2.5–5 μg/kg) before a sleep dose of etomidate, thiopental (thiopentone) or propofol given by slow injection. This approach provides a smooth induction with haemodynamic stability in most cases. Pre-treatment with opioids reduces the dose of induction agent required and limits, to some extent, the myocardial depression and fall in systemic vascular resistance associated with them. It may be preferable to give propofol as an infusion in a target-controlled device, particularly in high-risk cases. Etomidate is widely used for induction because it appears to have minimal cardiovascular effects, although reductions in blood pressure occur in patients with cardiac disease or some degree of hypovolaemia. Substantial falls in arterial pressures can occur in the elderly, in whom it should be used with care. Etomidate causes pain on injection, myoclonic movements and adrenal suppression even after a single dose.

Alternative approaches include the use of benzodiazepines, which are commonly used in North America. Cardiovascular stability is well maintained with intravenous diazepam and it may be used to facilitate insertion of invasive monitoring lines under local anaesthetic. Midazolam can be used for induction, but may cause hypotension resulting from falls in systemic vascular resistance and stroke volume, particularly in combination with opioids. Ketamine produces a substantial rise in arterial pressure as a result of sympathetic stimulation. In most cardiac patients, this is not ideal but occasionally these effects may be advantageous, for example in the patient with a large pericardial effusion and/or tamponade.

Muscular relaxation

Pancuronium is widely used by cardiac anaesthetists to facilitate intubation and ventilation. Its sympathomimetic and vagolytic actions were considered advantageous when the drug was first introduced and coronary artery surgery was in its infancy but these effects produce an increase in myocardial oxygen demand, which can result in ischaemia. The improved medical treatment of angina, particularly the use of β-adrenergic receptor blockers in the treatment of ischaemic heart disease, means that tachycardia and hypertension are unlikely to be a problem if this medication is taken up to the day of surgery.

Induction agents for cardiac anaesthesia

Drug effects	Cardiovascular	Pharmacokinetics	Infusion	Special considerations
Sodium thiopental (thiopentone)	Reduction in cardiac output due to direct cardiac depression with preservation of heart rate and SVR	Slow hepatic metabolism	Rapid accumulation	
Propofol	Significant reduction in SVR and thus MAP if given in bolus dose, largely avoided with a slow infusion	Rapid metabolism largely unaffected by renal or hepatic disease	Little accumulation in short-term infusion Used to minimize awareness during cardiopulmonary bypass and for sedation post-operatively	Best avoided in outflow tract obstruction (e.g. aortic stenosis or cardiomyopathy) No evidence of neuro-protection in cardiac setting
Etomidate	Minimal cardiovascular effects in normal patients Some reduction in MAP in those with cardiac disease and particularly in the elderly	Rapid metabolism by plasma and hepatic esterases	Associated with increased mortality in the critically ill	Significant adrenal suppression with even a single dose
Midazolam	Modest decrease in MAP and SVR	Rapid hepatic metabolism and renal clearance	Accumulates in long-term infusion, particularly in the critically ill	Can be used as a premedication and to facilitate line insertion under local anaesthesia

MAP, mean arterial pressure; SVR, systemic vascular resistance

Vecuronium is used increasingly because several studies have shown that residual neuromuscular blockade is common after administration of pancuronium and may cause delayed extubation if routine reversal is not used. Vecuronium, with a shorter half-life, has a stable cardiovascular profile, but may be associated with bradycardia if given shortly after fentanyl or remifentanil. Rocuronium has a similar haemodynamic profile and has been recommended for use in cardiac anaesthetic practice. Its rapid onset facilitates early intubation and its intermediate duration of action means that residual paralysis is unlikely to be a problem.

Atracurium is not widely used in cardiac anaesthesia except as a continuous infusion. It may be useful for short non-bypass procedures, but histamine release can cause hypotension.

Tracheal intubation

Oral intubation is preferred in adults and is well tolerated post-operatively. Nasal intubation may cause mucosal trauma, resulting in severe haemorrhage following administration of heparin.

Certain procedures require use of double-lumen endobronchial tubes. These include descending aortic surgery and thoracoscopic internal mammary artery harvest. The use of a double-lumen tube allows collapse of the lung on the operative side to facilitate surgery. A left-sided tube is usually selected to circumvent problems associated with right upper lobe ventilation.

Maintenance of anaesthesia

Surgery for ischaemic heart disease represents 75% of the total UK cardiac surgical workload, with 24,000 cases in the year 2000–2001. The following description of cardiac anaesthesia is largely applicable to these patients, but the principles are relevant to all cardiac surgical patients. Specific considerations for patients with valvular heart disease (about 20% of cases) are summarized in Figure 4.

Valve surgery and anaesthesia

Aortic stenosis

Heart rate/rhythm
- Sinus rhythm essential (ventricular filling critically dependent on atrial systole)
- Avoid tachycardia (shortens diastole)
- Sequential atrioventricular pacing required if heart block presents following cardiopulmonary bypass

Preload/contractility
- Maintain preload and contractility

Systemic and pulmonary vascular resistance
- May need to maintain systemic vascular resistance temporarily with vasoconstrictors to preserve coronary blood flow (e.g. before cardiopulmonary bypass)

Aortic regurgitation

Heart rate/rhythm
- Heart rate optimal at about 90 beats/min (sinus rhythm)
- Low heart rates associated with increased diastolic time and increased regurgitation

Preload/contractility
- Maintain preload and contractility
- May benefit from inodilator therapy

Systemic and pulmonary vascular resistance
- Forward stroke volume can be augmented with vasodilators

Mitral stenosis

Heart rate/rhythm
- Ideal heart rate 70–90 beats/min
- Many patients in atrial fibrillation at time of surgery – important to control ventricular rate in this situation

Preload/contractility
- Maintain preload and contractility
- Inotropic therapy often required following surgery (avoid tachycardia)

Systemic and pulmonary vascular resistance
- Long-standing mitral stenosis can lead to pulmonary hypertension
- May require pulmonary vasodilator therapy postoperatively and prolonged weaning from ventilation
- Inhaled nitric oxide therapy has been used in the latter context

Mitral regurgitation

Heart rate/rhythm
- Low heart rates deleterious: 80–100 beats/min (sinus rhythm) ideal range
- Patients often present with atrial fibrillation

Preload/contractility
- Maintain preload and contractility

Systemic and pulmonary vascular resistance
- Decrease in left ventricular afterload (decrease in systemic vascular resistance) can reduce the degree of regurgitation through the valve
- Pulmonary hypertension may occur with chronic mitral regurgitation (often combined with mitral stenosis) and require pharmacological treatment

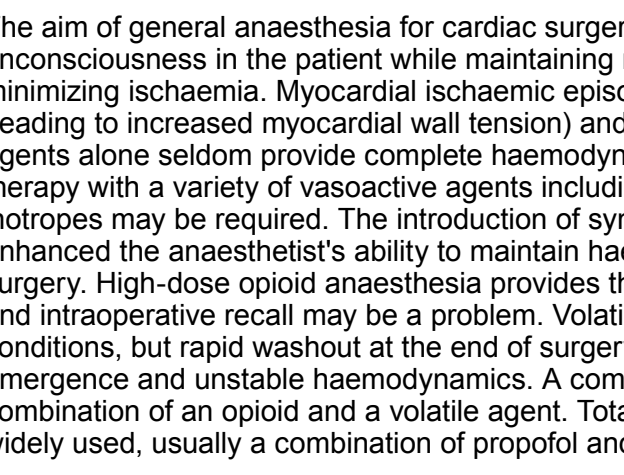
The aim of general anaesthesia for cardiac surgery is to produce a state of unconsciousness in the patient while maintaining myocardial oxygen balance and minimizing ischaemia. Myocardial ischaemic episodes are minimized if hypertension (leading to increased myocardial wall tension) and tachycardia are avoided. Anaesthetic agents alone seldom provide complete haemodynamic control, and additional drug therapy with a variety of vasoactive agents including nitrates, vasoconstrictors and inotropes may be required. The introduction of synthetic opioids 30 years ago, enhanced the anaesthetist's ability to maintain haemodynamic control during cardiac surgery. High-dose opioid anaesthesia provides this, but recovery is often prolonged and intraoperative recall may be a problem. Volatile agents provide good intraoperative conditions, but rapid washout at the end of surgery is associated with sudden emergence and unstable haemodynamics. A compromise anaesthetic technique is a combination of an opioid and a volatile agent. Total intravenous anaesthesia is also widely used, usually a combination of propofol and opioid.

The use of nitrous oxide is controversial in cardiac anaesthesia. It has myocardial depressant effects, which may be exaggerated if used in combination with opioids. To avoid this, an air/oxygen mix can be used as the carrier gas for volatile agents. This also eliminates the possibility that micro air emboli will be enlarged in the circulation by inward diffusion of nitrous oxide into the air bubbles during the period following cardiopulmonary bypass.

Inhalational agents: modern inhalational agents (e.g. isoflurane, sevoflurane, desflurane) have fewer side-effects than older agents such as halothane. On its introduction to clinical practice, isoflurane was heralded as the ideal inhalational agent for cardiac anaesthesia because it preserved cardiac output with reduced peripheral resistance and did not significantly depress myocardial contractility. A number of studies later suggested that isoflurane could cause a deleterious redistribution of coronary blood flow, increasing the flow to healthy areas of myocardium by diverting it from potentially ischaemic areas supplied by diseased coronary arteries – the ‘coronary steal effect’. These concerns have largely subsided and it is considered safe when used at moderate concentrations as part of a balanced anaesthetic technique. There is no recent evidence demonstrating any major advantage of any of the inhalational agents for cardiac anaesthesia. In practice, most units in the UK use isoflurane for adults and reserve sevoflurane for the induction of children.

During coronary artery surgery, myocardial ischaemia with subsequent reperfusion can lead to ischaemia-reperfusion injury of the myocardium with variable manifestations ranging from myocardial infarction and myocardial ‘stunning’ to reperfusion arrhythmias. Data show that inhalational agents (including isoflurane) given before an ischaemic insult confer significant protection against this injury. The mechanisms for this effect (Figure 5) include conservation of ATP levels, reduction of calcium overload and free radical scavenging, thus preserving myocardial myocyte function. This effect is not seen with intravenous agents such as propofol.

Possible mechanism for isoflurane’s myocardial protection



Activation of adenosine A1-receptors leads to a reduction in tumour necrosis factor-α (TNF-α), an increase in nitric oxide and activation of protein kinase C

Reproduced with permission from: Agnew N M, Pennefather S H, Russell G N. Isoflurane and Coronary Artery Disease. *Anaesthesia* 2002; **57:** 338–47.

Propofol is a well-established, non-cumulative intravenous anaesthetic agent, widely used in cardiac anaesthesia. It can cause significant systemic hypotension, particularly following a bolus injection. This effect is principally due to a decrease in systemic vascular resistance but there may also be an element of myocardial depression. Propofol should be used only in patients with good ventricular function and avoided in those with significant outflow tract obstruction (e.g. aortic stenosis, hypertrophic cardiomyopathy). Propofol is better tolerated if given slowly and is preferably administered as an infusion, possibly as part of a total intravenous anaesthetic (TIVA) technique. Propofol is commonly used to provide anaesthesia during the specific period of cardiopulmonary bypass and has an important role to play in the immediate postoperative period when ventilated patients can be sedated for a few hours with the non-cumulative drug.

Propofol has a neuroprotective effect in patients with severe head injuries. This effect has not been demonstrated in patients undergoing cardiopulmonary bypass.

Opioids: a range of synthetic opioids are available for use in cardiac anaesthesia. Fentanyl was first used for cardiac anaesthesia in 1978. Since then, its use has been extensively investigated along with two of its newer congeners, alfentanil and sufentanil. This group of drugs is reliable and effective for cardiac anaesthesia and is associated with minimal cardiovascular depression. In the UK, fentanyl is widely used for cardiac anaesthesia, but there has been a tendency to reduce the dose to facilitate weaning from ventilation. In this latter respect, much interest has centred around the use of the opioid remifentanil.

Remifentanil is a potent analgesic opioid agent with an ultra- short half-life (5 minutes) resulting from metabolism by plasma esterases. It is administered by infusion at a rate of 0.5–2 μg/kg/min. It has been successfully used with propofol and isoflurane to produce profound analgesia, haemodynamic stability and suppression of the stress response during cardiac surgery. Its unique properties allow patients to be weaned from ventilation within 30 minutes of stopping an infusion.

Initial enthusiasm for remifentanil has been tempered by a number of clinical observations. It has proved difficult to overlap the termination of remifentanil infusion with the commencement of an alternative analgesic (e.g. morphine or low-dose fentanyl). Proponents of TIVA consider this is only a question of attention to detail. However, if adequate analgesia is not established rapidly, the resultant pain is more resistant to treatment than if a longer-acting drug had been given throughout.

A bolus dose of remifentanil given at induction of anaesthesia can cause hypotension and bradycardia in patients with coronary artery disease. It is preferable to introduce the drug by infusion in these patients.

Neuraxial blockade

Interest in neuraxial blockade for cardiac surgery is increasing, but it is not widely used. The techniques used to provide intraoperative analgesia during cardiac surgery are intrathecal opioids and continuous epidural infusion of a low-dose local anaesthetic and opioid combination. Intrathecal opioids provide good intraoperative and early postoperative analgesia but can result in respiratory depression, which delays extubation.

In addition to excellent analgesia, thoracic epidural analgesia may beneficially affect the outcome of patients undergoing coronary artery bypass grafting through cardiac sympatholysis and attenuation of the cardiopulmonary bypass-related stress. Postoperative analgesia and respiratory function is also improved.

Thoracic epidural analgesia improves myocardial oxygen balance in several ways including selective vasodilatation of atherosclerotic coronary arteries and redistribution of blood to the subendocardium. In general, cardiac output and systemic vascular resistance are maintained. Hypertension is less likely to occur on cardiopulmonary bypass, and hypotension and bradycardia may, occasionally, be associated with thoracic epidural analgesia.

Spinal and epidural techniques have the potential to cause haematomata around the spinal cord and subsequent paralysis following the heparinization required for cardiopulmonary bypass. The incidence of major neurological complications of this nature is very small, but they are potentially devastating and may be under-reported. The optimum time for epidural catheter insertion and removal has been debated, but there is no consensus of opinion. Many practitioners recommend that several hours should elapse between insertion and heparin administration and site the epidural catheter the night before surgery in a patient first on the morning operating list. Others site the epidural just before induction of anaesthesia. Removal of epidural catheters should be carried out when coagulation is ‘at its most normal’, for example, 23 hours after the last dose of subcutaneous heparin. The timing of catheter removal is difficult because cardiac surgical patients are often treated with other anticoagulants and may also have a clotting defect following cardiopulmonary bypass. The place of thoracic epidural analgesia in cardiac anaesthesia remains uncertain with benefits demonstrated by some investigators as possibly justifying the potential complications and not by others. ◆

FURTHER READING

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Respiratory Management following Cardiac Surgery

Brian F Keogh

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Patients undergoing high risk, complex or re-do surgery, those with severely compromised cardiac function or those in whom unexpected perioperative difficulties have been encountered are generally referred to the intensive care team for postoperative management. Most cardiac surgical patients do not require this level of support and can be managed in postoperative cardiac care units, theatre recovery units or high dependency units as part of 'fast track' protocols. Trainee anaesthetists are often asked to direct ventilatory support and to assess suitability for extubation in this lower risk group.

Pulmonary effects of cardiac surgery

Respiratory function is subject to a variety of insults (Figure 1) even during routine cardiac surgery, though many patients suffer no adverse effects.

Effects of cardiac surgery on pulmonary function

- Reduced functional residual capacity
- Patchy atelectasis, particularly in dependent zones
- Increased V/Q mismatch and intrapulmonary shunt
- Ischaemia–reperfusion injury
- Increased pulmonary capillary permeability
- Increased extravascular lung water

1

The disturbance of lung water homeostasis associated with cardiopulmonary bypass (CPB) varies from a mild increase in extravascular lung water (EVLW) to severe acute lung injury or acute respiratory distress syndrome. It is exacerbated by any elevation in left atrial pressure. All patients undergoing CPB suffer increased EVLW and though this is less likely with non-bypass re-vascularization procedures, the risk is not eliminated. Extrapulmonary collections (blood, effusions) or pneumothoraces may combine to aggravate a reduction in functional alveolar volume.

These effects combine to decrease pulmonary compliance and increase the work of breathing. In weaning or spontaneously breathing patients, the metabolic cost of this increase may prove critical in a patient with borderline cardiac reserve. In such patients, a sudden rise in central venous pressure during weaning or following extubation is a warning sign of impending cardiopulmonary deterioration. Most cardiac surgical patients do not suffer such difficulties and proceed through respiratory weaning and extubation without notable compromise.

Approaches to respiratory support following cardiac surgery

The exact characteristics of ventilatory support in the postoperative period vary in different units. Flow-generated and pressure-generated mandatory breaths are equally applicable, though the latter may be uncomfortable for awake patients owing to the high initial inspiratory flow rate. Patient-initiated breaths should also be supported, most commonly with pressure support ventilation.

The pathophysiology outlined above results in a reduction of functional alveolar volume and ventilation–perfusion (V/Q) mismatch. Ventilatory conduct should encourage recruitment and maintenance of lung volume, while avoiding regional over-distension and the risk of barotrauma. Positive end-expiratory pressure (PEEP) is almost routinely applied to counteract atelectasis and to increase functional residual capacity, and it may have favourable effects on the redistribution of increased EVLW.

Typical initial ventilatory settings (Figure 2) allow an initial period of stabilization after surgery. It may be possible to wean some parameters (e.g. fraction of oxygen in inspired air (FiO_2), oxygen saturation (SpO_2)) rapidly. Values of 95% or above should be achieved, not because they are necessary for adequate oxygen delivery, but because lower values may reflect pulmonary pathophysiology and the need for intervention.

Typical initial ventilatory parameters following cardiac surgery

- Fraction of oxygen in inspired air (FiO_2) 0.6–0.8 (decreased if oxygen saturation in arterial blood (SaO_2) allows)
- Tidal volume 10–12 ml/kg
- Respiratory rate 10–12 breaths/min
- Inspiratory: expiratory ratio 1:2
- Positive end-expiratory pressure (PEEP) 5 cm H_2O
- Peak pressure limit 30 cm H_2O
- Pressure support ventilation setting 15 cm H_2O

2

Patients who are mildly desaturated may require an increase in PEEP or mean airway pressure (longer inspiratory:expiratory (I:E) ratio), lung volume recruitment manoeuvres (manual hyperinflation or brief increase in ventilator-delivered tidal volume) or reassessment of their haemodynamic status. Some patients require high levels of PEEP (> 10 cm H_2O) or mean airway pressure and the resultant increase in intrathoracic pressure may impair cardiac performance, particularly in the presence of hypovolaemia.

A chest radiograph is mandatory following cardiac surgery to check for fluid or air collections, to confirm the position of various tubes and catheters and to assess the state of the lung fields. It is often helpful in directing management. In addition to ventilatory manipulation (e.g. increase PEEP in bi-basal collapse) the chest radiograph may suggest the need for diuretic therapy or the introduction of an inodilator to reduce left atrial pressure.

Preoperative pulmonary function and blood gas measurements, if available, should be considered in determining target gas exchange values for an individual patient. In patients with known V/Q mismatch (e.g. those with chronic obstructive pulmonary disease (COPD)), other lung parenchymal diseases or restrictive disorders (e.g. obesity), lower levels of oxygen saturation in arterial blood (SaO_2) can be readily accepted. Bronchodilator therapy should be instituted as soon as possible after surgery in patients with COPD or airway irritability.

Weaning from mechanical ventilation

Weaning from ventilation following routine cardiac surgery does not necessarily involve a conscious decision but is usually integrated into normal clinical care. Effective analgesia must be continued throughout the weaning process. For weaning to proceed successfully, various general criteria (Figure 3) should be satisfied, of which a satisfactory haemodynamic status is paramount. An 'after-drop' in body temperature is commonly observed and temperature should approach normal levels before advanced weaning is attempted. In addition to general criteria, guidelines for acceptable respiratory parameters can be set (Figure 3) which act as alerts to initiate reassessment if they are not achieved. These are useful guidelines, which may be varied in individual patients or in unusual circumstances. For example, in a patient with known poor ventricular function, respiratory weaning and extubation may be undertaken successfully with moderate levels of inotropic support or even an intra-aortic balloon pump *in situ*.

Criteria for weaning from mechanical ventilation

General

- Stable cardiac rhythm
- Haemodynamic stability
- Low-dose or no inotrope requirement
- Acid–base status acceptable
- Haemostasis controlled (drainage < 100 ml/hour in adult)
- No residual neuromuscular blockade
- Approaching normothermia
- Adequate analgesia/controllable discomfort

Respiratory

- Partial pressure of oxygen in arterial blood (PaO_2) > 10 kPa with fraction of oxygen in inspired air (FiO_2) $\leq$ 0.5
- $PaCO_2$ < 6.5 kPa
- pH > 7.32
- Positive end-expiratory pressure (PEEP) $\leq$ 6 cm H_2O

3

Typical criteria for extubation are listed in Figure 4. As the level of respiratory support decreases, the acceptable level of partial pressure of carbon dioxide in arterial blood ($PaCO_2$) should be allowed to rise. $PaCO_2$ levels of 7.5–8 kPa are not unusual in weaning or extubated patients with acceptable cardiopulmonary parameters who are receiving adequate analgesia. The decision to extubate is clinically based and a comfortable, cooperative patient who is neither distressed nor tachypnoeic and has an acceptable respiratory pattern is likely to succeed, even if arterial blood gas values are not ideal.

Guidelines for extubation criteria

- General criteria apply (Figure 3)
- Partial pressure of oxygen in arterial blood (PaO_2) > 10 kPa with fraction of oxygen in inspired air (FiO_2) $\leq$ 0.5
- $PaCO_2$ < 8 kPa
- Respiratory rate < 20/min
- Minute volume requirement < 150 ml/kg/min
- Satisfactory respiratory pattern
- Comfortable, cooperative and neurologically intact patient

4

Post-extubation management

Patients must be encouraged to cough following extubation and it is vital that adequate analgesia is administered to allow effective propulsive coughing. Inevitably, some patients suffer areas of localized collapse, the left lower lobe being the most common, and this should be treated with intensive physiotherapy and humidified oxygen. High flow, continuous positive airway pressure (CPAP) systems are commonly used in patients with pulmonary collapse, pulmonary congestion and obesity, via face CPAP masks. This is usually well tolerated in cooperative patients, but may prove difficult or counterproductive in confused patients. Non-invasive positive pressure ventilation may also be used, via nasal or face mask, but requires patient education and compliance to be effective.

Respiratory issues in coronary re-vascularization

Internal mammary arteries are commonly harvested for conduit and ipsilateral lower lobe compression or collapse is common. Extreme care should be taken in lung hyperinflation if a left internal mammary pedicle graft has been performed because of the risk of traction disruption of the graft.

Patients may suffer myocardial stunning during surgery and may be at risk of functional mitral valve regurgitation, due to dilatation of the mitral valve ring. This may be exacerbated by respiratory weaning. A patient who becomes distressed during weaning, with a rise in right atrial pressure and relative hypotension, should be re-assessed with echocardiography. This condition requires venodilatation, usually with glyceryl trinitrate, in combination with low-dose vasoconstriction, in order to maintain coronary perfusion. It requires an index of suspicion and correct diagnosis, because fluid and inotropic therapy, both of which are commonly administered, can increase regurgitation.

Respiratory weaning – failure to progress

Unexpected failure to meet respiratory weaning targets should prompt patient reassessment. Simple factors include inadequate analgesia, sputum retention and regional pulmonary collapse. Neurological injury may also present at this time. Occult fluid or air collections should be excluded. Pericardial effusion or incipient tamponade may be associated with sudden deterioration in respiratory parameters. Similarly, deterioration in cardiovascular performance, associated with graft kinking or occlusion, or impairment of mitral valve function may initially manifest as tachypnoea and respiratory distress. Echocardiographic re-assessment of cardiac function is indicated, and may be urgently required in such patients. ◆

Clinical anaesthesia

Anaesthesia
and intensive care medicine
on CD-ROM

Airway Control

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Securing control of the airway is one of the most important skills required of the anaesthetist. Whether for elective or emergency surgery, and whether the need for airway control has been predicted or not, the safety of the patient depends on the anaesthetist's ability to intervene to ensure adequate oxygenation and ventilation should the need arise. The anaesthetist must:

- develop the skills of airway assessment and management
- be familiar with the equipment and techniques available for control of the airway
- be able to choose the appropriate measures for the individual patient.

This contribution focuses on these basic principles.

Assessment of the airway

The anaesthetist must assess the airway before undertaking any anaesthesia. When general anaesthesia is contemplated, assessment facilitates a planned approach to anticipated difficulties with laryngoscopy and intubation. When a regional or local technique is contemplated, the need for airway intervention may also arise, for example, following respiratory embarrassment as a result of a high spinal or epidural blockade level, over-zealous sedation, or more rarely, following an allergic reaction to a drug.

The patient's previous anaesthetic notes should be consulted if available. It is important to realize, however, that the patient's circumstances may have changed, and a previously easy intubation may have become difficult (e.g. as a result of pregnancy). A number of anatomical factors are associated with difficulty in laryngoscopy and intubation:

- obesity, pregnancy
- large protruding incisor teeth
- short neck, especially in a heavy patient
- reduced mobility of the neck (e.g. rheumatoid arthritis)
- instability of the neck
- reduced mouth opening
- intraoral masses
- large goitre.

Anatomical assessment

Whether laryngoscopy and intubation would be possible with reasonable ease should be assessed using a reliable and reproducible bedside method of airway assessment that has minimal false-positive and false-negative rates. No single test provides this information, but the modified Mallampati test in conjunction with an assessment of thyromental distance combines ease with reasonable accuracy.

The modified Mallampati test assesses the size of the base of the tongue in relation to the size of the oropharynx. The patient sits upright with the head in the neutral position. The assessor sits in front of the patient at the patient's eye level. The patient opens their mouth as wide as possible. Without phonating, the tongue is protruded as far as possible. The assessor inspects the pharyngeal structures visible and a score is allocated according to which structures are visible (Figure 1).

Modified Mallampati test

Class	Pharyngeal structures visible
1	Fauces, faucial pillars (the palatoglossal and palatopharyngeal arches), uvula, soft palate
2	Faucial pillars are obscured leaving the fauces, uvula and soft palate visible (i.e. posterior pharyngeal wall visible below soft palate)
3	Only the soft palate and the base of the uvula seen (i.e posterior pharyngeal wall not visible below soft palate)
4	Even the soft palate obscured

1

The measurement of thyromental distance as recommended by Frerk is obtained by maximally extending the head on the neck and measuring from the prominence of the thyroid cartilage to the bony point of the chin.

A modified Mallampati grade of 3 or 4 combined with a thyromental distance of 7 cm or less gives a bedside assessment system with a sensitivity of 81% and a specificity of 98% for difficulty with intubation.

The view of the laryngeal structures obtained at direct laryngoscopy is often classified according to the system described by Cormack and Lehane (Figure 2). In this system, grades 3 and 4 constitute difficult laryngoscopies. Fairly severe difficulty with intubation may occur with grade 3, and the use of a bougie/introducer, posterior to, but held up against the epiglottis may permit blind intubation. With a grade 4 view, intubation by standard methods is virtually impossible despite optimal positioning.

Cormack and Lehane classification system

Grade	Laryngeal structures visible
1	Most of the glottis visible
2	Only the posterior part of the glottis (posterior commissure, arytenoid cartilages) visible
3	Only the epiglottis visible, no part of the glottis seen
4	Not even the epiglottis seen

2

Airway patency

Partial obstruction of the airway in the awake patient may be caused by masses in the upper airway (e.g. tonsils, adenoids, tumour), foreign bodies, or epiglottitis. In the sedated or unconscious patient, laxity of the muscles that normally keep the tongue anterior to the posterior pharyngeal wall allows the tongue to fall back and obstruct the airway. Partial obstruction is recognized by noisy inspiration (stridor), tracheal tug, and dyssynchronous movements of the thorax and abdomen on inspiration.

In normal, unobstructed breathing, the abdomen expands as the diaphragm descends in inspiration and the thorax expands as indrawn gas fills the lungs. With obstruction, the abdomen still expands, but if inspired gas cannot be inhaled at a sufficiently fast rate, the sternum is drawn inwards by the increasing, unrelieved negative intrathoracic pressure. Partial obstruction and its cause (and therefore ease of reversal) must be recognized before embarking on anaesthesia. The technique of airway management is highly modified in the presence of partial obstruction.

Aspiration risk

For elective anaesthesia, the patient is fasted. Solid food, non-clear liquids (especially those containing milk) and chewing gum should not be consumed in the 6 hours before anaesthesia. Clear liquids are permissible up to 2 hours before induction.

For emergency anaesthesia, the interval between last food or drink and the injury or onset of illness is assessed. Gastrointestinal obstruction or other abnormal motility state (e.g. ileus, diabetes mellitus, renal failure, acute pain) all increase the risk of aspiration on induction of anaesthesia.

Equipment and techniques for routine airway management

Before embarking on general anaesthesia, the equipment required should be to hand and its correct function checked. A preoperative checklist such as that proposed by the Association of Anaesthetists of Great Britain and Ireland is particularly useful (see *Anaesthesia and Intensive Care Medicine* **1:2:** 65). The minimum equipment required includes:

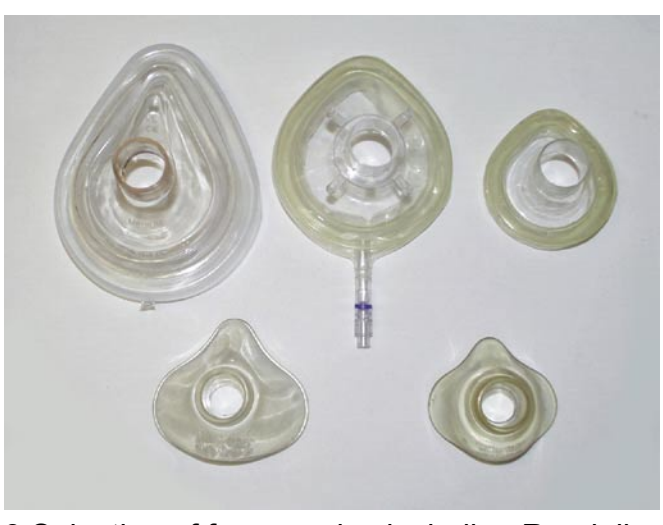
- source of pressurized oxygen (plus bag-valve-mask or anaesthesia circuit)
- selection of face masks
- selection of oropharyngeal and nasopharyngeal airways
- high-flow suction
- Yankauer suction catheter, and selection of narrow-bore suction catheters
- two laryngoscopes
- selection of tracheal tubes
- selection of laryngeal mask airways
- Magill's forceps
- sterile lubricating gel
- ties and padding to secure tracheal tube
- gum-elastic or other suitable bougie.

For non-emergency anaesthesia, several interventions to control the airway are available. These range from oxygen administration through a face mask, delivery of inhalational anaesthesia via an anaesthetic face mask or laryngeal mask airway, through to tracheal intubation.

Non-relaxant anaesthesia

If relaxant anaesthesia is not required (e.g. for body-surface surgery in the patient not at risk for aspiration) then inhalational anaesthesia via a face mask is appropriate. In the absence of flammable anaesthetic agents, the mask is usually clear plastic with an inflatable rim that provides a good seal in contact with the face. The size of the mask is determined by the patient's size and physical features, but a range of sizes (Figure 3) should be available. For paediatric anaesthesia, the mask should have as little dead space as possible (e.g. the Rendell-Baker–Souchet mask). Nasal masks are indicated for anaesthesia in the dental chair.

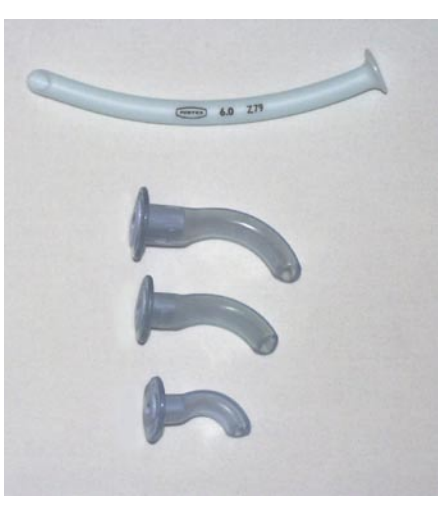
Induction in the absence of airway obstruction may be inhalational or by intravenous injection of a suitable induction agent. If there is any suggestion of airway obstruction then inhalational induction or another approach (e.g. awake fibre-optic intubation) is required.



3 Selection of face masks, including Rendell-Baker–Souchet paediatric masks (lower row).

Supporting the airway

Whatever the means of induction, once the patient is unconscious it is necessary to support the airway. There is a tendency for the airway to become partially obstructed at this stage because the tongue falls back against the posterior wall of the pharynx. Induction will normally have occurred with the patient supine, head resting on a pillow. This allows the anaesthetist to extend the head on the neck at the same time as applying a jaw thrust and opening the mouth. To achieve this triple manoeuvre, the mask is secured on to the face using one or both hands, with the thumbs on the upper part of the mask, index fingers on the lower part and the rest of the fingers effectively pulling the patient's mandible forward into the mask. It is crucial that unopposed downward pressure on the mask is not used to obtain a seal between mask and face because this will close the airway. Likewise, the third, fourth and fifth fingers must stay on the mandible and must not press on the floor of the mouth, which also tends to cause obstruction. If it is impossible to open the airway using these techniques, an artificial airway is required. Two methods are available: the oropharyngeal and the nasopharyngeal airway (Figure 4).



4a Nasopharyngeal airway.
b Selection of smaller oropharyngeal airways.

The oropharyngeal (Guedel) airway is a curved tube that has a flanged and reinforced oral end. The flange enables correct positioning at the incisor teeth, and the reinforcement prevents the patient from obstructing or severing the device by biting down. This airway is available in a range of sizes (size 3–4 is usually required for an adult, Figure 4b), and it is vital that the appropriate size is used for the patient. An easy way to determine size is to choose the airway in which the length is equal to the distance between the corner of the patient's mouth and the angle of the jaw. If the airway is too short it tends to push the tongue backwards and cause increased obstruction. If too long, the device tends to stimulate the larynx, provoking spasm, and it fails to sit securely with the flange at the front incisors. The Guedel airway is usually inserted upside-down (the pharyngeal opening facing the roof of the mouth, then rotated 180° as it passes the back of the tongue). A lightly anaesthetized patient may gag or cough with this intervention. It may also provoke laryngeal spasm.

The nasopharyngeal airway is a less stimulating intervention. It is a soft curved tube with a flanged nasal end and a bevelled pharyngeal end (Figure 4a). It is also available in a range of sizes. Sizes 6–8 mm (measured as internal diameter) are suitable for adults, the usual measure is the diameter of the patient's little finger. Before inserting the airway, a safety pin is inserted eccentrically at the flanged end, to prevent inhalation of the device. The airway should be coated with lubricating gel, and inserted into either nostril. It is advanced along the floor of the nose in a posterior direction, and should come to lie with the bevelled end in the oropharynx, behind the tongue and above the glottis. The eccentric positioning of the pin permits access of a catheter for suctioning secretions from the pharynx and airway.

Face mask: for brief procedures, anaesthesia can be maintained using a face mask, with or without airway adjuncts. For longer procedures, when it is desirable for the anaesthetist to have both hands free, the standard mask can be supported by a harness. It is now more common to insert a laryngeal mask airway for such procedures. This has the advantage of maintaining the airway without additional instrumentation, in addition to providing a more secure airway and providing hands-free operation.

The laryngeal mask airway (LMA) was designed to provide a connection between the artificial and anatomical airways in a less invasive way than with a tracheal tube, and yet with greater convenience and reliability than a conventional face mask. The standard LMA is made from silicone and is designed for multiple patient (up to 40) uses. It consists of a silicone bowl surrounded by a thin-walled elliptical ring that can be deflated to form a thin wedge shape, and which when inflated in the space posterior to the pharynx creates a seal around the laryngeal aperture. This seal permits ventilation of the airway under positive pressure. It also prevents insufflation of gas into the oesophagus and stomach, unless high inflation pressures (20–30 cm H_2O) are used. The device has a central aperture, with vertical bars, designed to prevent prolapse of the epiglottis into the tube that connects the mask to the anaesthetic circuit.

The LMA is available in a variety of sizes (Figure 5).

Correct placement is important to ensure a high-performance seal without overinflation of the cuff, and the appropriate size is chosen for the size of the patient (Figure 6).

The LMA is also available with a flexible, reinforced, non-kinking tube instead of the standard tube. This type is particularly useful for situations in which the head may be moved during surgery and for oral and ENT surgery. The intubating LMA is a development of the standard airway designed to act as a conduit permitting blind intubation of the trachea using a specially designed silicone tube.

A full description of the recommended technique for inserting the LMA is beyond the scope of this contribution. Briefly, the device is completely deflated (preferably using a cuff deflation tool, which will ensure deflation to the correct shape). The patient's head is supported on a pillow, in the classic intubating position. Extension of the head and flexion of the neck on the thorax is achieved by the non-dominant hand. The posterior surface of the LMA is lubricated with water-soluble gel. The LMA is held between index finger and thumb, with the index finger of the operator's gloved dominant hand at the junction of the mask and the tube. The aperture of the device faces caudally. An assistant holds the patient's mouth open, and the device is inserted under direct vision, with its posterior, lubricated surface firmly against the hard palate. The LMA is pushed, keeping it firmly against the palate at all times following the palate posteriorly and down into the hypopharynx. Resistance to insertion is met when the tip of the device is in the hypopharynx, with the tip resting at the upper oesophageal sphincter. It may be necessary to push the device using the non-dominant hand, if the inserting finger is not long enough. The device is released. The cuff is inflated with the recommended volume of air, at which point the tube may rise from the mouth as the device seats itself around the larynx. The tube of the LMA is connected to the anaesthetic circuit, if necessary using a swivel connector.

The LMA may be used to ventilate the anaesthetized muscle-relaxed patient, provided that the inflation pressures do not exceed about 20 cm H_2O. Above this pressure, the risk of gradual insufflation of the stomach with anaesthetic gas increases. This increases the risk of regurgitation and aspiration of gastric contents.

5a Standard laryngeal mask airways, sizes 2½, 3, 4. **b** Reinforced laryngeal mask airway, size 4.

Relaxant anaesthesia

Anaesthesia requiring a muscle-relaxant technique most commonly requires tracheal intubation. Indications for relaxant techniques and/or intubation are:

- provision of clear airway
- airway protection from blood, oral or gastric secretions
- facilitation of suctioning of airway
- prone or sitting patient, airway inaccessible
- abdominal, thoracic anaesthesia
- likelihood of postoperative respiratory support
- administration of positive end-expiratory pressure.

Tracheal intubation

Equipment: in addition to the equipment for inhalational anaesthesia using a face mask, a suitable laryngoscope, with a spare available, and a range of suitable tracheal tubes are necessary.

The laryngoscope consists of a handle (which houses the batteries) and a detachable blade, which has a screw-in bulb. Alternatively, the bulb may be in the handle, and a fibre-optic bundle transmits the light to the blade. Two basic types of laryngoscope are available (Figure 7):

- curved-blade (usually Macintosh)
- straight-blade (e.g. Wisconsin, Seward, Magill).

The curved-blade instruments are most commonly used for adults and larger children: the tip is placed in the vallecula, anterior to the epiglottis. Forward traction elevates the epiglottis without touching the posterior surface of the epiglottis. By contrast, straight-blade laryngoscopes are inserted posterior to the epiglottis and lift it from behind. These instruments are most often used for smaller children, because the epiglottis is longer and more floppy in this age group. The blades are available in a number of sizes, with the Macintosh 3 being suitable for most adults.

Tracheal tubes – an extensive range of tracheal tubes is available (Figure 8). They are most commonly made from polyvinylchloride or polyurethane and are bevel-ended. They may be plain or have a high-volume low-pressure cuff, which provides a seal enabling positive-pressure ventilation and preventing aspiration of secretions into the airway. Uncuffed (plain) tubes are used in children. This avoids the potential for ischaemic damage on the tracheal lining from high cuff pressure and maximizes tube size available. The presence of an air leak around the plain tube ensures that the fit is not too tight.

Tracheal tubes are usually inserted via the mouth, or if necessary via the nose (e.g. for intraoral surgery). Tube size is measured by the internal diameter, ranging from 2.5 mm to about 10 mm in 0.5 mm increments. The tube is usually cut to the appropriate length for the patient. Adult males usually require size 8–9 mm and adult females 7–8 mm, cut to 21–23 cm for oral intubation. For children, the tube size can be estimated from the formula (age/4 + 4 mm), and length (age/2 + 12 cm), with age being in years. This is an approximate size, and tubes 0.5 mm greater than and less than the estimated size should be available.

The tube is connected to the anaesthetic circuit at the proximal end with a tapered connector of suitable size (see *Anaesthesia and Intensive Care Medicine* **1:2:** 68). The distal end may have, in addition to the end hole, a side opening (Murphy eye) to allow passage of gas should the bevelled end be occluded by abutting on the tracheal wall.

Sizes of laryngeal mask airway

Size	Patient	Cuff volume (ml)
1	Neonates up to 6.5 kg	4
2	Patients 6.5–20 kg	10
2½	Patients 20–30 kg	14
3	Children and small adults	20
4	Normal adults	30
5	Large adults	40

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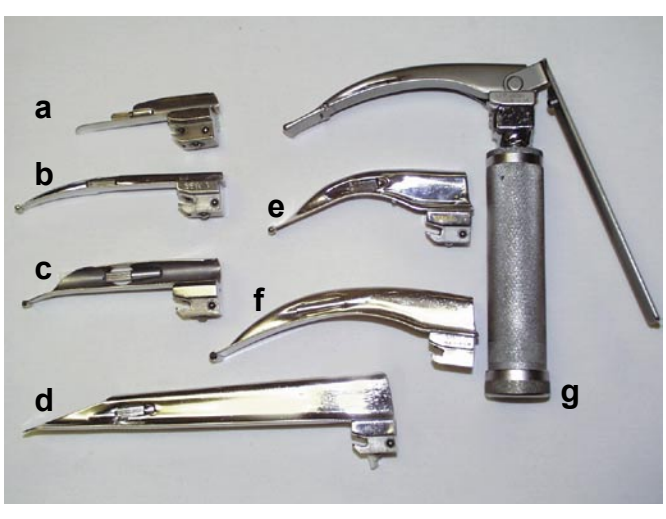
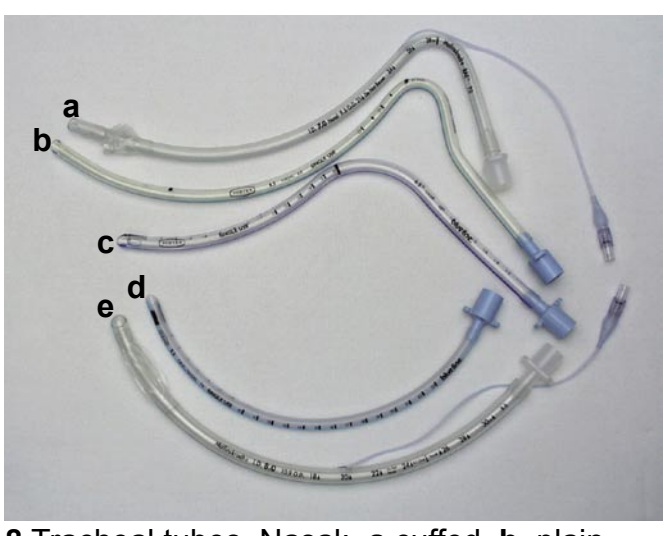


7 Selection of straight- and curved-blade laryngoscopes. **a** Wisconsin, **b** Seward, **c** Oxford, **d** Soper, **e** Macintosh size 2, **f** Macintosh size 3 **g** McCoy laryngoscope.



8 Tracheal tubes. Nasal: **a** cuffed, **b** plain. Oral: **c** North-facing plain polar. Magill pattern oral tubes: **d** plain, **e** cuffed.

Anaesthetic management

Positioning the patient correctly before intubation is crucial. Tracheal intubation requires approximate collinearity between the axes of the mouth, oropharynx and larynx. True collinearity of these structures is impossible, but appropriate positioning can make the difference between a relatively easy laryngoscopy and intubation, and failure to visualize the larynx at laryngoscopy. The classic intubating position is the sniffing position: the head is extended on the neck (atlantoaxial extension) and the neck is flexed on the thorax. For most adults this is easily achieved by having the patient lie supine on the trolley or bed and placing a pillow under the occiput. If the pillow is too caudad (elevating the shoulders) then extension of the neck on the thorax occurs. This almost always makes laryngoscopy more difficult. In small children, the relatively large head provides the correct position without the use of a pillow.

Induction – if the patient is not at risk of aspiration of gastric content, difficulty with laryngoscopy is not anticipated, and the airway is unobstructed, induction of anaesthesia is as for the mask techniques outlined above. Following induction, it is possible, providing the patient is deeply anaesthetized, to perform laryngoscopy and intubation. This practice is relatively uncommon. More usually, the anaesthetist confirms that it is possible to ventilate the patient using the mask (with an artificial airway if needed). Then an intubating dose of a muscle relaxant is given (e.g. suxamethonium, 1–1.5mg/kg). While the advantages of the speed of onset and quality of relaxation

obtained with suxamethonium are significant, its side-effects include myalgia (which can be quite severe), occasional profound bradycardia (especially in children, and particularly likely with second doses of the drug given shortly after a first dose), hyperkalaemia, and precipitation of malignant hyperthermia in susceptible individuals. To overcome these disadvantages, an intermediate-duration non-depolarizing drug such as vecuronium, 0.1 mg/kg, atracurium, 0.5 mg/kg, or rocuronium, 0.6 mg/kg, can be used. However, they commit the anaesthetist to providing ventilation by mask for a prolonged period if intubation proves more difficult than anticipated, or is impossible. With the exception of rocuronium they also take a longer time to achieve good intubating conditions, which makes them much less suitable for the patient at risk of aspiration of gastric content. The lungs are usually manually ventilated while awaiting the onset of muscle relaxation. A mixture of oxygen and the volatile agent chosen to maintain anaesthesia is used, together with nitrous oxide, if desired. The use of nitrous oxide reduces the interval allowable for laryngoscopy and intubation. The patient will become hypoxaemic more rapidly following cessation of ventilation if this gas is used, because available oxygen stores will be reduced. A peripheral nerve stimulator may be used to confirm the presence of adequate paralysis, as demonstrated by the absence of twitch response to a supramaximal stimulus.

Laryngoscopy is then performed. The right hand opens the patient's mouth and the assistant separates the patient's lips to expose the teeth. Using a curved-blade laryngoscope, held in the left hand, the blade is inserted into the right-hand side of the mouth, and advanced as far as the tonsillar bed. Sweeping the blade into the midline at this point should displace the tongue to the left, and give a view of the tip of the epiglottis. The blade is advanced, with force applied along the shaft of the laryngoscope directed upwards and outwards (at about 30–45° to the horizontal). The patient's upper incisors or gum must not be used as a fulcrum. The tip of the blade should enter the vallecula in front of the epiglottis, and the applied force elevates the epiglottis, exposing the larynx. The tracheal tube is picked up in the right hand and advanced from the right-hand side of the mouth, using the natural curvature of the tube to place the tip in the larynx under direct vision. Once the cuff of the tube is safely past the cords, the laryngoscope is carefully removed. The anaesthetic circuit is connected to the tube using a swivel connector and a catheter mount (if desired). The lungs are ventilated and the cuff of the tube inflated with just sufficient air (or gas mixture) to abolish the audible leak of gas on inflation of the lungs. Bilateral breath sounds and absence of sounds of gastric insufflation help confirm placement, however monitoring for appropriate and continuous concentration of carbon dioxide in the exhaled gas is mandatory.

Extubation – anaesthesia is maintained with inhalational agents, and the patient is ventilated using intermittent positive-pressure ventilation throughout the operation. At the end of the operation, residual neuromuscular blockade is reversed using a combination of a cholinesterase inhibitor and a muscarinic blocking drug (to prevent bradycardia). The drugs most commonly used are neostigmine, 0.05 mg/kg, with either atropine, 0.02 mg/kg, or glycopyrrolate, 0.01 mg/kg. Secretions and occasionally gastric content will have accumulated in the pharynx during the procedure. To prevent aspiration of these secretions and severe laryngeal spasm on removal of the tracheal tube, these are removed using a Yankauer sucker or equivalent, under direct vision (with a laryngoscope). The patient is ventilated with 100% oxygen. As the patient starts to breathe, the circuit is changed to permit spontaneous ventilation, with the reservoir bag providing visible confirmation of ventilatory effort and volume.

The tracheal tube is removed when the patient is breathing adequately and has regained protective airway reflexes (the patient is actively resisting the presence of the tube). The patient may be extubated in the supine position if the anaesthetist is satisfied that a clear airway can be maintained and the patient is not at risk for aspiration. If the patient is at risk, then extubation should take place in the lateral position, with the patient as fully awake as possible. Extubation should be performed during inspiration. Having deflated the cuff of the tracheal tube, the bag on the anaesthetic circuit is squeezed to expel secretions above the cuff into the oropharynx, away from the vocal cords. The tube is removed in a smooth movement, the breathing circuit rapidly reconnected to an anaesthetic mask, and the mask closely applied to the face.

Partial obstruction of the airway may occur at this stage if the tongue falls back into the pharynx, or more often because of mild laryngeal spasm. It may respond to the application of positive end-expiratory pressure. This may be achieved by partially closing the exhaust valve on the anaesthetic circuit, but the airway pressure must be monitored. If the airway is obstructed by the tongue, then an oral or nasopharyngeal airway may be required to relieve the obstruction. When the patient is breathing adequately, he is transferred to the recovery room, ensuring that he breathes supplementary oxygen during the transfer.

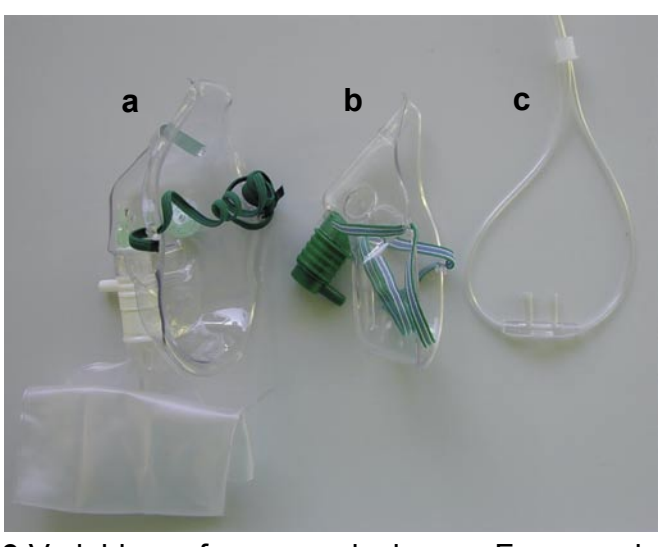
Recovery

Supplementary oxygen should be administered to all patients in the immediate recovery period. This is to prevent hypoxaemia that may otherwise occur from the ventilation–perfusion mismatch induced by surgery and anaesthesia, and the hypoventilation that may ensue from respiratory depressant drugs. Hypoxaemia may also be caused by dilutional hypoxia following cessation of nitrous oxide.

The duration of oxygen therapy may be limited to 15 minutes for young healthy patients undergoing minor day- case procedures, but extended for many hours or days for those with more serious pathology or complicated surgery. Therapy is guided by pulse oximetry or blood gas estimation, and oxygen therapy is usually titrated to achieve oxygen saturation greater than 95%.

Oxygen therapy devices may deliver either a variable or fixed concentration of supplementary oxygen to the inspired gas.

Variable performance devices include nasal prongs and simple 'Hudson'-type face masks with or without an oxygen reservoir (Figure 9). The oxygen flow delivered to the device is typically 2–4 litres/minute, which will be diluted by the air entrained during inspiration. The concentration of inspired oxygen depends on the oxygen flow rate, the patient's respiratory rate and peak inspiratory flow. Typically, 30–40% inspired oxygen is achieved when 4 litres/minute is delivered to a patient via a Hudson mask, and this concentration reduces as respiratory rate and inspiratory flows increase, due to increased air entrainment. The oxygen concentration delivered cannot be predicted accurately. This is usually of no consequence to a patient on the recovery ward, who simply needs supplemental oxygen, though the precise concentration is not critical. The inspired oxygen percentage can be increased further if an oxygen reservoir is used with the mask, and 80% inspired oxygen may then be achieved using a 12–15 litres/minute oxygen flow rate.

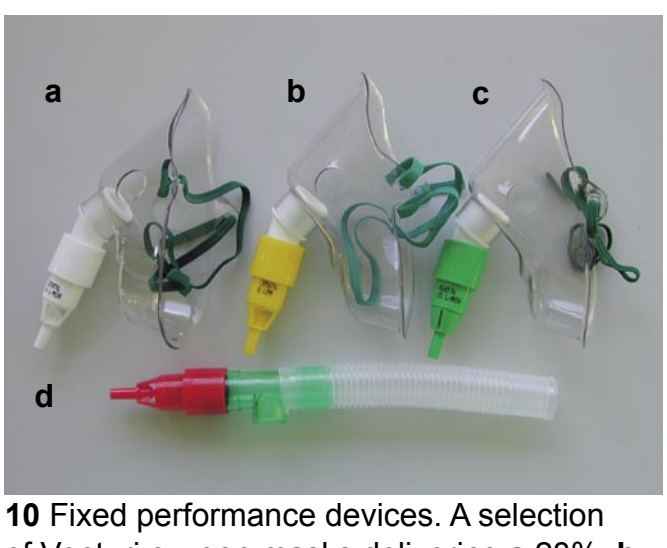


9 Variable performance devices. **a** Face mask with oxygen reservoir bag (folded); **b** simple Hudson-type oxygen face mask; **c** nasal prongs.

Fixed performance devices include face masks with Venturi-type injectors (Figure 10). They achieve a fixed inspired oxygen concentration by ensuring that a high flow rate of oxygen and entrained air is delivered, in excess of the patient's maximum peak inspiratory flow rate.

The use of a Venturi injector face mask delivers about 60 litres/minute of gas and so the inspired oxygen concentration is independent of the characteristics of inspiratory flow. Venturi devices are available to deliver fixed oxygen concentrations between 24% and 60%. The correct oxygen flow rate must be selected for the correct Venturi injector, and used with the correct mask. Details are printed on each Venturi, but typically 2 litres/minute delivers 24% oxygen, and 8 litres/minute delivers 35% oxygen. Venturi injector devices are not interchangeable with masks from different manufacturers, because the mask volume allows for adequate mixing of driving and entrained gases.

Fixed performance devices are often used in the high-dependency setting to enable accurate assessment of oxygenation, in patients with chronic lung disease who depend on a hypoxic respiratory drive, and on the general wards.



10 Fixed performance devices. A selection of Venturi oxygen masks delivering **a** 28%, **b** 35%, **c** 60% oxgen. **d** Venturi T-piece delivering 40% oxygen for use with laryngeal mask airway, tracheal tube or tracheostomy tube.

Anaesthesia for Laparoscopic Surgery

Michael W Platt

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Laparoscopic surgery is a revolution in modern surgical techniques and has reduced postoperative pain, respiratory complications and hospital stay considerably. However, it produces extra stresses on the heart and lungs, therefore patients should be screened carefully and the risks explained fully as part of obtaining consent for the procedure. Anaesthetists should consult their surgical colleagues about the relative risks in those with cardiac and respiratory disease and should be prepared to cope with complications as they arise.

History

The earliest recorded references to endoscopy are from Hippocrates in Greece (460–375 BC), who made reference to a rectal speculum. It was only in the 1970s that the problems of transmitting light, insufflation technology and optical technology were surmounted sufficiently for gynaecologists to embrace laparoscopic surgery. Laparoscopic techniques were not supported whole-heartedly by general surgeons until after 1987, when Mouret performed the first laparoscopic cholecystectomy in France. Following this, the rapid development of solid state video camera technology has further broadened the field of laparoscopic surgery.

The advantages of minimally invasive surgery are less ileus, the greatly reduced stress response to surgery and trauma, reduced acute phase reaction, reduced pain, reduced post-operative pulmonary dysfunction and reduced hospital stay. These also have economic advantages.

More procedures are being developed for laparoscopic surgery, including extraperitoneal inguinal hernia repair and retro-peritoneal nephrectomy and adrenalectomy. Routine general surgical laparoscopic procedures now include: oesophagectomy, Nissen's fundoplication, gastric banding, oversewing of peptic ulcer, intestinal resections, including hemicolectomy and col-ectomy, rectopexy and hernia repair.

Pathophysiology and complications of laparoscopy

The complications of laparoscopy include: haemorrhage, hypotension, decreased cardiac output, acidosis, pneumothorax, pneumomediastinum, subcutaneous emphysema, retroperitoneal carbon dioxide (CO_2), venous stasis, bradycardia, increased vagal tone, cardiac arrest, fatal venous CO_2 embolism, regurgitation and aspiration. Many of these complications are the result of peritoneal insufflation (pneumoperitoneum).

Pneumoperitoneum, the insufflation of the peritoneal cavity, is required to enable a gas milieu for visualization through the laparoscope (the operating telescope). CO_2 is used for laparoscopy because it is highly soluble in blood. Blood can carry large quantities of CO_2 as bicarbonate, carboxyhaemoglobin, and in plasma proteins. Carbon dioxide is eliminated rapidly and the lethal dose as an embolus is five times that of air. Usually a CO_2 gas embolism resolves rapidly, but if it is large, it can be fatal.

Pneumoperitoneum is achieved by insufflating the peritoneal cavity with CO_2 to a pressure of 10–18 mm Hg. The intra-peritoneal insufflation of CO_2 to these pressures causes respir-atory and haemodynamic changes.

Respiratory changes that occur as a result of pneumoperitoneum consist of a reduction of chest compliance by 30–50%. Airway pressures to maintain tidal volume rise to counter the reduction of chest compliance and the elevation of the diaphragm. Functional residual capacity of the lungs decreases and there is an increase in physiological dead space and shunt because of basal compression by the diaphragm and increased ventilation/perfusion mis-matching, which may result in a reduced arterial partial pressure of oxygen. Basal atelectasis may persist into the postoperative period. If minute volume is kept constant, end-tidal CO_2 increases due to absorption of CO_2 from the peritoneal cavity. The latter changes are usually countered by increasing the tidal volume and applying positive end-expiratory pressure (PEEP).

Haemodynamic changes also occur as a result of the pneumo-peritoneum. Compression of the inferior vena cava leads to a reduction in venous return, potentially followed by a fall in cardiac output. However, a reflex tachycardia and a massive increase in peripheral vascular resistance tends to maintain cardiac output at near-normal levels, by pulling blood centrally from the periphery, but with a concomitant increase in mean arterial blood pressure. This increase in myocardial work can result in myocardial ischaemia in those at risk and can lead to infarction, which may not occur until the postoperative period. Active vasodilatation and β blockade are often required to counter these effects.

Compression of the inferior vena cava causes reduced venous flow from the legs, resulting in venous stasis and an increased risk of venous thrombosis. Prophylactic anticoagulation and elastic stockings or pneumatic calf compressors should be used, especially in the elderly.

Respiratory and haemodynamic changes are affected by the patient's position. For example, head-up tilt, used for upper abdominal operations (e.g. cholecystectomy, Nissen's fundoplication) further inhibits venous return. Head-down tilt, used for colonic and pelvic surgery, promotes venous return, but aggravates respiratory changes, further reducing chest compliance and functional residual capacity and increasing basal compression.

Other complications of pneumoperitoneum include surgical emphysema, which can affect most tissues, including the conjunctivae and the scrotal sack. Cardiac arrhythmias can be secondary to vagal stimulation (bradycardia) or to hypercarbia (tachyarrythmias). Pneumothorax (including tension pneumo-thorax) may occur, particularly with upper abdominal procedures such as Nissen's fundoplication. Gastric reflux can occur because of increased intraperitoneal pressure, although retained gas in the stomach may obstruct the surgeon's view for upper abdominal operations. Pressure on the renal veins and arteries may cause a temporary reduction in renal function, due to reduced renal blood flow. Major CO_2 gas embolus seldom occurs and is usually the result of accidental direct injection of gas into a major vessel (e.g. the inferior vena cava). This may cause an obstruction to cardiac output when it reaches the heart. The treatment is to turn the patient onto the right side immediately and position them head down, causing the gas embolus to occupy the apex of the right ventricle, relieving the obstruction to ventricular outflow.

Anaesthetic technique

Preoperative assessment

Patients should be assessed carefully preoperatively, focussing on their cardiac function and reserve, because of the amount of extra cardiac work required during pneumoperitoneum. Patients with significant cardiac disease and limited cardiac reserve should be assessed by a cardiologist. It may be that an open procedure or even cancelling the procedure would be best for the patient. Patients with added risks of venous thrombosis should be treated prophylactically with fractionated heparin, elastic stockings and calf compressors during surgery. Surgery for patients with previously untreated hypertension should be postponed until treatment has stabilized. Respiratory function should also be assessed. Pulmonary function tests should be performed in those with significant pulmonary disease. Liver and renal function need to be ascertained because these organs may also be affected by pneumoperitoneum. Intercurrent medications (especially antihypertensives) should be given as normal on the morning of operation. A light sedative, such as a short-acting benzodiazepine, may be given before surgery.

Perioperative management

A routine intravenous induction is appropriate. It is preferable to intubate and ventilate patients undergoing laparoscopic surgery. This ensures a secure airway while ventilating with higher airway pressures and reducing the inherently small risk of aspiration from gastric regurgitation. A large-bore intravenous cannula should be placed to allow ready access for the management of major complications. In upper abdominal procedures a 12–16 FG oro- or nasogastric tube is passed to allow egress of gas from the stomach to facilitate the surgeon's view.

Maintenance may be by total intravenous or inhalational anaesthesia. Intermittent positive-pressure ventilation is preferable, to ensure adequate ventilation in the presence of the reduced compliance and elevated diaphragm caused by the pneumo-peritoneum.

Opioid supplementation aids analgesia and improves post-operative analgesia. This may be as intermittent morphine and diamorphine or as an infusion of a short-acting agent such as alfentanil or remifentanil.

Monitoring should be the minimum standard of non-invasive blood pressure, electrocardiograph, end-tidal CO_2, anaesthetic gases and pulse oximetry. For patients who require laparoscopic surgery, but who have very borderline cardiac function, invasive blood pressure and central venous pressure may be necessary, to allow closer control of cardiac function, in particular myocardial work. A pulmonary artery flotation catheter may be considered if there is concern regarding left heart function.

When peritoneal insufflation begins, there is often a reflex tachycardia and significant increase in blood pressure, even at deep levels of anaesthesia. To avoid hypertensive crises, with diastolic blood pressures above 120 mm Hg, it is advisable to have a vasodilator and β blocker available. Carefully titrated doses of labetalol can be effective, with its combined α and β effects. Occasionally, vagally-mediated bradycardia, even to the point of sinus arrest, may be seen. In this case, insufflation should cease immediately, while an appropriate vagolytic (e.g. atropine) is given. Ventilation should be adjusted to increase tidal volume and PEEP applied to counter the reduced compliance, elevated diaphragm and increased CO_2 load.

At the end of the procedure, it is preferable for the surgeon to infiltrate the small port wounds with long-acting local anaesthetic to reduce postoperative pain. The raw areas of tissue that occur after cholecystectomy can contribute to pain, due to carbonic acid formation by CO_2. Spraying the peritoneal cavity with bupivacaine may be effective in these cases.

Recovery

Pain in the immediate postoperative period can be severe, presumably due mainly to stretching of the tissues. Shoulder-tip pain is common, secondary to diaphragmatic irritation. Sitting the patient up and giving systemic analgesia should help this to settle. Occasionally, large doses of intravenous opioid are required for adequate relief. However, once the pain is controlled, recovery is rapid and the patient usually goes home in 2–3 days.

Postoperative complications

Surgical emphysema is occasionally alarming because it involves much of the trunk. It is advisable to deflate the scrotal sack before recovery. More generalized emphysema settles rapidly with time, but a pneumothorax should be excluded. The main problem with surgical emphysema is pain, which should be controlled systemically. Basal atelectasis with secondary pulmonary infection may also occur. It is more common in those with pre-existing pulmonary disease, and should be treated with antibiotics and physiotherapy. Aspiration may manifest as pleural effusions or rarely as Mendelson's syndrome. These may require the input of a respiratory physician, but are not usually a major problem in fasted patients.

The most serious complications are usually haemodynamic. Postoperative myocardial infarction can occur as a result of the increase in myocardial work during the procedure.

Deep venous thrombosis may occur due to venous stasis in the legs during surgery. This occasionally presents postoperatively with pulmonary embolus. ◆

FURTHER READING

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Anaesthesia for Reconstructive Free Flap Surgery

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Reconstructive free flap surgery is a complex method of wound closure for large wounds not amenable to linear (primary) closure. It involves the transfer of free tissue (skin, muscle, bone, bowel or a combination) to a site of tissue loss where its circulation is restored via microvascular anastomoses. A muscle flap produces a more even contour and better aesthetic appearance than that achieved by a simple skin graft and provides a better defence against infection. The defect may be caused by trauma, infection or extensive surgery (e.g. mastectomy, head and neck cancer). The site and size of the defect determines which flap is used. The most commonly used flaps are the gracilis muscle for lower leg trauma; latissimus dorsi and rectus abdominis for breast reconstruction; and pectoralis major and radial forearm flap for head and neck reconstruction.

In patients with lower third tibulofibular defects, free tissue transfer is typically required. The bony injury should be repaired and adequate debridement achieved before skin and muscle coverage begins. This should occur within the first 6 days after injury before colonization of the wound and the risk of complications increases. In patients with multiple trauma, any life-threatening injuries must be addressed first and the patient's haemodynamic status stabilized before reconstructive surgery is contemplated.

Flap transfer

The free flap is transferred with its accompanying artery and vein, which are then reattached to vessels at the donor site using microvascular techniques. The stages of flap transfer are:

- flap elevation and clamping of vessels
- primary ischaemia as blood flow ceases and intracellular metabolism becomes anaerobic (this is dependent on surgical time and lasts 60–90 minutes)
- reperfusion as the arterial and venous anastomoses are completed and the clamps released
- secondary ischaemia is subsequent to hypoperfusion of the flap (minimized by appropriate anaesthetic management).

Primary ischaemia

With cessation of blood flow, the flap becomes anoxic. In the presence of anaerobic metabolism, lactate accumulates, intra-cellular pH drops, ATP decreases, calcium levels rise and pro-inflammatory mediators accumulate. The severity of the damage caused by primary ischaemia is proportional to the duration of ischaemia. Tissues with a high metabolic rate are more susceptible to ischaemia, therefore skeletal muscle in a flap is more sensitive to ischaemic injury than skin. At the conclusion of primary ischaemia, the changes in the flap tissue include:

- narrowed capillaries due to endothelial swelling, vasoconstriction and oedema
- sequestration of leucocytes ready to release proteolytic enzymes and reactive oxygen intermediates
- diminished ability of endothelial cells to release vasodilators and degrade ambient vasoconstrictors
- end-organ cell membrane dysfunction and accumulation of intracellular and extracellular toxins
- up-regulation of enzyme systems to produce inflammatory mediators.

Reperfusion begins with the release of the vascular clamps. Normally, the re-establishment of blood flow reverses the transient physiological derangement produced by primary ischaemia. The flap recovers with minimal injury and normal cellular metabolism is restored. However, an ischaemia/reperfusion injury may result if factors in the flap are unfavourable. Prolonged ischaemia time or poor perfusion pressure make this more likely. Reperfusion injury occurs when the restored blood flow allows the influx of inflammatory substrates that may ultimately destroy the flap.

Secondary ischaemia occurs after a free flap has been transplanted and reperfused. This period of ischaemia is more damaging to the flap than primary ischaemia. Flaps affected by secondary ischaemia have massive intravascular thrombosis and significant interstitial oedema. Fibrinogen and platelet concentrations are increased in the venous effluent. Although skin flaps can tolerate 10–12 hours of ischaemia, irreversible histopathological changes in muscle can be seen after 4 hours.

Causes of flap failure: the general causes of poor flap perfusion may be classified as arterial, venous or resulting from oedema. The arterial anastomosis may be inadequate, in spasm or thrombosed. The venous anastomosis may similarly be defective, in spasm or compressed (e.g. by tight dressings or poor positioning). Oedema reduces flow to the flap and may be a result of excessive crystalloids, extreme haemodilution, trauma from handling or a prolonged ischaemia time. Flap tissue has no lymphatic drainage and is therefore susceptible to oedema.

Microcirculation: the blood flow through the microcirculation is crucial to the viability of a free flap. The microcirculation is a series of successive branchings of arterioles and venules from the central vessels. Regulation of blood flow and oxygen delivery is accomplished by three functionally distinct portions of the microcirculation: the resistance vessels, the exchange vessels and the capacitance vessels.

The resistance vessels are the muscular arterioles that control regional blood flow. Arterioles range in diameter from 20 μm to 50 μm and contain a relatively large amount of vascular smooth muscle in their walls. Alterations in vascular smooth muscle tone are responsible for active constriction and dilation in arterioles and thus control resistance to blood flow.

The capillaries constitute the network of vessels primarily responsible for the exchange function in the circulation. Small bands of vascular smooth muscle, the precapillary sphincters, are located at the arterial end of many capillaries and are responsible for the control of blood flow within the capillaries.

The venules act as the capacitance vessels, which collect blood from the capillary network and function as a reservoir for blood in the circulation.

The vascular bed of skeletal muscle has rich adrenergic in-nervation and therefore has a marked vasoconstrictor response to neural stimulation, primarily through the resistance vessels. Precapillary sphincters also constrict in response to sympathetic stimulation, but are sensitive to local factors such as hypoxia, hypercapnia, and increases in potassium, osmolality and mag-nesium, which may cause relaxation. Other vasoactive hormones (e.g. renin, vasopressin, prostaglandins, kinins) also have a role in microvascular control.

Transplanted vessels in a free flap have no sympathetic innervation but are still able to respond to local and humoral factors, including circulating catecholamines.

The flow behaviour (rheology) of blood in the microcirculation is determined by the red cell concentration, plasma viscosity, red cell aggregation and red cell deformability. Following all surgery under general anaesthesia, the changes in blood rheology include:

- increased platelet aggregation and adhesion
- an impairment of red cell deformability
- an increase in whole blood viscosity
- increased clotting factors
- increased plasma fibrinogen and red cell aggregation
- disturbance of fibrinolysis.

Normal levels of 2,3-diphosphoglycerate (2,3-DPG) are required for optimal red cell deformability. After blood transfusion, this deformability is impaired owing to the negligible amount of 2,3-DPG in stored blood.

Physiology

The physiological status of the patient has a major influence on the viability of the transferred tissues, so the conduct of anaesthesia and postoperative management have a direct effect on outcome. Surgery is long (often 6–8 hours) with multiple sites for tissue trauma, resulting in extensive blood and fluid losses as well as heat loss. The resulting hypovolaemic vasoconstriction and hypothermia, if not corrected, compromise blood flow to the flap and result in flap failure.

Even with good fluid management, blood flow to a flap may decrease by 50% for 6–12 hours postoperatively. The guiding principle of anaesthesia for free flap surgery is the maintenance of optimum blood flow. The determinants of flow are summarized by the Hagen–Poiseuille equation:

$$\text{Laminar flow} = \frac{\Delta P \times r^4 \times \pi}{8 \times \eta \times l}$$

where: ΔP is the pressure difference across the tube, r is the radius of the vessel, η is viscosity and l is the length of the tube.

From this we may deduce that the goals of anaesthesia for free flap surgery are vasodilatation, good perfusion pressure and low viscosity.

Vasodilatation

Vessel radius is the most important determinant of flow, for the vessels supplying the flap as well as those in the flap.

Temperature – the patient should be kept warm in theatre, the recovery room and the ward for the first 24–48 hours. This is best achieved by raising the ambient temperature in theatre and by using a warm air blanket. Active warming should begin before the start of anaesthesia because patient cooling occurs rapidly after induction of anaesthesia. In an awake patient, the central core temperature is higher than that of the peripheral tissue and skin temperature. After the induction of anaesthesia, vasodilatation modifies the thermal balance between compartments. The volume of the central compartment enlarges leading to a decrease in its mean temperature, while the temperature of the peripheral and skin compartments increases. At thermoregulation, the size of the central compartment becomes smaller owing to vasoconstriction, which leads to an increase in the mean temperature, although the peripheral and skin temperatures fall.

In addition to vasoconstriction, hypothermia also produces a rise in haematocrit and plasma viscosity, the aggregation of red blood cells into rouleaux, and platelet aggregation. These effects may reduce the microcirculatory blood flow in the flap.

Fluid – peripheral vasoconstriction due to an underestimation of fluid losses is common. There are two operating sites in free flap transfer: the donor site and the recipient site. Both have insensible fluid losses and both may have blood losses. A warm theatre environment also increases fluid loss. Modest hypervolaemia reduces sympathetic vascular tone and dilates the supply vessels to the flap. An increase in central venous pressure of 2 cm H_2O above the control measurement can double the cardiac output and produce skin and muscle vasodilatation. Figure 1 gives a guide to fluid management.

Guide to fluid management

Crystalloids
- 10–20 ml/kg to replace preoperative deficit
- 4–8 ml/kg/hour to replace insensible losses

Colloids
- 10–15 ml/kg for haemodilution
- To replace blood loss

Blood
- To maintain haematocrit at 30%

Dextran
- Often given postoperatively

1

Anaesthesia – isoflurane has the advantage over other volatile anaesthetics and propofol that it causes vasodilatation with minimal myocardial depression. Propofol inhibits platelet aggregation which could reduce the risk of thrombosis. This may be due to an effect of intralipid on the platelet–erythrocyte interaction, and by the increased synthesis of nitric oxide by leucocytes.

Vasospasm of the transplanted vessels may occur after surgical handling or after damage to the intima of the vessels, and can occur during surgery or postoperatively. The surgeons may use topical vasodilators such as papaverine, lidocaine (lignocaine) or verapamil during the operation to relieve the vasospasm.

Sympathetic blockade – epidural, brachial plexus or interpleural local anaesthetic infusions, used intraoperatively and postoperatively, provide sympathetic blockade to further dilate vessels. Concerns have been raised that the sympathetically-denervated transplanted vessels would be unable to dilate after lumbar epidural blockade, resulting in a 'steal' effect reducing flap blood flow. In fact, provided any hypotension due to the sympathetic block is treated appropriately, blood flow to the flap improves as a result of the increased flow through the feeding recipient artery. Other advantages of epidural analgesia include a reduction in intraoperative and postoperative blood loss and vessel spasm; a lower incidence of deep venous thrombosis; improved diaphragmatic function and more rapid post-operative recovery. Good analgesia reduces the level of circulating catecholamines and avoids the vasoconstrictor response to pain.

Perfusion pressure

The preservation of a good perfusion pressure with wide pulse pressure is essential to flap survival. Appropriate anaesthetic depth and aggressive fluid management are usually all that is needed. Most inotropes are contraindicated owing to their vasoconstrictive effects, but if required, dobutamine and low-dose dopamine could be used.

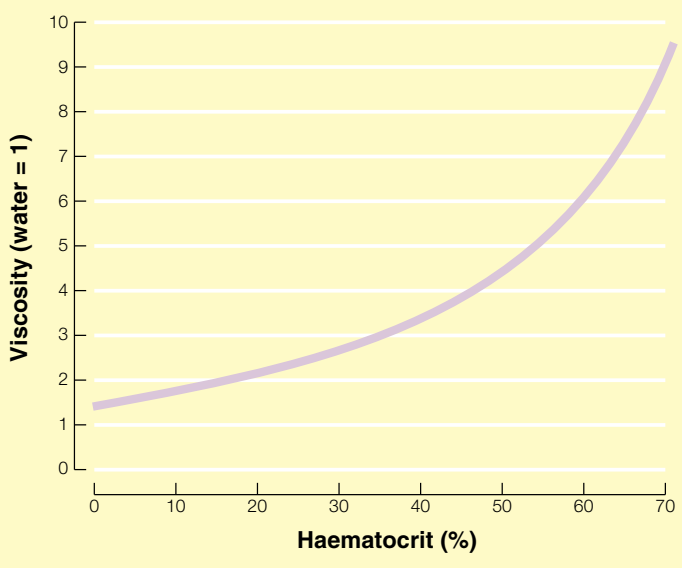
Viscosity

Isovolaemic haemodilution to a haematocrit of 30% improves flow by reducing viscosity, reducing reperfusion injury in muscle and increasing the number of patent capillaries, which decrease tissue necrosis. Further reductions in haematocrit do not provide much more advantage because the curve of viscosity versus haematocrit flattens off markedly (Figure 2). If the haematocrit falls further, the marginally improved flow characteristics from a lower viscosity may then be offset by a reduction in oxygen delivery:

$$DO_2 = CO \times [(Hb \times sat \times 1.34) + (PaO_2 \times 0.003)]$$

A low haematocrit also increases myocardial work, therefore care should be taken in patients with poor cardiac reserve.

Viscosity versus haematocrit



Source: MacDonald D J F. *Br J Anaesth* 1985; **57:** 904–21.

Practical conduct of anaesthesia

Monitoring

In addition to basic monitoring, these patients require invasive blood pressure monitoring to enable safe manipulation of the perfusion pressure. Direct measurement of arterial pressure gives a continuous record of the pressure and is more accurate than non-invasive indirect techniques. An arterial cannula also provides access to blood gas analysis and haematocrit estimations.

Central venous pressure reflects cardiac filling pressures and can be manipulated to increase cardiac output.

Core temperature measurement is essential when active warming is instituted. A nasopharyngeal or rectal probe is used intraoperatively for a continuous reading, while intermittent tympanic or axillary measurements are used in the recovery and ward areas.

Peripheral temperature is also measured because a fall in skin temperature can reflect hypovolaemia and vasoconstriction. A difference of less than 2°C between core and peripheral temp-eratures indicates a warm, well-filled patient. The temperature of the skin flap is sometimes monitored postoperatively because a drop in temperature may herald flap failure. However, this is not a sensitive test, because by the time the temperature has fallen the flap will have suffered sufficient vascular damage to render it virtually unsalvageable.

Urine output is another indicator of volume status. A urine output of 1–2 ml/kg/hour should be maintained intraoperatively and postoperatively with appropriate fluid management. Diuretics are contraindicated in these operations because volume depletion compromises flap survival.

Induction

Active warming starts before the patient is asleep. The ambient temperature in theatre is raised to about 22–24°C, a level high enough to reduce patient heat loss, but not too hot to be uncomfortable for the theatre staff. The patient is covered in a hot air blanket before induction of anaesthesia and this remains in place while the patient is prepared for theatre. Once in theatre, the blanket is moved to enable surgical access, but with as much surface area coverage as possible.

If appropriate, a regional block is inserted, preferably to cover the free flap recipient site (rather than the donor site) for the full benefit of the sympathetic block. The patient is intubated and ventilated; and a large gauge peripheral line, central line, arterial line, urinary catheter and core temperature and skin temperature probes are positioned.

Nitrous oxide diffusion into air in the stomach combined with gastric stasis results in gastric distension, with associated post-
operative nausea and vomiting. A nasogastric tube is therefore sited at intubation, left on free drainage, then aspirated and removed at the end of the operation.

Fluid, administered through a fluid warmer, is started in the anaesthetic room to compensate for preoperative dehydration.

Maintenance

Careful positioning of the patient is imperative for such a long operation. Limbs are positioned and supported to avoid neuro-logical damage or vascular compression. Eyes are taped and lightly padded to reduce the incidence of corneal abrasion and prevent drying of the cornea.

Prophylaxis against deep venous thrombosis is necessary for all patients. Subcutaneous heparin or low-molecular-weight heparin is given preoperatively, while anti-embolism (TED) stockings and compression boots are used intraoperatively.

The patient is ventilated to normocapnia. Hypocapnia increases peripheral vascular resistance and reduces cardiac output, while hypercapnia causes sympathetic stimulation. If the surgeon uses the microscope for vessel preparation or anastomosis on the chest or abdomen, the tidal volume is reduced to minimize movement in and out of the surgeon's field of vision. The respiratory rate is then increased to maintain minute ventilation.

Controlled hypotension is useful during the initial dissection and is most easily achieved using epidural local anaesthetic and/or isoflurane. An infusion of glyceryl trinitrate may be added if needed.

Crystalloids are used to replace the preoperative fluid deficit from starvation and to cover intraoperative insensible losses. The latter are high because the warm theatre increases evaporative losses from the two operating sites. Excessive use of crystalloid may precipitate oedema in the flap.

Hypervolaemic haemodilution is achieved using colloids.

Blood gas analysis and haematocrit measurement should be carried out at the start of the operation and repeated every 2 hours.

By the time the flap is reperfused, the patient should be warm, well-filled and sympathetically blocked with a high cardiac output.

Emergence and recovery

The patient should wake up pain-free. Analgesia is maintained postoperatively with local anaesthetic infusions for regional blocks, intravenous patient-controlled analgesia, or both. Coughing and vomiting increase venous pressure and reduce flap flow, so smooth emergence and extubation are needed. The principles of perioperative and postoperative care are listed in Figure 3. ◆

Principles of perioperative and postoperative care

- Maintain high cardiac output
- Normal arterial blood pressure (systolic >100 mm Hg)
- Low systemic vascular resistance
- Normothermia
- High urine output (> 1 ml/kg/hour)
- Effective analgesia
- Haematocrit 30–35%
- Monitoring of blood flow in flap (Doppler postoperatively)

FURTHER READING

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The Anaesthetic Machine

Michael O'Connor
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Many anaesthetic machines incorporate patient monitoring; conventionally this is considered separately and will not be discussed here.

Types of anaesthetic machine

Demand and intermittent flow machines
The patient's inspiration controls the flow of fresh gases. Such machines have been used for dental anaesthesia (e.g. the McKesson anaesthetic machine) and for military field anaesthesia (the Triservice apparatus).

Continuous flow machines (Boyle's machine)
Continuous flow machines are encountered in day-to-day hospital practice in the UK. The driving force for gas flow is compressed gases. This contribution discusses continuous flow machines.

Pressures in the anaesthetic machine

Units of pressure
To understand the anaesthetic machine, it is important to be able to relate the various different units that are used to describe pressure; 1 atmosphere pressure is approximately:

- 101 kPa
- 760 mm Hg
- 1035 cm H_2O
- 1 bar
- 15 psi.

Absolute and gauge pressure

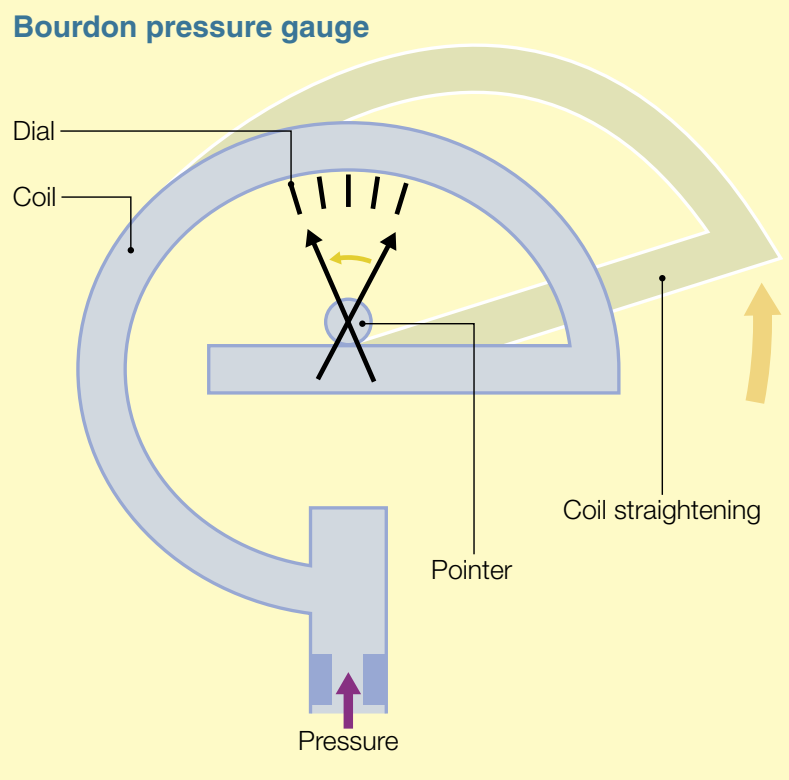
- Absolute pressure is pressure above that in a vacuum.
- Gauge pressure is pressure above atmospheric. Pressures in the anaesthetic machine are always quoted as gauge pressures.

All pipeline pressures are 400 kPa except for pressure in the air pipeline used to drive equipment such as orthopaedic drills, which is 700 kPa. Cylinder pressures are reduced to a machine working pressure of 400 kPa by pressure regulators (see below, page 66).

Pressure downstream of the flowmeters can range between zero (i.e. 1 atmosphere pressure), when the common gas outlet is open to the atmosphere, and about 33 kPa if the common gas outlet is completely obstructed and the safety valve in the back bar vents to the atmosphere.

Measurement of pressure
Cylinder and pipeline pressures are measured by a Bourdon pressure gauge (Figure 1). This is an aneroid (i.e. without liquid) gauge consisting of a coiled tube attached at one end to the gas supply and at the other to a pointer. The pressure of the gas causes straightening of the coil and thus movement of the pointer over the colour-coded, labelled and calibrated dial (Figure 2). The gauge is faced with heavy glass and designed such that leaks vent from the back of the valve casing and do not blow out the glass.

Bourdon pressure gauge



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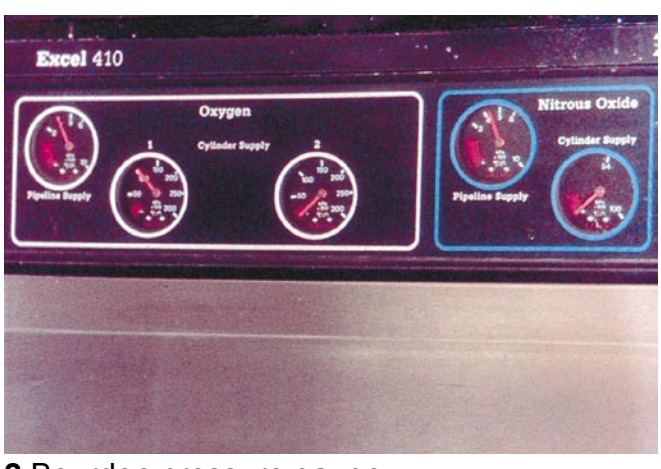
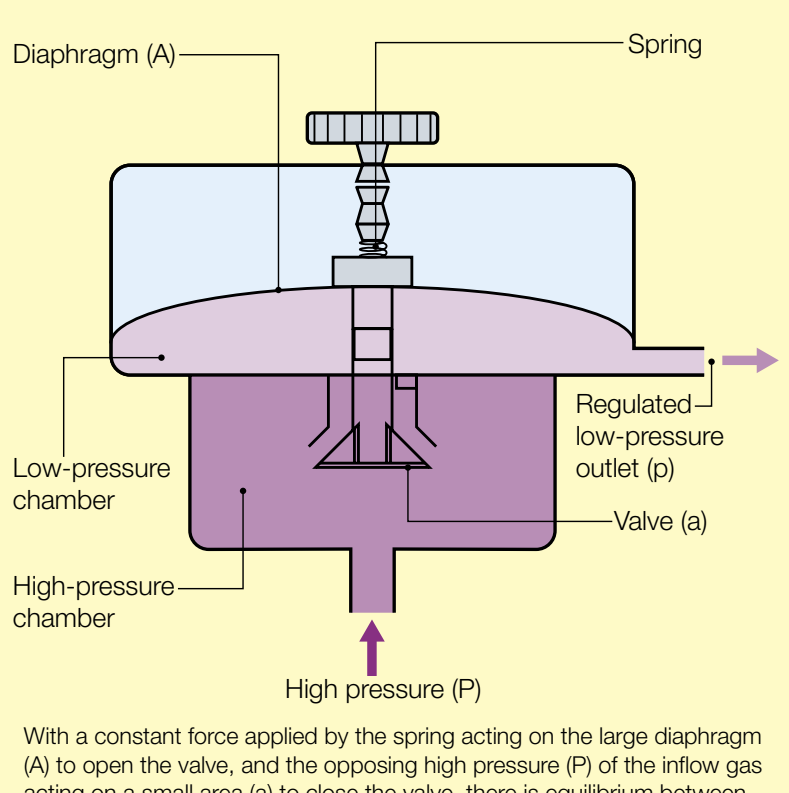


2 Bourdon pressure gauge.

Pressure regulators
Although sometimes referred to as pressure-reducing valves, the term pressure regulators is preferred because their function is not simply to reduce pressure, but in doing so to allow more accurate control of flow and to make up for the fall in cylinder pressures as they empty.

Figure 3 demonstrates the function of a pressure regulator. The principle is similar to that of the pressure-relief valve (see *Anaesthesia and Intensive Care Medicine* **1:3:** 107) except that there are two chambers, one of high pressure and the other of low, and two discs of different areas.

Pressure regulator



With a constant force applied by the spring acting on the large diaphragm (A) to open the valve, and the opposing high pressure (P) of the inflow gas acting on a small area (a) to close the valve, there is equilibrium between the high- and low-pressure chambers. To balance the equilibrium and keep the valve open, the pressure in the second chamber is thus reduced. Thus: P x a = p x A, where P = pressure in the high-pressure chamber; p = pressure in the low-pressure chamber; A = area of large diaphragm; a = area of small diaphragm.

Adjustment of the tension in the spring and thus the force it applies to the discs, regulates the pressure at the outlet to produce a constant operating pressure. As the inlet pressure falls during use of the cylinder, the force from the spring opens the valve wider, allowing more gas to flow into the second chamber and maintaining pressure at the outlet. The opposite happens if the inlet pressure rises, resulting in valve closure and thus less flow into the second chamber.

3

Flowmeters

Rotameters
Flow in most anaesthetic machines is measured by a variable orifice flowmeter known as a rotameter. A rotameter consists of a bobbin that floats in a glass tube with a diameter that increases with height up the tube. The pressure drop across the bobbin remains constant, and as flow increases it rises up the tube.

The two important properties of the gas flowing through a rotameter that influence its calibration are:

- viscosity
- density.

Gas flows in the annulus between the bobbin and the tube. At the lower end of the tube the annulus is long with respect to its cross-sectional area, and flow is laminar and dependent on the viscosity of the gas. Higher up the tube, the cross-sectional area of the annulus is greater, the gas is effectively flowing through an orifice, and flow is turbulent and dependent on the density of the gas (Figure 4).

Flowmeter

Laminar flow around the bobbin at the bottom of the tube, turbulent flow at the top. NB Pitch of the rotameter tube has been greatly exaggerated

4

Features of rotameters

- For any given gas, the flow through a rotameter depends on both its viscosity and its density. Rotameters therefore have to be calibrated individually for the gas they will be measuring.
- The bore may be varied to measure low flows accurately.
- The back plate may be luminous.
- Calibration is from the lowest accurate point, not zero.
- Accuracy is ± 2%.
- In many machines there is a constant low flow of oxygen.

Potential sources of inaccuracy in rotameters

- If the tube is not truly vertical, the annulus between the tube and the bobbin is altered.
- Static electricity can cause inaccuracies. To minimize this, glass is conductive and sprayed with antistatic material.
- Dust can collect on the bobbin or within the tube.
- Tubes may be damaged. In the UK, the oxygen rotameter tube is on the left (said to be because Boyle was left-handed). This can mean that any damage to the tubes would preferentially leak oxygen and result in the delivery of a hypoxic mixture. Many manufacturers now arrange the order in which the gases finally mix so that oxygen is the last gas added to the mixture.
- The top-sealing washer may be defective.
- The carbon dioxide bobbin may become stuck at the top of the tube.
- Back pressure from a minute volume divider such as a Manley ventilator increases the density of the gas and may cause the rotameter to under-read by about 7%.
- Atmospheric pressure affects density. Low pressure gives over-reading.
- Temperature affects density and viscosity. Increased temperature causes decreased density and increased viscosity.

Vaporizers

Vaporizers are discussed elsewhere.

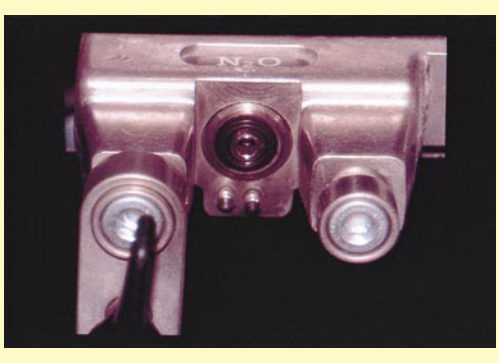
Safety

The anaesthetic machine has several in-built safety features that vary from machine to machine. The commonly found features that are of importance to anaesthetists are listed in Figure 5.

Perhaps the most important safety feature is that the machine should always be checked in a systematic fashion before use. The Association of Anaesthetists of Great Britain and Ireland has published a useful checklist, part of which is reproduced in Figure 6. These checks must be performed at the beginning of each theatre session.

Anaesthetic machine – safety features

- Non-interchangeable pipeline outlets (often referred to as Schrader connectors, though this is really a trade name)
- Pipelines are coloured and marked with the name of the gas
- Non-interchangeable screw thread connectors connect the pipeline to the anaesthetic machine
- The pin index system prevents accidental connection of the wrong cylinder to the wrong yoke
- Cylinders are coloured and marked with the name of the contents
- Grease can be flammable or explosive in contact with gases at high pressure. A Bodok seal (see below) makes a gas-tight connection between cylinder and yoke
- There are pressure gauges for pipelines and cylinders
- Rotameter knobs are identified by the oxygen knob being a distinctive colour and shape and more prominent
- The oxygen rotameter outlet may be diverted to enter the gas flow last
- Oxygen and nitrous oxide rotameters may be linked to prevent delivery of a hypoxic mixture
- The oxygen bypass can provide oxygen at high flow (> 30 litres/minute) directly to the common gas outlet
- There is an oxygen failure warning device triggered by a dropin the oxygen pressure, which also vents the flow of anaesthetic gases to the atmosphere to prevent delivery of a hypoxic mixture
- Vaporizer fillers are keyed to prevent a vaporizer being accidentally filled with the wrong agent
- Vaporizers may be arranged so that only one can be turned on at a time
- There is a machine pressure-relief valve in the back bar that prevents the pressure rising above about 33 kPa
- The machine is serviced regularly by a qualified engineer



Bodok seal.

Anaesthesic machine – safety checks

Anaesthetic machine

- Check that the anaesthetic machine and relevant ancillary equipment are connected to the mains electrical supply (where appropriate) and switched on
- Careful note should be taken of any information or labelling on the anaesthetic machine that might refer to its current status

Oxygen analyser

- The oxygen analyser should be placed where it can monitor the composition of the gases leaving the common gas outlet
- The analyser should be switched on, checked and calibrated according to the manufacturer's instructions

Medical gas supplies

- Identify and take note of the gases that are being supplied by the pipeline, confirming with a 'tug test' that each pipeline is correctly inserted into the appropriate gas supply terminal
- Check that the anaesthetic apparatus is connected to a supply of oxygen and that an adequate reserve supply of oxygen is available from a spare cylinder
- Check that adequate supplies of any other gases intended for use are available and connected as appropriate. All cylinders should be securely seated and turned ***Off*** after checking their contents. Carbon dioxide cylinders should not normally be present on the anaesthetic machine. A blanking plug should be fitted to any empty cylinder yoke
- All pressure gauges for pipelines connected to the anaesthetic machine should indicate 400 kPa
- Check the operation of flowmeters, ensuring that each control valve operates smoothly and that the bobbin moves freely through its range without sticking. With only the oxygen flow control valve open and a flow of about 5 litres/minute, check that the oxygen analyser display approaches 100%.

Turn off all flow control valves

- Operate the emergency oxygen bypass control and ensure that flow occurs without significant decrease in the pipeline supply pressure. Confirm that the oxygen analyser display approaches 100% during this test. Ensure that the emergency oxygen bypass control ceases to operate when released

Vaporizers

- Check that the vaporizer(s) for the required volatile agent(s) are fitted correctly to the anaesthetic machine, that any back bar locking mechanism is fully engaged and that the control knobs rotate fully through the full range(s). Ensure that the vaporizer is not tilted.

Turn off the vaporizers

- Check that the vaporizer(s) are adequately filled and that the filling port is tightly closed
- Set a flow of oxygen of 5 litres/minute and, with the vaporizer turned off, temporarily occlude the common gas outlet. There should be no leak from any of the vaporizer fitments and the flowmeter bobbin should dip.

Turn each vaporizer on in turn and repeat this test. There should be no leak of liquid from the filling port.

After this test, ensure that the vaporizers and flowmeters are turned off

Should it be necessary to change a vaporizer at any stage, it is essential to repeat the leak test.

Failure to do so is one of the most common causes of critical incidents

Removal of a vaporizer from a machine in order to refill it is not considered necessary

Source: Association of Anaesthetists of Great Britain and Ireland. *Checklist for Anaesthetic Apparatus, 1997.*

FURTHER READING

Association of Anaesthetists of Great Britain and Ireland. *Checklist for Anaesthetic Apparatus, 1997.*

Moyle J T B, Davey A. *Ward's Anaesthetic Equipment.* 4th ed. Philadelphia: Saunders, 1998.

Artificial Ventilation in the Operating Theatre

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Ventilators are used in two main settings: the operating theatre and the ICU.

- In the operating theatre, ventilators are used to maintain ventilation in anaesthetized, intubated, pharmacologically paralysed patients who have predominantly normal lungs. These ventilators are designed to interface with anaesthetic gas circuits to allow varying concentrations of oxygen, anaesthetic gases and volatile agents to be delivered to the patient. Most theatre ventilators are relatively simple, mechanical or electromechanical devices that do not have patient-sensing capabilities.
- Ventilators are often used in the ICU to ventilate patients with abnormal lungs, who require only air and oxygen as respiratory gases; these patients are seldom paralysed and often require only partial respiratory support. The ventilators used are almost all complex, computer-controlled devices with sensitive mechanisms to detect the patient's respiratory efforts.

This contribution discusses ventilators for theatre use, though many of the basic principles apply to ICU devices.

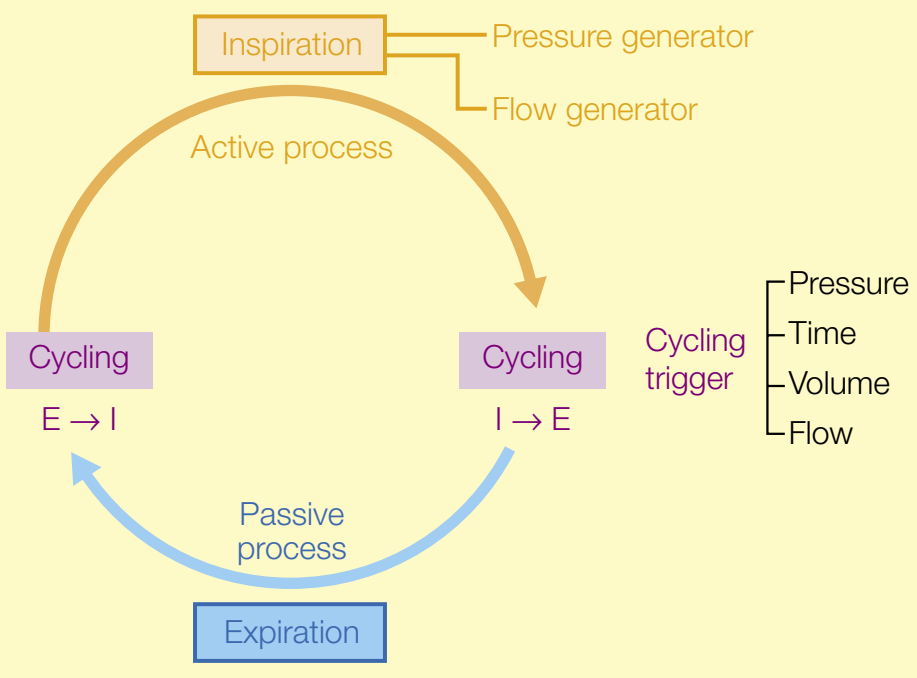
Classification of anaesthetic ventilators

Ventilators can be classified according to their function and operation.

- Functional classification is the most common and clinically useful system. It is based on the pattern of gas that the ventilator generates during inspiration, and the mechanism that cycles between inspiration and expiration (Figure 1).
- Operational classification is based on parameters such as power source or driving mechanism. Operational classification is not covered in this contribution.

Ventilator classifications were devised when most ventilators had only one mode of ventilation. Examples of such ventilators are the Manley ventilator (a time-cycled pressure generator), the Nuffield 200 ventilator (a time-cycled flow generator) and paediatric theatre ventilators (time-cycled pressure generators). Modern theatre ventilators and all ICU ventilators can operate in two or more ventilatory modes and so do not fit neatly into one single category of the traditional functional classification.

Functional classification of the respiratory cycle during intermittent positive-pressure ventilation



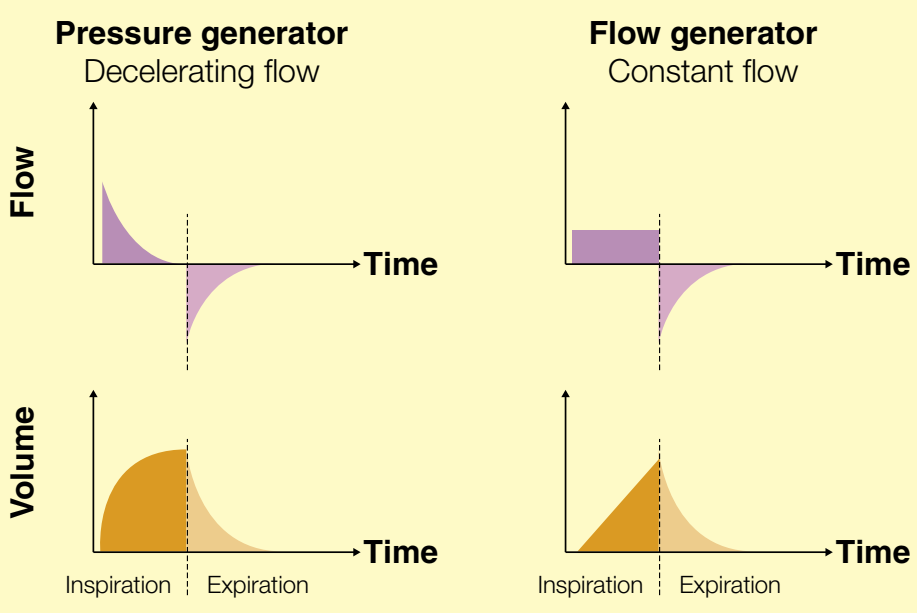
Based on Mapleson classification. I, inspiration; E, expiration

1

Functional classification of ventilators

The important difference between pressure and flow generators is the pattern of gas flow produced during inspiration. This influences the effects of changes in airway resistance, or lung and chest wall compliance, or if there is leak of delivered gases from the system. A summary of the important differences between pressure and flow generators is shown in Figure 2. Knowledge of the basic respiratory mechanics is vital to understanding ventilator–patient interactions.

Pressure generators and flow generators



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Resistance, compliance and time constants: the pressure required to cause gas to flow into the lungs has two components:

- that required to maintain gas flow along the airways, overcoming airways resistance
- that required to overcome the elastic recoil of the respiratory system, determined by compliance.

The interaction of these components determines the time constant (TC).

TC defines the rate of a simple (first-order) exponential process. It is equivalent to the time taken for the exponential process to complete if it were to continue at the same rate as that at which it began. TC describes how fast the lungs fill with a constant applied airway pressure or how fast they empty during expiration. (TC = compliance x resistance.) It increases with increasing resistance (e.g. in asthmatics) and decreases with decreasing compliance (e.g. in pulmonary fibrosis).

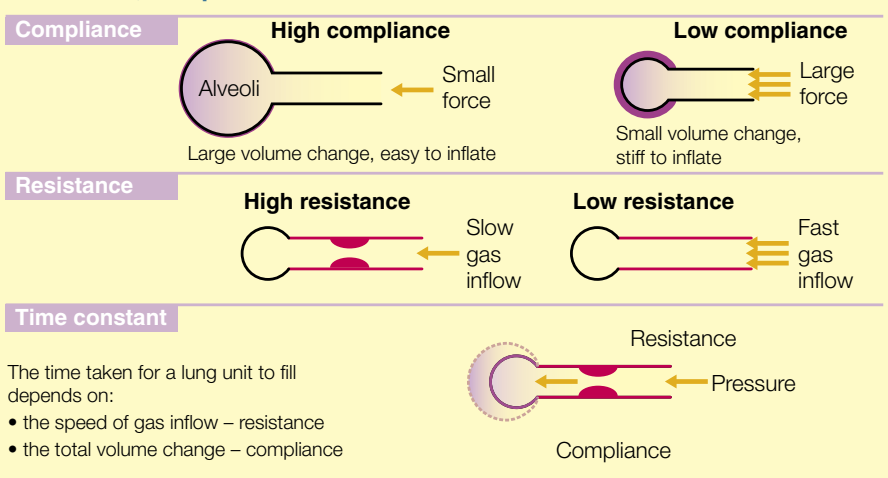
Resistance is a measure of the resistance to gas flow. The major site of respiratory resistance is in the medium-sized bronchi, but total respiratory resistance during positive-pressure ventilation also includes the contribution of the endotracheal tube and to a lesser extent the circuit. In a patient with normal lungs, this increases the total respiratory resistance from 2 to 4–6 cm H_2O/litre/second.

Compliance describes the elasticity of the respiratory system, or the ease with which it inflates, and is measured as the volume change per unit pressure. Total respiratory compliance consists of combined lung and chest wall compliance and is normally 50–70 ml/cm H_2O.

Within the normal working range of the lung compliance is constant though it decreases at extremes of volume. The contribution to compliance from the ventilator circuit is usually small. The exception is during anaesthesia in neonates and infants when the tidal volume is small compared with the circuit volume, and compression of gas within the circuit can make it difficult to ensure that accurate and adequate tidal volumes are delivered (Figure 3).

Effect on artificial ventilation − increased airways resistance and reduced lung and chest wall compliance are the most clinically significant changes in respiratory mechanics affecting artificial ventilation. Some causes are shown in Figure 4.

Resistance, compliance and time constant



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Causes of increased airways resistance and reduced respiratory compliance

Increased airways resistance	Reduced respiratory compliance
• Bronchospasm – asthma, chronic obstructive airway disease (COAD)	• Within lung – pulmonary oedema, adult respiratory distress syndrome, fibrosis, atelectasis
• Mucosal swelling – asthma, COAD	• Around lung – pleural effusion, upward compression from abdominal contents when supine, especially if obese
• Luminal obstruction – excessive secretions	• Chest wall – surgeon compressing chest, expiration retractors, scoliosis, contractures
• Foreign body – tumour	
• Emphysema – dynamic airway compression during	
• Low lung volume	

4

Pressure and flow generators: an understanding of the different types of ventilator and how they function helps predict the behaviour and limitations of each type of machine when resistance and compliance of the lungs change (Figure 5).

Pressure generators - a pressure generator applies a preset positive-pressure waveform to the airway for the duration of inspiration. In its simplest form this pressure is constant (Figure 6).

If the inspiratory time is sufficiently long, the respiratory compliance determines the tidal volume delivered when a given airway pressure is applied. The respiratory compliance decreases linearly with lung size, therefore a pressure generator set at 15−20 cm H_2O delivers an appropriate tidal volume to a small child or an adult with normal lungs.

Pressure generators can maintain the required airway pressure, even in the presence of a leak, within reasonable limits. As a result, the main use for pressure generators in anaesthetic practice is to ventilate children. The cricoid ring is the narrowest point of the airway in children. The insertion of endotracheal tubes can lead to compression of the tracheal mucosa against the cricoid cartilage, resulting in pressure necrosis. This can be avoided by using uncuffed endotracheal tubes; the presence of an air leak during inspiration confirms that the endotracheal tube is not lodged tightly in the cricoid ring.

The pressure generator ensures that adequate tidal volumes are delivered because a consistent pressure is maintained despite the leak. Paediatric patients, particularly neonates, are prone to ventilator-induced lung damage, and constant pressure generators ensure that even when lung dynamics change, the applied pressure remains constant.

Pressure generators are designed for use with normal lungs that remain normal during surgery (delivered tidal volume = pressure x compliance.) The main disadvantage of a pressure generator is that tidal volume is determined by compliance and reductions in compliance may cause significant reductions in delivered tidal volume and minute ventilation. Therefore, pressure generators may not be appropriate when precise control of arterial carbon dioxide tension ($PaCO_2$) is important, for example, during neurosurgery.

Flow generators (Figure 7) are devices that produce a constant gas flow independent of respiratory compliance or resistance. The volume delivered per unit time remains constant even in the presence of high airway pressures. All flow generators need a high-pressure gas source. This can be delivered by compressing bellows or by using proportional control valves, which control gas flow from the pipeline supply.

The delivered tidal volume is determined by control of the inspiratory flow rate and inspiratory time. The peak and mean airway pressure generated depends on the tidal volume, inspiratory flow rate, respiratory compliance and resistance.

The main advantage of a constant flow generator is that a constant tidal volume and minute ventilation are maintained even when the mechanics of the lung are changing. The tidal volume can be set precisely and minute ventilation is predictable and consistent, giving precise control of $PaCO_2$.

The main disadvantage is the potential for high airway pressures and barotrauma if changes in lung mechanics occur. There is also no ability to compensate for leaks. Flow generators are used mainly for adults, particularly where lung mechanics are abnormal, and when precise control of $PaCO_2$ is required.

Cycling parameters - cycling is the process of stopping one phase of ventilation and changing to the next. This occurs twice within each delivered breath. For the purposes of classification, cycling marks the end of inspiration and the beginning of expiration. Ventilators may be:

- time-cycled – cycling occurs after preset time
- volume-cycled – cycling occurs after preset volume delivered
- pressure-cycled – cycling occurs after preset pressure attained
- flow-cycled – cycling occurs when flow falls below a preset value.

Time cycling is the most common technique. Flow cycling is used in inspiratory pressure support in the ICU but seldom in theatre. Volume and pressure cycling are used infrequently. In most ventilators, cycling from expiration to inspiration is by time.

Advantages and disadvantages of pressure and flow generators

	Pressure generators	Flow generators
Advantages	• Protection from high airway pressures and barotrauma • Compensate for leaks	• Ability to maintain a constant tidal volume and minute ventilation even with significant changes in lung mechanics • Precise control of $PaCO_2$
Disadvantages	• Hypoventilation as a result of changes in lung mechanics	• Potential for high airway pressures and barotrauma • Inability to compensate for leaks

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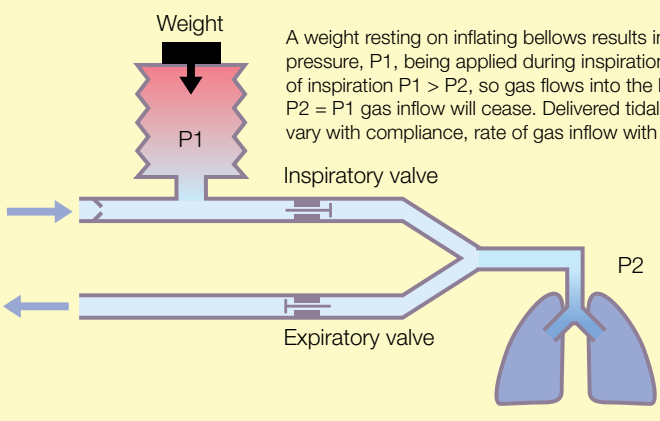
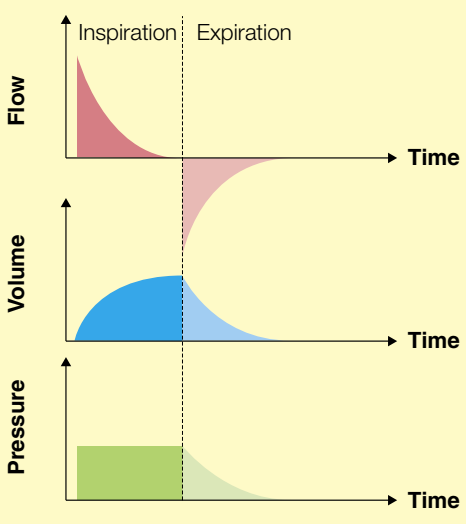
Constant pressure generator





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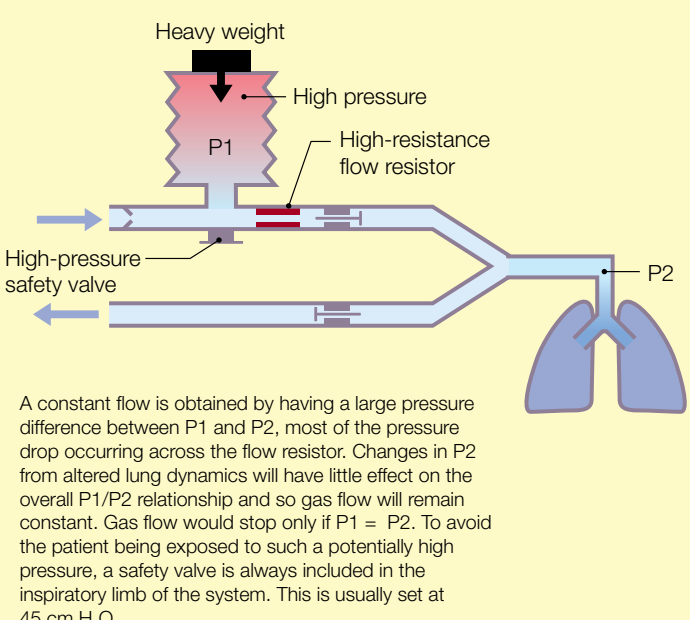
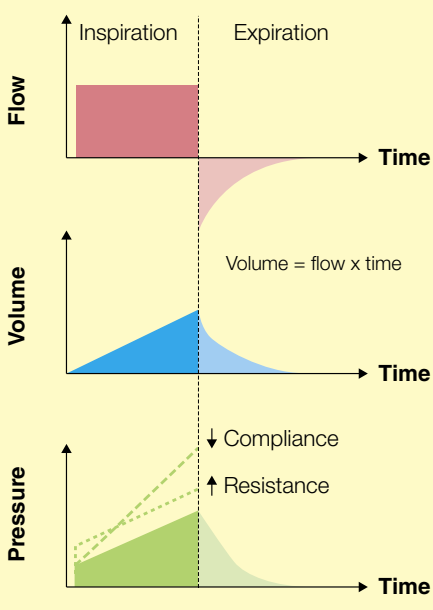
High-pressure, high-resistance flow generator



A constant flow is obtained by having a large pressure difference between P1 and P2, most of the pressure drop occurring across the flow resistor. Changes in P2 from altered lung dynamics will have little effect on the overall P1/P2 relationship and so gas flow will remain constant. Gas flow would stop only if P1 = P2. To avoid the patient being exposed to such a potentially high pressure, a safety valve is always included in the inspiratory limb of the system. This is usually set at 45 cm H_2O.



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Single- and double-circuit ventilators

In a single-circuit ventilation system the anaesthetic gas is also the driving gas. A well-known example is the Manley ventilator, where the fresh gas flow set on the rotameters is divided into tidal volume (hence the term minute volume divider). The fresh gas flow powers the ventilator and is also delivered to the patient.

In a double-circuit ventilation system the anaesthetic gas and the driving gas are in separate circuits. The clearest example of this is a 'bag in bottle' or bellows ventilator. The anaesthetic gas is contained within the circuit and a set of bellows, which act as a reservoir. After delivering the tidal volume, the bellows refill during expiration. The bellows are contained within an air-tight cylinder and a separate high-pressure driving gas is used to pressurize the cylinder periodically, compressing the bellows and thereby generating inspiratory gas flow. Most modern circle/ventilator systems are double circuits.

Bellows can be of the standing or hanging variety. Standing bellows rise as they refill; hanging bellows are mounted inverted and fall as they refill. The advantage of standing bellows is that a leak of anaesthetic gases will be noticed by a failure of the bellows to rise to the full height. This is especially useful during low-flow circle anaesthesia. Hanging bellows are usually weighted at the base and entrain room air if there is a circuit leak.

The Nuffield 200 series of ventilators are functionally double circuit. Although there is no physical separation of the driving and fresh gas flow, the configuration of these ventilators ensures that fresh (anaesthetic) gases and driving gas do not mix. This is achieved by using a connector hose with an internal volume that is greater than the tidal volume.

Pulmonary physiology and the effects of intermittent positive-pressure ventilation (IPPV)

When a patient breathes spontaneously the expansion of the chest wall creates a negative pressure relative to atmospheric pressure between the visceral and parietal pleura. The transpulmonary pressure gradient created causes the lung to expand and fill. Thus, during inspiration the intrathoracic pressure is negative.

During IPPV the patient makes no respiratory effort and the transpulmonary pressure gradient required to expand the lung is generated by raising the airway pressure. With inspiration, intrathoracic pressure is positive. During artificial ventilation the mean intrathoracic pressure is increased compared with spontaneous ventilation and this has effects on the respiratory, cardiovascular, renal and endocrine systems. The effects of IPPV are wide ranging and must be viewed in the context of the position of the patient on the operating table and the effects of general anaesthesia.

Normal respiratory physiology and the effects of general anaesthesia

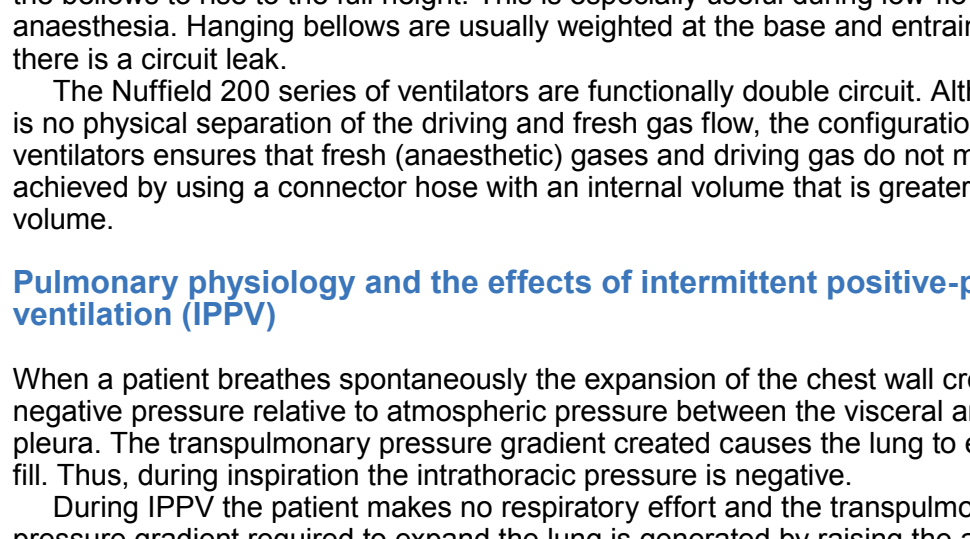
The primary function of ventilation is to move air in and out of the lungs so that carbon dioxide can be eliminated and arterial oxygenation maintained. In healthy individuals it is the requirement to eliminate carbon dioxide that is the prime determinant of minute ventilation. A normal tidal volume is about 500 ml in an adult (8 ml/kg); of this, about 150 ml (2 ml/kg) remains in the conducting airways (anatomical dead space), and the remaining 350 ml enters the alveoli and is available for gas exchange. The respiratory rate depends on the requirement for carbon dioxide elimination, but is usually 10−15 breaths per minute in adults. Effective ventilation maintains a normal arterial $PaCO_2$ of 4.5−5.5 kPa and an arterial oxygen tension (PaO_2) of 13.5 kPa in healthy young adults breathing room air.

Functional residual capacity (FRC): the various subdivisions of lung volume that can be determined by spirometry, whole-body plethysmography or helium dilution are shown in Figure 8. Of these, the most important for anaesthesia and the care of patients in the ICU is FRC. FRC is the end-expiratory volume of the lungs and is determined by the balance between:

- the elastic recoil of the lungs
- the outward recoil of the chest wall
- the respiratory muscle tone
- the position of the diaphragm.

FRC gradually reduces with age and is reduced on lying supine (by 500−800 ml) as a result of upward displacement of the diaphragm by the abdominal contents. This effect is enhanced in patients with abdominal distension or obesity. During general anaesthesia, reduction in diaphragmatic and chest wall tone and function lead to a reduction in FRC of about 20%. The effects of general anaesthesia and the supine position are additive, and can cause a significant reduction in FRC.

Lung volumes (70 kg adult)



Normal values

- Functional residual capacity 2.5 litres
- Inspiratory reserve volume 2.5–3.0 litres
- Tidal volume 0.5–0.6 litres
- Expiratory reserve volume 1.5 litres
- Residual volume 1.5–2 litres
- Vital capacity 3.5–5.5 litres
- Total lung capacity 6 litres

Minute ventilation 7.5 litres/minute
Alveolar ventilation 5 litres/minute
Vd/Vt 0.3

8

Closing capacity (CC) is the lung volume at which small airway closure begins. Closing volume is an alternative term that is equivalent to CC minus residual volume (RV). Normally CC is less than FRC, but they converge with increasing age. When FRC decreases to below CC, airway closure occurs during normal expiration and the resulting decrease in ventilation to areas of the lung distal to the closure worsens the ventilation-perfusion (V/Q) relationship. FRC usually remains greater than CC when supine until about 45 years of age but the additional reduction in FRC that occurs during general anaesthesia makes it more likely that FRC will fall below CC during anaesthesia. The resulting increase in V/Q mismatch leads to a decrease in arterial oxygenation, which is normally countered by increasing the inspired oxygen fraction.

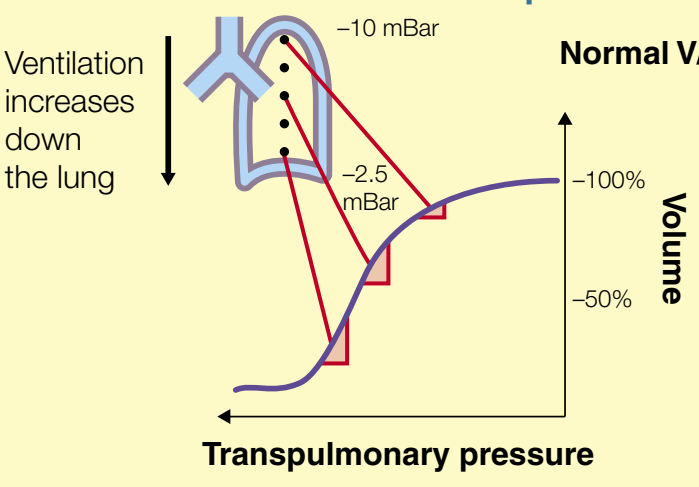
Distribution of ventilation and perfusion: during spontaneous ventilation in an upright position, distribution of ventilation and perfusion are not uniform throughout the lungs. Blood flow increases linearly from the top to the bottom of the lungs as a result of the effects of gravity on the low-pressure pulmonary circulation. The lower zones ventilate better than the upper zones because the dependent parts are on a more compliant (i.e. steeper) part of the pressure-volume curve. During normal inspiration, diaphragmatic contraction is enhanced in the parts of the diaphragm most displaced, aiding increased ventilation of the dependent parts of the lung (Figure 9).

Ideally, ventilation and perfusion at the alveolar level should be matched. Alveolar ventilation should equal perfusion and the V/Q ratio equal 1. In this situation no ventilation or perfusion is 'wasted'. However, the normal V/Q ratio is 0.8. The further the V/Q ratio deviates from 1, the more inefficient the ventilatory process becomes (Figure 10).

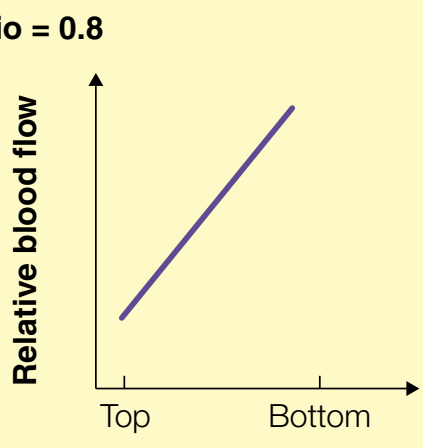
In the supine position, the gravitational effects on the lung are more limited, and perfusion is more homogeneous. However, the reduction of FRC, which is compounded by anaesthesia and the patient's position, leads to uneven ventilation because of airway closure and the tendency of the dependent portions of the lung to reduce in volume more than the superior parts (compression atelectasis).

Therefore, in the supine position (especially under anaesthesia) V/Q relationships worsen. This tends to cause hypoxaemia, which, because it is caused by a V/Q mismatch rather than a true shunt, can be reversed with added inspired oxygen.

Distribution of ventilation and perfusion in the lungs



Ventilation increases from the apex to the base. Dependent parts of the lung are on a more compliant part of the pressure–volume curve



Perfusion increases on moving down the lung. The low-pressure pulmonary circulation is affected by gravity

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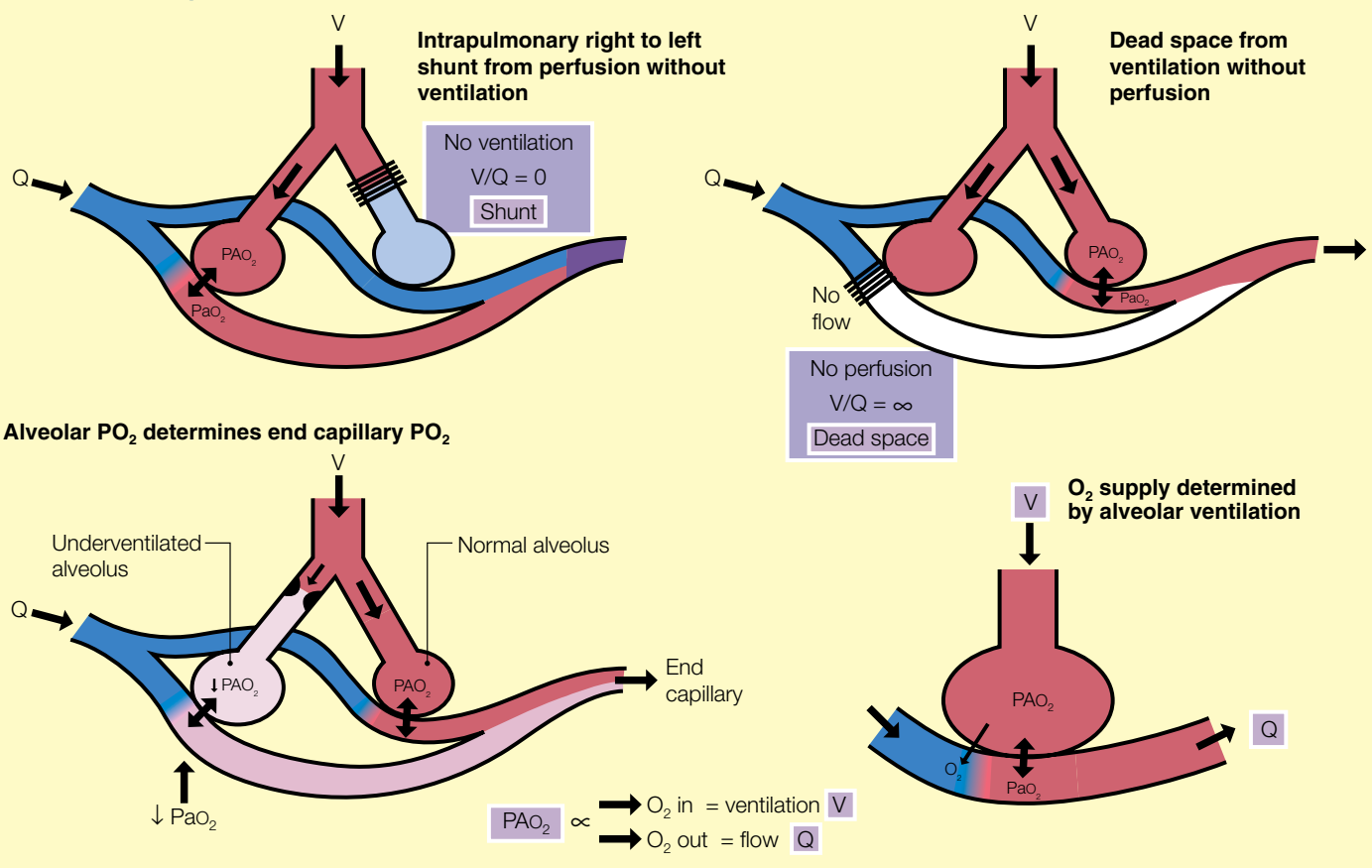
Ventilation and perfusion



In an ideal alveolus capillary P_{O_2} (Pa_{O_2}) comes close to alveolar P_{O_2} (PA_{O_2}). PA_{O_2} is determined by the balance between the rate of O_2 uptake by the pulmonary capillaries (Q) and continued supply of O_2 by alveolar ventilation (V). The rate of O_2 removal is determined by the rate of O_2 consumption (metabolic rate). In an under-ventilated alveolus, the supply of O_2 is reduced. If O_2 uptake continues, the result is for PA_{O_2} to fall and so Pa_{O_2} will fall

10

Hypoxic pulmonary vasoconstriction (HPV): when the alveolar PO_2 or, to a lesser extent, the mixed venous PO_2 decreases, smooth muscle contraction occurs in small pulmonary arterioles. This diverts blood from unventilated areas to better-ventilated areas and helps minimize the effects of V/Q imbalance. Volatile anaesthetic agents as well as many vasodilators (e.g. sodium nitroprusside) inhibit HPV, worsening the effects of V/Q mismatching.

Respiratory effects of IPPV

Changes in distribution of ventilation: the preferential ventilation of the non-dependent parts of the lung in the anaesthetized, supine position is increased by IPPV. The non-dependent areas are more compliant than the dependent zones after induction of anaesthesia and muscle relaxation, and so preferentially expand in response to positive pressure. This effect is further exaggerated if the lungs have an increased density, as in the adult respiratory distress syndrome or in patients with cardiogenic pulmonary oedema. It is also compounded by compression of basal areas of the lung as a result of the upward displacement of the paralysed diaphragm.

Changes in distribution of perfusion: normal distribution of perfusion is usually maintained during IPPV. However, in the presence of high intra-alveolar pressures, compression of the alveolar capillaries occurs and flow stops. Capillary pressures are lower in the upper zones because of the effect of gravity on the low-pressure pulmonary circulation, and these zones are particularly vulnerable to increases in airway pressure. These preferentially ventilated upper zones now have much reduced flow and V/Q mismatch is further increased. This is more likely to occur when mean airway pressures are high and with the use of positive end-expiratory pressure (PEEP).

PEEP is the application of a residual positive pressure to the airway at the end of expiration instead of atmospheric pressure. This improves oxygenation by increasing FRC and thus reduces the effects of airway closure and lung volume reduction on V/Q relationships. PEEP may also reopen previously collapsed lung units and maintain their patency (alveolar recruitment).

Barotrauma is the result of excessive pressure gradients between alveoli and the interstitium, with rupture occurring. Air can spread along perivascular spaces into the mediastinum, pericardium, up into the neck, down into the abdomen or into the pleural cavity (pneumothorax). Risk factors include:

- large tidal volumes
- excessive inflation pressures, especially > 40 cm H_2O
- use of PEEP
- non-uniform lung disease
- increased airway resistance.

Recently, the term ‘volutrauma’ has been used in the ICU setting. This refers to overdistension of ‘normal’ areas of the lung by the high pressures required to inflate the diseased areas.

Other respiratory effects of IPPV: during general anaesthesia with intubation and ventilation, there is loss of the ability to cough and so secretions are retained. Inhaled anaesthetics and cold, dry gases inhibit ciliary activity in the bronchial tree, again leading to a tendency to retain secretions. In addition, if the anaesthetic gases are not warmed and humidified, the respiratory tract can be a major source of heat loss.

Cardiovascular effects of IPPV

The major effect of IPPV is to reduce cardiac output via a reduction in venous return. In most patients, this can be counteracted by fluid loading (e.g. 500−1000 ml crystalloid). There are additive effects on the pulmonary circulation and heart, but their relative contribution is thought to be minor, and significant changes occur only with high mean airway pressures.

Cardiac output: a decrease in cardiac output occurs when beginning IPPV, which can cause significant hypotension. The increase in mean intrathoracic pressure during inspiration with positive-pressure ventilation causes the low-pressure veins in the chest to be compressed. Cardiac output falls because of the reduction in venous return to the heart. The decrease in cardiac output and mean arterial blood pressure can be particularly marked in patients who are hypovolaemic or have limited cardiovascular reserve and is further worsened by PEEP. The expected fall in cardiac output can be reduced by prompt infusion of fluids to increase central venous pressure and maintain venous return.

Effects of IPPV on pulmonary vascular resistance and the heart: increased pulmonary vascular resistance occurs when airway pressures are high, from direct compression of alveolar capillaries. As pulmonary vascular resistance increases, there is an increase in right ventricular afterload and right ventricular end-diastolic volume. If end-diastolic volume becomes significantly raised, bulging of the intraventricular septum into the left ventricular cavity can occur, reducing left ventricular compliance and reducing left ventricular stroke volume. In addition, the increased wall tension in the right ventricle, coupled with a reduced arterial pressure, can compromise right ventricular perfusion in compromised patients. The final effect is right heart strain further augmenting a reduction in cardiac output. Paradoxically, in patients with existing heart failure, the increase in transpulmonary pressure transmitted to the thorax can occasionally help to off-load the left heart by reducing venous return from the pulmonary veins, thus reducing left atrial pressures. Left ventricular performance may then improve.

Other effects of IPPV

Renal: mechanical ventilation causes a reduction in urine volume, and thus sodium and water retention. A fall in renal perfusion pressure associated with the reduced cardiac output and a rise in renal venous pressure as a result of impedance of venous return, along with increased levels of antidiuretic hormone associated with IPPV, are thought to be important. An increase in sympathetic stimulation triggered by baroreceptors sensing the changes in pressure and flow may also contribute. The renal effects are persistent and are not fully reversed with fluid infusion or improvement in cardiac output.

Liver: the reduction in cardiac output and increased venous pressure leads to a fall in hepatic blood flow proportional to the drop in cardiac output. Hepatic blood flow may be reduced by up to 50% and hepatic metabolism is reduced. This can be reversed by infusion of fluid. The increased venous pressure caused by the positive intrathoracic pressure can cause hepatic venous congestion, and hypocapnia will lead to vasoconstriction.

Endocrine: antidiuretic hormone levels are increased during IPPV, with corresponding increases in renin and angiotensin levels. This contributes to salt and water retention.

Practical aspects of positive pressure ventilation

Adequate ventilation requires an adequate tidal volume and minute ventilation to be delivered, time for gas distribution and gas exchange to occur, and sufficient time for expiration to be completed. Adequate ventilation results in a normal $PaCO_2$ tension (4.5−5.0 kPa), and in anaesthetic practice this is usually estimated by the end-tidal carbon dioxide tension ($P_{E'}CO_2$). In patients with normal lungs the arterial $PaCO_2$ is about 0.5 kPa greater than the $P_{E'}CO_2$. $P_{E'}CO_2$ is measured from alveolar gases from all ventilating lung units with a spread of V/Q ratios. Units with high V/Q ratios have a reduced alveolar PCO_2 and so ‘dilute’ the gas from units with a V/Q ratio close to unity. This relationship is lost in patients with lung disease; arterial blood gas monitoring may be required in these patients. The minute volume and tidal volumes used should aim for peak airway pressures of 15−20 cm H_2O in most patients.

Arterial oxygenation is determined primarily by the inspired oxygen, which should never be below 30% (FiO_2 0.3) initially. The required inspired oxygen is determined by the saturation recorded by the pulse oximeter; 95% or greater is appropriate. After monitoring the effect of the initial settings in each patient, appropriate alterations can be made to suit the individual.

Initial IPPV settings for routine general surgical cases

Adults:

- flow generator mode of ventilation
- tidal volume 8−10 ml/kg
- respiratory rate 10−12 breaths/minute
- inspiratory/expiratory (I:E) ratio 1:2
- Fi_{O_2} 0.4 (40% oxygen)
- maximum airway pressure 30 cm H_2O.

If a circle absorber system is in use, an initial fresh gas flow of 6 litres/minute should be used.

A tidal volume of 8−10 ml/kg is appropriate for adults. An I:E ratio of 1:2 allows sufficient time for equilibration in inspiration and time for full expiration, in relation to the TC of normal lung. A starting inspired oxygen concentration of 40% helps to prevent a fall in PaO_2 and overcomes the expected increase in V/Q mismatch that occurs during IPPV. Barotrauma is avoided if peak pressures are kept below 30 cm H_2O.

Flow generators are the preferred method of ventilation in adults. A reliable and predictable tidal volume and minute ventilation can be achieved even when there are alterations in lung mechanics from pre-existing lung disease or when temporary peroperative changes occur related to the effects of patient positioning and surgery.

Children:
- pressure generator mode of ventilation
- inspiratory pressure 20 cm H_2O irrespective of weight
- respiratory rate 30−40 breaths/minute for neonates; 20−25 breaths/minute for infants; 15−20 breaths/minute for older children
- I:E ratio 1:2
- Fi_{O_2} 0.5 (50% oxygen).

Owing to their increased basal metabolic rate relative to their weight, neonates and infants have an oxygen requirement (6 ml/kg/minute) twice that of adults. As a result, they have a high carbon dioxide production, hence the need for a high respiratory rate. Young children also have a reduced FRC, high CC and relatively high airways resistance with low respiratory compliance. Their increased metabolic rate and relatively low FRC means they have limited oxygen stores and so their arterial oxygen saturation falls rapidly if ventilation is inadequate. Loss of respiratory gases as an air leak from around their uncuffed endotracheal tube is expected and indeed desirable. It provides evidence that the endotracheal tube is not so tightly fitting as to cause tracheal mucosal compression at the level of the cricoid ring. Pressure generators, which compensate for gas losses and limit peak pressures, are commonly used in paediatric anaesthesia. At puberty, differential growth of the cricoid ring and laryngeal aperture means that the larynx becomes the narrowest part of the airway as in adults, so cuffed tubes may then be used.

Safety issues

Detection of ventilator disconnection

Anaesthetized, paralysed patients are wholly dependent on the ventilator and the anaesthetist to keep them alive. In this respect, a paralysed patient is much more vulnerable than one who is breathing spontaneously. The anaesthetist should be alerted to a disconnection promptly by a disconnect alarm, which may also indicate when inadequate ventilation is occurring.

Disconnections can be sensed by:
- loss of the rhythmic increase in airway pressure
- reduction in expired gas volume
- loss of expired carbon dioxide.

Monitoring of airway pressures and exhaled CO_2 are part of minimum monitoring requirements during mechanical ventilation.

Airway pressure sensors are either aneroid gauges or, more commonly, electronic pressure transducers. The gauge the anaesthetist uses for monitoring and the alarm system are often separate devices. Airway pressure alarms detect an increase above a threshold pressure. If an increasing pressure that exceeds the threshold is not detected in the preset time, an alarm is sounded. This system does not normally detect a blocked endotracheal tube, but an alarm for the excessive inspiratory pressures generated in this scenario is usually incorporated in the same system.

Expired tidal volume or expiratory flow over time can also be measured. A minimum preset volume must be exhaled at a frequency above the preset minimum rate or the alarm will be triggered. Expired tidal volume is usually measured by integrating the expired flow signal.

Capnographs are fitted with limit alarms and often with apnoea detectors, which detect apnoea from the carbon dioxide waveform. In addition, respiratory movements are sometimes sensed via ECG leads and as a very late indicator, pulse oximeters will alarm if significant arterial desaturation occurs.

Ventilator checks

The anaesthetist is responsible for the state of the equipment he or she uses. It is expected that equipment is systematically checked before use. Although on occasion this may be delegated to trained assistants, the final responsibility lies with the anaesthetist. To this end, guidelines for machine checks have been issued by the Associaton of Anaesthetists of Great Britain and Ireland (Figure 11). With the increasing use of sophisticated, electronically controlled anaesthesic machines and ventilators, a ‘generic’ checklist must be used only with reference to the manufacturer’s suggested protocol for each machine.

Ventilator checks

- Ensure that ventilator tubing is correctly configured and securely attached
- Set the controls for use and ensure that an adequate pressure is generated during the inspiratory phase
- Check that the pressure relief valve functions
- Check that the disconnect alarm functions correctly
- Ensure that an alternative means to ventilate the patient’s lungs is available

Source: Association of Anaesthetists of Great Britain and Ireland. *Checklist for Anaesthetist Apparatus*, 1997.

11

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Breathing Systems

Gordon W G French

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A 'breathing system' is the name given to apparatus that delivers and removes gas and vapour to or from a patient. The three main functions of the breathing system are:

- to supply adequate oxygen
- to remove carbon dioxide
- to supply adequate inhalational anaesthetic agent.

The perfect system has yet to be developed but the ideal breathing system should:

- be simple and safe
- deliver the intended mixture
- allow manual and intermittent positive-pressure ventilation (IPPV) in all age groups
- be efficient (able to use low gas flows)
- protect the patient from barotrauma
- be sturdy, lightweight yet compact
- be easy to scavenge
- be cheap.

Essential components of a breathing system

Tubing (hose): originally this was carbon-impregnated rubber (an antistatic design), corrugated to prevent kinking, but it was heavy and prone to perishing. Modern tubing is usually plastic, disposable or designed for single use, and often has a smooth inner bore that reduces resistance to airflow. Early systems had various means of inter-linking tubes, including tapered metal connectors that pushed into each other and screw mountings. These were manufactured in various sizes, with many systems being non-interchangeable, clearly a dangerous situation. The International Standards Organization (ISO.5356, 1987) and British Standard (BS 3849) recommend the following sizes for all breathing systems:

- 30 mm tapered connections for scavenging hose to breathing systems
- 22 mm taper for connections within breathing systems
- 15 mm connections between the breathing system and the endotracheal tube.

An upstream 'male' connector traditionally fits into a downstream 'female' part. The ISO 15 mm standard connector is cumbersome for small paediatric endotracheal tubes (2–6 mm internal diameter). Smaller, lighter 8.5 mm connectors may be used, which have adapters to connect to the 15 mm standard system. Tapered connections between plastic, metal and rubber can be 'locked' by giving them a slight twist after connecting. Systems designed for repeated use can usually be autoclaved, which does not affect their connectors. Single-use systems often distort if heated, making the connectors unsafe.

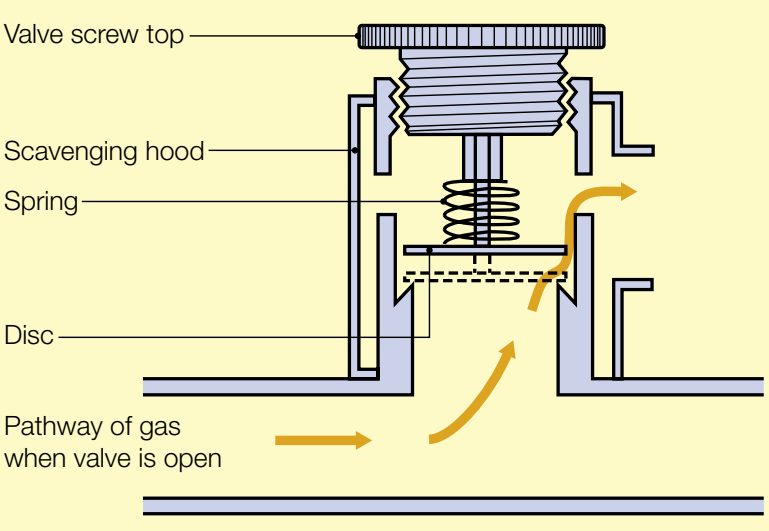
There is controversy among practising anaesthetists as to exactly what 'for single use only' means. Clearly it would be expensive to use a new breathing system for each patient, and almost certainly unnecessary. Many departments employ a cost-effective compromise by using a new disposable antibacterial filter for each patient, but only changing the actual breathing system weekly. It may be changed more often depending on clinical need (e.g. after use in a patient with known lung infection such as tuberculosis).

Reservoir bag: this stores fresh gas when the patient is exhaling and accommodates the high peak inspiratory flow rates during inspiration. Made of rubber or plastic, the common adult size is 2 litres and 0.5 litres for children, but some ventilators use other sizes up to 6 litres. The bag's motion allows observation of ventilatory patterns but does not reflect the tidal volume accurately. As the bag stretches, the pressure in its walls reaches a limit of about 40 cm H_2O (Laplace's law); further distension does not result in greatly increasing pressures. This partly protects the lungs from barotrauma should the breathing system outlet become obstructed, such as when the adjustable pressure-limiting (APL) valve is left fully screwed down. An open-ended reservoir bag is commonly used in paediatric circuits, allowing manual ventilation and assessment of the compliance of a child's lungs (e.g. Mapleson type F).

APL valve: this is a one-way, spring-loaded valve consisting of a thin, lightweight disc (made of hydrophobic material) held by an adjustable spring against knife-edged seating. This arrangement (Figure 1) reduces the area of contact between the disc and the seating, lessening any surface tension that condensed water vapour might create, causing the disc to stick. The disc prevents movement of air into the system when the patient inhales, but opens at low pressure (about 1 cm H_2O) to allow exhaled and surplus gas to be vented during expiration. When fully screwed down, modern valves open at about 60 cm H_2O positive pressure, acting as a safety feature.

Expired gases can be conveniently scavenged by surrounding the valve with a hood. If the valve is sucked open continuously by a faulty scavenging system, a huge increase in the dead space of the apparatus will result. The APL valve should be fully open during spontaneous respiration, partially closed during manual IPPV and fully closed during ventilator IPPV.

Cross-section of an adjustable pressure-limiting valve



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Classification of breathing systems

The historical development of breathing systems was largely based on the intuition and practical experience of individual anaesthetists. As a result, there are many different systems. One classification based on function is described below.

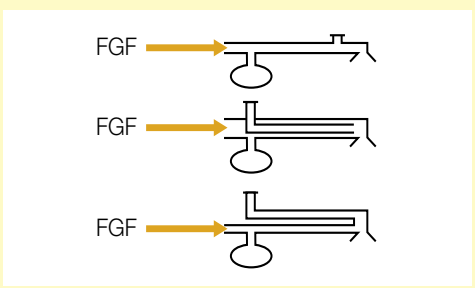
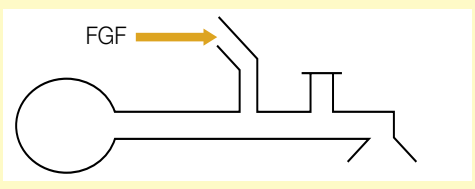
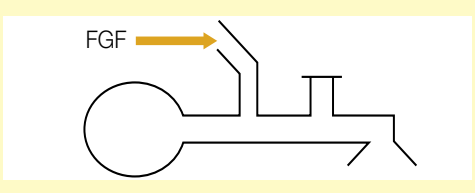
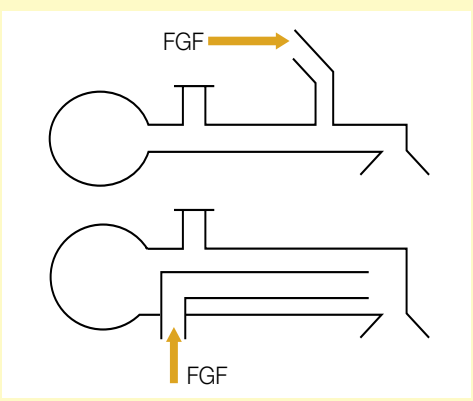
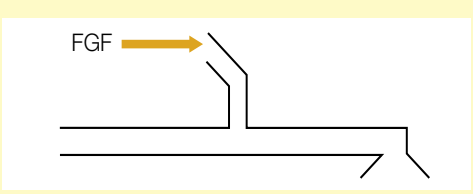
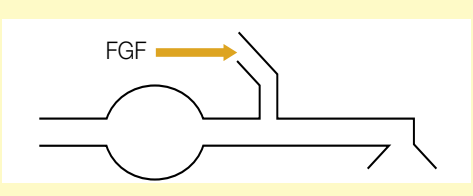
Non-rebreathing systems

Non-rebreathing systems use one-way valves to separate inspired and expired gases. When the patient inspires, the expiratory valve closes and the inspiratory valve opens, allowing inhalation of fresh gas. There is usually a reservoir bag on the inspiratory limb, which provides enough gas for the maximum peak inspiratory flow rate (often > 30 litres/minute), and collects fresh gas when the inspiratory valve is closed in expiration. It may also allow for manual-assisted ventilation. Resuscitation devices commonly include a bag constructed of foam-lined rubber or silicone, which remains inflated in the resting state, in addition to a thin-walled reservoir bag. Manual ventilation is provided by squeezing this bag, which automatically refills from the oxygen inlet and reservoir bag when hand pressure is released. The fresh gas flow (FGF) should at least equal the patient's required minute volume. Examples are resuscitation devices such as the Ambu bag, Laerdal silicone resuscitator, drawover units and the 'Triservice' apparatus.

Rebreathing systems

In rebreathing systems, the inspiratory and expiratory gases can mix in the tubing and re-inhalation of expired gas can occur. Rebreathing refers to inhaling part or all of the previously exhaled tidal volume. In particular, it is the inhaling of previously exhaled carbon dioxide (i.e. alveolar gas) which is of most concern to the anaesthetist. A system is efficient if it can preferentially vent alveolar gas, retaining dead space (non-carbon-dioxide-containing) gas and thus use an FGF that approximates to the patient's alveolar minute ventilation. The extent of carbon dioxide rebreathing thus depends on the FGF flushing the expired gas away before the next inspiration. The normal respiratory cycle consists of an inspiration followed immediately by expiration, but there is then an expiratory pause. It is during this period that the FGF flushes the system. In 1954, Mapleson classified five commonly used systems according to their efficiency at eliminating expired carbon dioxide in spontaneously breathing patients (Mapleson systems A–E). An F system was added in 1975 (Figure 2).

The Mapleson classification of anaesthetic breathing systems and adaptations

Mapleson type		Recommended fresh gas flow	General points
System A **a** Magill **b** Lack **c** Parallel Lack		**Spontaneous** AMV (70 ml/kg/minute) **IPPV** 2–3 x AMV	**a, b, c** Efficient for spontaneous, not for IPPV Heavy, especially at patient end Unsuitable for children < 25 kg because large dead space **b** Lack: coaxial, APL and reservoir bag at machine end Inspiratory gases through outer (30 mm) tube Expiratory via inner (14 mm) **c** Parallel Lack: separate inspiratory and expiratory tubes
System B		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	FGF near patient end. Performs similarly in both modes. Seldom used
System C		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	Similar arrangement to system B. The large-bore tubing to bag is shorter **a** Waters' 'to and fro' circuit: inefficient but small size and simplicity means useful for resuscitation and patient transfers **b** Waters' canister: heavy because incorporates a 1 lb soda lime container between bag and mask or ET tube Channelling occurs if incompletely packed. Nylon pot scourer compresses at bag end. Filter at patient end prevents soda lime dust movement. NB Filter to patient = dead space. Easily sterilized. Now little used. Superseded by circle absorber systems
System D **a** Bain		**Spontaneous** 2–3 x AMV **IPPV** AMV (70 ml/kg/minute)	Inefficient for spontaneous but good for IPPV Manley ventilator on spontaneous ventilation mode is a Mapleson D Safety problems include kinking of inner tube Disconnection of inner tube increases dead space. Both lead to hypoxia and hypercarbia **a** Bain: coaxial D. Length of tube does not affect properties (180–540 cm). FGF through inner tube (opposite to Lack) Ventilate with Penlon 200 replacing bag. Connecting tube long > 500 ml (usually 1 m) to prevent driving gas entering circuit. Lightweight, easy to scavenge. Ga in expiratory limb warm inspiratory gases
System E		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	Used for children up to 30 kg. Low resistance, small dead space, lightweight, no valves. Inefficient but used for spontaneous and IPPV. Expiratory limb is reservoir and should be > V_T to prevent air entraining Ayre's T-piece: developed for neuro/cleft palate surgery
System F		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	Jackson Rees modification. Reservoir bag allows rate and chest compliance to be monitored, ventilation by hand and continuous positive airway pressure application. Barotrauma and humidification a problem

AMV, alveolar minute volume; FGF, fresh gas flow; IPPV, intermittent positive-pressure ventilation; V_T, tidal volume

2

Mapleson A: classically describes the Magill system. The APL valve and any scavenging device make this system cumbersome at the patient's end. Lack solved this problem by creating a co-axial arrangement where the expiratory gases were carried up an inner hose to the APL and scavenging system, both of which were thus distant to the patient. However, this system is bulky, even though it is less weighty at the patient's end. In addition, if the inner tube breaks and this goes unrecognized, the system may become dangerous because carbon dioxide elimination is drastically reduced. It is also difficult to use with a ventilator. A parallel hose breathing arrangement (parallel Lack) eliminates this problem.

The Mapleson A system is an efficient system for spontaneous ventilation because it selectively vents alveolar gas through the APL valve. The first part of the exhaled tidal volume (non-carbon-dioxide-containing dead space gas) is retained in the system and is available for inhalation during the next breath. This efficiency is lost when the system is used for IPPV.

Mapleson B and C: in both systems the FGF, reservoir bag and APL are near the patient, creating a compact and portable system. However, they are both inefficient and only the Waters' 'to and fro' system is commonly used, mainly for patient transport and in postoperative recovery units.

Mapleson D: exhaled gas passes into a reservoir bag along with the fresh gas, so rebreathing occurs unless the FGF is high. The system is efficient for IPPV.

The Bain system is a coaxial version, which is particularly useful for limited-access surgery because of its light weight and the fact that the tubing can be lengthened without affecting the flow characteristics. The system can be connected to a ventilator by replacing the reservoir bag with tubing connected to a ventilator such as the Penlon Nuffield 200. The tubing should be of sufficient length to prevent the ventilator driving gas entering the breathing system (in practice > 500 ml or 1 metre of standard hose). In this system, the FGF is along a narrow internal tube (the opposite of the Lack system), and the expired gas moves along the outer tube, usefully heating up the dry FGF. It is vital that the inner tube is intact because disconnection leads to a huge increase in dead space and possible hypercarbia or hypoxia.

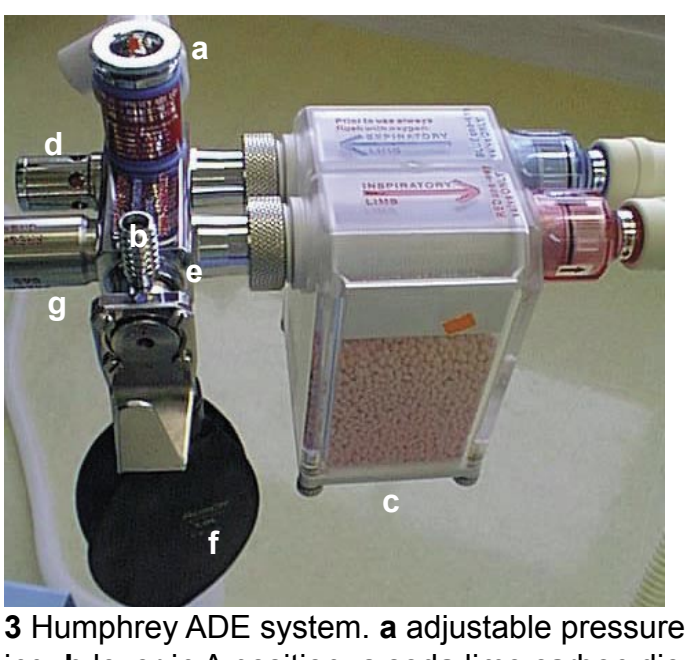
Mapleson E: the Ayre's T-piece is a valveless, lightweight system, with low internal resistance and dead space. In inspiration, gas is inhaled from both the inspiratory and expiratory limb. The volume of the expiratory limb needs to be at least equal to the tidal volume or air may be entrained. If it is too large, then rebreathing can occur because expired gas may not have vented to air before the next inhalation. Occluding the outlet intermittently allows IPPV.

Mapleson F: adding an open-ended reservoir bag to the expiratory limb of the Ayre's T-piece allows manual control of ventilation, observation of breathing and assessment of lung compliance. Some continuous positive airway pressure (CPAP) is also achieved with the system during spontaneous respiration, which, in an infant, may help to increase the functional residual capacity. Scavenging is a problem for both the Mapleson E and F systems. The routine use of capnography allows the FGF to be tailored precisely to achieve normocapnia in individual patients for all these systems.

Humphrey ADE system (Figure 3) is one of a number of hybrid systems that has become popular. It is a low-flow multipurpose system that appears to combine the best of the Magill, Lack and T-piece systems but not their disadvantages. It is cost effective in all modes, being more efficient than the Magill for spontaneous ventilation. The 15 mm, smooth-bore tubing has one-quarter of the resistance to flow of 15 mm corrugated tubing, which allows use in adults and children; 8.5 mm tubing is available for neonates. The reservoir bag, APL, scavenging shroud and a pressure-limiting valve are all located on the 'Humphrey block'. The system tubing connects to the patient via a symmetrical Y-piece, which probably accounts for much of its efficiency as it produces less turbulence than the conventional Magill–patient interface. One lever allows conversion from A mode to E mode, with only a slight increase in FGF being required to eliminate rebreathing. In E mode, the reservoir bag and APL are isolated from the system, and the expiratory tubing acts as the reservoir limb of a T-piece. This is open to the atmosphere via a port on the block to which a bag squeezer ventilator such as the Manley Servovent or Penlon Nuffield 200 or 400 can be attached. The D mode could be engaged by simply attaching a reservoir bag and APL to this port for spontaneous ventilation, but this is much less efficient than the A mode.

The APL valve provides positive end-expiratory pressure of 1 cm H_2O without increasing the airway resistance of the apparatus. The APL valve does not have to be screwed down for IPPV, except if used in the A mode. However, there is a long orange valve seat stem that can be temporarily held down instead. This also moves slightly during spontaneous respiration and gives a visual indication of respiratory movement. A separate 60 cm H_2O pressure-limiting valve lies behind the APL valve on the block. This is always in-line, whatever mode is being used. The system can be fixed on to the anaesthetic machine via a locking nut. A 500 g soda lime canister (lifespan 12 hours), which has a low resistance to flow and is autoclavable, can be fitted in front of the block. This circle system arrangement requires no other alterations in FGF for adults or children.

The entire system is MRI compatible, being made of plastic and brass. In addition, tubing lengths of over 3 m can be used without compromising its function. The main disadvantages are that it protrudes out of the anaesthetic machine, is heavy and can be knocked, which theoretically could fracture old anaesthetic machine outflow pipes.



3 Humphrey ADE system. **a** adjustable pressure limiting valve with scavenging; **b** lever in A position; **c** soda lime carbon dioxide absorber; **d** pressure relief (60 cm H_2O) valve; **e** port for ventilator; **f** reservoir bag; **g** fresh gas flow. Fresh gas flow: A mode (lever up) = 50 ml/kg/minute; E mode (lever down) = 70 ml/kg/minute. Children start at 3 litres/minute.

Systems using carbon dioxide absorbers

The circle system (Figure 4) was first described in the 1920s. It uses soda lime to absorb exhaled carbon dioxide. Partial rebreathing of other exhaled gases can thus be undertaken, depending on the arrangement of the components and the FGF.

Circle systems can be classified as follows:

- semi-open – no rebreathing, very high FGF, APL valve wide open
- semi-closed – rebreathing occurs, low flow, APL valve partly closed
- closed – FGF inflow exactly matches uptake by patient; complete rebreathing of exhaled gases after carbon dioxide uptake and APL valve fully closed.

A circle system consists of:

- FGF source
- inspiratory and expiratory unidirectional valves
- inspiratory and expiratory corrugated tubes
- a Y-piece connector
- an APL valve or pop-off valve
- a reservoir bag
- a canister containing a carbon dioxide absorbent.

Fresh gas enters the circle by a connection from the common gas outlet of the anaesthetic machine. Various arrangements of components are possible, but there are three golden rules to prevent carbon dioxide rebreathing.

- A unidirectional valve must be located between the patient and the reservoir bag on both the inspiratory and expiratory limbs of the circuit. These valves commonly have a clear plastic cover so that their correct movement can be observed during use.
- The FGF cannot enter the circuit between the patient and the expiratory valve.
- The APL valve cannot be located between the patient and the inspiratory valve.

The most efficient circle system has the unidirectional valves near the patient and the APL valve just downstream from the expiratory valve. This arrangement conserves dead space gas and preferentially eliminates alveolar gas. The advantages and disadvantages of a circle system are listed in Figure 5.

Nitrogen washout – at the start of anaesthesia, non-nitrogen-containing gas (unless medical air is being used) is inspired and body nitrogen passes into the lungs. This effectively reduces the oxygen concentration in the alveoli and circle system, producing a potentially hypoxic mixture. The use of high flows of gas at the start of anaesthesia can 'washout' this nitrogen. Pre-oxygenation with 100% oxygen for 7–10 minutes is also effective and can theoretically then allow low circle FGF to be used from the start. Basal metabolic oxygen requirements are about 250 ml/minute, but to allow for leaks in the circle and patient variability, 500 ml/minute oxygen is the minimum recommended flow rate. 'Low flow' anaesthesia is usually regarded as less than 1 litre/minute FGF.

The uptake of volatile agents is highest initially. Fast FGF inflows and large minute volumes produce fast induction of anaesthesia as well as facilitating denitrogenation. As equilibrium is reached, the expired concentration of volatile agent begins to reflect the inspired value, and flows can be reduced. The exhaled gases are added to the fresh gas and have a dilutional effect on the concentration of oxygen and vapour, which will be proportionally greater at low flows. A potentially hypoxic alveolar concentration of oxygen can develop as the FGF reduces. Using an inspired oxygen concentration of 50% to prevent these low oxygen levels in the circle was customary before the advent of in-line gas/vapour analysers. However, this was associated with an increased chance of awareness if the inspired volatile concentration was not increased to compensate for the lower inspired nitrous oxide and volatile concentrations.

Vaporizers can be placed outside (VOC) or inside (VIC) the circle (Figure 6). Most modern vaporizers tend to be outside the circle (e.g. Back bar units such as a TEC vaporizer) and are accurate at low flows. With this set-up, the concentration of volatile gas in the circle is reduced with increased patient uptake and low FGF (due to the dilutional effect of exhaled gas), until uptake reduces and equilibration begins to occur. With a vaporizer in the circle (e.g. Goldman vaporizer), both the fresh and exhaled gas (which already contains vapour) pass through the vaporizer. When the FGF is low and alveolar ventilation high, the concentration of volatile will rise. Thus the concentration of the alveolar and circle vapour is a function of ventilation. In spontaneous ventilation, with deepening anaesthesia and depression of ventilation, the concentration of volatile gas will fall and result in the patient becoming lighter, a useful safety feature. However, low flow controlled ventilation may result in high levels of volatile gas.

Future developments in circle technology may incorporate the VIC arrangement but use a system of vapour injectors instead of the vaporizer. This would be linked to a feedback mechanism incorporating circuit vapour analysis.

Carbon dioxide absorption – closed or semi-closed circle systems require carbon dioxide absorption to make rebreathing possible. Desirable features of a carbon dioxide absorption mechanism are lack of toxicity (intrinsic or with common anaesthetics), low resistance to air flow, low cost, ease of handling and efficiency. Soda lime and baralyme are the two formulations commonly used for carbon dioxide absorption (Figure 7). Both need water but because baralyme contains water as a barium hydroxide octohydrate salt it performs better in dry climates. Soda lime (but not baralyme) is capable of some regeneration after exhaustion. Maximum absorbency of both systems is 26 litres of carbon dioxide per 100 g absorbent.

Dyes (acids or bases) are also added, which change colour as the hydrogen ion concentration changes:

- ethyl violet (colourless to violet; fluorescent light deactivates it)
- phenolphthalein (white to pink)
- Clayton yellow (red to yellow)
- ethyl orange (orange to yellow)
- mimosa z (red to white).

The chemical reaction in soda lime is:

$CO_2 + H_2O \rightleftarrows H_2CO_3$

$H_2CO_3 + 2NaOH\ [KOH] \rightleftarrows Na_2CO_3\ [K_2CO_3] + 2H_2O + heat$

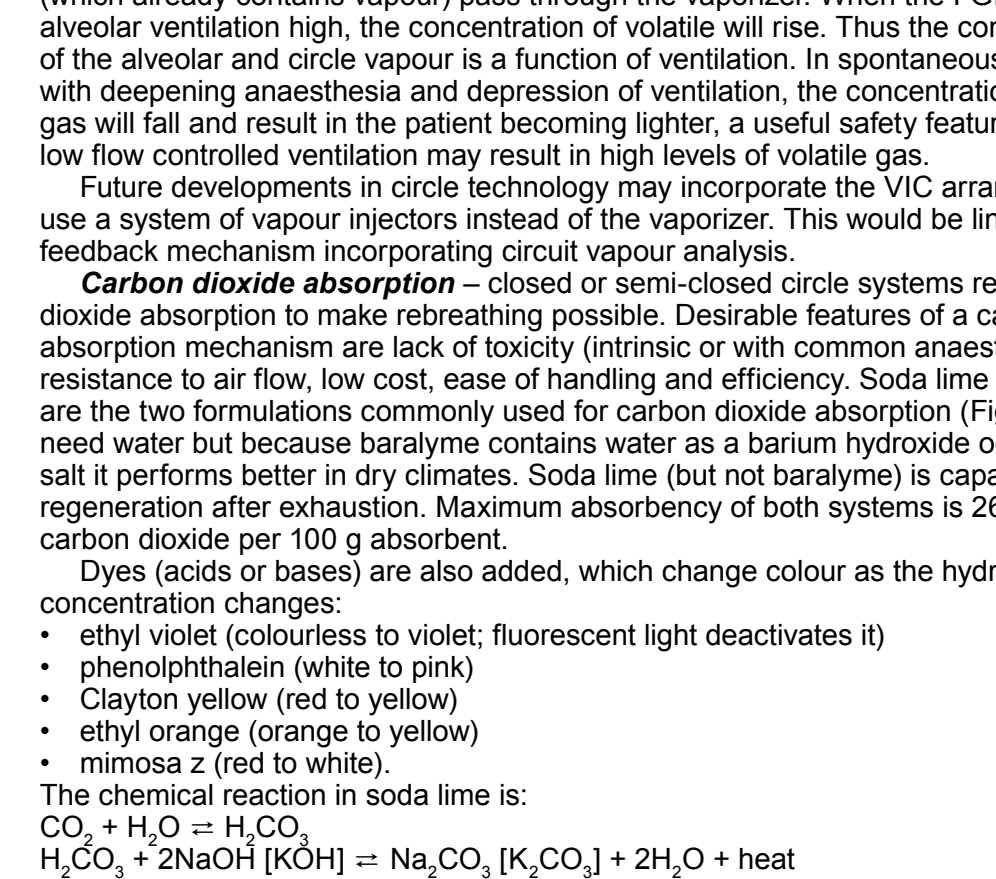
$Na_2CO_3\ [K_2CO_3] + Ca(OH)_2 \rightleftarrows CaCO_3 + 2NaOH\ [KOH]$

Some carbon dioxide reacts directly with calcium hydroxide but this is much slower. In baralyme the carbon dioxide acts directly with barium hydroxide and much more water is released. In the UK, the size of granules is 4–8 mesh (a compromise between surface area for absorption and air flow resistance). Mesh refers to the number of openings per linear inch in a sieve through which the granules pass. A 4-mesh screen indicates four quarter-inch openings per linear inch.

Soda lime and baralyme are not inherently toxic, but at low flows intrinsically produced acetone can accumulate and has been linked to nausea and vomiting. Carbon monoxide can also accumulate at low flows of dry gas (e.g. oxygen running overnight) leading to the formation of carboxyhaemoglobin.

The volatile agent trilene degrades into dichloroacetylene (a neurotoxin causing cranial nerve damage and encephalitis) and phosgene (a potent pulmonary irritant causing adult respiratory distress syndrome).

Sevoflurane and halothane are slightly unstable in soda lime, the rate of degradation increasing with temperature. Sevoflurane degrades into several compounds. Compound A (a vinylether) has been associated with lung haemorrhage and renal tubular necrosis in rats, but neither compound has been shown to cause problems in humans. Many of these problems are resolved by flushing the system regularly.



Properties of a circle system

Advantages	Disadvantages
• Heat/moisture conservation • Easy scavenging • Reduced cost • Small dead space • Good for long cases	• Multiple connections • Valves can stick • Open – leads to rebreathing • Closed – leads to asphyxia • Bulky • Inefficient for short cases • Soda lime changeover a hazard • Gas analyser necessary for accuracy • Potential for infection

5

Properties of vaporizers

Inside the circle	Outside the circle
• Low internal resistance • Low efficiency desirable • Higher concentrations at low fresh gas flow	• High internal resistance (plenum) • High efficiency desirable • Lower concentrations at low fresh gas flow (diluted)

6

Properties of soda lime and baralyme

Soda lime	Baralyme
• Calcium hydroxide (94%) • Sodium hydroxide (the catalyst) (5%) • Potassium hydroxide (1%) • Silica (calcium and sodium silicate harden it and reduce dust formation)	• Calcium hydroxide (80%) • Barium hydroxide (the catalyst) (20%) • More stable so does not contain silica • Denser and 15% less efficient than soda lime

7

System checks

All systems should be checked visually for broken parts and disconnections and a push-and-twist connector test performed. In addition, there are checks specific to individual systems.

- Occluding Mapleson types B and C causes their reservoir bags to fill, testing the air-tightness of the system. Releasing the valve causes the bag to deflate if the valve is functioning normally.
- The Bain system inner tube can be tested in two ways. Occluding the end of the inner tube causes the rotameter bobbin to dip and the pressure alarm/valve to blow if there are no leaks/disconnections up to that point. Occluding the patient end of the system will fill the reservoir bag, testing overall air- tightness. Releasing the occlusion causes the bag to deflate, then continue to empty as a result of the negative pressure caused by the Venturi-effect of the fast FGF leaving the inner tube. The connection of the inner tube can also be visually inspected because the outer corrugated tubing is often made from transparent plastic. This outer tubing may also be temporarily disconnected and a secure inner tube connection confirmed.
- To carry out the low-pressure circle leak test, the end of the system should be occluded and the APL valve closed off. The system is filled using the oxygen flush until the airway pressure gauge registers 30 cm H_2O. The pressure should remain at 30 cm H_2O if no leaks are present.

FURTHER READING

Humphrey D, Brock-Utne J G, Downing J W. Single Lever Humphrey ADE Low Flow Universal Anaesthetic Breathing System. *Can Anaesth Soc J* 1986; **33(6):** 698–718.

Cleaning, Disinfection and Sterilization of Equipment

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Hospital-acquired infections have significant implications for the morbidity and mortality of patients as well as for the economics of health care. The protection of patients and medical staff from medical equipment that has come into contact with patients or their body fluids, requires the adoption of various processes enforceable by law. Changes in these laws and guidelines, published by the Department of Health and the Medical Devices Agency, are expected in the near future. One of the reasons for the introduction of new guidelines is the development of new variant Creutzfeldt–Jakob disease, which is resistant to the standard methods of decontamination used in hospital sterile services departments.

Contamination is the soiling or pollution of an inanimate object with harmful, potentially infectious, material. In the clinical setting, this is most likely to be organic material or microorganisms. Contamination may place the patient at risk and may adversely affect equipment.

Decontamination is a method used to remove contamination and prevent microorganisms reaching a susceptible site in large enough numbers to initiate infection or other adverse effects. The three methods of decontamination routinely used are cleaning, disinfection and sterilization. The method of decontamination chosen takes into account the infection risk from the reprocessed piece of equipment. The risk is dependent on:

- the amount of contact the patient has with the piece of equipment (i.e. how invasive)
- the susceptibility of the patient (i.e. immunocompromised, potential hypersensitivity)
- the nature, extent and amount of microbial contamination on the piece of equipment (the bio burden).

The type of equipment and its intended use determine the method of decontamination used (Figure 1). The manufacturer should provide instructions for cleaning, disinfection and sterilization techniques that are effective without affecting the performance of the equipment.

It is essential that records are kept to demonstrate the number of times an item has been decontaminated and the effectiveness of each process. The documentation should allow patients to be traced in the event of any malfunction in the decontamination process.

Risk of contamination for equipment and suggested decontamination process

Risk	Application of equipment	Recommendation
High	• In close contact with a break in the skin or mucous membrane • For introduction into sterile body areas	Sterilization
Intermediate	• In contact with mucous membranes • Contaminated with particularly virulent or easily transmissible organisms • Before use on immunocompromised patients	Sterilization or disinfection (Cleaning may be acceptable in some agreed situations)
Low	• In contact with healthy skin • Not in contact with patient	Cleaning

1

'Single use' equipment

Manufacturers should state in the product literature any restrictions on the number of re-uses. Any device deemed by the manufacturer as unsuitable for reprocessing is labelled 'single use'. Devices labelled 'single patient use' may be used for an extended period of time or intermittently on the same patient. Users who disregard the manufacturer's guidelines, for example by reprocessing single use items or reprocessing more than the recommended number of times may be transferring legal liability for the safe performance of that product from the manufacturer to themselves or the organization for which they work.

Many anaesthetic departments routinely use disposable anaesthetic breathing systems marked as single use for extended periods with multiple patients. The wisdom of this practice is the subject of much controversy. The advantages of these breathing systems include safety (often pre-assembled with fewer opportunities for connection errors by the user), lightweight and low cost if used on several patients. The disadvantage is that this practice may contravene the manufacturer's recommendation for single use only and risk transmission of infection. The responsibility for use of equipment marked single use then lies with the hospital. Departments of anaesthesia should have an operational policy on the management of breathing systems marked for single use. This may include:

- the use of a new bacterial (heat and moisture exchanger type) filter for each patient
- change of all breathing systems weekly
- change of breathing system following use on a patient with known or suspected lung infection
- change of breathing system whenever there is visible contamination from blood or body fluids.

Cleaning

Cleaning physically removes contaminants without necessarily destroying microorganisms. It removes organic material and is required before disinfection or sterilization.

Manual cleaning

Manual cleaning does not disinfect. It should be used only when other mechanical methods are inappropriate or unavailable.

Immersion – wearing appropriate protective clothing, the cleaner should submerge the device in compatible water/detergent solution at the correct dilution and not exceeding 35°C. It is important to ensure that the cleaning solution reaches all surfaces of the device, including lumen surfaces. Endoscopic equipment that may be totally immersed for cleaning is marked with a blue line, usually around the eyepiece adjacent to the focussing ring. The device should be brushed or agitated to remove any visible contaminants. The device should be thoroughly drained and rinsed in clean water. This method is generally satisfactory for the routine cleaning of laryngoscopes between patients. Disinfection with an alcohol spray is then commonly used.

Non-immersion – wearing appropriate protective clothing, the cleaner should immerse a cleaning cloth into the detergent solution and wring it out. The equipment should be cleansed by wiping its surfaces. The surfaces should be hand dried using a cloth, hot air dryer or drying cabinet. This method of cleaning is often used for electrical or electronic equipment which cannot be immersed in water.

Mechanical cleaning

Mechanical cleaning uses automated washers to clean equipment and often combines cleaning with disinfection.

Thermal washer – cleaning occurs by continually spraying the equipment with water and detergent during a timed cycle. During the first process, cleaning occurs at 35°C. The second wash heats the surface of the equipment to a minimum temperature of 71°C for a minimum of 3 minutes, 80°C for 1 minute, or 90°C for 1 second to disinfect it.

Chemical washer – the first part of the cleaning process is the same as the thermal washer. Disinfection occurs by exposing the equipment to an approved disinfectant for a particular period of time at less than 60°C. The residue disinfectant is then removed by a rinse cycle.

Ultrasonic cleaners are often incorporated into washer disinfectors. These work by rapidly forming bubbles in the liquid, which immediately collapse (cavitation). This cavitation agitates the liquid, producing a highly effective cleaning system. The process does not disinfect.

Disinfection

Disinfection is used to reduce the number of viable micro-organisms, but it may not kill all microbial agents such as some viruses and bacterial spores.

Low temperature steam disinfection

Low temperature steam disinfection is also known as pasteur-ization. It kills most vegetative microorganisms and viruses by exposure to moist heat. The equipment is exposed to dry saturated steam at a temperature of 73°C for at least 10 minutes at below atmospheric pressure. The low temperature steam kills vegetative microorganisms and some heat-sensitive viruses. It cannot be used for sealed, oily or greasy pieces of equipment or those with sealed cavities due to the variation in pressure.

The advantages of this system are its broad spectrum of disinfection, it is non-toxic, non-corrosive and the equipment is relatively safe and simple to use. The disadvantages are that it requires a trained operator and that much equipment is unsuitable for disinfection in this way. The capital cost of the disinfector is high and the equipment is fixed and not portable.

Boiling water disinfection

Boiling water is an effective disinfectant against many microorganisms. Immersing a piece of equipment in soft water and boiling at 100°C for at least 5 minutes produces disinfection. Boiling inactivates most non-sporing microorganisms, fungi, viruses and some heat-sensitive spores. This method is not used if a better method is available. It is unsuitable for heat-labile pieces of equipment, hollow or porous items into which the water will not penetrate, or tubing over 1 metre in length.

The advantages are that boiling water has a broad disinfecting effect. The process is non-toxic and inexpensive. The disadvantages are that boiling water is a potential cause of injury. Following disinfection, items are wet and unfit for immediate use and must be allowed to dry and cool, which may allow recontamination. There is also no method of checking the efficacy of the process.

Washer disinfectors

Washer disinfectors are described above. They inactivate all microorganisms except bacterial spores and some heat-resistant viruses. They are unsuitable for equipment that may be heat labile or corroded by chemical disinfectant, and for hollow or porous equipment that does not allow all surfaces to come into contact with the chemical disinfectant or heat.

These methods are safe for the operator. There is minimal handling of the equipment by staff and therefore a low risk of recontamination. Another advantage is that they combine cleaning and disinfection. The disadvantages are the high cost of the equipment and the requirement for trained staff.

Liquid chemical immersion

Liquid chemical immersion relies on good contact between the chemical disinfectant and the equipment. The equipment therefore requires thorough cleaning beforehand. It is then immersed in the chemical disinfectant, ensuring that the disinfectant reaches all surfaces. The equipment is immersed for a predetermined time depending on the chemical disinfectant used. The spectrum of activity also depends on the type of chemical disinfectant used (Figure 2).

The method is unsuitable if the corrosive nature of the chemical disinfection may damage the equipment or if the equipment has areas inaccessible to liquid. It requires trained staff wearing protective clothing. It is potentially toxic, corrosive or volatile. Also, the equipment may have to be hand dried after disinfection allowing possible recontamination.

Equipment disinfectants commonly used and their spectrum of activity and physical properties

Disinfectant	Microbiological activity					Stability	Inactivation by organic matter	Corrosive/ damaging matter	Irritant
	Spores	Mycobacteria	Bacteria	Viruses[1] Enveloped	Viruses[1] Non-enveloped				
• Glutaraldehyde 2%	+++ (slow)	+++	+++	+++	+++	Moderate (fixative)	No	No	Yes
• Peracetic acid 0.2–0.35%	+++	+++	+++	+++	++	Poor (< 1 day)	No	Slight	Slight
• Alcohol (ethyl alcohol) 60–80%	None	++	+++	+++	++	High	Yes (fixative)	Slight	No Flammable
• Peroxygen compounds	None	+	+++	+++	++	Moderate (7 days)	Yes	Slight	No
• Chlorine-releasing agents >1000 ppm average Cl_2	+++	+++	+++	+++	++	Poor (< 1 day)	Yes	Yes	Yes
• Clear soluble phenolics 0.6–2%	None	+++	+++	+	None	Good	No	Slight	Yes
• Quarternary ammonium compounds	None	Variable	Moderate	+	+++	Good	Yes	No	No

[1] Activity varies with concentration of product.

Sterilization

Sterilization is used to produce an object free from viable microbial organisms including viruses and bacterial spores. There are several types of sterilizer (Figure 3).

Steam

When steam is pressurized it reaches a temperature greater than that of boiling water at atmospheric pressure and destroys or renders non-viable, bacteria, viruses and their spores. For this process to be effective, direct contact between the pure dry saturated steam and the object being sterilized is required at the specific temperature and in the absence of air. The temperature reached by the object determines the time required for sterilization. The lowest temperature recommended is 121°C for 15 minutes; the highest temperature of 134°C requires only 3 minutes.

This process is effective against all microorganisms with a significant safety factor. Problems occur with wrapped items because all air must be removed. To overcome this, porous load sterilizers are used, which incorporate a vacuum pump. Air is removed before steam is added. This is the most commonly used method for sterilization in hospitals today (Figure 4). However, it cannot be used for any material that cannot withstand the temperatures or pressures required for sterilization (e.g. thermo-labile plastics, fibre-optic endoscopes).

The advantages of this process are that steam is non-toxic, non-corrosive and a highly effective sterilizing agent. This system can be incorporated into a fully automated process on a large scale, coping with a high turnover of equipment. Disadvantages are that the operator must wear protective clothing to avoid direct contact with the steam.

Different types of hospital sterilizers

Types of sterilizer	Use	Minimum time / temperature
• Steam sterilizer		
Porous load	Wrapped instruments, dressings, utensils	134–138ºC for 3 minutes
Fluid cycle	Fluids in sealed containers	121–124ºC for 15 minutes,
	or 115ºC for 30 minutes	
Unwrapped instruments	Unwrapped instruments and utensils	134–138ºC for 3 minutes
• Hot air sterilizer	Oils, powders, heat-resistant instruments that must be kept dry	160ºC for 2 hours
• Low temperature steam formaldehyde sterilizer	Heat-sensitive equipment	73ºC for 3 hours
• Ethylene oxide	Heat-sensitive equipment	Various temperatures and times

Dry hot air

In this process, sterilization takes place by raising the ambient temperature. Typical processes consist of 160°C for 2 hours, 170°C for 1 hour, 180°C for 30 minutes. If all the items are completely clean and dry before this sterilization process starts, then all microorganisms will be killed. However, it cannot be used for materials that would be damaged by these temperatures (e.g. rubber, plastic).

Dry heat can be used to sterilize stable powders, waxes and non-aqueous liquids. It is also effective for non-stainless metals, hollow needles and glass syringes. However, the sterilization time is long compared with other methods, and items have to cool slowly afterwards. Many pieces of equipment cannot withstand these high temperatures for the allocated time.

Ethylene oxide

Ethylene oxide at ambient pressure and temperature vaporizes easily and thus has good penetrative properties. It is also non-corrosive and has a wide spectrum of activity against bacteria, spores, fungi, viruses and other living cells. Sterilization is usually carried out at 20–60°C for 2–24 hours.

Ethylene oxide is most often used under three different conditions:

- normal atmospheric pressure using undiluted ethylene oxide – the gas is very flammable, and so is often diluted to reduce explosion risk
- ethylene oxide with a diluent gas such as nitrogen at a pressure of 2 bar
- ethylene oxide diluted with carbon dioxide at a pressure of 6 bar.

This process should not be used if heat sterilization is possible. Organic material has a marked protective effect and therefore prior cleaning is essential. Ventilatory or respiratory equipment is contraindicated. Ethylene oxide does not penetrate plastic; therefore items must be wrapped in sterilization paper.

Ethylene oxide is a highly effective sterilizing agent. In particular it is used to sterilize single use medical items that would be damaged by the excessive heat used in other sterilization methods. Disadvantages of ethylene oxide are that it is toxic and long periods of aeration are required after sterilization therefore turn-around time is long. The process is expensive and there are significant health and safety issues concerning ethylene oxide and the equipment required to use it. Because of this, ethylene oxide is not often used in hospitals but is commonly used by industry.

Low temperature steam and formaldehyde

This process uses a combination of dry saturated steam and formaldehyde, which together kill vegetative bacteria, spores, fungi and most viruses. Objects are placed in the sterilizer to allow maximum contact with the steam. Air is actively removed from the container and replaced by dry saturated steam at 73°C at subatmospheric pressure. Formaldehyde is entrained as the steam enters the sterilizer.

The subatmospheric pressure may damage hollow objects. Formaldehyde may be corrosive with certain materials and some fabrics may absorb formaldehyde. This method cannot be used for items contaminated with body fluids, because the proteins in the fluids congeal and produce hard fixed deposits.

Advantages of the process are that it can provide dry, packaged items in a sterile form and the process is fully automated. Disadvantages are that the process is complex and formaldehyde is toxic, irritant and possibly mutagenic. The equipment required is also expensive, with the added problem of toxic waste products.

Irradiation

Irradiation uses γ rays or accelerated electrons. A dose greater than 25,000 Gray produces sterility. Irradiation is often used to sterilize single use items on an industrial scale. It has a broad spectrum of activity. Irradiation can cause significant degradation of materials and is unsuitable for the resterilization of hospital equipment.

The advantages are that it is reliable on an industrial scale for heat-labile pieces of equipment. However, irradiation can damage equipment particularly on re-exposure. Monitoring the process and the required safety equipment is expensive.

Special circumstances

Recent work has identified that the prion strain causing bovine spongiform encephalopathy (BSE) in cattle has infected humans, manifesting itself as a novel human prion disease, new variant Creutzfeldt–Jakob disease (vCJD). The abnormal prion protein is a new class of transmissible agent that demonstrates resistance to the standard methods of sterilization used in hospital sterile services departments.

Affected individuals accumulate prion protein in lympho-reticular tissues (e.g. appendix, tonsils), as well as in the CNS. The number of people incubating the disease is unknown, and there are concerns that prions might be transmitted iatrogenically via contamination of surgical instruments. Such risks remain unquantified, and there have been no identified cases involving vCJD transmission via surgical instruments. All neurosurgical instruments used on patients suspected of carrying vCJD are destroyed. However, there are significant implications for the safety of surgical instruments in ENT and other surgical practice.

The Spongiform Encephalopathy Advisory Committee (SEAC) has recommended that, where feasible, the move to single use instruments is appropriate. From January 2001, the Department of Health requires tonsillectomy and adenoidectomy to be performed using single use instruments in England and Wales. The recommendations are that instruments used to dissect or cut lymphoid tissue are to be disposed of. Anaesthetic equipment may also provide theoretical risk for prion disease transfer. This risk is as yet unquantified and accepted practice is continuing to evolve. It is likely that, in the near future, anaesthetic practice will change to incorporate disposable, single patient use equipment wherever possible (e.g. disposable laryngoscope blades and laryngeal mask airways).

Critical Incidents: The Cardiovascular System

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Hypertension

Hypertension is a common critical incident during anaesthesia. Whether it is harmful depends on its severity, cause and duration, and on the condition of the patient. These factors also determine how actively it needs to be treated. Hypertension is difficult to define because of observer and subject variation, and the arbitrary nature of cut-off values, but definitions include:

- elevation of blood pressure at least 15% above patient's baseline
- systolic blood pressure greater than 160 mm Hg and/or a diastolic blood pressure greater than 95 mm Hg. Figure 1 lists the causes of hypertension during or persisting after anaesthesia.

Causes of hypertension during or persisting after anaesthesia

- Inadequate anaesthesia/analgesia
- Tracheal intubation/extubation
- Inadequate muscle relaxation
- Pre-existing hypertensive disease
- Hypoxaemia
- Hypercapnia
- Aortic clamping
- Raised intracranial pressure, cerebral ischaemia or cerebrovascular accident
- Drugs (e.g. ketamine, adrenaline (epinephrine))
- Metabolic disorders (e.g. malignant hyperpyrexia, thyroid crisis, phaeochromocytoma, carcinoid syndrome)
- Postoperative urinary retention, pain, anxiety

1

Complications

Cardiovascular – hypertension may precipitate myocardial ischaemia (especially subendocardial), infarction or failure.

Neurological – cerebral haemorrhage may result, especially in patients with vascular malformations. Cerebral oedema or encephalopathy are less common complications of uncontrolled hypertension.

Haemorrhage at the operation site or from pre-existing vascular malformations.

Renal – severe hypertension may precipitate acute renal failure.

Management

Management of hypertension should be directed towards the underlying cause. The usual cause is inadequate anaesthesia for the level of surgical stimulation being employed and treatment requires an increase in the inhalational or intravenous anaesthetic drug, or an increase in analgesia. Confirmation of the diagnosis may require a trial of therapy. If the cause of the hypertension cannot be diagnosed or removed, an appropriate antihypertensive drug may be used. The following are examples of drugs commonly used.

- Labetalol – combined α- and β-blockade; dose 5–20 mg i.v. over 2 minutes with increments up to 200 mg. Onset 5–30 minutes, duration 50 minutes.
- Metoprolol –β_1 (cardioselective) blockade; 2 mg increments slow i.v., maximum dose 15 mg.
- Esmolol – rapid onset; short half-life of 9 minutes; 500 µg/kg loading dose; 50–200 µg/kg/minute infusion.
- Nifedipine – calcium-channel blocker, sublingual or intranasal; onset 1–5 minutes following a 10 mg dose.
- Phentolamine – α-blockade; 0.5–2 mg i.v., repeated as necessary, rapid onset, short half-life 10–15 minutes.
- Hydralazine – direct-acting arteriolar dilator, peak action after about 20 minutes following 10–20 mg slow i.v. injection over 20 minutes. Onset occurs after 15–20 minutes; duration is 2–6 hours.
- Glyceryl trinitrate – arterial and venous dilator; use 1 mg/ml solution i.v. (preferably a central vein) via syringe driver, dose 10–200 µg/minute, maximum effect after 1–2 minutes.
- Sodium nitroprusside – arteriolar dilator; very rapid response, administered by continuous intravenous infusion via a dedicated vein, 0.5–1.5 µg/kg/minute. Direct arterial blood pressure recording is mandatory. Doses greater than 4 µg/kg/minute may cause cyanide poisoning.

Hypotension

Mild-to-moderate falls in blood pressure are common during anaesthesia, but seldom result in any harm to the patient. It is difficult to determine what is a dangerous level of hypotension; it depends on the duration of hypotension and the patient's preoperative medical condition. Two signs of inadequate myocardial perfusion are the development of ST segment depression and ectopic beats. Increased ventilation–perfusion mismatch secondary to pulmonary hypotension causes a fall in oxygen saturation (SpO_2). In awake patients receiving regional anaesthesia, nausea and dizziness are common symptoms of excessive hypotension. The lower limit of cerebral, renal and hepatic autoregulation occurs at a mean arterial pressure of about 60 mm Hg in otherwise healthy individuals.

Causes

Anaesthesia

- Volatile agents produce a dose-related fall in blood pressure (vasodilatation, myocardial depression, impaired baroreceptor response).
- Induction agents cause a dose-related fall in blood pressure owing to a complex combination of effects involving myocardial depression, vasodilatation, altered baroreceptor reflex and bradycardia (especially propofol).
- Opioids may precipitate histamine release and vasodilatation. Larger doses are associated with bradycardia.
- Non-depolarizing muscle relaxants may produce hypotension secondary to histamine release.
- Positive-pressure ventilation increases intrathoracic pressure and produces a decrease in venous return and cardiac output.
- Spinal and epidural anaesthesia produce sympathetic blockade. This results in vasodilatation, reducing venous return, cardiac output and systemic vascular resistance. Although reflex vasoconstriction occurs above the level of the block, blood pressure usually falls. Higher blocks (T4 or above) obtund the cardiac sympathetics, preventing a compensatory tachycardia.
- In obstetrics, aortocaval compression impairs venous return and in combination with spinal and epidural anaesthesia may produce profound hypotension.

Hypovolaemia, regardless of aetiology, becomes less concealed following induction of anaesthesia owing to impairment of compensatory mechanisms. Hypotension then ensues. Hypovolaemia may occur in patients with:

- trauma or burns
- gastrointestinal disease (e.g. haematemesis, melaena, small bowel obstruction, acute inflammatory bowel disease)
- dehydration from poor fluid intake, vomiting or diarrhoea
- metabolic disorders (e.g. diabetic ketoacidosis, diabetes insipidus, hypercalcaemia).

Surgical causes of hypotension include:

- haemorrhage
- head-up position
- excessive intra-abdominal pressure during laparoscopic surgery may impair venous return causing hypotension
- release of aortic cross-clamping or lower limb tourniquets causes an acute fall in systemic vascular resistance and blood pressure secondary to vasodilatation in the ischaemic tissues.

Cardiovascular disease may lead to hypotension:

- ischaemic heart disease with impaired cardiac contractility (including unstable angina and recent myocardial infarction)
- heart failure
- valvular heart disease (mitral or aortic stenosis and regurg-itation)
- dysrhythmias (fast atrial fibrillation, complete heart block)
- hypertension, especially if poorly controlled
- others (e.g. myocarditis, cardiomyopathy, constrictive pericarditis, myocardial contusion, tamponade, aortic coarctation, congenital cardiac anomalies).

Cardiovascular medication such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, nitrates, α_1-antagonists (prazosin) and centrally acting α_2-agonists (e.g. clonidine, methyldopa) may cause hypotension.

Autonomic neuropathy produces impaired baroreceptor response and may be present in a variety of disease states:

- diabetes mellitus (incidence and severity increase with the duration of the disease)
- Guillain–Barré syndrome
- spinal cord injury and following cerebrovascular accident
- Parkinson's disease
- AIDS.

Other causes

- Anaphylaxis may result in massive histamine-mediated vasodilatation, producing cardiovascular collapse.
- Pulmonary embolus from deep vein thrombosis, or emboli from air, carbon dioxide or fat may reduce cardiac output. Hypotension is accompanied by desaturation and a fall in end-tidal carbon dioxide.

Management

- Identify and remove the precipitating cause.
- Increase fraction of oxygen in inspired air (F_iO_2) to maintain SpO_2.
- Position patient supine, possibly with the legs raised to improve venous return. The head-down position is no longer recommended because it also raises cerebral venous pressure and therefore cerebral perfusion pressure may not be improved.
- Give a rapid intravenous infusion. The type and amount of fluid depends on aetiology and patient factors. A useful guide is to infuse 10 ml/kg of colloid or 20 ml/kg crystalloid initially and assess the response.
- Vasopressors may be considered, particularly if the cause of hypovolaemia is non-haemorrhagic (e.g. ephedrine, 3–6 mg i.v., metaraminol, 0.5–1.0 mg i.v., or phenylephrine, 0.5–1.0 mg i.v.).
- Consider an infusion of a positive inotrope (e.g. adrenaline (epinephrine), dobutamine) or vasoconstrictor (e.g. noradrenaline (norepinephrine)).

Massive haemorrhage

Bleeding is a significant cause of mortality and morbidity because of the loss of blood volume and its constituents and also the effects of infusions of products aimed at compensating for the loss. Massive blood transfusion can be defined as the transfusion of blood, blood products and fluids equivalent to the circulating blood volume in any 24-hour period. The most profound physiological, haematological and biochemical effects occur in those who have the most rapid loss and replacement therapy.

Causes of massive haemorrhage include:

- trauma
- major elective surgery such as orthopaedic or vascular surgery, especially rupture or dissection of the aorta
- during pregnancy and the puerperium (e.g. massive antepartum or post-partum haemorrhage)
- urgent operations and/or procedures in patients with abnormalities of haemostasis or coagulation.

Management

Measuring blood loss: the quantity of blood lost can be estimated by a number of methods.

- Weighing swabs and measurement of blood aspirated into suction apparatus. With major haemorrhage, these methods become less useful because a considerable amount of blood is spilled on to the drapes and floor. In traumatized patients, major blood loss may have occurred before arrival in hospital or may be concealed in the chest or abdomen, or in the limbs and pelvis at the site of fractures.
- Measuring packed cell volume. Blood lactate concentration gives an indication of the adequacy of organ perfusion.
- Clinical observation. The monitoring of cardiovascular variables such as heart rate, arterial pressure, capillary return, central venous pressure, and in some cases pulmonary capillary wedge pressure and cardiac output, allows a clinical impression of the adequacy of volume resuscitation to be made.

Compensatory mechanisms initially maintain the blood supply to vital organs. Unless adequate and appropriate corrective measures are taken, these mechanisms will decompensate. With increasing volumes of blood loss, there is an increase in heart rate, decrease in stroke volume, reduced pulse pressure, increased respiratory rate and a reduction in cerebral blood flow leading to a reduction in conscious level. These compensatory mechanisms are less efficacious in the elderly and very young and may be impaired by disease or medication. Figure 2 shows the relationship between the changes in vital signs and the volume loss from the circulation.

Relationship between the changes in vital signs and the volume loss from the circulation

	Blood loss (ml)			
	≤ 750	**750–1500**	**1500–2000**	**≥ 2000**
Loss as % of blood volume	≤ 15	15–30	30–40	≥ 40
Heart rate	< 100	> 100	> 120	≥ 140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal	Decreased	Decreased	Decreased
Capillary return	Normal	Slowed	Slowed	Slowed
Respiratory rate (breaths/minute)	14–20	20–30	> 30	≥ 35
Urine output (ml/hour)	> 30	20–30	5–15	Negligible
Mental status	Normal	Anxious	Confused	Drowsy
Suggested volume replacement	Crystalloid	Crystalloid/colloid	Blood	Blood

Active management: the rapid and effective restoration of an adequate circulating blood volume is the primary responsibility of the anaesthetist during periods of heavy blood loss.

Establish adequate venous access by siting at least two large-bore cannulae to allow rapid fluid infusion. The most important pre-determinants of the flow rate of fluid are the diameter of the cannula and the ability to apply a continuous pressure of 2–300 mm Hg via a pressurized infusion system. Crystalloids and synthetic colloids may be used initially and should be followed by the administration of blood if bleeding continues.

Commence intravenous fluids – internationally accepted practice is to use Hartmann's solution as the initial resuscitation fluid for trauma and burns. The success of initial resuscitation in an acutely hypovolaemic patient probably depends more on adequacy of repletion than on which fluids are used. For a given blood volume expansion about twice the volume of crystalloid compared with colloid is required. In practice, combined therapy using both crystalloids and colloids is often used.

Fluids should be warmed – a transfusion system should have the ability to transfuse blood at fast flow rates (up to 500 ml/minute) and at temperatures greater than 35°C. Some systems use a constant-pressure infusion device combined with an efficient blood warmer and a purpose-designed blood-warming coil (e.g. *Level One*™). Priming or flushing blood through the system after fluid containing calcium has been used (such as *Haemaccel*) should be avoided, because this may cause blood clot formation in the tubing by reversal of the anticoagulant effect of citrate.

Blood should be taken for grouping and cross-matching, for coagulation studies and for biochemical analysis. Accurate identification of transfusion specimens and of designated units of blood, platelets and fresh frozen plasma (FFP) is particularly important in patients undergoing massive transfusion. It should be noted that most incompatible blood transfusions occur in emergency situations. For operations where significant blood loss is anticipated, replacement therapy should be available in advance of surgery.

Red cell transfusions are given to increase the haemoglobin concentration and thus improve or normalize the delivery of oxygen to the tissues. The haemoglobin concentration at which blood transfusion is commenced depends to a certain extent on the individual patient (e.g. elderly patients are at greater risk of complications from anaemia). A haemoglobin value below 8.5 g/dl would be an indication to transfuse in all apart from the younger fitter patient. A postoperative haemoglobin level of about 10 g/dl is widely accepted as a general guideline in adult surgical patients. However, it is more appropriate to base transfusion decision on a clinical assessment of the patient. If a major surgical procedure is planned, it may be possible to decrease the amount of donor blood transfusions by using an automated cell saver system.

About 80% of patients who have massive haemorrhage develop diffuse ooze from raw or cut surfaces. The causes are multifactorial but include relative hypothermia, abnormal platelet function, dilution of clotting factors, consumption of factors and enhanced fibrinolysis. It is critically important to monitor platelet numbers and the coagulation process during major bleeding and its resuscitation. The platelet count falls steadily with the transfusion of each successive unit of blood. Platelet infusion is indicated if there is:

- a platelet count less than 50 x 10^9/litre and there is impending surgery or an invasive procedure
- diffuse microvascular bleeding and transfusion greater than one blood volume and a platelet count of 50 x 10^9/litre or less, or the result is unavailable
- diffuse microvascular bleeding following cardiopulmonary bypass and the platelet count is 100 x 10^9/litre or less, or the result is unavailable
- bleeding in a patient with a qualitative platelet defect, regardless of platelet count.

Moderate deficiency of coagulation factors is common in massively transfused patients, but does not contribute to microvascular haemorrhage until levels fall below 20% of normal. These levels are reliably reflected by prolongation of the prothrombin (PT) and activated partial thromboplastin times (aPTT) to values of more than 1.5 times the control value. If the PT and aPTT are more than 1.5 times normal, 4 units of FFP should be given. If PT and aPTT are prolonged and fibrinogen is less than 0.8 g/litre, cryoprecipitate is indicated.

Arterial and central venous lines may be sited to allow rapid blood sampling, for acid–base and potassium status, and the direct measurement of arterial and central venous pressures. The central venous catheter also provides access for intermittent bolus administration of drugs or drug infusions.

A urethral catheter should be passed unless contraindicated by pelvic or urethral injury, and urine output monitored.

Core temperature should be measured continuously and every effort made to prevent heat loss. Hypothermia causes platelet dysfunction, reduced metabolism of citrate and lactate and an increased tendency to cardiac arrhythmias. This may result in bleeding diathesis, hypocalcaemia, metabolic acidosis and cardiac arrest.

Arrhythmias

Arrhythmias are one of the most commonly reported critical incidents. About 12% of patients undergoing anaesthesia develop arrhythmias; this increases to 30% in patients with cardiovascular disease. Treatment may not be required; this depends on the nature of the arrhythmia and its effect on cardiac output. Single supraventricular or ventricular ectopic beats, and slow supraventricular rhythms, do not require treatment unless cardiac output is compromised.

Management

Fluid, electrolyte and acid–base disturbances should be corrected preoperatively. Particular attention should be paid to the level of potassium ions in the plasma because they have a vital role in the generation of the resting membrane potential and thus muscle and nerve function. Patients with hypokalaemia may be prone to the development of supraventricular or ventricular extrasystoles and tachycardias. ECG changes of hypokalaemia include a long PR interval, ST depression, T wave flattening and a prominent U wave. Rapid treatment is indicated if arrhythmias are present. Intravenous administration of potassium supplements should not exceed 0.5 mmol/kg/hour.

Continuous intraoperative ECG monitoring is essential. The ECG gives no indication of cardiac output or tissue perfusion, therefore the detection of an abnormal cardiac rhythm should be followed by clinical assessment of the circulation. An absent pulse, severe hypotension or ventricular tachycardia or fibrillation should be treated as a cardiac arrest.

Correcting the precipitating factor is often the only treatment required. Hypoxaemia and inadequate anaesthesia or analgesia must be excluded. Factors associated with the development of arrhythmias are listed in Figure 3.

Intervention with a specific antiarrhythmic agent or cardioversion is indicated if there is:

- a risk of developing ventricular tachycardia or fibrillation (e.g. frequent, multifocal ectopic beats, or 'R on T' complexes)
- a significant decrease in cardiac output (causing dizziness or hypotension)
- evidence of myocardial ischaemia (causing chest pain or ST segment changes).

Factors associated with the development of arrhythmias

Preoperative conditions

- Ischaemic heart disease
- Pre-existing arrhythmias
- Congestive heart failure
- Hypertension
- Valvular heart disease
- Electrolyte disorders
- Medications (theophylline, β_2-agonists, tricyclic antidepressants)
- Others (thyrotoxicosis, myocarditis, cardiomyopathies, trauma, drug and solvent abuse)

Anaesthetic factors

- Hypoxaemia
- Hypo/hypercapnia
- Hypo/hypertension
- Laryngoscopy
- Drugs (e.g. volatile anaesthetic agents, suxamethonium, central venous pressure lines)

Surgical factors

Catecholamines

- Exogenous (e.g. infiltrated adrenaline (epinephrine))
- Endogenous (inadequate analgesia, inadequate anaesthesia)

Autonomic stimulation

- Oculocardiac reflex
- Laryngoscopy, bronchoscopy, oesophagoscopy
- Carotid artery and thyroid surgery
- Peritoneal and visceral traction
- Peritoneal insufflation

Direct stimulation of the heart

- Cardiac and thoracic surgery

Embolism

- Thrombus, fat, air, carbon dioxide, amniotic fluid

Others

- Limb reperfusion
- Aortic cross-clamping

Bradycardia can be treated with an anticholinergic agent such as atropine, 0.6 mg i.v., or glycopyrrolate, 0.2–0.4 mg i.v. If the bradycardia is refractory to treatment, cardiac pacing or an intravenous infusion of isoprenaline, 0.5–10 µg/minute, may be indicated. An anticholinergic drug may be given prophylactically if there is risk of bradycardia (e.g. strabismus surgery or following a second dose of suxamethonium).

Sinus tachycardia associated with myocardial ischaemia may be controlled by administration of a β-blocker such as metoprolol, 2 mg increments slow i.v., maximum dose 15 mg, or esmolol, 500 µg/kg, loading dose followed by 50–200 µg/kg/minute infusion.

Junctional rhythms are usually associated with the use of halothane. A reduction in concentration and/or changing the volatile agent is indicated. An anticholinergic drug may restore sinus rhythm.

Accelerated nodal rhythms may be precipitated by an increase in sympathetic tone in the presence of sensitizing volatile agents. Treatment includes adjusting the depth of anaesthesia and/or changing the anaesthetic agent.

Supraventricular tachycardia (SVT) can occur in susceptible patients, such as Wolff–Parkinson–White or other 'pre-excitation syndromes'. Treatment of SVT consists of:

- carotid sinus massage
- adenosine, 3–12 µg i.v.
- DC cardioversion if haemodynamic decompensation is present
- if there is no decompensation give verapamil, 5–10 mg slow i.v. over 30 seconds; the injection should stop when the SVT is controlled
- in sepsis-related or refractory SVT, volume loading plus amiodarone, 300 mg i.v. by infusion over 20 minutes, then 900 mg over 24 hours
- if the patient is thyrotoxic a β-blocker is useful.

Atrial fibrillation or flutter is often seen as a paroxysmal increase in the ventricular rate in patients with pre-existing atrial fibrillation or flutter. Having corrected any precipitating factors, the therapeutic options include:

- digoxin, 10 µg/kg by slow i.v. injection over 20 minutes, repeat after 4 hours according to response, maintenance dose 125–500 µg/day. Peak effect after 2 hours. Slows the ventricular rate and is a positive inotrope
- amiodarone produces a more rapid ventricular response and may re-establish sinus rhythm, give 300 mg i.v. by infusion over 20 minutes, then 900 mg over 24 hours
- β-blockers, especially in thyrotoxicosis, in combination with digoxin (e.g. propranolol 1 mg slow i.v. repeated every 2 minutes, maximum 5 mg)
- cardioversion is an option if the ventricular rate is fast with a clinically reduced cardiac output.

Premature ventricular contractions are common in healthy patients. Perioperatively they seldom progress to more serious arrhythmias unless there is underlying hypoxaemia or myocardial ischaemia. An underlying cause should be sought before antiarrhythmic agents are considered. If associated with a slow atrial rate, increasing the sinus rate with an anticholinergic drug will abolish them. Halothane lowers the threshold for catecholamine-induced ventricular arrhythmias; this is exacerbated by hypercapnia. Halothane should be used with care in patients receiving sympathomimetic drugs (including local anaesthetics containing adrenaline), and in patients taking tricyclic antidepressants and aminophylline.

Ventricular tachycardia and fibrillation should be treated as a cardiac arrest.

Malignant hyperthermia

Malignant hyperthermia is a rare inherited complication of general anaesthesia triggered by inhalational agents or suxamethonium in susceptible patients. The inheritance is complex and it is a genetically heterogeneous condition. These patients have a defect in intracellular calcium binding within the sarcoplasmic reticulum of skeletal muscle cells. Calcium ions are released on exposure to trigger agents, which initiates widespread skeletal muscle contraction and generalized membrane permeability. There is severe metabolic disturbance and catabolism runs unchecked, because raised levels of myoplasmic calcium ions result in increased production of pyruvate and heat. A successful outcome relies on making an early diagnosis, discontinuation of trigger agents, prompt treatment with intravenous dantrolene and supportive care. The mortality today has decreased to about 25% owing to increased awareness, monitoring and prompt treatment. The mode of presentation is variable and a high index of suspicion is required for early diagnosis.

Signs of malignant hyperthermia include:
- unusual muscle rigidity following suxamethonium (especially masseter spasm)
- unexplained tachycardia and arrhythmias
- rise in end-tidal carbon dioxide
- metabolic acidosis
- fall in oxygen saturation
- hyperkalaemia
- rise in core temperature (about 1–2°C/hour)
- evidence of a coagulation disorder, oozing from wound sites.

Management

Immediate actions
- Discontinue inhalational agents and inform the surgeons. Stop surgery if feasible, make the operating site safe and close wounds.
- Continue sedation or anaesthesia with a total intravenous technique. Hyperventilate with 100% oxygen using a clean breathing system. Change the circle system using fresh soda-lime, or use a non-rebreathing system.
- Immediately instruct staff to prepare dantrolene and commence as soon as available in an intravenous infusion of 1 mg/kg repeated at 10 minute intervals up to 10 mg/kg.
- Remove drapes, fully expose the patient and promote surface cooling with avoidance of vasoconstriction.
- Insert an arterial line to aid monitoring, and allow regular estimation of arterial blood gases, potassium and creatine kinase.
- Monitor the patient's core temperature.

Intermediate actions
- Control life-threatening dysrhythmias (e.g. β-blockers).
- Control hyperkalaemia with intravenous glucose or insulin.
- Control metabolic acidosis by hyperventilation, consider sodium bicarbonate (2–4 mmol/kg) if acidosis is severe (e.g. pH < 7.0).

Later actions
- Send blood for clotting screen (PT, aPTT, fibrinogen).
- Catheterize the patient. Test their urine for myoglobin. Collect samples for vanillylmandelic acid estimation to exclude phaeochromocytoma. Promote diuresis with intravenous fluids and mannitol, 0.5 g/kg over 20 minutes.
- Request a chest radiograph. Send blood for full blood count, biochemistry and thyroid function tests.
- Notify the intensive care unit.
- Repeat the creatine kinase estimation in 24 hours.
- Consider other diagnoses such as recreational drug ingestion (e.g. Ecstasy), neuroleptic malignant syndrome or myopathy.

Future care

The patient and their family should be counselled as to the likely diagnosis and the implications for future anaesthetics. Wearing a Medic-Alert bracelet should be encouraged. The patient and immediate family should be referred for further investigation and muscle biopsy to:

UK MH Investigation Unit, Academic Unit of Anaesthesia
Clinical Sciences Building
St James's University Hospital Trust
Leeds LS9 7TS
Tel: 0113 206 5274
Emergency hotline: 07947 609601

Future anaesthetic care can be provided safely with the avoidance of trigger agents – the volatile anaesthetics and depolarizing muscle relaxants. Prophylactic dantrolene is not recommended. Phenothiazines, antidepressants and haloperidol have been suggested as possible trigger agents, because of the similarity between malignant hyperthermia and the neuroleptic malignant syndrome, but this is unlikely. All other anaesthetic drugs appear to be safe.

Critical Incidents: The Respiratory System

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A critical incident during anaesthesia is any event that may result in actual or potential harm to the patient if uncorrected. It may cause severe morbidity or even mortality. It is often preventable by a change in practice. Incident reporting is the key to preventing future disaster. There is observer bias concerning which incidents are recorded, and the problem for anaesthetists is to distinguish between a critical incident and the normal course of clinical practice.

This contribution deals with life-threatening problems in the management of the respiratory system including the clinical and physiological presentation of some commonly encountered critical incidents and their treatment. All may be a cause of alarming cyanosis under anaesthesia. Not all the problems discussed can be prevented and so some may not meet the precise definition of critical incidents. The recommendations aim to provide the anaesthetist with fast and effective solutions that may be used in clinical, examination or simulation situations. In all cases, the trainee anaesthetist must request senior help at the earliest opportunity.

Aetiology

The 2000 report of the National Confidential Enquiry into Perioperative Deaths (NCEPOD) cites hypotension, hypoxaemia, arrhythmia and cardiac arrest as the most common critical events that occur during or immediately following surgery. It also concludes that modern anaesthetic equipment, when properly checked, is very reliable. Human factors often play a major role in the aetiology of adverse events (Figure 1).

Factors involved in avoidable deaths

- Error of judgement
- Error of clinical expertise
- Lack of experience
- Lack of assistance
- Lack of equipment
- Equipment failure

1

Preparation is an important factor in predicting and treating these events and should involve:

- thorough preoperative patient assessment
- check of all anaesthetic equipment
- appropriate selection of drugs
- appropriate level of clinical expertise.

The Association of Anaesthetists of Great Britain and Ireland (AAGBI) has recently published new recommendations for standards of monitoring during anaesthesia and recovery. The Royal College of Anaesthetists (RCA) has a web page (http://www.rcoa.ac.uk/critincident/ciweb.html) that deals with the processing of critical incidents. The RCA is committed to setting up a national database so that even rare incidents can be reported and acted on. Critical incidents should be discussed locally at regular departmental audit meetings to complement the process of clinical governance.

Respiratory obstruction and increased peak airway pressure

Obstruction to the airway is an immediate threat to life and is the most common critical incident registered. The 'airway' can be considered as the conducting pathway responsible for the delivery of oxygen from anaesthetic machine to the alveolar/blood interface. Thus, obstruction may occur from outside or within the patient. The anaesthetic machine, breathing system and connections must be checked to ensure their patency and correct function before anaesthesia.

Obstruction of the airway within the patient may arise from the upper, supraglottic region, to the lower bronchiolar region. It may be caused by the devices used during anaesthesia or result from airway anatomy, pathology or trauma. Figure 2 shows some of the likely causes of airway obstruction in the perioperative period.

Possible causes of airway obstruction

Supraglottic

- Tongue
- Periglottic abscess, tumour, haematoma
- Regurgitation of solid material
- Blood or secretions
- Laryngeal mask airway (LMA) or tracheal tube luminal occlusion or misplacement

Laryngeal

- Laryngospasm
- Tumour or oedema
- Post-thyroidectomy (laryngeal nerve injury)
- LMA or tracheal tube luminal occlusion or misplacement

Tracheal or bronchial

- Aspiration
- Asthma
- Anaphylaxis
- Pneumothorax
- Pulmonary oedema
- Tracheal obstruction by retrosternal goitre
- LMA or tracheal tube luminal occlusion or misplacement

2

Respiratory obstruction during induction of anaesthesia

Preoperative evaluation of the airway is vital and should include mouth opening, dentition, Mallampati score, jaw movement, thyromental distance and neck movement. The aim is to predict which patients may present difficulty with direct laryngoscopy and intubation and those in whom difficulty may arise with airway maintenance following loss of consciousness, such as those with:

- obesity or a 'bull neck'
- limited mouth opening (e.g. trismus, following infection, trauma)
- restricted head and neck movement (e.g. severe ankylosing spondylitis, rheumatoid arthritis)
- stridor resulting from tumour, trauma, infection or haem-atoma
- upper airway soft tissue swelling (e.g. burns, pre-eclampsia). About 10% of reported critical incidents occur in the anaesthetic room. Patient monitoring during induction of anaesthesia should follow the guidelines established by the AAGBI. The patient must be monitored adequately during this stage of anaesthesia. If the required equipment is unavailable, induction should take place in the operating theatre.

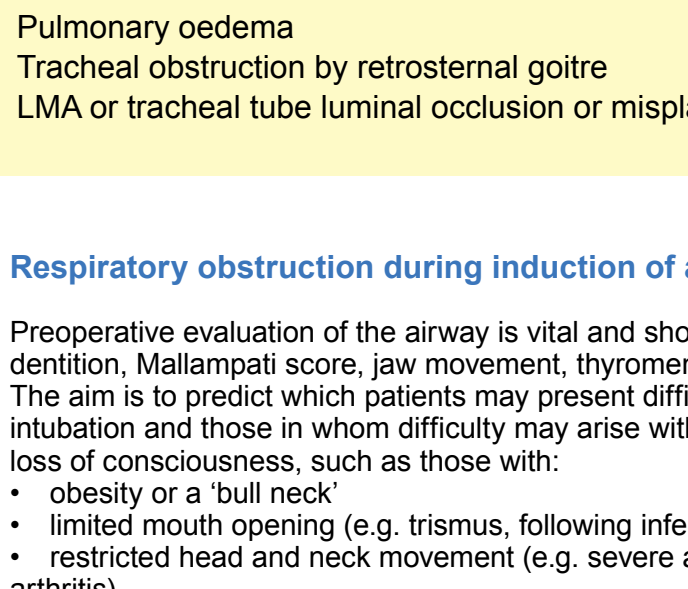
Induction of anaesthesia in patients with upper airway obstruction requires specialized expertise. Management must involve a clear plan of how to proceed in the event of total airway obstruction during induction. These patients are best managed in the operating theatre with surgeons gowned and ready to perform immediate tracheostomy under local anaesthesia if necessary.

In routine practice, airway obstruction that occurs following induction is apparent from:

- paradoxical (see-saw) chest movement (when breathing spontaneously)
- noisy airway
- absent or diminished movement of the reservoir bag
- absent or diminished capnograph trace
- increased airway pressure (when mechanically ventilated)
- progressive oxygen desaturation.

Simple airway manoeuvres such as chin lift and jaw thrust, often combined with the insertion of a correctly sized oropharyngeal or nasal airway are necessary to maintain airway patency following induction. In apnoeic patients or those requiring assisted ventilation, bag and mask ventilation by two operators is more effective than that provided by one operator (Figure 3), allowing more effective face mask application and upper airway management. Manual ventilation with bag and mask is then easier to perform. If management is difficult, it is important to switch to 100% oxygen and call for senior help early on.

Two operators providing bag and mask ventilation



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If airway obstruction persists, a laryngeal mask airway (LMA) often corrects the situation. While tracheal intubation provides a definitive airway, it may be difficult to insert in a patient who has not received muscle relaxants. Neuromuscular blockade should never be administered unless airway patency can be assured. However, if airway maintenance is lost following the administration of muscle relaxants then swift direct laryngoscopy and tracheal intubation should be attempted. Some patients (e.g. those with adenotonsillar hypertrophy, the obese or heavy snorers) are often easy to intubate despite having a difficult airway to maintain with bag and mask. The LMA is also the technique of choice following a failed intubation if subsequent airway management is difficult. Numerous reports testify to the ability of the LMA to provide a clear airway following a failed intubation. The *Combitube* may also be useful, though it is less commonly used in the UK. Both are 'supraglottic' airway devices, therefore it is unlikely that the *Combitube* will provide a clear airway if the LMA does not.

Can't intubate, can't ventilate (CICV)

The inability to intubate or ventilate a patient is rare, with an estimated incidence of 1/10,000 anaesthetics. It occurs when alveolar ventilation cannot be maintained despite best attempts at intubation and bag-mask ventilation (Figure 4).

Analysis of closed-claims in the USA revealed that the most common predisposing factor in the development of CICV was repeated and continued attempts at intubation. With each successive period of re-oxygenation between intubation attempts, bag-mask ventilation became increasingly difficult as laryngeal oedema evolved. The anaesthetist should limit intubation attempts to a maximum of three. The decision must be made early to abandon further attempts at intubation and the anaesthetist must use an alternative airway device, or wake the patient. The main causes of CICV are:

- repeated failed attempts at intubation
- airway or neck trauma
- burns to the head and neck
- pregnancy (especially pre-eclampsia)
- tumour (e.g. larynx)
- infection.

Requirements for optimum best attempts

Optimum best bag-mask ventilation

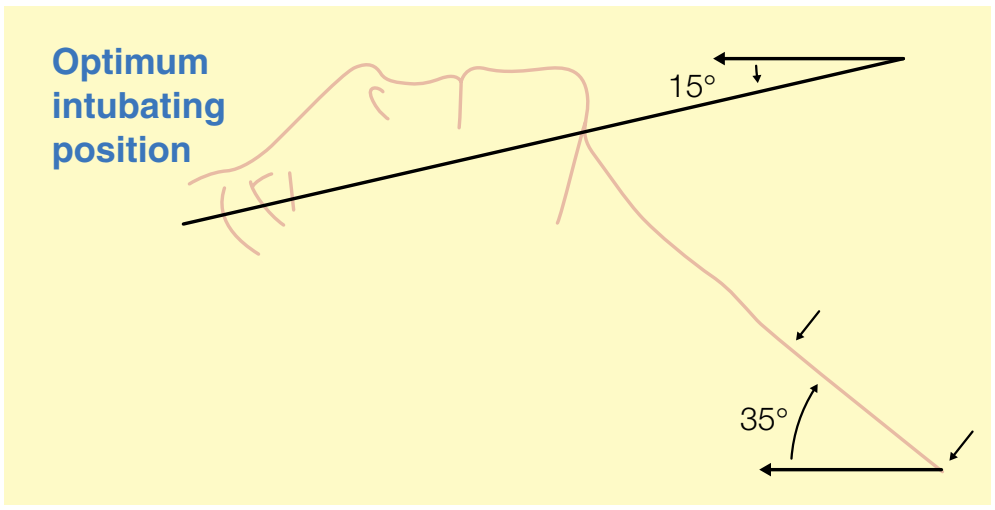
- Correctly sized oral or nasal airway
- Two-operator technique

Optimum best laryngoscopy

- Trained anaesthetist (3 years' training)
- Optimal intubating position
- Optimal external laryngeal manipulation
- Optimal laryngoscope

4

The optimal intubating position is shown in Figure 5. Flexion of the cervical spine, and extension of the head at the atlanto-occipital joint, aligns the glottis with the visual axis. In the obese or pregnant woman at term, this may require at least one pillow under the shoulders and two pillows beneath the head and neck. Anaesthetic induction and tracheal intubation should be avoided when patient positioning is not ideal.



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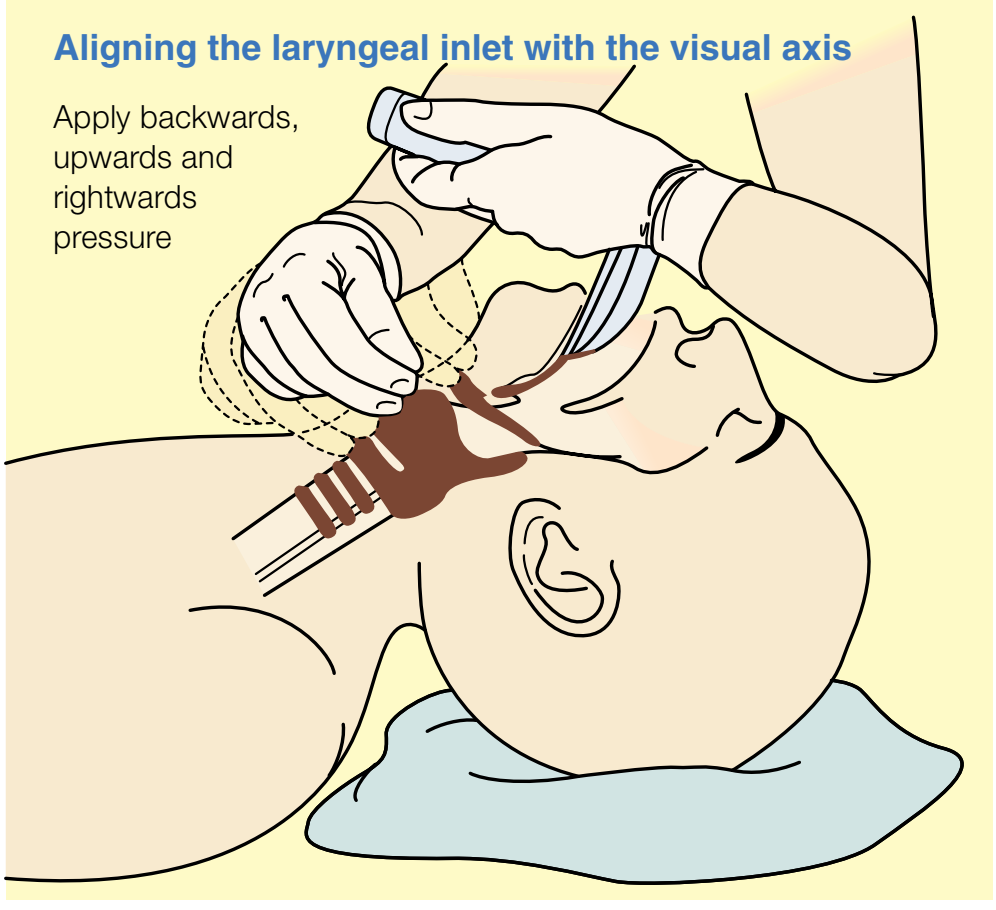
The larynx should be manipulated from the front of the neck by the operator's free hand to help provide the best view. This position is maintained by the anaesthetic assistant while intubation is performed. Optimum external laryngeal manipulation does not mean 'cricoid pressure', which may further distort the view and make direct laryngoscopy more difficult. Optimum manipulation involves direct manipulation of the thyroid cartilage of the larynx. The application of backwards, upwards and rightwards pressure aligns the laryngeal inlet more closely with the visual axis. Correct optimum external laryngeal manipulation is shown in Figure 6.



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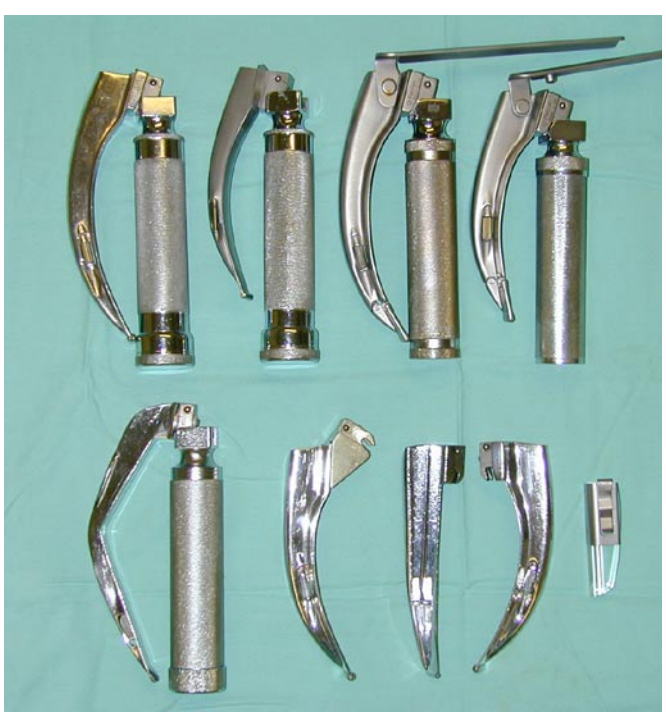
The choice of laryngoscope blade is important. A useful guideline is to change the length of blade once, and the type of blade once, to achieve the best view. A variety of blades is available in clinical practice. The standard Macintosh blade (size 3) may need to be changed to a longer blade (size 4) or to a levering blade such as the McCoy. The McCoy blade can be successful in improving the laryngoscopic view by one grade (Cormack and Lehane grade 3 to 2). The Belscope blade has a 45° angle and a detachable prism, and may similarly improve a grade 3 view. The Polio blade is inclined at an angle greater than 90° to the handle, which may aid insertion into the mouth (Figure 7).



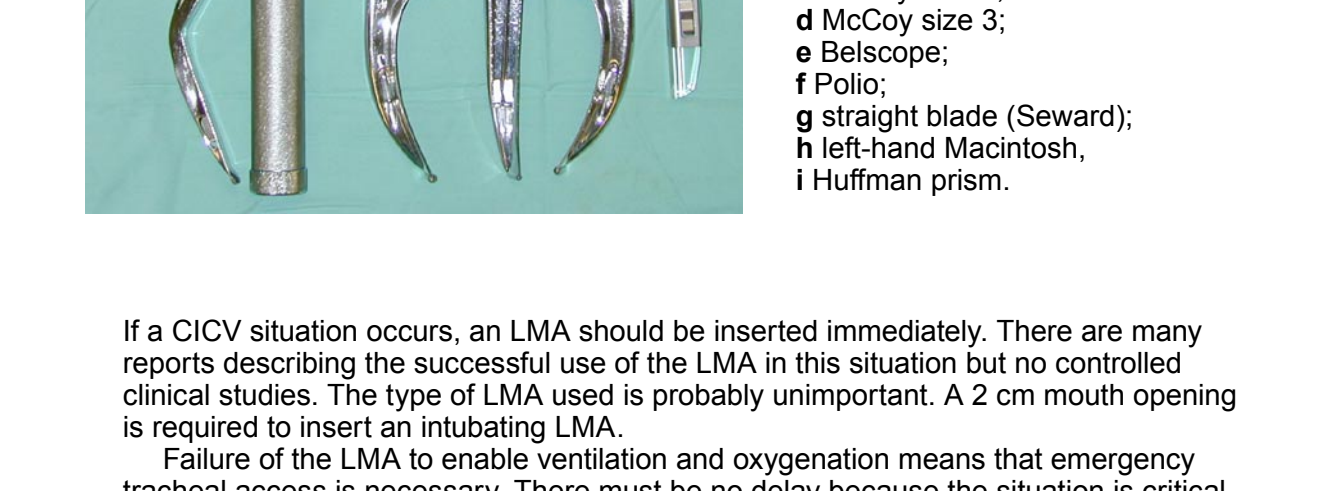
7 Laryngoscope blades:
a Macintosh size 4;
b Macintosh size 3;
c McCoy size 4;
d McCoy size 3;
e Belscope;
f Polio;
g straight blade (Seward);
h left-hand Macintosh,
i Huffman prism.

If a CICV situation occurs, an LMA should be inserted immediately. There are many reports describing the successful use of the LMA in this situation but no controlled clinical studies. The type of LMA used is probably unimportant. A 2 cm mouth opening is required to insert an intubating LMA.

Failure of the LMA to enable ventilation and oxygenation means that emergency tracheal access is necessary. There must be no delay because the situation is critical in a patient with marked hypoxia. Tracheal access is best achieved via the cricothyroid membrane by needle puncture, percutaneous cricothyrotomy or surgical cricothyrotomy. The precise technique depends on: the equipment available; the experience of the anaesthetist; and the nature of the emergency.

It is impossible to give firm recommendations but whatever the means used, the immediate aim is to achieve oxygen delivery to the trachea (and alveoli) via the cricothyroid membrane. This membrane lies subcutaneously between the cricoid and thyroid cartilages of the larynx and in the adult measures 1 x 3 cm. It will accept a tracheal tube of maximum size 7.0 internal diameter (ID). Paired cricothyroid arteries arise from the superior border and pass laterally. The patient's head and neck should be extended to bring the cricothyroid membrane closer to the skin surface to facilitate access. Placing a sandbag or 1 litre fluid bottle between the patient's scapulae may help to achieve this.

Needle cricothyrotomy is minimally invasive but requires a jet ventilator to achieve satisfactory alveolar ventilation. A cannula is inserted via the cricothyroid membrane (Figure 8), free aspiration of air confirms correct placement. Resistance through the cannula is too high to enable conventional bag ventilation. Simple emergency systems can be constructed using green oxygen tubing connected to a flowmeter (e.g. 10-15 litres/minute). A side hole or three-way tap allows for intermittent insufflation by finger occlusion of the hole. The green oxygen tubing is inserted into the barrel of a 2 ml syringe which then allows connection to the cannula. The free end is connected to an oxygen flowmeter or to the anaesthetic machine via a 15 mm connector. Oxygen insufflation techniques provide tracheal oxygen delivery but not satisfactory carbon dioxide elimination. It is recommended that all sites where anaesthesia is administered have access to a jet ventilator. The inspiratory time of about 1 second should be followed by a 3 second expiratory time. It is unlikely that airway obstruction is absolute and passive exhalation will occur via the glottis. If this is deemed inadequate a second cannula should be placed to allow exhalation and prevent overinflation and barotrauma. A needle cricothyrotomy is a temporary measure and preparations should be made for a formal tracheostomy.



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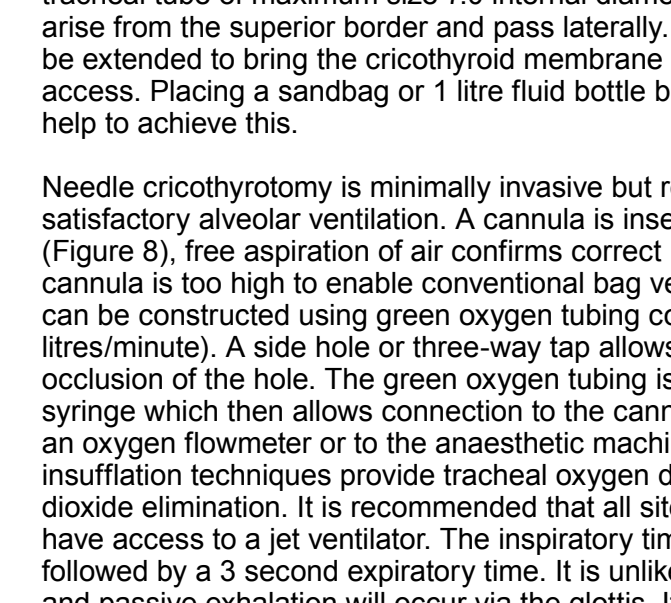
Specific cricothyroid cannulae are available for emergency tracheal access (Figure 9). The Ravussin 13 G jet ventilation catheter (VBM Medical) is flanged to simplify fixation, and has both Luer-lock and 15 mm connections. The Cook 6 F emergency transtracheal catheter is spiral reinforced and kink-resistant; a standard 14 G intravenous catheter is easily kinked and difficult to fix. The main complication of the technique is incorrect needle position and subcutaneous/mediastinal emphysema.



9 Cricothyrotomy needles.
a 13 G Ravussin jet ventilation catheter (VBM Medical);
b 6 F Cook emergency transtracheal catheter;
c 14 G Venflon cannula.

Percutaneous cricothyrotomy allows emergency placement of a tracheal tube to allow more conventional ventilation via bag and mask. Several commercial kits are available, which differ in insertion technique (Seldinger or non-Seldinger), size of tube (3.5-6.0 ID), and time taken for tube placement. There are insufficient data to make recommendations concerning the optimum technique and the anaesthetist should be familiar with the equipment available in their hospital. A non-Seldinger kit (e.g. VBM Quicktrack, 4.0 mm ID) generally allows the most rapid access by direct cricothyroid puncture using a large diameter sharpened stylet. A Seldinger technique (e.g. Cook Melker kit 3.5-6.0 mm ID) may be safer to perform but requires several stages including the use of a dilator. All techniques require familiarization. Complications include bleeding, malposition and subcutaneous emphysema.

Surgical cricothyrotomy rapidly provides a definitive airway, though it requires more surgical experience and bleeding is likely to be considerable. It is ideally suited to the emergency trauma setting in the presence of severe maxillofacial, neck or laryngeal injury. Thorough training is necessary for this seldom performed but life-saving procedure. Practising on the sheep's larynx provides a realistic training model.

With finger and thumb either side, the cricothyroid membrane should be stabilized. A 22 scalpel blade is used to make a 2 cm vertical skin incision to part the skin. The scalpel should then be horizontally inserted into the cricothyroid membrane, perpendicular to the skin. This incision should be enlarged laterally. The scalpel handle should be inserted through the cricothyroid incision and rotated through 90°, then removed. A well-lubricated size 7.0 ID cuffed tracheostomy tube should be inserted. The main complications are bleeding and malposition.

Respiratory obstruction during the intraoperative period

If respiratory obstruction occurs during surgery, the following procedure will help to diagnose the cause of obstruction (Figure 2) and guide appropriate action to correct the situation. Surgery can then recommence.

- 100% oxygen should be commenced.
- The surgeons should be alerted to the problem and advised to stop surgery. The surgical stimulation may have caused the obstruction. Procedures such as dilation of the cervix or anus may precipitate severe stridor especially if anaesthesia is 'light'.
- The anaesthetic delivery circuit should be checked rapidly.

If it is patent, the obstruction must be within the patient.

- Access to the airway may be difficult, especially in head and neck surgery. Extreme circumstances of continued patient deterioration require the complete uncovering of surgical drapes and exposure of the airway.
- The upper airway should be checked for secretions, signs of regurgitation or obvious tube or LMA obstruction. The mouth and trachea should be suctioned if indicated.
- The capnograph confirms alveolar ventilation by displaying a carbon dioxide trace. Absence of a trace is a sign of complete airways obstruction. The normal capnograph trace may change in airways obstruction with a characteristic marked upslope to the alveolar plateau.
- The urgency of the situation is indicated by the oxygen saturation. If there is any doubt about the tracheal tube position, immediate replacement is needed. An LMA will need repositioning or changing to a tracheal tube. Careful observation of the chest wall during manual ventilation may show unilateral or little chest movement. Auscultation of the chest may detect unilateral air entry, wheeze or absent breath sounds. Withdrawing the tracheal tube slightly may alleviate this if the distal end has migrated to the endobronchial position, or is in contact with the carina.
- Fibre-optic bronchoscopy will confirm the position of the tracheal tube and that there is no intraluminal obstruction such as a sputum plug, blood clot or in rare circumstances, an endoluminal tumour.

Bronchospasm during anaesthesia

Bronchospasm is reversible airways obstruction most commonly associated with patients who have asthma or chronic chest disease. The incidence of asthma is 5-10% with a higher prevalence in children. Smokers and patients with upper respiratory tract infection are also at increased risk of bronchospasm. Bronchospasm occurs as a result of smooth muscle constriction within the respiratory subepithelial layers in the bronchioles. It may be accompanied by other pathological effects (e.g. mucosal oedema, cellular infiltrates, mucus secretion, desquamation of surface epithelial cells, goblet cell hyperplasia) which exacerbate smooth muscle contraction. Contraction is stimulated by neural or paracrine effects. Chemical mediators such as histamine and products of arachidonic acid, the leukotrienes, may act locally to initiate bronchoconstriction.

Bronchospasm is not the only cause of intraoperative wheeze (Figure 10). Luminal occlusion from eccentrically inflated tube cuffs (cuff herniation) used to occur with red rubber tracheal tubes, but modern disposable materials have made this complication less common, however the tracheal tube cuff should not be over-distended. The old adage 'if in doubt – take it out' remains true. A monophonic wheeze developing immediately after intubation may indicate tube occlusion, or a distal position next to the carina or within a bronchus.

Bronchospasm is suggested by:

- increased respiratory effort, tachypnoea and intercostal recession (if spontaneously breathing)
- expiratory wheeze (wheeze throughout the respiratory cycle may indicate obstruction within the breathing equipment)
- rise in inspiratory airway pressure (if mechanically ventilated). Management of wheeze while under anaesthesia is as follows.
- The surgeons should be alerted and asked to stop surgery.
- 100% oxygen should be delivered and anaesthesia deepened. Bronchospasm may result from a depth of anaesthesia that is too light for the degree of surgical stimulation. This includes stimulation of the airway by the anaesthetist. All modern inhalational agents are bronchodilators.
- The breath sounds over both lung fields and over the stomach should be listened to. Capnography confirms tracheal intubation. Tracheal tube position should be adjusted if necessary. Signs of pulmonary oedema or tension pneumothorax should be sought.• The position of the tracheal tube should be adjusted if necessary.
- The airway should be checked and the trachea should be suctioned looking for signs of aspiration.
- Full monitoring should be in place. Extreme tachycardia and cardiovascular collapse suggest anaphylaxis.

The treatment of bronchospasm includes the following.

- The inspired concentration of volatile anaesthetic agent should be increased.
- The patient should be treated with continuous inhaled salbutamol nebulizers, 5 mg, and ipratropium, 500 µg, until the wheeze settles. This is best delivered using a separate oxygen cylinder with nebulizer attachment, connected to the tracheal tube on the patient side of any heat/moisture exchange filter.
- If wheeze persists, aminophylline, 250−500 mg (5 mg/kg) i.v.in 500 ml normal saline over 20 minutes can be given (if notalready treated with theophylline or aminophylline preparations); continue with an infusion of 0.5 mg/kg/hour if needed.
- If bronchospasm is severe, salbutamol, 250 µg bolus i.v. over 5−10 minutes may be given, and continued as an infusion of 5 µg/minute, adjusted according to the heart rate and bronchospasm response.
- It may be necessary to adjust ventilator settings. A longer expiratory time may be needed to allow more complete exhalation, though a short inspiratory time will produce higher peak inspiratory pressures. An I:E ratio of 1:2 or 1:1.5 is usual.
- Hydrocortisone, 200 mg i.v., is not immediately effective but provides bronchospasm relief within 6–12 hours.
- Management of anaphylaxis will be covered in **CLINICAL ANAESTHESIA.**

Causes of intraoperative wheeze

- Endobronchial intubation
- Mechanical obstruction of the tracheal tube
- Bronchospasm
- Anaphylaxis
- Pulmonary oedema
- Tension pneumothorax
- Aspiration of gastric contents

Failure to breathe

A delay in the return of spontaneous respiration following anaesthesia is most commonly the result of an imbalance between the:

- patient requirements of anaesthesia and analgesia (differences caused by normal variation and the effects of coadministered drugs or disease)
- doses of drugs used
- timing of their administration.

In all patients, maintain ventilation to ensure satisfactory oxygenation and carbon dioxide removal. The patient is likely to be unconscious and usually all that is required is more time. If there is continued apnoea, inconsistent with the clinical picture, then a careful evaluation of the cause is needed. The patient should be reassured if they are conscious.

Assess neuromuscular block − a train-of-four ratio of 75% is usually adequate for satisfactory ventilation following anaesthesia. The presence of four good twitches with absent fade implies adequate reversal. Modern nerve stimulators (e.g. the train-of-four watch) can provide more accurate assessment of neuromuscular function by measurement of thumb acceleration (and thus force, because the mass of the thumb is constant). The standard 1 ml ampoule of glycopyrrolate, 0.5 mg/neostigmine 2.5 mg, is the correct reversal dose for a 50 kg patient. The ability to sustain a 5-second head lift from the pillow is a useful clinical indicator of neuromuscular recovery. Figure 11 shows factors that prolong the action of a non-depolarizing neuromuscular block.

Factors that may increase duration of non-depolarizing neuromuscular block

- Hypokalaemia
- Hypothermia
- Hypocarbia
- Neuromuscular disease (e.g. myasthenia gravis, Eaton-Lambert syndrome)
- Inhalational anaesthetic agents
- Aminoglycosides
- Calcium antagonists
- Magnesium
- Local anaesthetics
- Lithium
- Frusemide

Partial reversal of neuromuscular block presents as respiratory inadequacy together with jerky, uncoordinated gross muscular movement. Laryngeal muscle weakness can produce airway obstruction and stridor. The best treatment is to:

- reassure the patient (they may be distressed and feel unable to breathe, with tachycardia and hypertension) and administer 100% oxygen
- help allay anxiety by giving midazolam, 2 mg i.v. or reintroduce general anaesthesia for a short period of time
- correct any underlying cause
- administer further neostigmine (with glycopyrrolate) to a total of 70 µg/kg i.v. (maximum dose 5 mg) if necessary.

Plasma cholinesterase activity − if suxamethonium (or mivacurium) has been used and return of adequate neuro-muscular function is delayed, it is likely that plasma cholin-esterase activity is decreased. This may be an inherited abnormality of cholinesterase activity or an acquired reduction in enzyme activity (Figure 12). The genetic variants have autosomal dominant inheritance, and the prevalence of homozygotes for the atypical gene is 1:2500 of the Caucasian population. Only homozygotes display significantly prolonged apnoea. This may produce many hours of continued paralysis. The patient will come to no harm providing ventilation is supported and adequate sedation is continued (e.g. propofol, 4−6 mg/kg/hour). Neuromuscular block should be monitored with a nerve stimulator and eventually wears off. Infusion of fresh frozen plasma containing cholinesterase enzyme speeds recovery of neuro-muscular function. The benefits must be balanced against the cost and infection risk. Acquired conditions (Figure 12) that reduce plasma cholinesterase activity may slightly increase suxamethonium duration.

Factors that may cause decreased plasma cholinesterase activity

Congenital

- Autosomal dominant inheritance of abnormal enzyme Four alleles have been identified: $E1^n$ normal, $E1^a$ atypical, $E1^f$ fluoride-resistant, $E1^s$ silent

Acquired

- Infections
- Malignancy
- Chronic disease
- Liver disease
- Renal failure
- Pregnancy, oral contraceptives
- Hypothyroidism
- Drugs (monoamine oxidase inhibitors, ecothiopate eye drops, organophosphorus compounds, chemotherapy)

Doxapram is a central respiratory stimulant that may reverse the respiratory depression caused by general anaesthetic agents and potent analgesics. It does not reverse the other effects of opioids. It acts by direct stimulation on the carotid body chemoreceptors. A maximum dose of 1.5 mg/kg slow i.v. can be given.

Benzodiazepines − flumazenil can be used to reverse the central sedative effects of benzodiazepines. It has a shorter half-life than midazolam and diazepam, and therefore re-sedation is possible. Flumazenil, 200 µg i.v., should be given followed by 100 µg i.v. every minute as necessary. The maximum total dose is 1 mg. While benzodiazepines may contribute to postoperative sedation, they seldom cause apnoea unless large doses are used or the patient is elderly and frail.

Opioid drugs − if excessive narcotic is suspected, then give naloxone by titrating dose to effect. Dilute 400 µg in 10 ml normal saline and give 1−2 ml every few minutes to achieve the desired effect. It is important not to use excessive naloxone to prevent reversal of the analgesic effect. Pain, hypertension and tachycardia may result. The patient must be observed closely for the next 4−6 hours because the duration of the naloxone effect may be shorter than that of the opioid.

Check end tidal carbon dioxide tension ($P_{E'}CO_2$) – hyperventilation during anaesthesia results in reduced respiratory drive. Spontaneous ventilation is unlikely to occur until the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and $P_{E'}CO_2$ have normalized. The addition of 5% carbon dioxide to the inspiratory gas mixture was common in older anaesthetic practice to stimulate respiratory drive. Hazards associated with carbon dioxide use, in particular the inadvertent use of carbon dioxide from incorrect flowmeter settings, have removed the use of this gas from modern practice.

The $P_{E'}CO_2$ should be allowed to rise by itself by either reducing minute volume, or adding dead space into the breathing system (e.g. disconnection of the absorber from a circle system).

Body temperature – hypothermia delays recovery from anaesthesia, prolongs the duration of neuromuscular blockade and is an important cause of postoperative hypoventilation. The fall in core temperature that occurs with anaesthesia should be anticipated and minimized using passive or active rewarming (see *Anaesthesia and Intensive Care Medicine* **1:3:** 122). Continued ventilation in the recovery area or ICU may be required until rewarming is completed and spontaneous ventilation is satisfactory.

Neurological vital signs − an intracranial bleed during surgery is a rare cause of continued unconsciousness and apnoea. It may occur as a result of an undetected head injury in patients undergoing surgery for trauma, or coincidentally in patients with cerebrovascular disease. A CT scan is required for diagnosis.

Investigations in the patient who fails to breathe following anaesthesia should include:

- blood gases, electrolytes and glucose
- body temperature
- neuromuscular function (nerve stimulator)
- ECG and chest radiograph
- CT head scan
- blood for serum cholinesterase activity if indicated.

Air embolism

If bubbles of gas enter the circulation, they may accumulate in the right ventricle. Unlike liquid, gases are compressible, and therefore adequate ejection of blood is not achieved, reducing stroke volume and cardiac output. This can present clinically as a minor fall in blood pressure, hypoxaemia or complete cardiovascular collapse with electromechanical dissociation. If a patent foramen ovale is present, or any other shunt-causing communication between the right and left sides of the heart, the air could enter the systemic circulation and cause neurological injury or coronary artery embolism and infarction (paradoxical air embolism). The effects of air embolism depend on the:

- volume of air entrained
- rate at which it enters the circulation
- general condition of the patient.

Experiments in dogs suggest that volumes greater than 20 mlare potentially fatal.

Some operations carry an increased risk of air embolus (Figure 13). Air may be entrained into an open vein when the venous pressure is subatmospheric. Air embolism occurs in 25−50% of all craniotomy operations in the sitting position and the incidence has reduced now this position is seldom used. The prone position with head tongs appears to be safer for posterior fossa surgery.

Procedures with increased risk of air embolus

- Posterior cranial fossa neurosurgery (especially in the sitting position)
- Lumbar laminectomy and head and neck surgery when the vertebral column is positioned above the level of the heart
- Hepatic surgery that carries a risk of opening the inferior vena cava
- Any patient with a central venous pressure catheter in situ that may result in accidental entrainment of air
- Varicose vein ligation
- Surgery combined with low venous pressures (e.g. in children)

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Signs that alert the anaesthetist to the development of air embolism are usually detected by monitoring. Early diagnosis allows prompt institution of preventive measures before the situation becomes critical. The signs of air embolus include:

- sudden fall in $P_{E'}CO_2$ despite unchanged ventilatory settings (if breathing spontaneously the patient may develop respiratory distress)
- turbulent blood flow (monitored by precordial Doppler probe; conventional auscultation may reveal continuous ‘millwheel’ murmur as a late sign)
- fall in oxygen saturation
- pulmonary artery pressure increases during air embolism (it is not often monitored)
- arterial hypotension
- tachycardia, dysrhythmias or cardiac arrest.

Management (Figure 14) comprises prevention of further air entrainment, attempts to remove the air and supportive measures.

Management of air embolus

- Ventilate the patient with 100% oxygen. Stop nitrous oxide administration
- Flood the surgical site with normal saline, wet packs, and apply bone wax to any area of exposed bone cortex. Manually compress the proximal veins to stop further air entrainment
- Attempt to increase venous pressure
  - Position patient head down (or surgical site down)
  - Give rapid fluid bolus (250−500 ml) and observe effects
  - Use vasopressors if the arterial blood pressure is severely affected
  - Compression of the abdomen
  - Activation of antigravity venous compression device (G suit) if fitted
- If a central venous catheter (CVC) is in situ, try to aspirate air from all lumens. Insert a CVC (right internal jugular or subclavian) if one is not present
- The left lateral position may transfer air from the pulmonary artery to the right ventricle, thereby improving pulmonary flow (there is little evidence that this is of benefit)
- Give cardiopulmonary resuscitation if required

14

Pneumothorax

The pleural cavity usually exists only as a potential space between the parietal pleura (attached to the innermost intercostal muscle, the transversus thoracus), and the visceral pleura (continuous with the lung parenchyma). A pneumothorax occurs when this potential cavity is opened, either by breaching the chest wall structures (an open pneumothorax), or by injury to the lung parenchyma (a closed pneumothorax).

- The clinical management is concerned with releasing the accumulation of air from the cavity and correcting the chest wall injury. Understanding the anatomy of the chest cavity allows cause and effect to be identified rapidly.
- The dome of the lung protrudes superiorly above the thoracic inlet to the level of the 6th cervical vertebra. The tip of a needle inserted towards the internal jugular vein could pass more posteriorly where it may cross the pleural space and enter the apices of the lung parenchyma. This is possible even with a relatively high approach.
- The inferior part of the chest cavity extends to the costo-diaphragmatic recess. This reaches to the crura of the diaphragm at the level of the 12th thoracic vertebrae. The cavity can be entered inadvertently in this low position by surgery to the renal bed or lower thoracic and upper lumbar vertebrae.
- The mediastinal pleura lies against the vertebral bodies, oesophagus, aorta, large veins, heart and trachea. Damage to many of these mid-chest structures could allow air or blood to enter the pleural cavity. Trauma from accidents or surgical instrumentation of the oesophagus or trachea may cause this.

The signs and causes of a developing pneumothorax while under general anaesthesia are shown in Figure 15; some or all may be present depending on the nature of the pneumothorax (simple or under tension), its speed of onset, the general health of the patient and whether they are breathing spontaneously or are mechanically ventilated.

Signs and causes of pneumothorax

Signs

- Hypoxaemia
- Wheeze
- Increasing airway pressure
- Unilateral chest wall motion
- Reduced air entry
- Hyperresonance
- Distended neck veins
- Shock
- Shifted trachea away from affected side

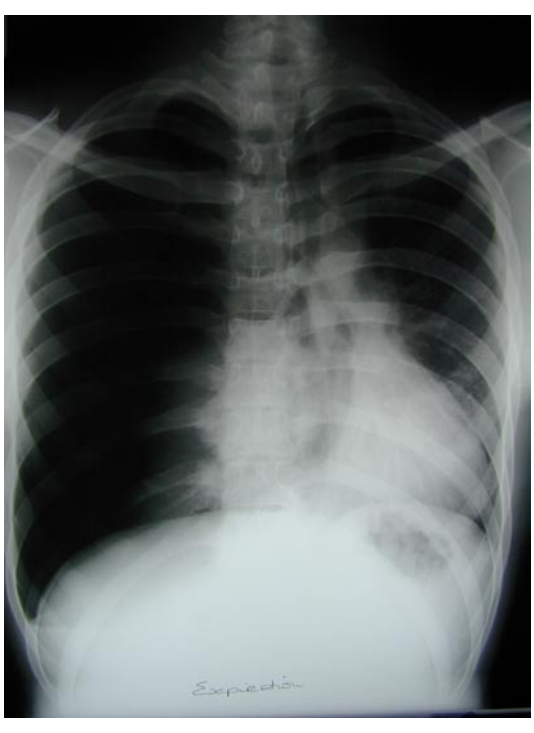
Causes

- Central venous catheter insertion
- Penetrating or blunt chest trauma
- Diaphragmatic, tracheal, oesophageal or cardiac surgery
- Chest drain clamping
- Spontaneous bullae rupture

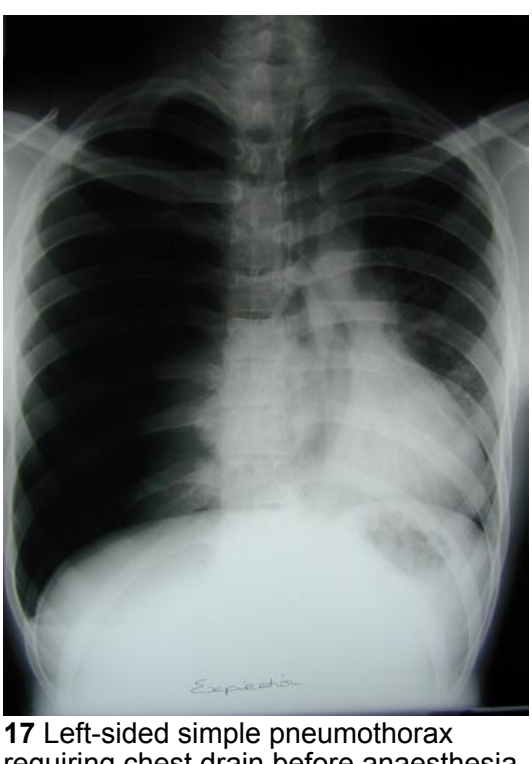
15

In trauma patients, pneumothorax should be identified and treated by chest drain insertion before anaesthesia to avoid the dangers of tension pneumothorax following the start of positive pressure ventilation (Figures 16 and 17). If there is obvious chest injury, but no clinical sign or chest radiograph appearance of pneumothorax, ‘prophylactic’ bilateral chest drains may be indicated. The risks of chest drain insertion must be balanced against the consequences of a tension pneumothorax developing during interhospital or intrahospital transfer or during the perioperative period.

Immediate management of a tension pneumothorax is chest decompression using a 14 G cannula inserted in the midclavicular line and second intercostal space. This should be followed immediately by formal chest drain insertion.



16 Right-sided tension pneumothorax requiring immediate needle decompresion followed by chest drainage. Gross mediastinal deviation is shown to the left.



17 Left-sided simple pneumothorax requiring chest drain before anaesthesia.

Electrical Hazards: Their Causes and Prevention

John Moyle

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Before 1940 there was little electrical equipment in the operating theatre apart from crude radiofrequency diathermy. Since then there has been an invasion of electronic monitoring equipment and many surgical tools are electrically powered. The operating theatre and ICU are unique in electronic engineering because deliberate electrical contact is made with the human body.

The body should be protected from electric current. The body may be considered as an electrolyte solution, which is a good conductor of electricity, contained in a leather bag. Dry leather is a good electrical insulator but conducts electricity easily when damp especially with electrolyte-containing liquids such as sweat.

Electrical injury is caused primarily by the intensity of the current passing through. Current is dependent on the potential difference or 'voltage' across the body and the resistance of the tissues through which it passes (Ohm's law).

$$I = \frac{E}{R}$$

where: E, potential difference (volts); R, resistance (ohms); I, current (amperes)

Severity of injury also depends on the current pathway through the body, environmental factors and the pre-existing health of the patient.

Pathophysiological effects

The pathophysiological effects of electricity range from a mild 'tingling' feeling to ignition in extreme cases. Any electrical current passing through a resistance loses some energy by conversion to heat. The amount of heat generated depends on the current and the value of the resistance; this may be beneficial and forms the basis of coagulation by radiofrequency diathermy. Electricity may stimulate excitable tissues, both nerves and muscles. In a controlled way, this effect may be used medically (e.g. peripheral nerve stimulator, defibrillation). Direct currents, even of low intensity, may cause electrochemical effects. Very high currents, generated by high voltages, cause arcing or sparking and char the tissues. This effect may be harnessed when radiofrequency diathermy is used to cut tissues.

Complications of the inadvertent application of electric currents to the body are:

- cardiopulmonary arrest
- cardiac arrhythmia
- skin and tissue damage
- associated injuries caused by gross muscle contraction.

In the hours after an electric shock there may be further heart rhythm disturbances, hypoxia and electrolyte disturbances, and acute renal failure due to myoglobinuria. It is difficult to predict the effect of electricity on the body because of variables such as body size, proportion and general health. Pre-existing heart problems make the heart more susceptible to arrhythmias.

The current pathway through the body dictates the type of injury. Current passing through the head or across the thorax may cause loss of consciousness and respiratory arrest with or without ventricular fibrillation. Current passing from hand to hand (Figure 1) may cause ventricular fibrillation. Current passing vertically through the body is more likely to cause cardiac muscle damage and injury to other vital organs especially the spinal cord. These injuries depend on the intensity and duration of the current.

The resistance of the human body is not uniform, therefore electricity does not pass evenly through it. Skin resistance is low and allows electricity to pass easily, especially when wet with sweat. Blood has a relatively low resistance, therefore highly vascular areas or inflamed areas of skin have lower resistance. The highest skin resistance is found over heavily calloused areas such as the palm or sole.

The pathway of the current inside the body depends on the resistance of each tissue type. Tissues with the lowest resistance (the best conductance) are nervous tissue, blood, mucous membranes and muscle; the poorest conductors are tendon, bone and fat.

Direct and alternating currents have different effects on the body. Direct current of sufficient intensity causes short duration muscle spasm which may throw the victim from the source. There may be a disturbance of heart rhythm and blunt mechanical trauma. Alternating current, especially at 50 Hz (60 Hz in North America) is approximately three times more dangerous than direct current. Alternating current (40–110 Hz) causes continuous muscle spasm or tetany. As the flexor muscles are more powerful than the extensors, tetany may cause the victim to grip the offending conductor more tightly, thus prolonging the duration of current. Local diaphoresis also reduces skin resistance at the point of contact thus increasing the current.

50 Hz (or 60 Hz) is a bad choice of frequency for the public utility electricity supply because it is the frequency to which the body is most sensitive. At higher frequency the body is progressively less sensitive to the excitable effects of electricity. Radiofrequency surgical diathermy uses frequencies greater than 100 kHz at which comparatively large current may be passed, taking advantage of the heating effects of electricity without affecting excitable tissues.

Effects of hand-to-hand 50 Hz alternating current

1 mA	Tingling sensation
5 mA	Pain
15 mA	Severe pain with local muscle spasm
50 mA	Respiratory muscle spasm
80–100 mA	Dysrhythmias, pump failure, ventricular fibrillation

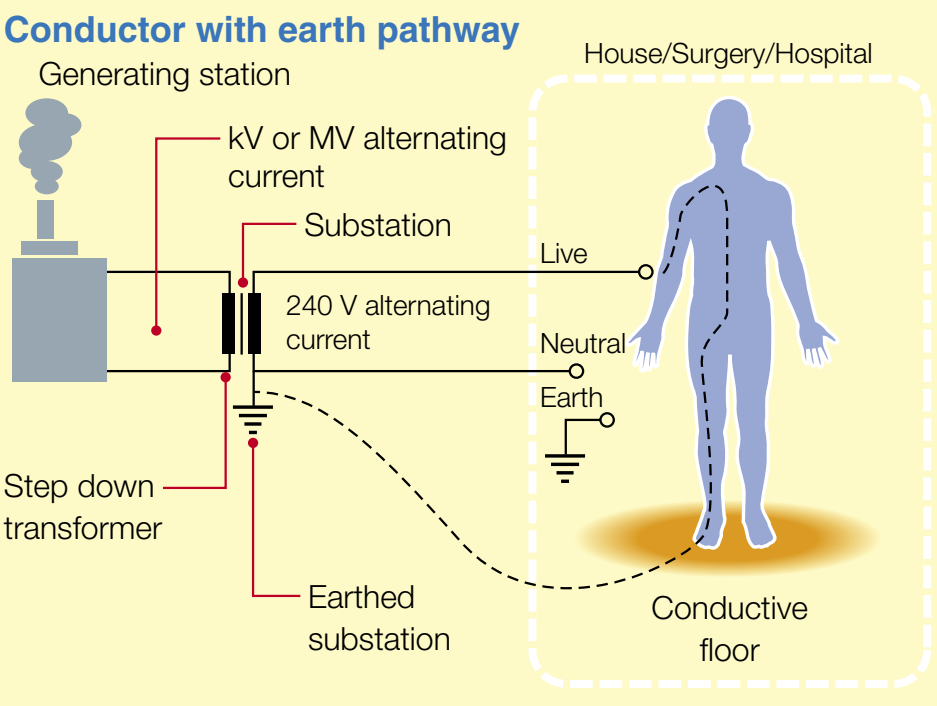
1

Electrical safety

The basic principle of electrical safety is to prevent the body becoming part of an electrical circuit. This requires good design of equipment, cables and connectors. Even with the highest quality of design, the user has the responsibility of using and handling equipment sensibly.

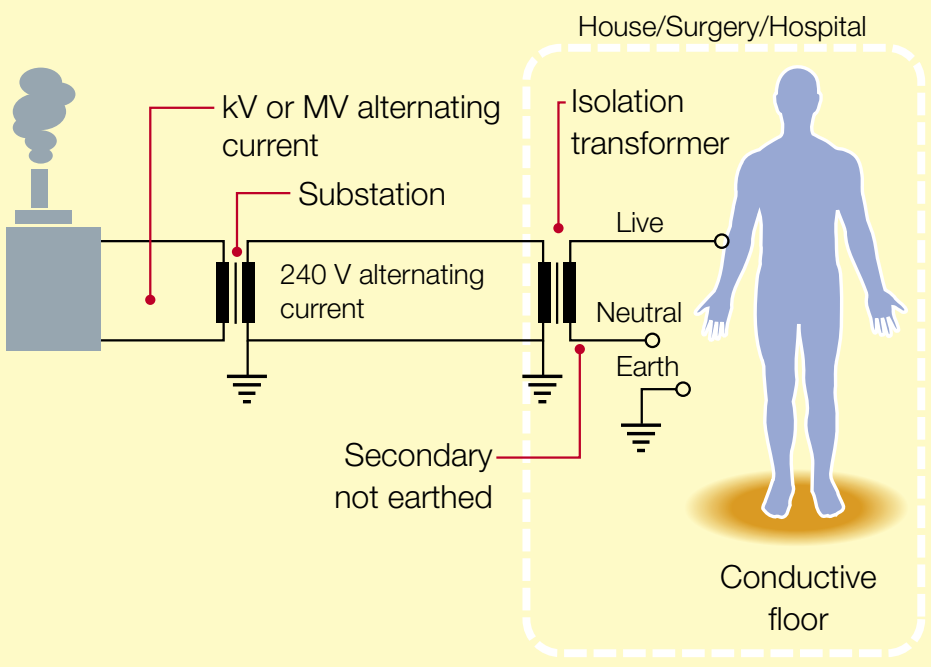
The conventional single-phase mains supply has two conductors: live and neutral. The live conductor is at a voltage dependent on the supply, normally 220–240 volts (110 volts in the USA) with respect to the neutral conductor which is 'tied' to earth at the substation. A safety or earth conductor may also be present which is connected to earth locally and therefore may be at a slightly different potential from the neutral conductor. It is unusual to get an electric shock from the neutral conductor alone but a circuit may be completed between a live conductor or component and either the neutral conductor or, more commonly, an earth pathway (Figure 2). This condition may be eased by the use of an isolation transformer (Figure 3) which will protect against electrocution via earth but not between earth and neutral. Isolation transformers are the most common form of basic protection with medical equipment and are often contained inside the equipment. (Further isolation is required when connection is made directly to the patient, this is described below.)

Conductor with earth pathway



2

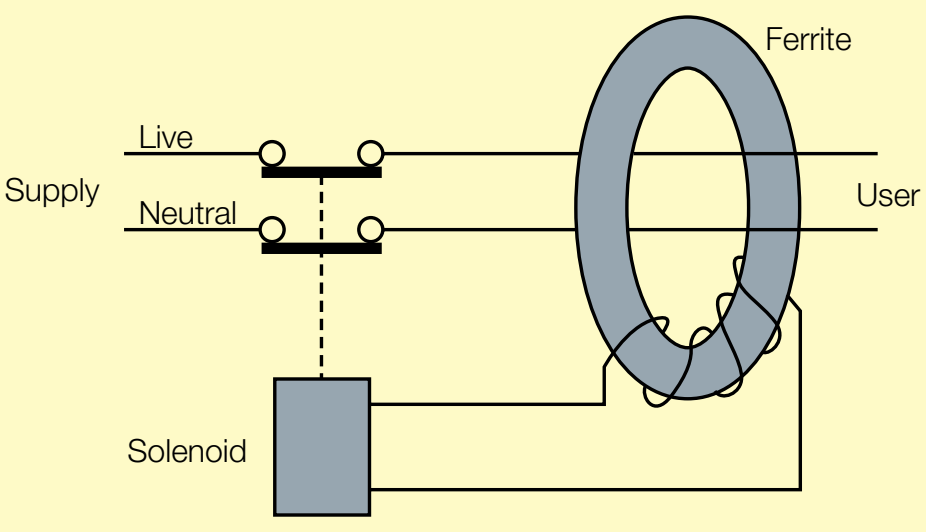
Conductor with isolation transformer



3

Electrocution depends on the duration of exposure and current. The shorter the duration, the higher the current required before damage is done. The earth leakage or residual circuit breaker stops the current passing through the body before any serious damage occurs. This phenomenon is used as the final level of protection from electrocution in the domestic situation and is commonly used commercially for power tools. The principle of the earth leakage circuit breaker (ELCB) is shown in Figure 4. The ferrite ring forms the core of an electrical transformer. The live and neutral conductors pass together through the ring, forming a single-turn primary of the transformer. The secondary of the transformer consists of many turns of much finer wire and is connected to a solenoid. When the solenoid is energized it breaks the supply. In the normal state, current passes down the live conductor, through the appliance and back through the neutral conductor. The current in the neutral is equal and opposite to that in the live and so their magnetic fields are cancelled out and no current is generated in the secondary winding. If some current leaks out of the appliance due to a fault or someone touching a live part, there is an imbalance between the live and neutral and a much amplified current is generated in the secondary, energizing the solenoid and disconnecting the supply.

Earth leakage circuit breaker



4

Microshock: electrocution of the intact human body is commonly referred to as macroshock to distinguish it from microshock in which smaller currents can lead to cardiac dysrhythmia or arrest because one of the points of contact is on or in the heart. 50 Hz mains electricity at a current as low as 50 μA by this route may have serious consequences. Contact may be made with the heart during thoracotomy but a more common and less obvious route is via electrolyte solutions in catheters in or near the heart. Therefore, any equipment that might make connection with the heart must be specially designed to protect against the unintentional passage of these very small currents. Such equipment includes ECG recorders, intravascular pressure monitoring systems, pacemakers and defibrillators.

Leakage current may be defined as electric current that has passed through insulators. It is difficult to design equipment with perfect insulation. The reduction of leakage in medical equipment requires special design features. The designer has to ensure that no electrically live parts are accessible. Any outer metal casing has to be connected to earth; an extra layer of insulation may also be used – the 'double insulation' often used on power tools. These techniques may make a piece of medical equipment safe to be in the patient environment. However, if there is any possibility of connection with the heart, special isolation techniques have to be employed by the equipment designer to ensure that any leakage current is less than 10 μA. This is a stringent limit to achieve.

Safety standards

All medical equipment manufacturers have to comply with published international standards. Each nation also has its own standards organization; in the UK it is the British Standards Institute (BSI). To make standards applicable on a worldwide basis, all national organizations cooperate to write international standards. The International Standards Organization (ISO) deals with everything excluding electricity; the International Electrotechnical Committee (IEC) deals with the standards of anything electrical. Both the ISO and the IEC are based in Geneva.

IEC-60601 is the basic standard for medical equipment. It classifies equipment in two ways; the method of electrical protection and the degree of protection.

- Class I equipment uses a 'protective' earth connection to the outer conductive casing.
- Class II protection is by double insulation. The degree of protection required is classified as B, BF or CF (C, intra cardiac or near cardiac; F, floating) as shown in Figure 5. Figure 6 shows the same symbols, with the indication that the equipment may withstand a defibrillator pulse without damage.

Three types of protection required

Type B applied part

- Maximum leakage current 0.1 mA
- Single fault condition 0.5 mA
- Allowed in patient care area but not in direct contact with patient
- Can be used in X-ray and suction equipment and operating theatre lights

Type BF applied part

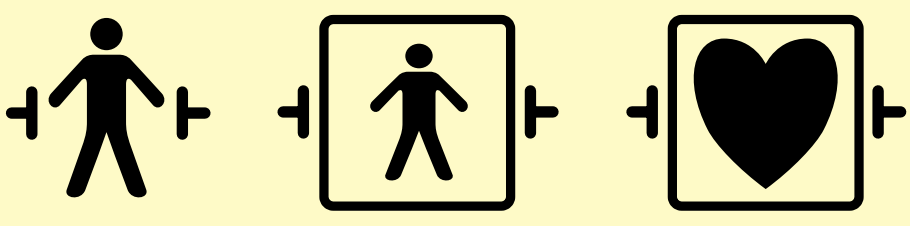
- Maximum leakage current 0.1 mA
- Single fault condition 0.5 mA
- Floating/Isolated
- May be deliberately in contact with patient but not in direct contact with heart
- Can be used in temperature measurement, non-invasive blood pressure measurement, ultrasonography, pulse oximetry, capnography

Type CF applied part

- Maximum leakage current 0.01 mA
- Single fault condition 0.05 mA
- Floating/Isolated
- Suitable for direct cardiac application
- Can be used in ECG, EEG, direct blood pressure measurement, electromagnetic blood flow

5

Symbols indicating equipment is able to withstand a defibrillator pulse



B BF CF

6

Two values of leakage current are given for each category; the lower refers to the equipment in its normal state; the higher value is the maximum allowable leakage current with a single fault condition (SFC). The Standard lists the allowable SFCs for each type of equipment. All medical equipment has to be marked with symbols to show the degree of protection. Figure 7 includes other relevant safety markings that are published in IEC 60601.

Electrical symbols

~	Alternating current
3~	3 Phase alternating current
3N~	3 Phase alternating current with neutral
⎓	Direct current
⏚	Protective earth (ground)
⏚	Earth (ground)
N	Neutral conductor (only on permanently installed equipment)
⏚	Equipotentiality

7

Fires and Explosions

John Moyle

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Less emphasis is placed on the risk of fire and explosion in the operating theatre today than previously mainly because the use of flammable agents has decreased; for example, ether and cyclopropane are no longer used in anaesthesia. This has lead to a false sense of security and little attention to fire safety. It must not be forgotten that alcohol as an antiseptic and dry drapes are flammable and that the microenvironment around a patient may have an increased concentration of oxygen. Nitrous oxide supports combustion better than oxygen. There are also new sources of ignition, such as the intense energy at the end of fibre-optic 'light pipes' and surgical lasers as well as the dangers associated with the use of surgical diathermy.

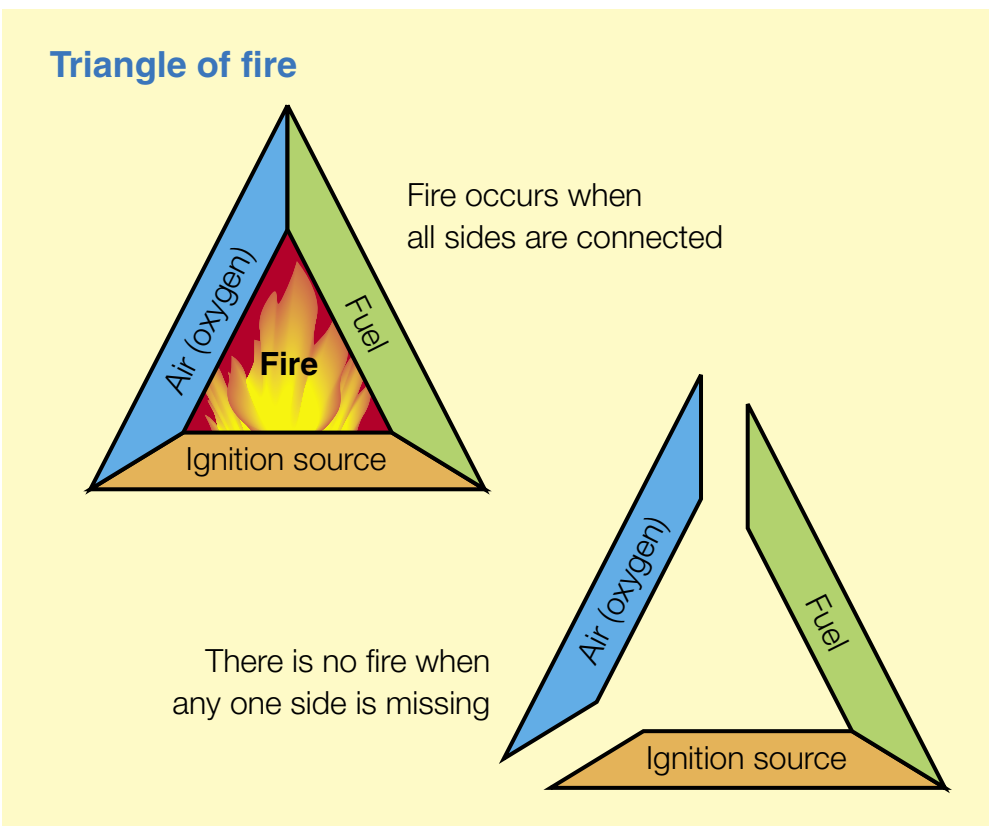
Fire and explosion

Fire or explosion occurs when a substance combines with an oxidizing agent with the release of energy. The reaction requires activation energy to trigger it (Figure 1). If the reaction occurs slowly, heat may be the only obvious evidence, though it usually leads to fire. If the reaction proceeds rapidly, large amounts of heat, light and a rapid increase in pressure occur, making sound; this is an explosion. Fire burns slowly at atmospheric pressure at a temperature of 200–500°C. An explosion is a fast, sudden increase in pressure to a high level at a much higher temperature than fire.

If the rate of liberation of heat is equal to the amount of heat required to maintain the process, the flame will stay still as long as the reactants are made available by convection. If the rate of generation of heat is larger than that required to continue activation, the flame will travel through the mixture. The greater the difference, the greater the likelihood of the reaction travelling so fast that a shock wave occurs; this is an explosion.

On a molecular basis, combustion is a chemical process. In oxidation, the intermolecular bond energy of the end products is less than the bond energy of the reactants and the excess energy is dissipated as heat. To induce the initial deformation of the molecules which allows the rearrangement of these bonds, activation energy has to be added to the system; in the case of fires and explosions this is usually in the form of heat. When the oxidation process begins, positive feedback has to occur to maintain the reaction; if not, the process would cease immediately, before the reaction was complete.

The speed of reaction is greatest for a stochiometric mixture: defined as a mixture in such proportions that none of the reactants is left at the end of the reaction.



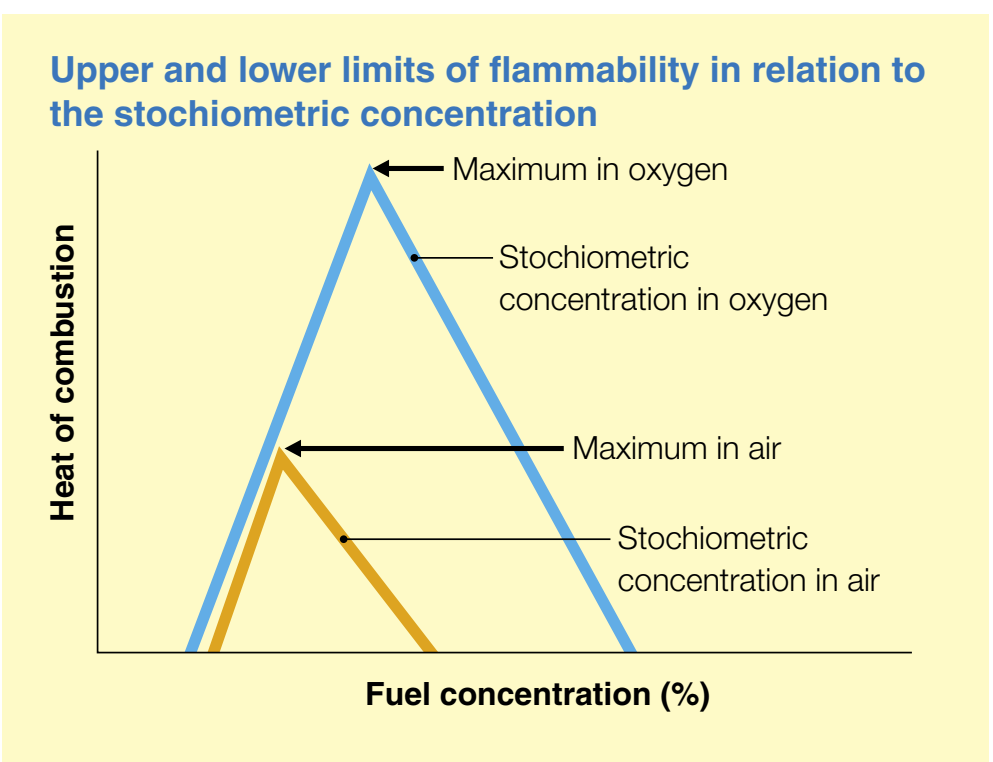
1

Fuel

A gas or vapour may be flammable over a range of concentrations with lower and upper limits of flammability. The stochiometric concentration occurs between these limits. Limits of flammability vary depending on the atmosphere in which the flammable gas or vapour is found (Figure 2).

Anaesthetic gases and vapours are not the only flammable substance that may put the patient at risk.

- Methane and hydrogen are found in bowel gas.
- Alcohol forms the basis of many skin preparation solutions and is in the exhaled gases of the inebriated. Isopropyl alcohol is commonly used to clean the skin before cannulation. Methyl alcohol is used in spirit burners and by down-and-out alcoholics.
- Drapes are often applied to the patient before the alcohol in skin preparation solution has evaporated completely. There may be a high concentration of the vapour, and even some of the liquid alcohol, beneath the drapes.
- Some surgeons use hydrogen peroxide to clean wounds. It rapidly decomposes by enzyme catalysis when poured on to open wounds, producing a froth of hydrogen and oxygen; the gas given off is highly flammable.
- Dry cotton or paper drapes are flammable.
- The plastic compounds used in the manufacture of conventional tracheal tubes may become flammable in high concen-tration of oxygen and high ignition energy levels.



2

Oxygen

Oxygen in the air is the usual source of oxygen involved in a fire. Figure 3 shows that the risk of ignition of any flammable gas or vapour is increased with increased concentration of oxygen above ambient level. Any fire burns more vigorously if the concentration of oxygen is increased.

Nitrous oxide is not combustible but it vigorously supports combustion.

Risks of fire and explosion arise from the strong oxidizing action of nitrous oxide and from its thermodynamic instability. At about 400°C, nitrous oxide breaks down to oxygen and nitrogen and if this comes into contact with combustible material, fire or explosion may result. The concentration of oxygen and nitrous oxide is increased around the mouth and upper airways if a tracheal tube or laryngeal mask does not seal perfectly. There is often an increased concentration of oxygen and nitrous oxide trapped between the patient and the surgical drapes.

Limits of flammability of gases and vapours encountered in the operating theatre[1]

Gas or vapour	Air		Oxygen		Nitrous oxide		30% oxygen 70% nitrous oxide		20% oxygen 80% nitrous oxide	
	L[2]	U	L	U	L	U	L	U	L	U
Diethyl ether	1.9	48	2.0	82	1.5	24				
Cyclopropane	2.4	10	2.5	60	1.6	30				
Ethyl chloride	4.0	15	4.0	67	2.0	33				
Enflurane			4.0				5.75		4.25	
Isoflurane			6.0				7.0		5.25	
Halothane							4.75		3.25	
Methoxyflurane	7.0		5.0	28	4.6					
Trichloroethylene			9.0	65						
Fluoroxene				4.0						
Hydrogen	4.0	74	4.6	94	5.8	86				
Methane	5.3	15	5.4	59	4.0	40				
Sevoflurane			12		11					
Isopropyl alcohol	2.5	12								
Methyl alcohol	6.0	36.5								
Ethyl alcohol	3.3	19								

[1]This is a compilation of information from a number of sources
[2]L, lower limit; U, upper limit.
All values are percentages.

3

Ignition source

Sources of ignition may be sparks generated by static electricity, flames or hot surfaces. Even shaking a bottle containing an organic compound in combination with a peroxide, may cause ignition.

The flash point of a liquid is the lowest temperature at which it gives off enough vapour to form an ignitable mixture with air. At flash point, the vapour will burn, but only briefly because inadequate vapour is produced to maintain combustion. The flash point of a liquid is always quoted but is of less significance to theatre staff than the autoignition temperature.

The autoignition temperature is the minimum temperature above which a flammable mixture is capable of extracting enough energy from the environment to self-ignite. Figure 4 shows the flash points and autoignition temperatures of some compounds in the operating theatre.

If anaesthetic agents that are flammable at clinical concen-trations are used, care must be taken to keep any possible source of ignition outside the zone of risk. There are two zones of risk around the anaesthetic machine, breathing circuit and head and neck of the patient:

- 5 cm if only air is used as the source of oxygen
- 25 cm if nitrous oxide and/or oxygen are used.

Equipment must be marked as AP where air is the only source of oxygen and APG when nitrous oxide or high oxygen concentrations are used.

Possible sources of ignition

Open flames are an obvious source of ignition; they comprise spirit and gas burners, matches and cigarette lighters.

Hot surfaces may cause ignition if the temperature is above the autoignition temperature of the liquid, vapour or solid. In some cases the high temperature of a surface is obvious because it glows or is incandescent.

Hot wire filaments used for cautery may be of high enough temperature to cause ignition. Miniature filament bulbs used in old-fashioned endoscopes may have a surface temperature of 250°C; sufficient to ignite diethyl ether in air.

Light sources – powerful light sources and fibre-optic light-guides have replaced miniature light bulbs but they should always be extinguished when not in use because the energy emitted from the light-guide when not connected to an instrument is intense enough to cause a burn on a surgical drape or the skin. The likelihood of igniting a drape is higher if the concentration of oxygen or nitrous oxide is high in the atmosphere trapped beneath it.

Surgical lasers – see below.

Sparks due to current electricity, as in radiofrequency surgical diathermy and static electricity, are the most obvious sources of ignition in surgical practice. Even sparks that are so small as to be almost invisible may be of sufficient energy to cause ignition.

Sudden increase in gas pressure causes gases to heat. Therefore it is important that no oil, grease or other flammable substance comes into contact with oxygen or nitrous oxide under high pressure.

Lasers

The energy emitted from the tip of a laser applicator is extremely high. The risk of causing ignition is higher than with any other source of emission. Extreme care must be taken to ensure that a laser beam does not come into contact with anything flammable. Any drapes or swabs in the vicinity must be kept wet with water. Care must also be taken to ensure that the beam is not inadvertently reflected on to a flammable surface. If the laser is being used in the mouth, the trachael tube should be of a non-flammable type or be suitably protected. In the case of laser in the bronchi or trachea the oxygen concentration should be 21% or only slightly higher.

Precautions

- Avoid the use of flammable liquids, gases and vapours.
- Keep unsuitable equipment out of zones of risk when flammable anaesthetic agents are in use.
- Observe antistatic precautions.
- Remember bowel gases are flammable.
- Relative humidity should not be less than 50% (a dry atmosphere promotes the generation of static electrical charge).
- At least 15–20 changes of air per hour in the operating theatre will reduce the risk of build-up of flammable vapours.
- High energy light sources must not remain on dry drapes (these sources are of high enough energy to damage tissues).
- Radiofrequency surgical diathermy is a potent source of ignition energy; evaporation of flammable skin preparation solutions must be complete and the atmosphere cleared of the vapour before diathermy is used.

Flash points and autoignition temperatures of flammable liquids encountered in the operating theatre

Compound	Flash point (°C)	Autoignition temperature (°C)
Methyl alcohol	–16	385
Ethyl alcohol	12	363
Diethyl ether	–45	160
Isopropyl alcohol	11.7	455.6

Induction of Anaesthesia

James Austin

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Induction is the process that produces a state of surgical anaesthesia in a patient. The term is used only in the context of general anaesthesia and not with local anaesthesia. It is the first step in the process of anaesthesia whereby the patient is rendered unconscious, preventing both awareness of, and response to, surgical stimuli. Anaesthesia and physiological sleep are different because sleep has structured, specific EEG patterns and endocrine changes, whereas anaesthesia is associated with a diffuse damping-down of EEG function and a stress-type endocrine response.

The process of induction should ensure patient safety, produce a state of unconsciousness, ensure optimal conditions for the surgeon and prepare the patient for waking and recovery.

Before anaesthesia is induced, the anaesthetist must:

- assess the patient as completely as circumstances allow, and institute preoperative preparations (e.g. intravenous fluids, sedative drugs, analgesics)
- discuss the surgery with the surgeon, particularly in complex or unusual cases
- plan the anaesthetic technique
- ensure all necessary equipment and drugs are available, and that the equipment is working.

On arrival in the anaesthetic suite, the anaesthetist must ensure:

- the correct patient has arrived
- the correct operation is planned on the correct side
- consent has been given
- jewellery or prostheses have been removed or declared
- blood for transfusion is available if required.

Anaesthetic room

In the UK, most inductions take place in a dedicated anaesthetic room; however, in many other countries induction takes place on the operating table in theatre. The main advantage of using a dedicated induction room is the quicker change-around as the theatre is cleaned and prepared between patients. If staffing permits, induction may take place while the previous case is being completed. A separate induction room also avoids the psychological stress (for some patients) of seeing the operating theatre. The anaesthetic room must be equipped with the necessary anaesthetic and monitoring equipment for the induction to be completed safely. The duplication of equipment between anaesthetic room and operating theatre may be a financial constraint in some locations. In urgent cases, with potentially unstable patients or with the morbidly obese, theatre is the best place for induction, because it saves the time, physical hazards and period of reduced or absent monitoring associated with transfer.

Equipment checks: successful induction requires planning and attention to detail. Before the procedure begins, checks of the anaesthetic machine must have been completed and the following must be available:

- the patient must be on a tilting bed or trolley
- two working laryngoscopes (in case of bulb failure), including standard and long blades (sizes 3 and 4)
- a selection of laryngoscope blade types (e.g. the Macintosh and the McCoy levering blade)
- a selection of tracheal tube sizes, with their cuffs checked
- suction equipment
- equipment to deal with difficult or failed intubation, including oral and nasal airways, gum-elastic bougie, laryngeal mask
- standard monitoring equipment (e.g. pulse oximeter, ECG, capnometer, blood pressure monitor).

Monitoring

In addition to the clinical observations made by the anaesthetist, the Association of Anaesthetists of Great Britain and Ireland has published recommendation for standards of monitoring equipment during anaesthesia and recovery. Monitoring should be instituted before induction whenever possible and should consist of a pulse oximeter (ideally with continuous display of pulse rate and plethysmography), an ECG and non-invasive arterial blood pressure monitoring. Following unconsciousness, other variables should also be monitored, including:

- carbon dioxide (using a capnometer)
- the anaesthetic vapour concentration
- body temperature
- neuromuscular function if muscle relaxants are used (assessed using a nerve stimulator)
- invasive arterial or central venous pressures and urine output monitoring may be required.

Induction methods

Most anaesthetic inductions are performed using intravenous or inhalational (‘gas’) induction; each has advantages and disadvantages (Figure 1). Less commonly, induction may be carried out by the intramuscular route in uncooperative patients, children or those with difficult venous access. Ketamine,10 mg/kg, provides up to 30 minutes of surgical anaesthesia, but induction times are unpredictable (15–45 minutes) and recovery is slow. Rectal induction with thiopentone, methohexitone, chloral hydrate or benzodiazepines was popular for children at one time, but is seldom used now. Oral induction is effectively a heavy sedative or ‘premedicant’, rather than induction, and recovery time is prolonged.

There are several tasks to be accomplished with any form of induction:

- last-minute preliminary checks (as specified above)
- establish monitoring
- establish intravenous access
- produce unconsciousness
- secure the airway
- establish ventilation
- commence analgesia (systemic or local)
- position the patient
- establish maintenance of anaesthesia.

Intravenous and inhalational induction

Intravenous	Inhalation
Advantages	*Advantages*
• Rapid onset • Patient comfort • Airway protection in rapid-sequence induction	• Does not require IV access • Useful for children • Useful for adults with needle-phobia
Disadvantages	*Disadvantages*
• Contraindicated in patients with a ‘difficult airway’	• Slow induction • ‘Excitement’ phase • Risk of vomiting • Risk of arrhythmias • Volatile agents contraindicated in patients susceptible to malignant hyperpyrexia

1

Intravenous induction

Pulse oximetry and ECG monitoring should be established before intravenous access because occasionally a cardiovascular event (e.g. vasovagal syncope) occurs during cannulation. Intravascular access commonly consists of a simple venous cannula; however, complex cases may require an arterial line, a central venous line and/or a pulmonary artery catheter. These may be sited with local anaesthesia before induction, to provide additional monitoring if haemodynamic instability is expected.

Following intravenous access, preliminary drugs (e.g. analgesics, antibiotics, anti-emetics) may be given. These vary according to the clinical circumstances and a detailed discussion is beyond the scope of this article. A regional analgesic block, if required, may also be given at this stage. Whether to insert the block before or after the patient is anaesthetized is the subject of some controversy (Figure 2).

Advantages of regional nerve blockade performed either before or after induction

Before induction	After induction
• Patient cooperation with correct positioning • Patient may provide feedback to minimize neural damage by needle or injection • Less requirement for anaesthetic monitoring	• Patient preference • Correct positioning may be easier (e.g. patients with painful fractures or skeletal deformity)

2

Pre-oxygenation: some anaesthetists routinely pre-oxygenate their patients before induction. The correct technique is for the patient to breathe 100% oxygen via an anaesthetic circuit and close-fitting mask for about 3 minutes of tidal volume breathing. Alternatively, pre-oxygenation by three vital capacity breaths has been demonstrated to be effective. The aim is to replace nitrogen-containing air in the resting volume of the lungs (the functional residual capacity, FRC) with a high oxygen concentration. The gas within the FRC acts as an important oxygen store, and therefore pre-oxygenation lengthens the time before hypoxaemia occurs following the onset of apnoea. This may provide valuable time in which the airway can be secured if an unexpectedly difficult airway is encountered. Mask phobia and the difficulties in achieving a mask seal in non-compliant patients and children are the only significant contraindications to pre-oxygenation. Pre-oxygenation is mandatory in rapid-sequence induction.

Intravenous drugs: slow, smooth injection of an intravenous anaesthetic agent usually results in loss of consciousness in less than 1 minute. Thiopentone, for example, starts to work in a period of one ‘arm–brain circulation time’. This is the period of time taken for the drug to travel from the site of injection (the arm) to the site of action (the brain) and is about 15 seconds in a healthy patient. The dose is carefully titrated according to patient response. Typical induction doses for healthy individuals are shown in Figure 3, but dose reduction may be required in:

- patients who are less fit
- the elderly or frail
- neonates
- patients with hypotension or poor cardiac reserve
- patients with chronic renal or liver disease
- patients with raised intracranial pressure
- patients who have been premedicated.

It can be difficult to judge when enough induction agent has been given. Care and experience are needed to titrate dose to effect but some indicators include:

- loss of response to verbal command
- loss of eyelash reflex (in which brushing the eyelash produces a blink response)
- relaxation of a motor posture (e.g. a raised arm or a grip on an object)
- cooperation with bag/mask ventilation.

The eyelash reflex has conventionally been regarded as a good end-point for thiopentone induction, but it is less reliable in propofol induction, for which loss of verbal response or motor relaxation is a more useful end-point.

Induction doses of intravenous drugs

Drug	Typical adult induction dose (mg/kg)	Notes
• Propofol	1.5–2.5	Popular and widely used drug associated with rapid and ‘clear-headed' recovery. Rapid metabolism and lack of cumulative effects has made it popular for total intravenous anaesthesia
• Thiopentone	3–5 (2.5% solution)	The ‘gold-standard’ against which all other drugs are judged. Smooth induction in one arm–brain circulation time
• Methohexitone	1–1.5 (1% solution)	Lowers the convulsive threshold, mainly used in anaesthesia for electroconvulsive therapy
• Etomidate	0.2–0.3	Marked cardiovascular stability makes this drug popular for use in unstable patients
• Ketamine	0.5–2	Useful for sedation with profound analgesia. Increases pulse rate and blood pressure and useful for the induction of patients suffering from acute trauma
• Midazolam	0.15–0.5	A benzodiazepine that may provide stable induction for the elderly and frail, in combination with an opioid

3

Further procedures: the induction agent may be followed by a muscle relaxant, particularly if tracheal intubation is planned. It is important to confirm that the patient's lungs can be ventilated via a bag and mask before paralysing. A muscle relaxant should not be given until it has been confirmed that ventilation is possible. Once anaesthesia is adequate, a clear airway is established using a simple face mask (with or without an oral or nasal airway), laryngeal mask airway or tracheal intubation. If the level of anaesthesia proves to be inadequate to allow an airway or tracheal tube to be tolerated, it may be deepened either with supplementary doses of intravenous agent, or by ventilating with volatile anaesthetic. With the airway secure, ventilation can continue by the patient's own effort, by manual 'hand' ventilation, or by mechanical ventilator.

At this stage, further invasive procedures may take place, such as additional vascular access, regional blocks, bladder catheterization, passing of a nasogastric tube or insertion of a temperature probe.

Transfer to theatre: if anaesthesia has been induced in the anaesthetic room, the patient is now transferred to theatre. This is potentially hazardous because for a short time the patient is separated from monitoring equipment and the mechanical ventilator. The patient is also potentially unstable because of the effects of induction drugs and is at risk of injury during the physical transfer. It is the anaesthetist's responsibility to guarantee the patient's safety. It should be ensured that ventilation and anaesthetic maintenance are re-established in good time, that tubes and lines are not dislodged, and that changes in clinical condition are detected promptly, in particular, cardiovascular instability, desaturation or signs of waking from anaesthesia.

Once in theatre, the priorities are:

- prompt transfer on to the operating table
- prompt re-establishment of ventilation
- prompt re-establishment of anaesthetic maintenance if using volatile anaesthetic drugs
- check correct drug delivery if using intravenous maintenance technique
- prompt re-establishment of monitoring equipment
- safe positioning of the patient
- commencement of maintenance fluids and temperature control.

Rapid-sequence induction

Rapid-sequence induction is used to decrease the risk of aspiration if the patient may have a full stomach, for example in an emergency. In patients presenting for elective surgery, a period of starvation of 2 hours for clear fluids, or 6 hours for food, is considered appropriate. Bowel obstruction, incompetent lower oesophageal sphincter, pregnancy and gastroparesis caused by disease, pain or drugs such as opiate analgesics are also causes of a potentially 'full stomach'.

The incidence and severity of aspiration of gastric contents are made worse by the nature, volume and pH of the gastric solution. Mendelson's studies on aspiration pneumonitis showed that aspiration of solid particles produced more damage than purely fluid aspirates. A potential gastric aspirate greater than 25 ml in volume and/or with a pH less than 2.5 is considered dangerous, though there is little direct clinical evidence for this. In these 'at-risk' patients it is sensible to attempt to raise gastric pH, and to try to promote gastric emptying. Pre-medication with ranitidine, 50 mg i.v., to decrease gastric acidity, and metoclopramide, 10 mg i.v., to enhance gastric emptying and increase the tone of the lower oesophageal sphincter is popular with some anaesthetists; both take at least 1 hour to take effect. A non-particulate antacid, such as sodium citrate, 30 ml of 0.3 M solution orally, given on leaving the ward or arriving in the anaesthetic room, further neutralizes residual stomach acid, but at the expense of raising gastric volume further.

Some anaesthetists advise that a nasogastric tube should be passed to drain the stomach, but it is uncomfortable and may induce vomiting. The counter argument is that any vomiting is better done while the patient is fully awake with protective airway reflexes. If a nasogastric tube is already in place it should be aspirated. If the gastric contents are still acidic on litmus test, consideration should be given to instilling sodium citrate. The old practice of inducing vomiting with ipecac or apomorphine is no longer advised.

The 'rapid sequence' of drug administration aims to produce unconsciousness and intubation conditions as rapidly as possible. The airway is swiftly protected by a cuffed tracheal tube without prior inflation of the lungs via bag and mask. This is to prevent possible gastric distension with an increased risk of gastric reflux. It is performed with the help of a trained assistant, competent in the technique of cricoid pressure.

Muscle relaxants are administered before the airway is controlled, and in this way rapid-sequence induction breaks an important rule of anaesthesia. Careful preoperative assessment of potential airway difficulty is therefore vital, and rapid-sequence induction must not be performed if this assessment predicts difficulty with intubation. The trainee anaesthetist must seek further advice, because an awake intubation technique may then be indicated.

Pre-oxygenation is mandatory, though it may be difficult to achieve in children. Pre-oxygenation reduces the need to ventilate the lungs before intubation. The correct technique is described above. Oxygen must be delivered via an anaesthetic breathing system capable of delivering 100% oxygen; standard 'Hudson' type face masks are inadequate.

Drug injection: the chosen drug is rapidly adminstered (Figure 3). Thiopentone is the drug of choice because of its rapid onset of action in one arm–brain circulation time, but propofol or etomidate are alternatives, albeit slightly slower-acting. The use of rapid-acting opioids such as alfentanil, 10 μg/kg, or fentanyl, 1 μg/kg, helps to reduce the pressor response to laryngoscopy.

Cricoid pressure: or Sellick's manoeuvre, is traditionally practised in rapid-sequence induction and is applied by the anaesthetic assistant as the patient starts to lose consciousness. Pressure is applied to the cricoid cartilage to compress it against the oesophagus, preventing passive regurgitation of stomach contents.

If active vomiting occurs, it is recommended that cricoid pressure be removed to prevent oesophageal rupture – suction, head-down tilt and turning the patient's head to one side is then used instead. Otherwise, cricoid pressure is removed only on the instruction of the anaesthetist, once the airway has been secured with a cuffed tube. Occasionally, it may be removed to facilitate an intubation that is being made more difficult by its continued application.

Muscle relaxation: suxamethonium, 1.5 mg/kg, is the drug of choice. Its rapid onset produces ideal intubating conditions, with a peak effect of muscle relaxation within 50 seconds of injection. It is important to allow the drug time to work, and not to begin the intubation sequence before muscle fasciculations have subsided.

The duration of apnoea is usually about 5 minutes in healthy individuals, and thus spontaneous respiration may be re-established early in the event of a failed intubation. Suxamethonium is contraindicated in patients with:

- previous allergy
- susceptibility to malignant hyperpyrexia
- myotonia
- severe burns, muscle damage or paraplegia (of over 1 week's duration)
- known raised serum potassium.

In these patients, rocuronium, 0.6–0.9 mg/kg, may provide relaxation as rapidly as suxamethonium, but with longer duration. Rocuronium is also the drug of choice in patients with reduced or absent plasma cholinesterase activity, in whom suxamethonium has a long and unpredictable duration of action.

Intubation: the trachea is intubated with a cuffed tube following unconsciousness and muscle relaxation. Uncuffed tubes are used in children to avoid local pressure on the tracheal wall and to maximize the internal diameter of tube available. If difficulty is encountered with direct laryngoscopy, then simple steps may be taken to facilitate intubation:

- manipulate the larynx (the assistant providing the cricoid pressure may be distorting the view of the larynx)
- change to a larger blade laryngoscope
- change to a different type of blade (e.g. a McCoy levering blade)
- use the gum-elastic bougie (this thin, flexible stylet may be used to pass through the cords providing a 'track' over which the tracheal tube can be railroaded).

Before the cricoid pressure is released, the correct position of the tube must be checked carefully by auscultation and capnometry. Once the cuff has been inflated and the airway has been secured, a nasogastric tube should be passed and aspirated, if not done previously. The rest of the anaesthetic proceeds as usual; but at the end of the procedure extubation should take place with the patient awake, with their protective airway reflexes re-established, positioned on their side in a head-down tilt, and with suction available.

Failed intubation drill – if the trachea is not successfully intubated, a failed intubation drill must be followed:

- cease further attempts at intubation
- call for help
- maintain cricoid pressure
- insert an oral airway
- hand-ventilate via bag and mask using 100% oxygen
- await return of spontaneous respiration
- once spontaneous ventilation has returned, turn the patient into the lateral position with head tilted down and await return of consciousness.

A decision to abandon further attempts at intubation must be made early and certainly before arterial desaturation supervenes. The prime concern of the anaesthetist is patient safety. The safest option following failed intubation is to wake the patient. Once the effects of the intravenous induction agent and muscle relaxant have worn off, consideration must be given to how to proceed. This requires consultation with a senior anaesthetist and may involve an awake intubation technique.

Inhalational induction

Gas induction, controversially, is often used as a means of inducing anaesthesia (particularly in a child) without having to site an intravenous cannula first. However, in the event of difficulties (e.g. laryngospasm, arrhythmias) instant intravenous access should be available, because otherwise the anaesthetist controlling the airway will be unable to attempt rapid cannulation. For this reason, some anaesthetists seldom perform gas induction; others permit gas induction if a second anaesthetist is present to assist with intravenous cannulation. Gas induction of children and adults has taken place without intravenous access for over 150 years, in most cases safely and without incident.

Indications: gas induction (with intravenous access) is indicated for patients in whom airway difficulties are expected. In these cases, the patient continues to breathe spontaneously throughout and apnoea is avoided, since it may then be impossible to manually ventilate the lungs with bag and mask.

Upper airway obstruction is an important indication for inhalation induction, and in these circumstances fibre-optic techniques for intubating the trachea are contraindicated for fear of producing complete airway obstruction. However, in patients with an unobstructed 'difficult' airway, the increasing availability of fibre-optic intubation equipment and the growing skill of anaesthetists in awake intubation techniques may reduce the need for gas induction. The difficult airway may best be secured even before anaesthesia is induced.

Technique: there is controversy over whether to induce in 100% oxygen or to use nitrous oxide as well.

- Concurrent use of volatile and nitrous oxide exploits the second-gas effect for a cumulatively more rapid induction. The rapid absorption of the second gas (nitrous oxide) has the effect of increasing the alveolar concentration of the first agent. The partial pressure of anaesthetic gas in the alveolus reflects the partial pressure of anaesthetic in the brain and hence the anaesthetic effect.
- 'Pre-induction', with 33% oxygen and 66% nitrous oxide only, may render a child sleepy enough not to resist when the odour of the volatile agent is added. Clearly the more nitrous oxide is used the more anaesthetic effect is achieved; but likewise the less reserve there is against desaturation. A minimum of 30% oxygen should be given.
- Induction in 100% oxygen is least smooth, but should laryngospasm occur, it is an advantage to have as much of the lung FRC filled with oxygen as possible. This maximizes oxygen stores and thus delays the onset of hypoxaemia.

Conventional practice for inhalational induction with halothane is to start with a low inspired concentration of 0.5%, and to increase it by 0.5% every four breaths up to 4%.

Sevoflurane has greatly enhanced gas induction, because it is faster, better tolerated by patients, and is less arrhythmogenic than halothane. It has been suggested that the lower incidence of arrhythmias has contributed to a decrease in dental anaesthetic deaths in recent years. The high blood-gas solubility of sevoflurane accounts for its rapid onset and offset. Because sevoflurane is less pungent it is often used in high concentrations (maximum 8% on most vaporizers) for faster induction.

Enflurane is seldom used for gas inductions because it is slow; isoflurane and desflurane are almost never used because they are pungent and irritating to the airway.

The last-minute checks before inhalational induction are the same as those for the intravenous route. Monitoring should be established; some children make this difficult, but ECG should be the minimum monitoring instituted. Induction should ideally take place via a tight-fitting face mask (even small leaks may significantly delay induction). However, the use of a cupped hand may be less threatening to a small child in the first instance.

'Single-breath induction' has been described with halothane and sevoflurane. A Mapleson A breathing system containing a 4-litre reservoir bag is filled with a maximum concentration of volatile anaesthetic (4% halothane or 8% sevoflurane) in 66% nitrous oxide and 33% oxygen. The patient is asked to exhale to residual volume, then, via a tight-fitting mask, to inhale a full vital-capacity breath of gas, and then to hold their breath for as long as possible. This technique produces a faster induction than conventional tidal volume inhalational induction in cooperative adults. In the case of single-breath 8% sevoflurane, the speed of induction is comparable with induction with intravenous propofol. It may be a useful technique to use in cooperative needle-phobic adults, but it offers few other advantages.

Four main variables determine the speed of inhalational anaesthetic induction.

- The inspired partial pressure of the anaesthetic agent relative to its minimum alveolar concentration (MAC) alters the speed of induction. MAC is the partial pressure of the agent, expressed in volumes %, which at equilibrium prevents gross muscle movement in response to a skin incision in 50% of patients. It is thus the effective dose in 50% of patients and is a measure of anaesthetic potency.
- The faster the patient breathes, or the greater the alveolar ventilation, the faster the alveolar partial pressure of the agent approaches the inspired partial pressure. In a child, crying speeds up gas induction by increasing minute ventilation.
- The higher the cardiac output the more anaesthetic agent is removed from the alveoli and hence the slower the partial pressure rises in the alveoli. Thus, an anxious, hyperdynamic patient is slow to induce, whereas a shocked patient with a low cardiac output is quicker.
- The higher the solubility of an agent (i.e. a high blood-gas solubility coefficient), the more the agent will dissolve in blood and thus a lower partial pressure will be generated. Agents with a low solubility (e.g. sevoflurane) result in more rapid induction.

During a gas induction, most patients pass briefly through a phase of excitability during which they may be agitated and at increased risk of laryngospasm or, more rarely, arrhythmias. If a child is being induced, it is useful to warn the parents of this disinhibition in advance. The disinhibition is not remembered by the patient.

Once the patient is unconscious, anaesthesia should be deepened, assisting the ventilation by hand, using bag and mask if necessary. If not already obtained, intravenous access should be secured, which requires the help of an assistant. Muscle relaxants may then be given intravenously to assist in securing the airway. If the patient is sufficiently deeply anaesthetized, as evidenced by a regular respiratory pattern and a forward gaze in eyes with small pupils, the airway may be secured (even by intubation) purely under inhalational anaesthesia. Nevertheless, it is valuable to have intravenous access before attempting to manipulate the airway, in case any untoward airway reflexes are produced (e.g. arrhythmias, laryngospasm). With the airway secured, the remainder of the induction sequence proceeds as above.

Historical note

In 1937, Arthur Guedel published *'Inhalational Anaesthesia – a Fundamental Guide',* three chapters of which were devoted to his observations of premedicated patients' responses to gas inductions with nitrous oxide, the ethers, chloroform and cyclopropane

Guedel's stages of anaesthesia

Stage	Definition	Features
1 Analgesia	From beginning to loss of consciousness	Sedation Loss of eyelash reflex[1]
2 Delirium	Loss of consciousness to onset of rhythmic breathing	Agitation, vomiting, arrhythmias Eyes deviated
3 Surgical		
• 1st plane	Onset of rhythmic breathing to loss of eyeball movement	Loss of eyelid reflex Loss of conjunctival reflex[1]
• 2nd plane	Loss of eyeball movement to onset of intercostal paralysis	Loss of laryngeal and gag reflexes Loss of corneal reflex[1]
• 3rd plane	Onset to completion of intercostal paralysis	
• 4th plane	Complete intercostal paralysis to respiratory arrest	Dilated pupils Loss of carinal reflex[1]
4 Respiratory paralysis	Respiratory arrest to death	Loss of anal reflex

[1] Not described in Guedel's original monograph

Induction in children

Children from about 3 months of age until the teenage years are generally more anxious, or less able to control their anxiety, than adults. The preoperative visit is important in children because meeting the anaesthetist and having the procedure explained calms the fears of children and parents. If the child is old enough, address your conversation to him or her. Explain in detail what will happen, and invite the parents and child to ask questions. Where possible, bring relevant equipment, particularly a face mask for gas induction, for the child to become familiar with.

Topical local anaesthetic cream such as EMLA (a eutectic mixture of lignocaine and prilocaine) or amethocaine gel is desirable if awake intravenous access is planned. Marking visible veins in advance helps the nurse to cover the right spots. Both preparations are similarly effective in clinical practice though onset and duration of action differ (Figure 4).

It has become common for parents to accompany children to the anaesthetic room, and this is generally helpful. Smaller children may best be anaesthetized on a parent's lap – a well-positioned hug serves to comfort the child and to restrain them during intravenous cannulation or gas induction. Strapping for the cannula, and the induction drugs, should be on hand for swift application once access has been obtained.

- For gas induction, a sideways hug helps to immobilize all the limbs, while the anaesthetist's hands control the head.
- For intravenous cannulation, a 'face-to-face' hug (Figure 5), with the child's arm under the parent's arm, helps to immobilize the arm and restrict the child's view of cannulation.
- The older child may prefer or need to be anaesthetized on the trolley. If the trolley permits, it is useful to raise the back until just before (or even during) induction itself. This more upright position allows the child a better view of their surroundings, and hence a feeling of more control and less anxiety.

Children should be treated with respect at all times. They should be spoken to in non-condescending language they can understand – if something is going to be unpleasant, it should be acknowledged. The alternative is for the child to become suspicious and uncooperative for even the most innocuous procedure. There is no formula that will ensure every paediatric induction is smooth and trouble-free; some children will be understandably fractious despite all efforts to calm them.

Comparison of EMLA cream and amethocaine gel

	EMLA cream	Amethocaine gel
Constituents	Lignocaine 2.5%, prilocaine 2.5% as an oil/water emulsion	Amethocaine 4%
Presentation	White cream, 5 g per tube	Clear gel, 1.5 g per tube
Application	2 g minimum 1 hour before venepuncture, maximum 5 hours	1 g 30–45 minutes before venepuncture. Remove after 45 minutes
Duration	Efficacy declines soon after cream is removed	Efficacy remains 4–6 hours after application
Skin effects	Usually transient paleness May produce redness and oedema	Usually transient redness May produce itching and oedema
Contra-indications	Not for children < 1 year	Not for children < 1 month

4

5 Hugging the child face to face helps to immobilize the arms.

Further Reading

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Induction of Anaesthesia in Special Circumstances

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A full stomach

The pulmonary aspiration of acid gastric contents has long been recognized as a major risk of anaesthesia. Patients are normally asked to fast preoperatively to allow sufficient time for gastric emptying. However, induction of anaesthesia in the presence of a full stomach may be unavoidable when normal gastric emptying is impaired, or when the urgency of surgical intervention overrides the requirement for a patient to have fasted adequately. Gastric stasis, ileus and reverse peristalsis may accompany obstruction or perforation of the gastrointestinal tract. Trauma, pain and its treatment with opioids delays gastric emptying. Gastric motility may also be abnormal in the presence of diabetes mellitus or obesity and in these circumstances no period of fasting may be considered to be safe. The hazards of induction of anaesthesia in these circumstances are listed in Figure 1.

If the patient has a full stomach an attempt to reduce intragastric volume and acidity before anaesthetic induction is desirable. Gastric fluid may be removed through a gastric tube, or if there is time and no contraindications by giving a prokinetic agent (e.g. metoclopramide, 10 mg i.v.). The pH of the gastric contents may be increased by the ingestion before induction of a non-particulate alkali, usually 30 ml of a 0.3 molar solution of sodium bicarbonate.

Induction of anaesthesia in the presence of a full stomach

Hazards	Management
Pulmonary aspiration of gastric contents	Reduce gastric volume Raise intragastric pH with alkali Use of cricoid pressure Rapid sequence induction
Unanticipated failure to intubate	Preoxygenation Rapid sequence induction Failed intubation drill

1

Rapid sequence induction

Rapid sequence induction is the anaesthetic technique indicated in the presence of a full stomach (Figure 2). It aims to reduce to a minimum the period during which the airway is unprotected after induction of anaesthesia and before inflation of the cuff of a correctly placed tracheal tube.

During preparation for rapid sequence induction, a skilled assistant should carefully identify and hold the cricoid cartilage between the thumb and forefinger, ready to apply cricoid pressure as anaesthesia is induced. Cricoid pressure (Sellick's manoeuvre) correctly applied with adequate, but not excessive, force compresses and occludes the upper oesophagus between the flat posterior surface of the cricoid cartilage and the body of the sixth cervical vertebra, preventing reflux of gastric contents without distorting the view at laryngoscopy. If a gastric tube is already in place, it should not be removed but should be allowed to act as a gastric vent.

The main risk of rapid sequence induction is that there is no prior opportunity to ensure that intubation or mask ventilation will be possible after induction. Good preparation for intubation is vital and it is essential that all equipment is checked, suction equipment and aids to oxygenation are ready and the patient is in an optimum intubating position.

The patient's lungs should be preoxygenated. This is achieved by allowing the patient to breathe 100% oxygen through a tightly fitting mask and anaesthetic circuit for about 3 minutes. When apnoea occurs at induction, the lung rests at end tidal volume where there is equilibrium between the elastic recoil of the lungs and the chest wall. Arterial oxygen desaturation follows when the oxygen content within the functional residual capacity (FRC) of the lungs is exhausted. During preoxygenation, the nitrogen in the FRC will be displaced, increasing the oxygen content of this reservoir substantially and delaying the onset of cyanosis after induction of apnoea. Despite these measures, arterial oxygen desaturation is accelerated by the presence of a reduced FRC (e.g. obesity), a raised metabolic oxygen demand (e.g. sepsis) or a combination of the two (e.g. late pregnancy).

Rapid sequence induction requires the use of rapidly acting induction and paralysing agents injected intravenously in quick succession. Most intravenous induction agents cause loss of consciousness within one arm–brain circulation time in the following doses: thiopental (thiopentone), 2–4 mg/kg, etomidate 0.2–0.3 mg/kg, propofol 2–3 mg/kg. In UK practice, suxamethonium, 1.5 mg/kg, remains the neuromuscular blocking agent of choice because it provides optimum intubation conditions in the shortest time.

Once the correct position of the tracheal tube is verified clinically and by capnography and after the cuff has been inflated, cricoid pressure can be released.

In case of failure to intubate, the duration of action of the induction and paralysing agents is critical. Despite the additional time made available by preoxygenation, it may be impossible to see the larynx or intubate the patient. It is then essential to revert to a well-rehearsed failed intubation drill. The effects of the common induction agents wear off in a few minutes and the choice of suxamethonium is reinforced by its short duration of action. The temptation to give a second dose of the drugs and prolong attempts at intubation should be resisted. At this point, resumption of patient oxygenation is the priority.

Rapid sequence induction

- Selection of intubation aids and equipment for cricothyroid puncture
- Skilled assistant applying cricoid pressure
- Patient on surface that can be tipped head down
- Suction switched on with catheter under pillow
- Optimal patient intubating position
- Good quality venous access with running intravenous infusion
- Preoxygenation with 100% oxygen through close fitting face mask
- Single sleep dose of intravenous induction agent
- Single adequate intravenous dose of suxamethonium (e.g. 1.5 mg/kg)
- Failed intubation drill

2

After head injury

Induction of anaesthesia and tracheal intubation after head injury (Figure 3) is indicated when:

- the patient's airway or oxygenation is compromised
- the patient has a depressed level of consciousness (Glasgow Coma Score of 8 or less)
- in the presence of agitation
- before emergency surgery
- in preparation for safe transfer to either CT scanner or to a neurosurgical centre.

It is vital to prevent secondary brain injury due to hypoxia, hypotension, hypercapnia or uncontrolled rises in intracranial pressure. The patient is assumed to have a full stomach so a rapid sequence induction with preoxygenation and cricoid pressure is indicated. In addition, patients presenting with a severe head injury must be assumed to have suffered a cervical spine injury. Cricoid pressure is applied using a two-handed technique, the second hand supporting the back of the cervical spine. Another assistant is required to provide manual in line stabilization of the spine during induction because any cervical collar has to be temporarily removed to facilitate intubation. Coexisting facial injuries need to be assessed carefully because they may affect intubation by displacing, distorting or obstructing the airway.

Careful monitoring of cardiovascular status is required. It may not be practical to monitor blood pressure invasively before induction, but non-invasive measurements should be made frequently. Suppression of the hypertensive response to intubation requires an intravenous induction agent, though the dose may have to be reduced in the presence of depressed consciousness. Lidocaine (lignocaine), 1 mg/kg, may also be given for this purpose. After induction there should be a smooth transition to maintenance sedation, which may include opiates, to avoid fluctuations in blood pressure.

Suxamethonium is associated with a transient rise in intracranial pressure, but this potential for harm is outweighed by its advantage of rapidly producing optimal intubating con-ditions and thereby reducing the risk of hypoxia. A peripheral nerve stimulator will help to ensure adequate neuromuscular blockade before intubation, and that a non-depolarizing agent is given in time to prevent coughing and facilitate controlled ventilation as the effect of suxamethonium wears off.

Tracheal and gastric tubes should not be placed nasally, for fear of breaching a skull base fracture. Constriction or distortion of neck veins that could result in cerebral venous hypertension should be avoided when securing the tracheal tube and applying a cervical collar. Arterial hypotension must be actively investigated and treated, while moderate hypertension should be tolerated because this may be a normal response to intracranial hypertension, preserving cerebral perfusion pressure.

Induction in head injury

Hazards	Management
Full stomach	See Figure 1
Cervical spine injury assumed	In line stabilization of neck Two-handed Sellick manoeuvre
Rising intracranial pressure	Adequate dose of induction agent Adequate neuromuscular blockade Smooth transition to maintenance sedation and paralysis
Reduced cerebral perfusion pressure	Avoid hypotension
Facial injuries	Intubation facilitated or made more difficult
Skull base fracture	Avoid nasal intubation

3

Upper airway obstruction

The management of the patient with obstruction of the upper airway, including the larynx, is a vital skill for anaesthetists (Figure 4). Adequate diagnosis of the airway pathology and the derangement of normal anatomy should precede discussion of the management plan between senior anaesthetic and ENT staff. An alternative strategy must also be agreed so that there is a back-up plan before proceeding. The management plan should be explained clearly to the patient, whose cooperation will be required.

Induction in airway obstruction

Hazards	Management
Potential for airway obstruction in expert hands	Senior help present
Abnormal anatomy	Information from imaging or endoscopy
Loss of muscle tone in upper air-way at induction may precipitate complete obstruction	Inhalation induction or awake tracheostomy
Obstruction during inhalation induction	Back-up plan in place with scrubbed ENT surgeon for surgical airway

4

Assessment of the patient may elicit stridor (inspiratory noise) at rest, which suggests that the airway is more than 50% narrowed. Results of radiographs, CT or MRI scans or nasendoscopy should be available. In their absence it may be appropriate to perform endoscopic examination by fibrescope via a topicalized and vasoconstricted nasal passage. The site of obstruction must not be approached with the fibrescope because attempted fibre-optic intubation may be impossible and may be hazardous, but endoscopy may provide important reconnaissance information. If there is doubt about the feasibility of intubation, then an awake surgical tracheostomy under local anaesthesia should be considered.

If intubation is likely to be possible, an alternative strategy must be in place before embarking on induction of anaesthesia. A scrubbed ENT surgeon must be present ready for immediate intervention and opening of a surgical airway.

The usual technique for induction of anaesthesia in the presence of upper airway obstruction is an inhalation induction. Most experience has been obtained with halothane although use of sevoflurane is growing. Gradual induction of anaesthesia while maintaining spontaneous ventilation and airway muscle tone may allow adequate depth of anaesthesia for intubation without airway closure. Should there be no obstruction, no manipulation of the airway or laryngoscopy is allowed before adequate depth of anaesthesia is achieved as judged by the pupils coming to lie centrally. It is vital that no neuromuscular blockade or intravenous sedation is used before the airway is safely secured.

Obstruction of the airway during inhalation induction prevents further uptake of anaesthetic agent, therefore allowing anaesthetic depth to lighten and the patency of the upper airway to be restored. An awake surgical tracheostomy should then be performed under local anaesthesia.

FURTHER READING

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Maintenance of Anaesthesia

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This contribution is an overview of what is meant, and required, by maintenance of anaesthesia. Many of the topics are covered in greater detail in separate contributions; the aim here is to put these topics in context.

Maintenance of general anaesthesia involves four priorities:

- keeping the patient safe
- keeping the patient comfortable
- presenting the best possible operating conditions for the surgeon
- preparing the patient for the postoperative period.

Keeping the patient safe

There are several aspects involved in keeping the patient safe:

- airway, breathing and circulation
- temperature control
- monitoring
- positioning.

Airway: this will usually have been established at the time of induction. However, it should not be assumed that this remains secure. Airway disconnection or obstruction may occur and the anaesthetist must be able to detect and correct these incidents promptly, assisted by monitors such as the capnograph, pulse oximeter, disconnect alarm and airway pressure monitor. Movement of the tracheal tube (either towards the right main bronchus or withdrawal from the trachea) or dislodgement of the laryngeal mask airway (LMA) are particularly likely to occur when patients are transferred to the operating table or when changes are made to patient position. These periods require increased vigilance by the anaesthetist. The integrity of the airway should be rechecked both clinically and by monitoring after each patient movement.

Tracheostomy, rigid bronchoscopy or 'one-lung' thoracic surgery may require intraoperative changes to the airway. The anaesthetist must be prepared for such changes and, if necessary, should formulate a plan with the surgeon in advance as to how the airway will be managed.

Breathing will often depend on whether muscle relaxants are being employed as part of the anaesthetic technique. Although the use of muscle relaxants is not essential for controlled ventilation, they are usually employed for ventilated patients. Surgical factors often influence the decision to use muscle relaxants. For example, abdominal surgery is greatly facilitated by muscle relaxation. In specialized surgery, such as ophthalmic surgery or neurosurgery, where the slightest move or cough may have disastrous consequences and carbon dioxide must be controlled, paralysis is ideal. Otherwise, anaesthetists have widely differing views as to whether breathing should be controlled. Some anaesthetists use muscle relaxants almost routinely for any operation lasting longer than about 30 minutes, on the basis that carbon dioxide retention is avoided, potent short-acting opioids can be used without fear of respiratory depression, and good lung aeration with avoidance of atelectasis may be easier to achieve. Others control ventilation less often unless indicated for reasons of airway management or the requirements of surgery. Some advantages and disadvantages of paralysis and ventilation are listed in Figure 1.

The technique of 'paralysing and ventilating' may be preferred when a tracheal tube is present. It is likely that a relaxant will already have been given to enable intubation. Also, the presence of a tube within the trachea is a potent stimulus, and unless local anaesthesia has been applied to the respiratory tract, a deeper level of anaesthesia may otherwise be needed for the patient to breathe spontaneously without coughing. Lighter planes can be tolerated when a laryngeal mask or oropharyngeal airway are employed, because these devices are less stimulating to the patient. Paralysing and ventilating may also be used for longer operations, where carbon dioxide control and prevention of atelectasis is important.

However, avoiding relaxants wherever possible can reduce two important complications of general anaesthesia:

- unrecognized awareness – patient movement usually warns of light anaesthesia before the patient becomes aware
- accidental hypoxia – the spontaneously breathing patient may maintain oxygenation even in the event of circuit disconnection.

Use of muscle relaxants and controlled ventilation

Advantages	Disadvantages
• May allow 'lighter' anaesthesia because reflex activity is abolished by neuromuscular blockade	• May allow unrecognized awareness as a result of inadequate anaesthesia
• Facilitates abdominal surgery by relaxation of abdominal muscles	• Reliance on ventilation equipment and circuit integrity to maintain alveolar ventilation
• Intracranial and intraocular pressure control by regulation of $PaCO_2$	• Possible side-effects of muscle relaxant drugs (e.g. histamine release, vagal blockade, malignant hyperpyrexia)
• Allows effective ventilation during, for example, thoracic surgery, prone positioning or long procedures	• Need for reversal of neuromuscular blockade
• Allows use of potent opioids to reduce the surgical stress response in major surgery	• Possible contraindication in patients with a difficult airway. Absence of spontaneous respiration may render ventilation impossible
• May improve surgical conditions by facilitating a hypotensive technique and lowered $PaCO_2$	• When there is requirement to monitor neuromuscular function (e.g. facial nerve during surgery on the parotid gland or acoustic neuroma)
• Decreases intraoperative atelectasis	
• Decreases energy requirements and tissue carbon dioxide production	• Contraindicated in some myopathies

1

Ventilator settings – most anaesthesia ventilators are time-cycled and volume- or flow-driven. A rate, usually with a ratio of inspiratory time to expiratory time (I:E), and a tidal volume or flow need to be set. Most adults have a minute volume of 80–100 ml/kg, therefore a tidal volume of 8 ml/kg (e.g. 500–600 ml) and a rate of 10 breaths/minute is a good starting point; this can be adjusted according to the observed end-tidal partial pressure of carbon dioxide ($P_{E'CO_2}$). For routine surgery, a $P_{E'CO_2}$ of about 4.5 kPa should be aimed for. If metabolic rate and cardiac output (and hence pulmonary perfusion) are assumed to be constant, then $P_{E'CO_2}$ varies inversely with the alveolar ventilation.

In general, an I:E ratio of 1:2 is often the best compromise between maintaining low inflation pressures (e.g. 15–20 cm H_2O), satisfactory oxygenation (Sp_{O_2} > 95%) and adequate carbon dioxide removal ($P_{E'CO_2}$ 4.5 kPa). However, this can be decreased to 1:1.5 or even 1:1 to prolong inspiratory time. This may be useful in some patients to help decrease high airway pressures (e.g. > 25–30 cm H_2O) or improve oxygenation (e.g. in the obese). Some patients with asthma or chronic airway disease may benefit from a longer expiratory time to allow the lungs to empty, and an I:E ratio of 1:3 or 1:4 may be preferable.

Children have a proportionately higher minute ventilation than adults – up to 200 ml/kg in infancy, approaching adult values weight-for-weight by about age 10 years. Given that their tidal volume is slightly less weight-for-weight than adults (7 ml/kg), this increased minute volume must be provided for by an increase in rate. For example, in a 5 kg infant, a minute volume of 1000 ml might be provided by 30 breaths each of about 33 ml/minute.

However, paediatric ventilation is complicated by the obligatory leak around the uncuffed tube. Volume control is unlikely to inflate the lungs to the set volume (especially if a Newton valve is used with T-piece ventilation). This is usually overcome by increasing the tidal volume by titrating against inflation pressure and/or $P_{E'CO_2}$. Some modern anaesthesia ventilators have pressure control capabilities (e.g. the *Draeger Julian*). Specific compliance varies little with age, therefore pressure control mode can be used to deliver an inflation pressure of 15–20 cm H_2O. This provides an adequate tidal volume for any age, despite small to moderate leaks, as long as lung compliance is normal.

Regardless of the mode of ventilation, a fresh gas flow must be selected. This depends on the breathing system in use as well as the size of the patient. A high flow should be used initially (e.g. 6 litres/minute), regardless of the circuit being used. This allows time for denitrogenation and equilibration of inhaled anaesthetic agent during this early period of rapid anaesthetic uptake. After about 10 minutes, flows can be reduced considerably if the system permits. The circle system with carbon dioxide absorber is widely used, and modern lightweight valves and low-resistance tubing make it suitable for paediatric use well below the traditional lower patient weight limit of 20 kg. With appropriate monitoring of gas concentrations within the circle, this permits total fresh gas flows of 1 litre/minute or less. Higher flows are required for T-pieces such as the Bain and Jackson Rees systems. Formulae exist for each of these circuits to predict the flow of fresh gas required per kilogram patient weight to eliminate rebreathing for controlled and spontaneous respiration. However, a more practical approach is to reduce the fresh gas flow gradually, stopping when rebreathing of carbon dioxide begins to appear on the capnograph.

General anaesthesia, particularly when using volatile anaesthetic agents, causes the development of atelectasis in the dependent parts of the lung and impairs the pulmonary vascular response to hypoxia (hypoxic pulmonary vasoconstriction). These two factors produce a small but noticeable degree of shunt, usually about 10%. This can be corrected by giving anaesthetized patients higher inspired oxygen than the 21% present in air; 30% is usually given, though this can be titrated against observed oxygen saturation.

Circulation: appropriate fluid management is an important component of anaesthetic maintenance. Intravenous fluid requirements may range from none in short and relatively non-invasive procedures, to many times the circulating volume in long and traumatic procedures. Fluid requirement consists of:

- replacement of existing deficit – crystalloid or blood
- metabolic maintenance requirements – crystalloid
- replacing additional ongoing losses – crystalloid, colloid or blood.

Existing deficit – in the adult elective surgical patient, who has been starved for at least 4 hours preoperatively (and sometimes much longer), a deficit of 500 ml of crystalloid can be assumed. This deficit is generally well tolerated and does not necessarily need replacing, but it decreases the patient's margin of reserve against any further losses, or against ongoing postoperative dehydration as a result of nausea or vomiting. Many anaesthetists routinely administer 500–1000 ml of crystalloid in all patients except those at risk from fluid overload (e.g. those with renal or cardiac failure). There is evidence to suggest that this may improve the quality of early recovery and help to decrease postoperative nausea.

In the emergency patient, fluid deficit may be considerable, as a result of either trauma-related blood loss, or anorexia, vomiting and/or interstitial (third-space) fluid loss from surgical pathology. In either case, the deficit should be assessed and replaced with the appropriate fluid. The larger the deficit, the more important that it be replaced before induction, whenever circumstances permit. The exception to this rule is during major ongoing blood loss, such as a ruptured aortic aneurysm or major trauma, where the priority is stopping the bleeding rather than prolonging attempts to normalize the circulation preoperatively.

Maintenance – for many patients this is the least important component of intraoperative fluid management – the average adult requirement of about 100 ml/hour is negligible in the context of a short procedure and other fluid losses. However, in small children, maintenance requirements are proportionately larger and more significant. Paediatric maintenance fluid is usually calculated according to: 4 ml/kg/hour for the first 10 kg, plus 2 ml/kg/hour for the next 10 kg, plus 1 ml/kg/hour for the remainder. Thus, a 25 kg child would have a maintenance requirement of 40 + 20 + 5 = 65 ml/hour. The smaller the child, the less reserve there is for managing without ongoing maintenance fluids, and the greater the impact of preoperative starvation.

Infants have small glycogen reserves, and therefore need intravenous dextrose (e.g. as 5% dextrose in 0.18% saline) as maintenance to sustain their blood sugar levels. For longer procedures, careful attention must be paid to electrolyte balance, because infants have less ability to correct excessive salt loads or water loads.

Ongoing losses – the most significant aspect of intraoperative fluid management can be the most difficult to estimate.

Losses from extravascular spaces (e.g. gastrointestinal, evaporative, third-space fluid losses) are usually crystalloid losses. Evaporative losses can be large – an adult may lose in excess of 1 litre/hour from a laparotomy or thoracotomy wound, and even larger amounts from extensive open skin wounds such as burns or large graft sites. There is no way of measuring these losses directly, and measures such as blood pressure, pulse rate or central venous pressure (CVP) provide only an indirect measure of total body water. Urine output may be the most useful clinical measure. Blood tests such as plasma urea, sodium and haematocrit may provide information regarding the hydration state, and plasma electrolytes and haematocrit are now commonly available from blood gas machines.

Losses also occur from the intravascular space (i.e. blood). Losses in suction bottles may be complicated by wash, faeces, urine or amniotic fluid. Visual estimates of blood loss on swabs are often inaccurate – weighing of swabs is more precise, but still neglects losses on drapes, gloves and instruments. A dilutional technique relies on washing all swabs, instruments and gloves in a fixed volume of water, which can then be measured colorimetrically to give an accurate measure of blood loss. Such instruments are not widely available. Intravascular loss may be estimated indirectly from clinical measures such as blood pressure, pulse rate or CVP, though other anaesthetic factors such as the balance between surgical stimulation and depth of anaesthesia complicate these measures. Estimation of haemoglobin is useful only when adequate intravascular volume has been replaced. Blood losses may initially be replaced by colloid solution (e.g. a gelatin solution or hydroxyethyl starch), but larger losses (> 20% blood volume) may require replacement by packed-cell blood. Very large losses (> 1 blood volume) may require supplementation with fresh frozen plasma and/or platelets to maintain clotting function.

In practice, it is likely that fluid losses are under-replaced in many patients. This is offset by the hormonal 'stress response' to surgery: aldosterone, cortisol and antidiuretic hormone levels rise and atrial natriuretic peptide falls; all contribute to postoperative water retention.

Temperature control: there is now good evidence that the maintenance of a physiological body temperature reduces postoperative morbidity. Patients suffering from head injury or undergoing certain neurosurgical procedures are possible exceptions. Shivering increases oxygen consumption, and predisposes to myocardial ischaemia, dysrhythmias, hypotension and acidosis. Hypothermia also increases susceptibility to infection and tends to lengthen hospital stay.

Temperature control is of particular importance in patients at the extremes of age (who have less intrinsic control over body temperature and a larger surface area-to-volume ratio through which to lose heat), in operations involving open body cavities, and in all patients undergoing lengthy procedures. About 20% of trauma patients who arrive at hospital are hypothermic (core temperature < 35°C).

A change in core temperature as a result of general anaesthesia is a three-phase response.

- The first phase is a brisk fall in core temperature as a result of vasodilatation, caused by redistribution of heat to the peripheries. Core temperature may be as low as 35.5°C in some patients after transfer to the operating theatre from the anaesthetic room.
- The second phase is a slower but more sustained fall as a result of accelerated loss of heat to the environment from the warmer peripheries.
- The third phase is a stable equilibrium at a lower core temperature.

It is important to note that the anaesthetic itself brings about these changes, which are independent of the nature of the surgery, though surgery may modify the pattern. The use of spinal or epidural anaesthesia instead of general anaesthesia reduces, but does not abolish, the three-phase response described above.

Passive rewarming is the prevention of heat loss, typically by raising the temperature of the environment. Passive rewarming can serve to modify only the second phase of the heat loss response. Covering with blankets or the use of foil 'space' blankets decreases heat loss by reduced transfer of heat by convection, conduction, evaporation and radiation.

Dry inspired anaesthetic gases need to be humidified, and a heat and moisture exchange filter in the breathing system reduces heat loss by evaporation from the respiratory tract (latent heat). Low flows in a circle system (e.g. 1 litre/minute) further reduce the quantity of dry gas needing to be humidified and help retain heat and moisture within the breathing system.

A 'normal' operating room temperature of 21°C is a compromise between that which is warm enough for the patient, but cool enough for the comfort of theatre personnel. An increase in theatre temperature (e.g. to 25°C) helps to reduce the gradient for heat loss in patients at high risk (e.g. young children, patients with extensive burns).

Active rewarming is the addition of heat into the patient. It may be used to prevent or reverse the first phase of the temperature drop. The local environmental temperature can be raised so much that the transfer of heat is reversed. Warm air convection blankets (e.g. the *Bair Hugger*) are considered as active rewarming.

Intravenous fluid warmers play an increasingly important role the greater the volume of intravenous fluid given. A fluid-warming device should be used in all at-risk patients and especially when stored blood is administered. Ventilatory gases may be warmed using a heated humidifier. Overhead radiant heaters may be used when a large area of the body needs to be exposed, and neonates may undergo surgery on an open incubator such as the *Resuscitaire*.

Cardiopulmonary bypass represents the ultimate in active rewarming, but is practical only in cardiothoracic surgery or in uncommon resuscitation situations.

Care is needed not to overheat the patient and temperature monitoring is necessary when active rewarming methods are used. Monitoring probes are available for a variety of body cavities, including nasopharynx, oesophagus, rectum, bladder and tympanic membrane. In routine clinical practice, core temperature is usually measured by nasopharyngeal or rectal temperature probes. Surface temperature monitors do not reflect core temperature, but the core–peripheral gradient may provide a useful measure of peripheral vasodilatation. A gradient of less than 2°C implies good peripheral perfusion.

Monitoring: the Association of Anaesthetists has published recommendations on standards of monitoring. A summary is given in Figure 2.

Blood sugar should be monitored in infants and diabetic patients. The blood sugar of diabetic patients should be known before anaesthesia is given, and should be estimated every 1–2 hours during routine surgery.

The Association of Anaesthetists summary of standards of monitoring

- The Association of Anaesthetists of Great Britain and Ireland strongly recommends that the standard of monitoring used during general anaesthesia should be uniform in all circumstances irrespective of the duration of anaesthesia or the location of administration
- An anaesthetist must be present throughout the conduct of general anaesthesia
- Monitoring should be commenced before induction and continued until the patient has recovered from the effects of anaesthesia
- These recommendations also apply to the administration of local anaesthesia, regional analgesia or sedation where there is a risk of unconsciousness or cardiovascular or respiratory complications
- The anaesthetist should check all equipment before use. Monitoring of anaesthetic machine function during the administration of anaesthesia should include an oxygen analyser with alarms. During spontaneous ventilation, clinical observation and a capnometer should be used to detect leaks, disconnection, and rebreathing and high pressure in the breathing system. Measurement of airway pressure, expired volume and carbon dioxide concentration is strongly recommended when mechanical ventilation is employed
- A pulse oximeter and capnometer must be available for every patient
- It is strongly recommended that clinical observation of the patient should be supplemented by continuous monitoring devices displaying heart rate, pulse volume or arterial pressure, oxygen saturation, the electrocardiogram and expired carbon dioxide concentration. Devices for measuring intravascular pressures, body temperature and other parameters should be used when appropriate. It is useful to have both waveform and numerical displays
- Intermittent non-invasive arterial pressure measurement must be recorded regularly if invasive monitoring is not indicated. If neuromuscular blocking drugs are used, a means of assessing neuromuscular function should be available
- Additional monitoring may be required in certain situations. These recommendations may be extended at any time on the judgement of the anaesthetist

2

Positioning: an unconscious patient cannot move to relieve an uncomfortable position, and it is the anaesthetist's responsibility to prevent discomfort from becoming damage. The anaesthetist is also responsible for protecting the patient during movement on and off the operating table, and during changes of position. Traditionally, the anaesthetist has particular responsibility for the head and airway. It must be ensured that all members of the team are working to a common agenda and with coordinated timing. It is usually easiest and safest to disconnect as much equipment as possible before moving the patient.

Prophylaxis against venous thromboembolism – the thrombotic process often starts intraoperatively. It is difficult to identify patients at high risk, though coexisting medical illness, major surgery, malignancy, trauma (especially hip and pelvis), obesity, high-dose oestrogen therapy and age greater than 40 years are well-known risk factors. Thromboprophylaxis should commence before anaesthesia; gradated compression stockings and low-dose unfractionated heparin, 5000 IU s.c. twice daily, continued until full mobilization, is popular and effective. When positioning for surgery, raising the heels on foam pads prevents venous stasis in the calves. Intermittent pneumatic compression pumps assist venous return, but it is not known whether this reduces the incidence of postoperative pulmonary embolism.

Keeping the patient comfortable

Traditionally, the main components of anaesthetic maintenance are unconsciousness (hypnosis), analgesia and absence of movement. Some advantages and disadvantages of using muscle relaxants have been discussed. Keeping the patient unconscious and relieving the pain of surgery are now considered.

Maintenance of unconsciousness is usually achieved by anaesthetic drug delivery via the inhalational or intravenous route, or both. The intramuscular route is seldom used in hospital practice owing to the relatively slow onset of drug action, unpredictable duration and delayed recovery. Ketamine, 10 mg/kg, is the only useful intramuscular agent, with an onset of 5–10 minutes producing up to 30 minutes of anaesthesia. It has a role in the provision of emergency anaesthesia in difficult locations.

Inhalational route – this is the most widely used technique, using a volatile anaesthetic agent with or without nitrous oxide. It therefore requires a supply of compressed gas, a vaporizer and a breathing system for drug delivery. Compressed gas may not be required if a 'drawover' type vaporizer is used.

The potency of an inhaled anaesthetic agent may be described in terms of its minimum alveolar concentration (MAC). MAC is defined as the alveolar concentration of the anaesthetic agent which at equilibrium is required to prevent gross reflex muscular movement in response to a standardized skin incision in 50% of healthy, unpremedicated patients. It is therefore a measure of anaesthetic potency, and is the effective dose in 50% of the population (ED_{50}). It should be borne in mind that not all operations are 'a standardized skin incision'. The amount of anaesthetic needed to remove a foreign body from the nose is very different from that needed for an anal stretch. It is important to know the MAC of individual inhalational agents and the factors on which they depend (Figures 3 and 4).

Of any given inhalational anaesthetic, 0.7–1.3 MAC will anaesthetize 95% of the population. MACs are also additive: 0.5 MAC of nitrous oxide (52%) plus 0.5 MAC of isoflurane (0.6%) is equivalent to 1 MAC of any other inhalational agent given alone.

The principle of MAC acts as a useful guide. It allows the anaesthetist to select a vapour concentration that is likely to maintain unconsciousness. The state of anaesthesia is related to the partial pressure of anaesthetic within the brain, which is taken to be equivalent to the alveolar partial pressure. This can be measured by analysis of the end-tidal partial pressure of the anaesthetic agent. What is dialled on the vaporizer or the nitrous flowmeter is not necessarily what is in the patient's alveoli – the fresh gas flow takes time to equilibrate both with the dead space of the circuit and with the uptake by the patient. Observing how the ratio of end-tidal to inspired partial pressure varies with time can assess this rate of uptake (or 'wash-in').

MAC is useful to estimate the amount of anaesthetic required. In clinical practice this must be adjusted against indicators such as pulse rate, blood pressure, respiratory rate, patient movement, pupillary size, lacrimation and sweating. Many of these variables may be abolished by factors other than anaesthetic depth. Tachycardia may be prevented by co-administered β-blockers, hypertension masked by hypovolaemia, respiratory rate and patient movement abolished by paralysing drugs, and pupillary size altered by use of opioids or anti-muscarinic drugs. Thus, lacrimation and sweating, though crude indicators of inadequate anaesthesia, reflect the need for clinical observation in addition to monitoring.

Minimum alveolar concentration (MAC) of inhalational anaesthetic agents

Anaesthetic agent	MAC in oxygen (%)	MAC in 70% nitrous oxide
• Halothane	0.75	0.29
• Enflurane	1.68	0.57
• Isoflurane	1.15	0.50
• Sevoflurane	2.0	0.8
• Desflurane	6–9	2.5–3.5

3

Factors affecting minimum alveolar concentration

Decrease	Increase	No change
• Increasing age	• Decreasing age	• Gender
• Alcohol (acute ingestion)	• Alcohol	• Duration of anaesthesia (chronic ingestion)
• Nitrous oxide	• Hyperthermia	• Time of day
• Analgesics	• Hyperthyroidism	• Hypercarbia
• Sedatives and hypnotics	• Hypocarbia	
• Hypotension		
• Hypothermia		
• Hypothyroidism		
• Hypoxia		

4

Intravenous route – a popular alternative to inhalational anaesthesia is total intravenous anaesthesia (TIVA). Many intravenous anaesthetics have been used for TIVA, including barbiturates, ketamine, etomidate and propofol. The pharmaco-kinetic profile of propofol makes this drug the most commonly used for TIVA. It has a high clearance (1300–1900 ml/minute), short metabolic half-life (60–100 minutes) and inactive metabolites. For short procedures, propofol may be administered following initial intravenous induction by intermittent bolus with no special infusion equipment (e.g. 50 mg as required every 3–5 minutes).

For longer procedures, the advent of reliable electronic syringe pumps, and in particular the development of target-controlled infusion (TCI) software, have contributed to the widespread use of TIVA techniques. Some advantages and disadvantages of inhalational or TIVA maintenance are shown in Figure 5.

Consider a three-compartment model: vascular space, richly perfused organs, and poorly perfused organs plus clearance. A large initial bolus of propofol is needed to fill the vascular compartment, namely the induction dose. Thereafter an initially high rate of infusion is needed to keep up with losses to the richly perfused compartment until it approaches saturation. Then a slower rate is required to keep up with losses to the poorly perfused but difficult to saturate compartment, and with metabolic clearance.

The 'Bristol regimen' reflects these kinetics. This regimen aims to maintain a plasma propofol concentration of about 3 μg/ml by giving patients receiving 67% nitrous oxide an initial bolus of 1 mg/kg, followed immediately by infusion at 10 mg/kg/hour for 10 minutes, then 8 mg/kg/hour for 10 minutes, then 6 mg/kg/hour thereafter. A dose of 10 mg/kg/hour is equal to the patient's weight (in kg) as ml/ hour of 1% propofol – hence a 60 kg patient will initially receive 60 ml/hour of 1% propofol. At the end of the operation, switching off the propofol allows rapid redistribution from the vascular compartment (and therefore from the richly perfused compartment also) to the still unsaturated third compartment. It is this rapid redistribution that allows a prompt wake-up even after a long period of TIVA.

TCI microprocessor-controlled technology (e.g. as incorporated in the Graseby 3500 'Diprifusor' syringe pump) requires manual input of patient age, weight and desired plasma concentration. The pump then administers propofol according to the three-compartment pharmacokinetic model incorporated into its software. Change to a higher propofol concentration is achieved by a rapid zero-order infusion, and the plasma concentration is calculated until the new predicted value is reached. Change to a lower concentration is achieved by temporary cessation of drug infusion until the predicted plasma level falls to the required level, followed by continuation of infusion at a lower rate. The system is used in a similar fashion to adjusting the vaporizer setting during inhalational anaesthesia; the predicted plasma concentration of drug is analogous to the end-tidal concentration of the inhalational agent. Maintenance of satisfactory anaesthesia requires a plasma concentration of propofol of 2–6 mg/ml, depending on patient fitness, coexisting drug therapy and degree of surgical stimulation.

Comparison of inhalational anaesthesia and total intravenous anaesthesia (TIVA) maintenance techniques

Inhalational maintenance

Advantages
- Cost-effective (especially when used with low-flow circle systems)
- Predictable population pharmacokinetics and confidence in anaesthetic depth achieved
- Ease of measurement of end-tidal partial pressure
- Minimal metabolism of modern agents, no accumulation and clearance independent of patient hepatic and renal function

Disadvantages
- Requires conventional tidal ventilation for drug delivery
- Requires specialized equipment (e.g. vaporizer, anaesthetic machine, agent analyser)
- Concern regarding tissue and organ toxicity (especially hepatotoxicity following repeat halothane exposure)
- All volatile anaesthetics are known triggers for malignant hyperpyrexia
- Environmental pollution

TIVA

Advantages
- Independent of airway for drug delivery. May be advantage in, for example, jet ventilation techniques
- No specialized equipment is essential. More suitable technique for patient transport and difficult locations
- Rapid increase in anaesthetic depth possible by administration of intravenous bolus
- Low incidence of postoperative nausea and vomiting and better quality of early recovery (especially for propofol)
- No contraindication in malignant hyperpyrexia

Disadvantages
- Requires patent and dependable intravenous access. Undetected failure may result in awareness
- Drug accumulation with prolonged infusion
- Inability to measure plasma concentration directly has led to concerns about possibility of awareness

5

Analgesia: modern inhalational or intravenous anaesthetic drugs possess little analgesic activity, with the exception of ketamine. For all but the simplest procedures, analgesia must be provided by systemic analgesics (usually opioids) or by local anaesthetics. Analgesia has several effects.

- It reduces the required MAC (or plasma concentration) of co-administered anaesthetic drugs. Analgesia is an important component of the balanced anaesthetic technique.
- It reduces the immediate autonomic activity in response to pain. Sympathetic stimulation otherwise results in cardiovascular and respiratory responses that may lead to myocardial ischaemia and dysrhythmias.
- It reduces the neuroendocrine 'stress response' caused by surgery.

Opioid analgesics such as fentanyl, 15 μg/kg, reduce circulating concentrations of the stress hormones that increase after moderate and major surgery (e.g. noradrenaline, adrenaline, cortisol, growth hormone, glucagon, antidiuretic hormone). The stress response is largely detrimental and leads to increased catabolism, metabolic rate and oxygen consumption. This response is not significant in minor surgery.

The short-acting synthetic opioid drugs such as fentanyl and alfentanil are widely used to provide intraoperative analgesia. Fentanyl, a synthetic opioid structurally related to pethidine, is the most popular (1–2 μg/kg for minor procedures, onset 1–2 minutes, duration 30 minutes). Its potency and minimal effect on pulse and blood pressure make it commonly used for the provision of intense analgesia during surgery. These drugs are unsuitable for routine use in postoperative analgesia because of their short duration of action and their tendency to produce marked respiratory depression. They are commonly substituted by longer-acting analgesics (e.g. morphine 0.1–0.2 mg/kg i.v.) towards the end of the procedure to provide pain relief following surgery.

Pre-emptive analgesia – laboratory work suggests that noxious stimuli produce hypersensitivity in the pain pathways both centrally and peripherally. Larger doses of analgesics are then required to have an effect. If systemic analgesia or local anaesthetics are used to prevent the initial pain, this hypersensitivity is reduced. This is the basis of pre-emptive analgesia, but its clinical significance is disappointing.

Providing the best possible operating conditions

The surgeon hopes for two things from his patient during the operation: not to move, and not to bleed. If the anaesthetist has succeeded in keeping the patient safe and comfortable as described, then the patient is unlikely to move. The anaesthetist can also help to minimize bleeding.

Tourniquets are ideal for extremity surgery. Traditionally, a 90-minute time limit is imposed on upper limb tourniquets (usually at 250 mm Hg), and a 120-minute limit on lower limb tourniquets (usually at 300 mm Hg). This is arbitrary; the longer the tourniquet is on, the greater the potential for damage. The main risk is ischaemic damage to nerves directly under the tourniquet; distal ischaemia is likely to take 4–6 hours to become significant. If antibiotics are necessary, they should be given at least a few minutes before exsanguination.

Sickle-cell disease is an absolute contraindication to tourniquet use, because sickling of haemoglobin S may be induced by the local hypoxia and acidosis.

Positioning – adequate venous drainage from the operative site is ensured by careful attention to patient positioning. Raising the operative site above heart level decreases arterial and venous pressures. Arterial pressure falls by 2 mm Hg for each 2.5 cm vertical height. Head-up tilt is commonly used in head and neck surgery to decrease bleeding, but there is a risk of venous air embolism.

Hypotensive anaesthesia – moderate reduction of systolic blood pressure (e.g. to 70–80 mm Hg) in otherwise fit patients may greatly improve the operative field. It must be used with caution in patients with coronary, cerebral, renal or peripheral vascular diseases who are at risk from ischaemic events. Techniques for deliberate hypotension are outside the scope of this contribution.

Non-steroidal anti-inflammatory drugs used intraoperatively may increase blood loss during surgery.

Blood gases – carbon dioxide is a local vasodilator, and moderate hypocapnia (e.g. P_{CO_2} 4.0–4.5 kPa) contributes to a dry surgical field.

Preparing the patient for the postoperative perio

The maintenance period is often a convenient time to complete the necessary anaesthetic record and drug prescription charts. During anaesthesia, it should be considered what else may be done while the patient is unconscious to enhance his or her postoperative course. This includes the following.

Venous access must be sufficient for postoperative requirements. A central venous line should be sited if access is likely to be difficult or prolonged, or to enable central venous monitoring. A subcutaneous cannula for analgesic administration may avoid the need for injections, especially in children.

A nasogastric tube is more comfortably inserted while the patient is asleep, and its position can be checked during laparotomy.

Analgesia – ideally, the plan for postoperative pain control should be formulated before anaesthesia, and discussed with the patient. 'Balanced analgesia' is the concept of using several analgesics with differing modes of action, thus reducing dose-related side-effects and enhancing overall analgesic effect. Typically this may involve local or regional analgesia in combination with opioids, non-steroidal anti-inflammatory drugs and simple analgesics (e.g. paracetamol).

Antiemetics should be given in particular to patients receiving opioids, and those at high risk of postoperative nausea and vomiting (PONV). High risk includes patients with a history of previous PONV or motion sickness, certain operations (e.g. gynaecological, middle ear or strabismus surgery) and female gender.

Oxygen – all anaesthetics (with the exception of ketamine) induce about 10% shunt. Atelectasis, impaired hypoxic pulmonary vasoconstriction, diffusion hypoxia from nitrous oxide use, opioid-mediated hypoventilation and other factors contribute to making the postoperative patient prone to hypoxia. Added oxygen (e.g. 30–40% via a simple face mask) should be administered in the immediate recovery period to all patients for about 15 minutes, guided by pulse oximetry. Subsequently, the need for added oxygen must be determined for each patient depending on factors such as age, pre-existing disease and the nature of anaesthesia and surgery.

Fluids – there must be clear instructions for postoperative fluid intake. Elective day-surgery patients will drink when ready, but in-patients and those undergoing major procedures require intravenous fluids to replace continuing fluid losses and provide maintenance. How far in advance fluids can be prescribed depends on the accuracy of prediction of future needs.

Thromboprophylaxis – stockings for prevention of thrombo-embolic disease and/or regular heparin should be prescribed where indicated by local policy.

Antibiotics – should be prescribed at the surgeon's discretion.

Monitoring – the anaesthetist should understand the routine standard of monitoring on the postoperative ward and ensure that it meets the needs of the patient. Specific requirements must be clearly communicated, such as hourly urine output, hourly blood pressure, overnight Sp_{O_2} or any other observ-ations in an at-risk patient. Action that should be taken if the observation deviates from the desired targets should be documented.

Medical Gas Storage, Suction Devices and Humidifiers

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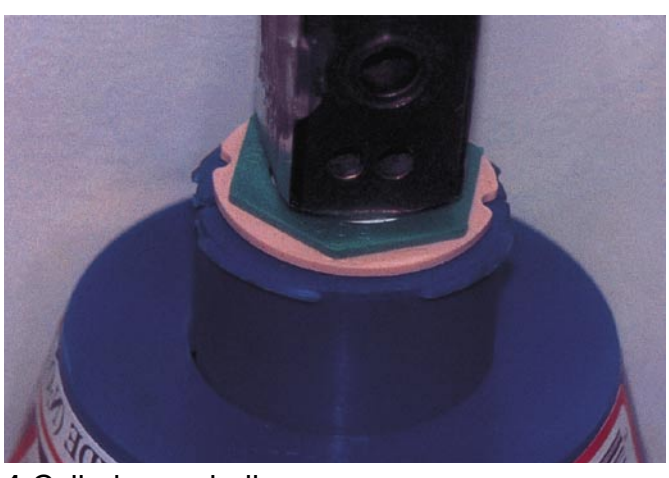
Cylinders

Medical gas cylinders are made of molybdenum steel to ensure they are strong and able to withstand high pressures, but are also relatively light in weight. They are constructed as a seamless tube and consist of a body, shoulder and neck. They are colour coded according to British and International Standards (BS1319C and ISO32) to identify their gas contents (see Figure 7, page 109). Cylinders are manufactured in different sizes from A, the smallest, to J, the largest. Size E cylinders are usually attached to the anaesthetic machine and size J cylinders make up manifolds.

The cylinder valve fits into the cylinder neck by a screw thread mechanism, to permit safe, controlled use of its contents. The junction between the cylinder and valve melts in the presence of intense heat, thus allowing escape of gas and minimizing the risk of explosions. Between the neck and cylinder valve is a plastic disc, the colour and shape of which denotes the year in which the cylinder was last examined (Figure 1).



1 Cylinder neck disc.

Cylinder body
The cylinder body is colour coded and engraved with:
- test pressure
- date of last test performed
- chemical symbol of contents
- tare weight (i.e. weight of empty cylinder).

It is also labelled (Figure 2) with the name and symbol of the gas it contains, its volume, pressure and minimum purity (Figure 3). The label gives additional information relating to storage, use (in conjunction with the Medical Gases Data Sheet) and safety matters. The safety points highlighted are:
- compressed gas
- flammability status
- avoidance of oil or grease because spontaneous combustion can occur with high-pressure gases.

2 Cylinder label.

Cylinder size, volume, pressure and purity of contents

Gas	Cylinder size (litres)	Volume of gas at 15°C	Pressure (kPa)	Purity (%)
Oxygen	E	680	13700	99.5
Nitrous oxide	E	1800	4400	98.0
Air	E	640	13700	21.0 (oxygen)
Carbon dioxide	C	450	5000	99.0

3

Storage
- Cylinders must be stored under cover, in a dry, clean and well-ventilated area, away from extremes of temperature.
- Smoking or the use of a naked flame in the storage area is prohibited.
- Moisture or exposure to chemicals can lead to the corrosion of the cylinder or its valve.
- Cylinders should be kept in the upright position or horizontal on shelves to avoid direct damage to the valves.
- Cylinders should be used in a sequential manner to ensure that no cylinder remains in storage for too long.
- Full and empty cylinders should be kept apart.

Testing
During manufacture, one in every 100 cylinders is cut into strips and tested for tensile strength. Cylinders in circulation are tested on a 5-yearly basis by:
- exposure to hydraulic pressure of about 22,000 kPa (far in excess of the pressures encountered in daily use)
- filling with water under pressure to assess expansion and elastic recoil
- internal endoscopic inspection.

Test date details are recorded on the plastic disc between the cylinder valve and the neck and engraved on to the cylinder body.

Filling
Medical gases are stored either in the gaseous state (oxygen and air) or as a mixture of the liquid and vapour (nitrous oxide and carbon dioxide). Cylinders that contain liquid should be used only in the upright position. Gases and vapours stored in cylinders must be free of water vapour to avoid the formation of ice (secondary to a fall in temperature on cylinder opening), which may block the exit valve. For cylinders containing gas alone, the contents can be assessed directly by measuring the pressure using a Bourdon gauge (see *Anaesthesia and Intensive Care Medicine* **1:2:** 65). In the case of cylinders containing both the liquid and vapour phases the situation is more complex. The contents of these can be determined only by subtraction of the tare weight from the cylinder weight because the pressure within will not fall until the liquid has completely vaporized, assuming the temperature stays constant.

During nitrous oxide use, the liquid within the cylinders cools owing to the uptake of latent heat of vaporization. Condensation or ice may form on the outside of the cylinder. In such circumstances, the cylinder gauge pressure may fall despite there being liquid nitrous oxide in the cylinder owing to the fall in saturated vapour pressure of nitrous oxide following the drop in temperature of the liquid. However, once the gas flow is turned off the temperature returns to that of the atmosphere and the gauge pressure returns to that at the beginning of use. Carbon dioxide is used at low flows so the chances of ice forming are low. Liquid is less compressible than gas, therefore cylinders containing nitrous oxide or carbon dioxide are only partially filled with liquid. Any change in pressure within the cylinder is minimized, thus reducing the chance of cylinder rupture should the temperature rise.

The filling ratio is that between the mass of liquid contained in the cylinder and the mass of water that it could contain if filled to the top. The filling ratios for nitrous oxide and carbon dioxide are both 0.75 in temperate climates and 0.67 in the tropics.

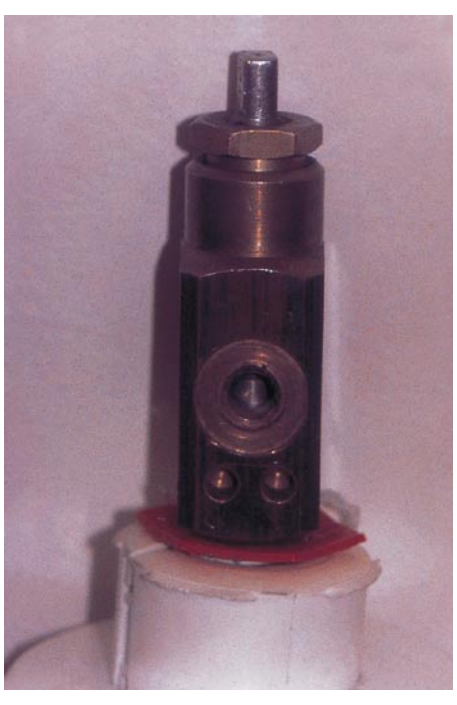
$$\text{Filling ratio} = \frac{\text{Mass of liquid}}{\text{Mass of water}}$$

Cylinder valve
Cylinder valves are made of brass and screw into the cylinder neck. There are four types of valve:
- pin-index valve block
- bull-nose valve
- hand-wheel valve
- star valve.

A pin-index valve is used on all cylinders that are to be attached to an anaesthetic machine. It is an international system (ISO2407) designed to prevent the fitting of the incorrect gas to the yoke and is fully detailed in the British Standard BS1319.

The system is made up of two components.
- Two pins projecting from the yoke, which are arranged in a gas-specific configuration in relation to the valve outlet
- Two holes within the valve block on the cylinder with a corresponding pattern for the designated gas (Figure 4).

This arrangement ensures that it is impossible to fit the incorrect cylinder to the yoke. The pin-index valve block on the cylinder is engraved with:
- tare weight
- chemical symbol for contents
- cylinder owner
- pressure of hydraulic test.



4 Pin-index valve holes on the cylinder.

Cylinder use
New or refilled cylinders are supplied from the manufacturer with a plastic dust cover over the valve to avoid dirt contamination. Before use, this cover should be removed and the valve transiently opened to expel any dirt or grease from the outlet. This reduces the chance of debris entering the anaesthetic machine and is known as 'cracking' the cylinder.

The cylinder is mounted on to the anaesthetic machine by engaging the pins on the yoke with the holes in the valve block. It is secured by tightening the wing nut.

Before use, the cylinder should be opened gently to ensure that there are no leaks, either from the cylinder valve itself or at the point of attachment to the yoke on the anaesthetic machine. A possible reason for gas leakage at the pin-index junction is the absence of the Bodok seal. This is an aluminium-rimmed neoprene washer that sits between the outlet on the valve block and the yoke on the anaesthetic machine. Gentle opening of cylinders minimizes sudden surges of high-pressure gas that may damage the pressure gauge or regulator.

Suction systems

Suction systems form part of the piped medical gases and vacuum systems (see page 107) and must comply with specifications detailed in BS4957. Portable and fixed suction systems are available to accommodate the differing circumstances of use. General operating principles are the same for both systems. Outlets from the central piped vacuum system must have the capability of maintaining a vacuum of at least 53 kPa below atmospheric pressure (101.3 kPa) and supporting a flow of 40 litres/minute.

Suction apparatus and nozzle: suction nozzles are made of either firm plastic (e.g. Yankauer) or metal. They should have a smooth tip to prevent damage to the soft tissues of the oropharynx. The tip often has more than one hole to allow continuation of suction should one hole become blocked. Suction tubing is constructed of semi-rigid plastic to minimize kinking, with a smooth internal surface to limit resistance to flow. The tubing must be of sufficient length to be practical to use, but it should be remembered that the length and width of a tube influences the laminar flow within it, according to the Hagen–Poiseuille equation:

$$\text{laminar flow} = \frac{\Delta P \pi r^4}{8 \eta L}$$

where: ΔP = pressure gradient along tube, r = tube radius, L = tube length, η = viscosity of liquid.

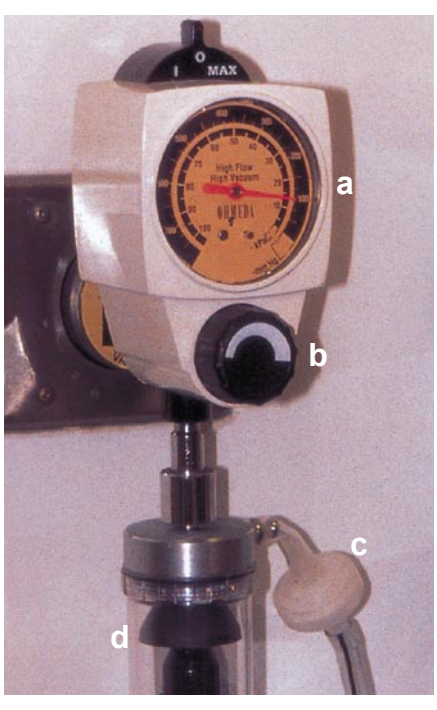
Thus, short, wide tubing maximizes laminar flow.

Reservoir: the reservoir must be of sufficient size to contain the estimated volume of suctioned material, but not so large that it increases the time taken for the vacuum to build up. Most reservoir vessels are constructed of clear material to allow the contents to be visualized and are graduated to permit accurate assessment of aspirate volume. Disposable liners are commonly used to reduce staff exposure to potentially infective material. A floating ball valve within the collection vessel prevents material from entering the control unit and the vacuum source if the container overfills.

Vacuum control regulator unit: this unit is usually situated between the reservoir and the vacuum source (Figure 5). Its function is to allow adjustment of the degree of vacuum applied to the distal suction tubing. The vacuum control adjuster acts as a variable orifice (either directly or by way of a spring acting on a diaphragm) to adjust the force of vacuum, which is indicated on a gauge. Within the unit is a filter and some form of float valve to provide protection from particulate matter.

Distribution pipeline network: between the terminal outlet and the control unit there is a colour-coded (yellow) flexible hose with a specific Schrader probe connection, as for piped medical gases.

Terminal outlet: the terminal outlet of the vacuum pipeline consists of a labelled, self-sealing valve, fronted in yellow, that accepts a probe with indexing collar to prevent misconnection.



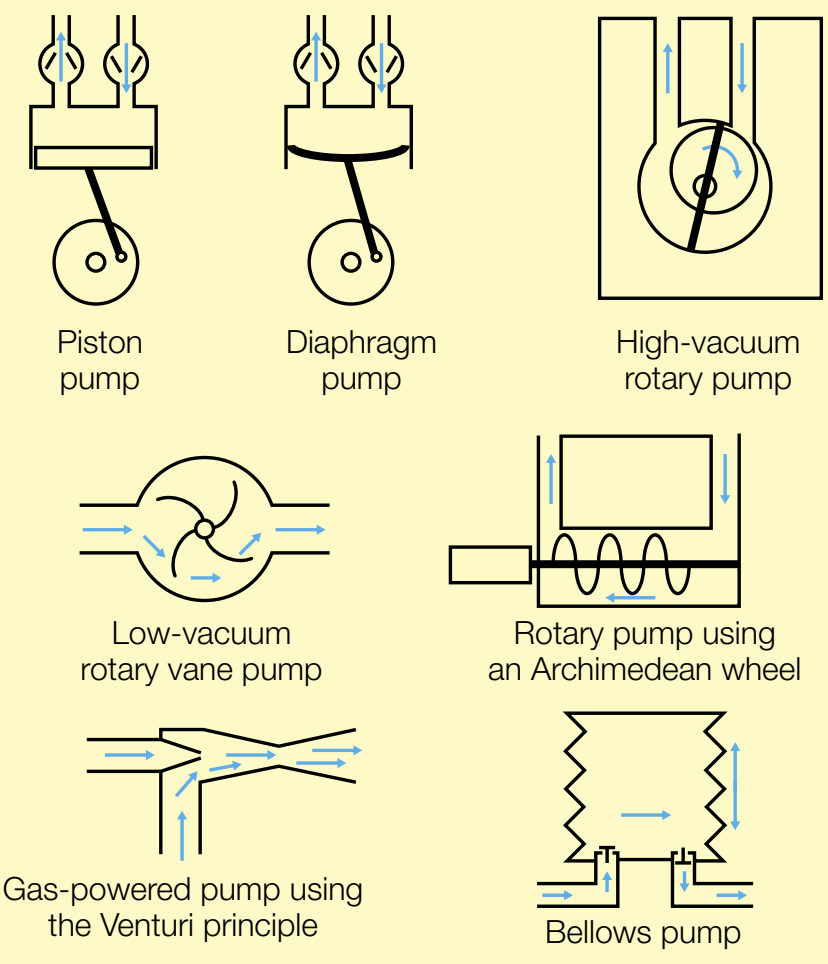
5 Vacuum control regulation unit.
a vacuum gauge, **b** vacuum control, **c** filter, **d** float valve.

Filter unit: filters are sited within the control unit, but also in the case of piped medical gases and vacuum systems between the terminal outlet and the central vacuum source. They remove particulate matter and bacteria from the system to prevent blockage and contamination.

Central pump: the role of the pump is to generate subatmospheric pressure within the system. Pumps are commonly driven by electrical, pneumatic or manual means (Figure 6). The piston, diaphragm and rotary devices shown in Figure 6 all require some form of energy source (usually electricity) to drive mechanical pumps. In contrast to these, the gas-powered pump works on the Venturi principle and the bellows require manual input to generate subatmospheric pressure.

The type of pump is determined by the specific requirements of the suction unit. For example, most portable units use a manual pump, whereas a rotary-driven pump may be used when a large volume of aspirate is anticipated. The pump expels its exhaust gases, via a silencer, to the atmosphere at a suitable site, such that staff and patients are not exposed to the pollution.

Vacuum pumps



Adapted from: Moyle J T B, Davey A. *Ward's Anaesthetic Equipment.* 4th ed. London: WB Saunders, 1998. By courtesy of the publisher.

6

Humidification devices

Humidification strictly refers to the addition of water vapour to air. Humidification of dry, cold anaesthetic gases as they enter the patient's airway is important because dry gases result in drying of the mucosal surfaces, abnormal ciliary function and increase in the viscosity of respiratory tract secretions. Loss of these protective mechanisms can cause mucus plugging, atelectasis, reduction in gas exchange and an increased susceptibility to infection. Also, heat energy due to latent heat of vaporization is lost by the patient in warming and humidifying dry, cold anaesthetic gases.

Aims: under normal circumstances, the upper respiratory tract warms and humidifies the air to an absolute humidity (i.e. mass of water vapour in a given volume of air at specified temperature and pressure) of 34 g/m^3 at 34°C in the trachea and 44 g/m^3 at 37°C in the alveoli. These values equate to fully saturated air whereby the air contains the maximum possible water vapour at specified temperature and pressure. Achievement of these values is the 'gold standard' for humidification. The different efficiencies of various humidifiers are shown in Figure 7.

Approximate efficiency of humidifiers

The exact values depend on the model of humidifier used.

Adapted from: Davis P D, Parbrook G D, Kenny G N C. *Basic Physics and Measurement in Anaesthesia.* 4th ed. Oxford: Butterworth-Heinemann, 1995. By courtesy of the publisher.

7

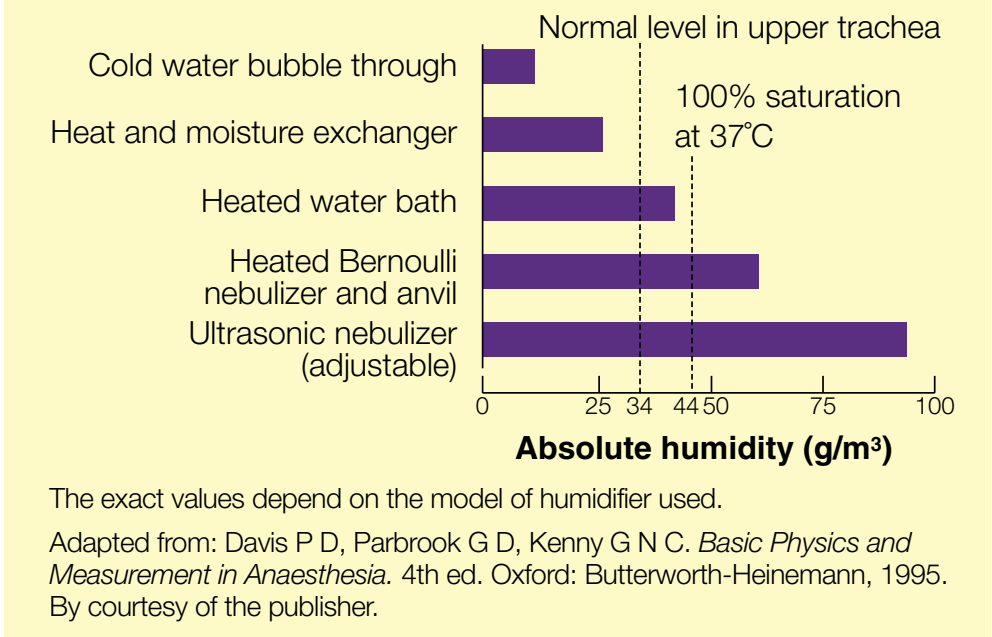
Types of humidifiers

Heat and moisture exchanger (HME) is the most commonly employed humidifier in day-to-day anaesthetic practice (Figure 8). It consists of a sealed unit that is placed within the breathing circuit. The exchanger contains a structure usually of either sponge or mesh, of large surface area, on to which water is absorbed. Absorption is maximized if the mesh is made of a hygroscopic material such as paper coated with calcium chloride or glass fibre. An additional role of some devices is to act as bacterial filters because over 99.99% of bacteria will not pass through pores of less than 0.2 microns. HMEs work on the principle that the moisture from expired gas condenses on to the mesh material within the device as it cools. The mesh is also warmed as the cooling moisture emits latent heat. As gas is inhaled it is warmed and humidified, thus exchanging heat and moisture. The advantages of the system are that it is:

- lightweight
- compact
- disposable
- efficient (60–70% relative humidity at 30–34°C, equating to absolute humidity of about 25–35 g/m^3)
- passive (requires no external power source)
- inexpensive.

The disadvantages are:

- increased dead space
- increased resistance to breathing
- single-patient use.



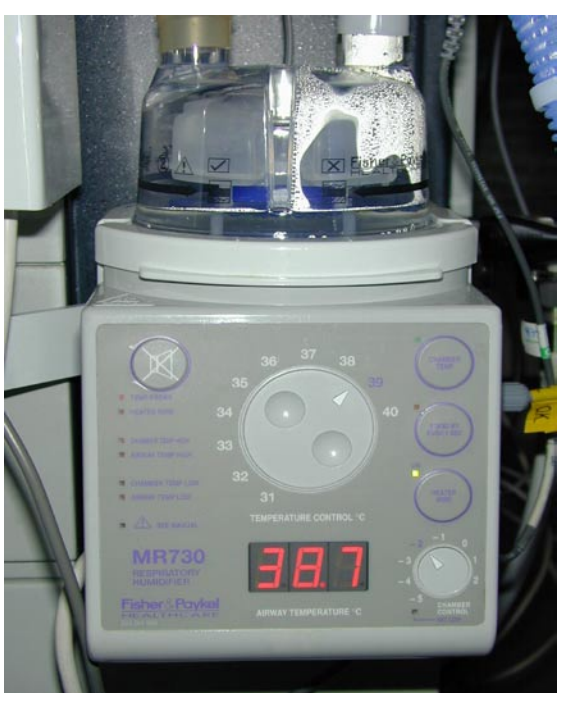
8 Heat and moisture exchanger.

Cold water bath humidifier (Figure 9): this operates by bubbling inspiratory gas through or over a cold water bath. The advantages are it is simple and safe. The disadvantage is that it is inefficient.

Hot water bath humidifier (Figure 10): inspiratory gases are bubbled through, or pass over, a warm water reservoir. The contact surface area is increased in some devices by the use of wicks or multiple bubble holes. The water temperature must be rigidly regulated to attain a balance between maximum humidification, bactericidal activity and heating, with the risk of thermal injury to the patient. This is achieved by the use of a thermostatic control and temperature monitoring within the circuit close to the patient. A water trap must be included on the patient side of the system and the whole apparatus must be below patient level to limit the risk of condensed water in the tubing entering the breathing circuit directly. The system is efficient but the disadvantages are:

- risk of scalding
- bacterial growth if temperature falls below 60°C
- condensation of water within tubing.

9 Cold water bath humidifier.



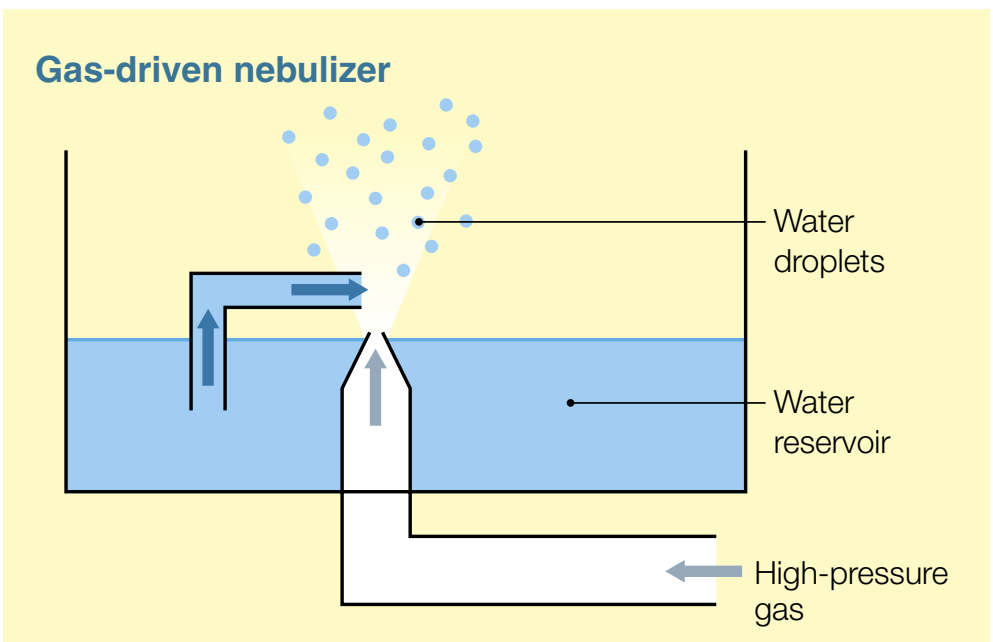
10 Hot water bath humidifier.

Nebulizers: the principle of nebulizers is to add tiny droplets of water to the inspired gas. Strictly speaking nebulizers are not humidifiers because they add water droplets not vapour to the gas. Nebulizers have the potential to produce water droplets of varying sizes. The result of this is that very small droplets pass into the alveoli and thus risk fluid overload, whereas large droplets risk being deposited in the breathing circuit or upper airway. Ideal droplet size is 1–5 microns. Nebulizers are highly efficient but they can be expensive and water overload may occur, especially in ultrasonic devices. There are three commonly encountered methods by which nebulizers produce water droplets.

Venturi principle – water is entrained into a jet of gas that breaks it into droplets (Figure 11). Some systems also contain a solid object (anvil) into which the droplets are propelled, thus further reducing their size. Droplet size averages 2–4 microns. Back pressure from a breathing system can affect the efficiency of the device by reducing water entrainment. Some nebulizers incorporate a heater to increase their efficiency.

Spinning disc – a rapidly rotating disc that throws off tiny water droplets.

Ultrasonic – high-frequency ultrasound waves fragment water into tiny droplets. The water may be dropped on to a vibrating surface or the device may be immersed in a water bath. Droplets 1–2 microns in size are produced.



11

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Medical Gases and their Delivery

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Medical gas

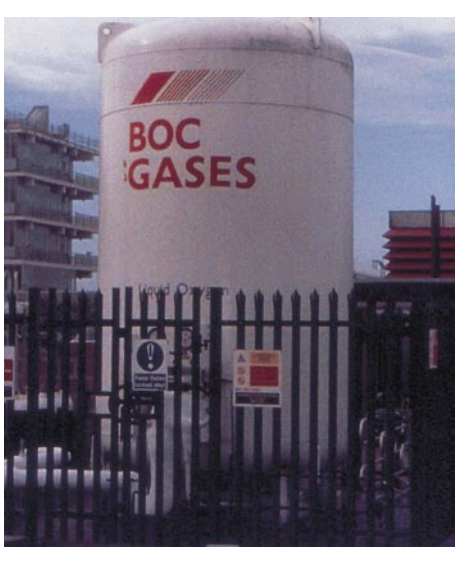
In the UK, most hospitals have piped medical gases and vacuum systems (PMGV) for convenience and economic reasons. The vacuum component of this system is discussed on page 114.

The pipeline network carries medical gases from central bulk storage sites to hose outlets in the walls of anaesthetic rooms, theatres and wards. The responsibility for this section of the PMGV is principally that of the hospital pharmacy, supplies and engineering departments. Anaesthetists have responsibility for the section of pipeline between the terminal outlet and the anaesthetic machine. The bulk store for medical gases is usually a series of cylinder manifolds (Figure 1). In the case of oxygen, the cylinder manifold is often used as a reserve because most hospitals store oxygen in a vacuum-insulated evaporator (VIE) (Figure 2). The cylinder manifold is divided into a primary unit, which is in use, and a secondary unit in reserve. As the pressure in the primary unit falls, the supply is automatically switched to the secondary unit and an alarm sounds to alert the staff to replace the empty cylinders. When there is actual or impending supply failure the alarm usually sounds in the switchboard area of the hospital.

The pipes are constructed of high-grade copper alloy to prevent degradation of gases and are de-greased to reduce the risk of combustion or explosion. They are labelled at regular intervals along their length and are separated from other pipelines within the hospital to avoid confusion. Within the network of pipes there are valves to control the supply to individual theatres or a complete department, in the event of fire or pipeline damage. These are lever-operated, non-lubricated valves housed in clearly accessible units usually behind a breakable glass cover (Figure 3).

The pressure within the pipelines is regulated at about 400 kPa.

1 Cylinder manifolds.



2 Vacuum-insulated evaporator.

3 Pipeline lever safety valve.

Terminal outlet connection

Outlet points (Figure 4) for each of the piped medical gases have specifically labelled, shaped, colour-coded and non-interchangeable Schrader sockets to prevent connection of the incorrect gas supply to the flexible hoses supplying the anaesthetic machine. These must comply with the British Standard codes (BS5682) and be labelled as such. Each terminal outlet is a self-sealing valve unit of specific size to receive the corresponding collar-indexed probe of the flexible hose.

To ensure correct connection and function of the outlet valve, the probe is firmly inserted and a sharp tug applied to ensure full engagement and opening of the valve. This simple procedure is known as the 'tug test'.

4 Terminal gas outlets.

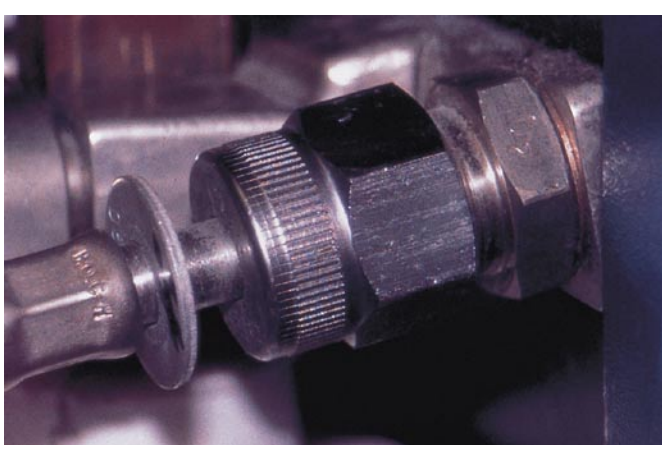
Flexible pipeline

A flexible pipeline carries medical gases from the terminal outlet to the anaesthetic machine. The terminal outlet probe (Schrader probe; Figure 5) is fitted with an indexing collar of a specific diameter for each gas, which will fit only the corresponding gas socket on the terminal outlet valve. In addition, each collar has a notch that fits over a pin within the socket to prevent rotation of the hose once installed. The entire assembly is constructed so that rapid probe insertion or withdrawal can be performed single-handedly and that once withdrawn the terminal outlet unit is self-sealing.

The flexible hose is made of a high-quality copper alloy with antistatic and bacteriostatic properties. It is colour coded and labelled in accordance with the gas it carries.

The hoses are connected to the anaesthetic machine by a non-interchangeable screw thread unit. This unit consists of a probe unique to each gas and a nut to screw the assembly on to the machine. A stainless-steel ferrule is crimped over the whole unit to seal the connection and prevent its removal (Figure 6).

5 Schrader probe.



6 Non-interchangeable screw thread.

Safety

Pipelines and flexible hoses: guidance for manufacturers, installers and maintenance engineers is in accordance with BS5682 (1987) and Health Technical Memorandum 2022 (1994). Pipelines for each of the medical gases are manufactured in different locations within the factory to prevent accidentally mixing up their unique features, for example, connection of the wrong terminal probe, non-interchangeable screw thread fitting or incorrect colour coding.

Pipelines and flexible hoses are steam cleaned, dried and sealed at both ends after internal inspection before being transported to their installation site. This is to prevent contamination and particulate matter from entering the gas supply. In the event of damage to, or technical failure of any part of the pipeline, it must be returned directly to the manufacturer for repair or replacement.

The pharmacy, supplies and engineering departments within each hospital are responsible for the pipeline supply. This includes testing of gases for purity and identity after installation of new pipelines.

The anaesthetist is responsible for ensuring that the flexible hoses are correctly engaged and that the corresponding gas passes into the anaesthetic machine. Correct engagement is checked by using the 'tug test' and the identity of the gas by using the 'single-hose test'. This is done by attaching the oxygen pipeline to the anaesthetic machine, turning on all the flowmeters and ensuring that gas flows only through the oxygen flowmeter and that it is detected by an oxygen analyser fitted at the common gas outlet.

Cylinder gas supply: cylinders and their use in conjunction with the anaesthetic machine are covered elsewhere in *Anaesthesia and intensive care medicine*.

Medical gas pressure

Working pressures within cylinder and piped medical gas supplies are outlined in Figure 7.

Pressure monitoring and display of both pipeline and cylinder gases is performed by Bourdon gauges. The Bourdon gauge is an aneroid (i.e. without liquid) gauge consisting of a coiled tube, attached at one end to the gas supply and at the other end to a pointer. The pressure of the gas causes straightening of the coil and thus causes movement of the pointer over the colour-coded, labelled and calibrated dial. The gauge is faced with heavy glass and designed such that leaks vent from the back of the valve casing and do not blow out the glass.

Cylinder and pipeline colour coding and pressures

	Body colour	Shoulder colour	Pressure (kPa) at 15°C
Cylinder			
• Oxygen	Black	White	13700
• Nitrous oxide	Blue	Blue	4400
• Carbon dioxide	Grey	Grey	5000
• Air	Grey	White/black	13700
Pipeline			
• Oxygen	White		400
• Nitrous oxide	Blue		400
• Air (clinical use)	Black		400
• Air (power tool use)	Black		700

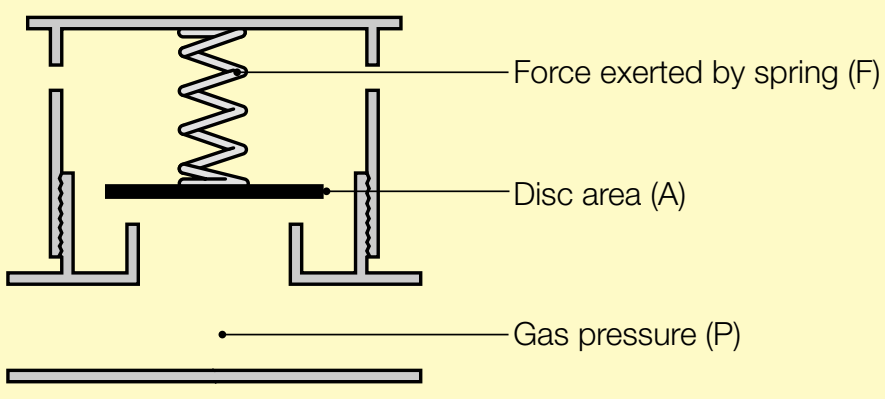
7

Pressure regulators: throughout the medical gas supply network the pressure within the system is closely regulated. This is vital for the protection of both equipment and patient. Measures to maintain a near-constant pressure are found in many sites and usually take the form of a pressure relief valve or a pressure regulator (see *Anaesthesia and Intensive Care Medicine* **1:2:** 66). Both devices are also present within the anaesthetic machine.

Pressure relief valves are designed to allow escape of gas above a certain set pressure. In the case of the VIE this protects the oxygen storage equipment from damage from pressure above 1690 kPa. Similar valves are positioned downstream of pressure regulators within the pipeline supply in case of regulator failure. These are set slightly above 400 kPa.

The principle on which the valve works relates to an equilibrium between two opposing forces: that exerted by the spring and that generated by the gas itself (Figure 8).

Pressure relief valve



$F = P \times A$

As the disc area is constant, and the force exerted by the spring to close the valve is pre-set, once the gas pressure within the system exceeds this closing force, the valve opens and gas escapes

Adapted from: Aitkenhead A R, Smith G, eds. *Textbook of Anaesthesia.* 3rd ed. London: Churchill Livingstone, 1998. By courtesy of the publisher.

8

Medical gases

Oxygen

Manufacture: industrial manufacture is by the fractional distillation of liquid air. This involves the removal of carbon dioxide and then the separation of oxygen and nitrogen by means of their different boiling points.

Oxygen may also be produced by oxygen concentrators, which extract oxygen from air. This process involves the passing of air through a sieve of zeolite (aluminium silicate), which absorbs the nitrogen, leaving oxygen and a trace of argon. The equipment for this process used to be bulky, but recently smaller units suitable for home use have been developed. A maximum concentration of 95% pure oxygen can be produced using these devices.

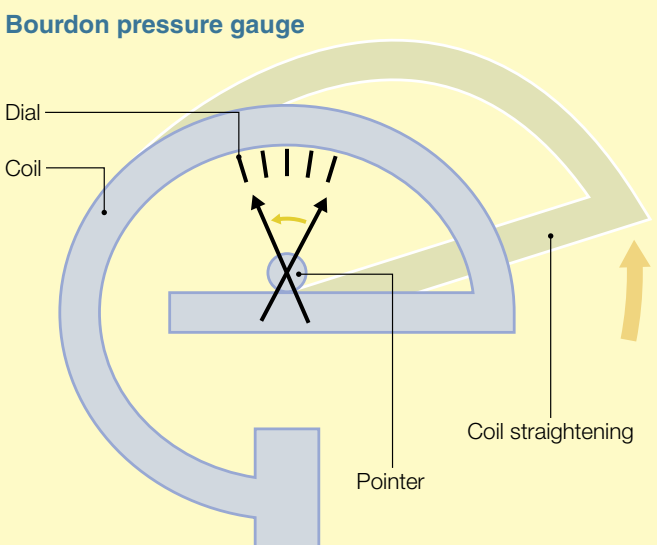
Storage: oxygen is stored either as a gas in cylinders or as a liquid in a VIE. In the UK, cylinders used for oxygen storage are black with a white shoulder (Figure 9); in the USA they are green. The oxygen is stored at a pressure of 13700 kPa at 15°C. Where piped medical gases are used, oxygen is also stored in cylinder manifolds. In cylinders, oxygen is a gas and the volume of oxygen remaining in the cylinder is directly related to the measured pressure, according to Boyle's law.

9 Cylinders. From left: oxygen, nitrous oxide, air, carbon dioxide.

The VIE (Figure 10) is a thermally insulated device similar to a large vacuum flask. Oxygen is stored within this vessel at about –160°C and at a pressure of 5–10 atmospheres (500–1000 kPa). The low temperature is maintained by the vacuum surrounding the main chamber and by heat energy being lost from the liquid oxygen as it evaporates (latent heat of vaporization). Under normal working conditions, oxygen evaporates and passes through the pressure regulator to reduce its pressure to 400 kPa, and then enters the pipeline supply. If demand for oxygen is low, the internal pressure gradually rises until a safety valve opens at 1690 kPa to release gas to the atmosphere. When demand for oxygen is great, the control valve opens allowing liquid oxygen to pass through the pressure-raising superheater and vaporizer, evaporate and enter the pipeline supply. The superheater is a coil of uninsulated copper pipe.

The VIE (Figure 2) can be found outside all hospitals that use piped gases and may be supported by a tripod structure. Two of these legs support the weight of the evaporator, while the third is a weighing device to allow the mass of liquid contained to be measured. Modern designs stand on four legs and the contents are calculated by measuring the pressure difference between the top and bottom of the vessel.

Bourdon pressure gauge



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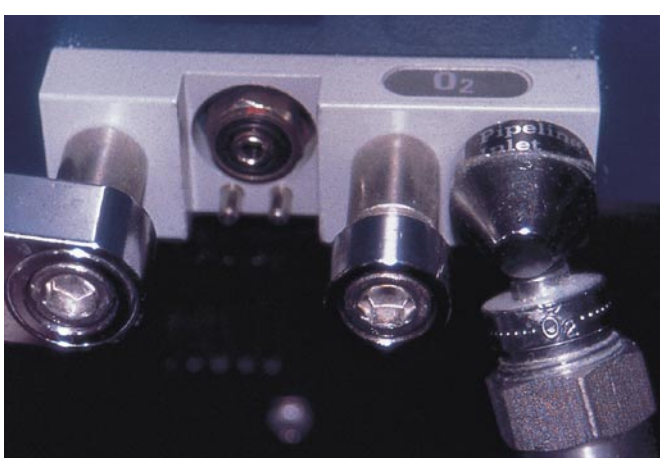

11 Cylinder yoke.

Delivery: oxygen is delivered from a central supply (i.e. a manifold or VIE) or directly from cylinders. Central oxygen supply is via the pipeline system described above. Direct cylinder supply of oxygen to the anaesthetic machine involves the connection of the cylinder valve to the cylinder yoke (Figure 11) on the back of the machine.

Carbon dioxide

Manufacture: carbon dioxide is manufactured by heating calcium or magnesium carbonate in the presence of their oxides. Other sources are as a by-product of the manufacture of hydrogen, fermentation of beer or the combustion of fuel.

Storage: in the UK, carbon dioxide is stored in grey cylinders (Figure 9) at a pressure of 5000 kPa at 15°C, as a liquid in equilibrium with its vapour.

Distribution: unlike the other medical gases, carbon dioxide is not distributed via a central pipeline. The attachment of carbon dioxide cylinders to anaesthetic machines has declined in recent years to minimize the risk of accidental administration during anaesthesia. The present guidelines issued by the Association of Anaesthetists of Great Britain and Ireland state that carbon dioxide cylinders should not be routinely fitted to the anaesthetic machine.

Air

Manufacture: air for medical use is compressed, cleaned and filtered before use.

Storage: compressed air for anaesthetic use is stored in grey cylinders with black and white shoulders (Figure 9) at a pressure of 13,700 kPa at 15°C. In the USA, the cylinders are yellow.

Distribution: pipeline air is sourced from either a manifold (Figure 1) or, more economically, from an air compressor. It is important to know that air for clinical use is regulated to a pressure of 400 kPa, whereas that for the use of surgical power tools is supplied at 700 kPa. The terminal outlet for compressed air is colour coded black and white, labelled and has a non-interchangeable connection (Figure 4).

Cylinders are attached directly to the anaesthetic machine by connection of the cylinder valves to the cylinder yoke. A larger portable cylinder may be attached via a flexible hose.

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Perioperative Fluids

E Anne Thornberry

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Any surgery under anaesthesia can upset the patient's normal fluid status through preoperative restriction of oral intake of fluids. The degree of disruption depends on the patient's medical condition, the nature of the surgery and the choice of anaesthetic. Factors to consider when planning perioperative fluid management are listed in Figure 1.

Maintenance requirements: normal values for daily fluid and electrolyte requirements are shown in Figure 2. Dextrose 4% with saline 0.18% contains 30 mmol/litre of sodium and is often used for basal fluid therapy.

Determinants of perioperative fluid requirements

- Maintenance requirements
- Preoperative deficits
- Blood loss
- Third-space losses
- Transcellular fluid losses
- Effects of anaesthetic agents and technique

1

Maintenance fluid and electrolytes

Adults
- 40 ml/kg/day

Children
- 100 ml/kg/day for first 10 kg
- 50 ml/kg/day for second 10 kg
- 25 ml/kg/day for each subsequent kg

Na^+ = 1–1.5 mmol/kg/day
K^+ = 1 mmol/kg/day

2

Preoperative deficits

Preoperative assessment of the fluid status of the patient requires an appropriate history, examination and investigations.

History and examination

The following questions should be asked.
- How long has the patient been starved?
- Do they have an intravenous infusion in progress?
- Have they any reason to expect excessive losses?
- Are they taking diuretics?
- Are they pyrexic?
- Have they been vomiting or do they have a nasogastric tube *in situ*?
- Have they got diarrhoea or had a bowel preparation?
- Could they have third-space losses or occult bleeding?
- Have they any symptoms of fluid overload?

The physical examination includes evaluation of the mucous membranes and skin turgor, and measurement of the vital signs, including orthostatic changes. Ascites, pulmonary oedema and pleural effusions should be sought. Measurement of urine output may be useful.

Investigations

A normal haematocrit value may indicate that the patient has a normal fluid status or it may reflect someone with anaemia who is also dehydrated. A raised serum urea with a normal creatinine level may indicate dehydration. Raised urinary sodium levels, specific gravity and osmolality all reflect the normal homeostatic response to water depletion and can be used to monitor progress with resuscitation. The signs and symptoms of water depletion are described in Figure 3.

Estimation of total body water deficit

Deficit of body weight	For example in a 70 kg man	Signs and symptoms
Up to 5%	3.5 litres	Thirst Dry mouth
5–10%	3.5–7 litres	Decreased skin turgor Decreased intraocular pressure Tachycardia Orthostatic hypotension Tachypnoea Oliguria Skeletal muscle weakness Drowsiness
10–15%	7–10.5 litres	Severe hypotension Tachycardia Anuria Confusion/coma

3

Signs and symptoms of uncorrected acute blood loss

Volume lost	For example in a 70 kg male	Signs and symptoms
10%	490 ml	Thirst Venoconstriction
20%	980 ml	Mild increase in heart rate Systolic blood pressure normal Slight rise in diastolic pressure Decreased urine output
30%	1470 ml	Tachycardia > 120/minute Moderate hypotension Tachypnoea Cool, clammy, pale Anxious/aggressive Oliguria
40%	1960 ml	Severe hypotension and tachycardia Tachypnoea Anuria Mental confusion
50%	2450 ml	Coma

4

Fluid losses

Blood loss: the signs and symptoms of unreplaced blood loss (Figure 4) can help to estimate acute losses if accurate measurements cannot be made. Estimates of intraoperative blood losses are derived from measuring or estimating observed losses. Prediction of postoperative losses requires knowledge of the type of surgery and expected postoperative bleeding, combined with measurement of losses in the drains, vital signs, and haemoglobin and haematocrit levels.

Third-space losses are caused by sequestration of extracellular fluid into the tissues. The composition of this fluid is the same as that of interstitial fluid and losses after major bowel resection may be as great as 8 ml/kg/hour. The extent of third-space losses depends on the severity of injury to the tissues.

Transcellular fluid losses: nasogastric aspirate can be measured but pleural effusions and ascites must be estimated. Losses from evaporation occur from the surgical site and during a laparotomy these can be as much as 10 ml/kg/hour.

Effects of anaesthetic agents and techniques

Ventilation with dry anaesthetic gases increases the pulmonary losses from evaporation. General and regional anaesthesia tend to decrease the patient's blood pressure by a reduction in sympathetic tone, vasodilatation or myocardial depression. Vasopressors and intravenous fluids are used to minimize these effects, complicating the assessment of perioperative fluid status. Central venous pressure monitoring can be invaluable in helping to manage more complex cases.

Choosing perioperative fluids

Crystalloids

Dextrose solutions disperse through all the body fluid com-partments and are required to replace combined intracellular plus extracellular water depletion. Once any deficit has been replaced, dextrose is used only perioperatively as part of the basal water requirements or in a diabetic regimen.

Physiological saline disperses throughout the extracellular fluid compartments and is commonly used perioperatively to replace blood loss, transcellular losses, evaporation and third-space losses. Only one-third remains in the intravascular compartment and therefore three times the volume of the blood loss must be given if saline is used as a replacement. When large volumes of saline are administered there is a risk of developing hyperchloraemic acidosis.

Ringer's lactate (Hartmann's solution) behaves as normal saline in distribution. It is often used as the first-choice replacement fluid because the electrolyte content more accurately mimics the extracellular fluid. Its constitution varies between laboratories but in general it contains 137 mmol/litre sodium, 4 mmol/litre potassium, 3 mmol/litre calcium and 142 mmol/litre chloride. There are fewer risks of electrolyte disturbances if large volumes are administered but it is hypotonic and large volumes reduce plasma osmolality.

Colloids

The contents of the commonly used colloids are listed in Figure 5.

Properties of commonly used colloids

	Average molecular weight	Sodium (mmol/litre)	Potassium (mmol/litre)	Chloride (mmol/litre)	Calcium (mmol/litre)
Haemaccel	35,000	145	5.1	145	6.2
Gelofusine	35,000	154	0.4	154	0.4
Hetastarch	450,000	154	0	154	0
Dextran 70 in saline	70,000	150	0	150	0
Albumin 4.5%	70,000	150	2	120	0

5

Colloids used for intravenous therapy have an increased osmolality with respect to plasma and can increase plasma volume by more than the volume infused by attracting water from the interstitial fluid compartment. Consequently they are used predominantly to replace intravascular losses and are unsuitable for the treatment of dehydration. The length of time a colloid stays in the intravascular compartment depends on the shape, size and charge of the molecules suspended and the porosity of the capillary endothelium.

Gelatins are colloid solutions derived from animal gelatin. They have an average molecular weight of 35,000 but there is a wide variation in molecule size. The two commonly used gelatins are *Haemaccel*, which is urea linked, and *Gelofusine*, which is a succinylated gelatin. Their intravascular persistence is low, about 2–3 hours with *Gelofusine* and less for *Haemaccel*. Gelatins are the colloids most likely to induce an anaphylactoid reaction. Cross-matching is unaffected by the use of gelatins. *In vitro* studies suggest they interfere with clotting and platelet aggregation but in clinical practice little effect is seen.

Hydroxyethyl starches (HES) are modified natural polymers of amylopectin, which are metabolized by amylase. They are divided into high, medium and low molecular weight starches according to the range of molecular weights in the solution. *Hetastarch* is a 6% solution with an average molecular weight of 450,000 and a mean molecular weight of 70,000. The intravascular persistence of *Hetastarch* is over 24 hours. Some enters the interstitial space and is taken up by the reticulo-endothelial system where it can persist for years. Hexastarch and pentastarch are lower metabolic weight starch solutions. High molecular weight HES solutions can cause a coagulopathy by reducing factor VIII and von Willibrand factor. The lower the average molecular weight of the solution the less effect it has on coagulation. The maximum recommended dose is 33 ml/kg/day, though this has often been exceeded without any adverse effects. Anaphylactic reactions have been reported, but the incidence is low.

Dextrans are branched polysaccharides produced by the action of bacteria on a sucrose medium. Dextran solutions are divided by their average molecular weight into 10% Dextran 40 (molecular weight 40,000) and 6% Dextran 70 (molecular weight 70,000). Dextran reduces blood viscosity, reduces platelet adhesiveness and increases fibrinolysis. Doses higher than 1.5 g/kg can increase bleeding. Only Dextran 70 is used for short-term plasma expansion. Severe anaphylaxis is uncommon but has been reported.

Albumin has a molecular weight of 69,000 and is a naturally occurring plasma protein that contributes significantly to the maintenance of plasma oncotic pressure. It has been used as a colloid to treat critically ill patients with hypoalbuminaemia but there is no evidence that this improves outcome. Recent research has suggested it may worsen outcome but this is not proven. The increasing cost of production of albumin has significantly reduced its use in clinical practice.

Crystalloid–colloid controversy
It has been argued that colloids are more appropriate than crystalloids for the replacement of intravascular losses because they stay in the intravascular compartment longer, necessitating a smaller volume of replacement and a more rapid result. As stated above, the intravascular persistence varies significantly between the different colloids, while this argument holds for hydroxyethyl starches it is not so strong for the gelatins.

Opponents of colloids emphasize the incidence of ana-phylaxis with colloids, which does not exist with crystalloids. The pragmatists suggest that the normal physiological response to an acute intravascular deficit is to draw water in from the interstitial fluid compartment and therefore it makes sense to initiate resuscitation with a crystalloid and then to continue with a colloid if the loss becomes significant.

Blood and blood products
Red cell transfusions: the indication for a red cell transfusion is to increase the oxygen-carrying capacity of the blood by raising the haemoglobin concentration of patients with acute or chronic anaemia. The extent to which it should be raised depends on the balance between oxygen consumption and supply, with the aim of avoiding tissue hypoxia. Factors that affect perioperative oxygen consumption are body temperature, sympathetic activity, metabolic activity, heart rate and drug therapy.

New safety requirements are making blood products more complex and expensive to produce. Recent research suggests the traditional trigger of a haemoglobin concentration of 10 g/dl for perioperative transfusion is too high. The rate of blood loss also needs to be taken into consideration when deciding to transfuse. Suggested British Society for Haematology guidelines are summarized in Figures 6 and 7.

Need to transfuse based on an estimate of lost circulating volume

Volume lost	Indication for transfusion
15%	Only if superimposed on existing anaemia or Patient unable to compensate because of severe cardiac or respiratory disease
15–30%	As above or In the presence of continuing blood loss
30–40%	Transfusion should be considered
> 40%	Transfuse

6

Need to transfuse based on consideration of haemoglobin concentration

Haemoglobin concentration	Indication for transfusion
< 7 g/dl	Transfuse
7–10 g/dl	Transfuse patients who would tolerate anaemia poorly (e.g. those with cardiac or respiratory disease, those over 65 years of age)
> 10 g/dl	No indication

7

Concerns about the safety of transfusion have encouraged the development of alternative strategies to minimize the need for homologous transfusions. These include the use of autologous pre-donation of blood, acute normovolaemic haemodilution, intraoperative cell salvage, preoperative administration of erythropoietin and the development of blood substitutes.

Fresh frozen plasma is valuable because it contains all the clotting factors. It is used to correct a coagulopathy due to a concurrent illness, the use of anticoagulants or a dilutional coagulopathy. A coagulation screen should be requested to establish the need for fresh frozen plasma, although in the presence of a massive haemorrhage, fresh frozen plasma may be given before laboratory results are available if there are clinical signs of impaired coagulation.

Platelets should be given only if there is clinical and laboratory evidence of abnormal coagulation.

Blood substitutes
There are three different areas of research in progress: free haemoglobin solutions, encapsulated haemoglobin cells, and perfluorocarbon emulsions.

Haemoglobin-based oxygen carriers: free haemoglobin has been used as a red blood cell substitute for decades but initially there were many adverse effects including hypertension, bradycardia, renal dysfunction and a short intravascular retention time. A problem was the lack of 2,3-diphosphoglycerate (2,3-DPG) and the higher pH of plasma compared with that inside the red blood cell. There is also an increase in oncotic activity which limits the concentration of free haemoglobin that can be used to about 5–7 g/dl.

Some of the adverse effects of free haemoglobin have been reduced by a variety of modifications including polymerization and conjugation to increase the intravascular retention time and the introduction of haemoglobin into cell-like structures, using stable, porous membranes that allow molecules such as glucose to enter. Some products have reached the stage of clinical trials.

Perfluorocarbon emulsions: perfluorocarbons are synthetic carbon–fluorine compounds. They dissolve gases including oxygen and carbon dioxide. They are not metabolized *in vivo* and most are excreted unchanged via the lungs. A small amount is taken up by the reticulo-endothelial system and excreted later. They are immiscible in water and have to be emulsified. Initial emulsifiers caused numerous adverse effects. Second-generation perfluorocarbons have reduced the complications, but high doses can still interfere with coagulation, elevate liver enzymes and produce a febrile response. They are in phase III trials as a blood substitute. ◆

FURTHER READING

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Positioning the Surgical Patient

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The correct positioning of a patient for surgery is a balance between optimizing surgical exposure and minimizing complications for the patient. The surgeon may request a particular position and it is often the role of the anaesthetist to ensure that this is accomplished safely. The anaesthetist must consider the limits of position that may be tolerated and ensure access to the airway, monitoring and vascular devices as far as possible. In general, complications may arise from physiological consequences of the position and the effects of direct pressure on soft tissue structures.

Supine position

Indications: the supine position is the standard for most surgical procedures. The orthopaedic fracture table is a modification that enables traction to be maintained on a lower limb and provides access for an image intensifier.

Physiological consequences: when an individual is upright, ventilation per unit lung volume is greater in the lower part of the lung, because here the weight of the lung makes the intrapleural pressure–volume curve steeper (see Figure 2). The apex of the lung is on a flatter part of this curve, representing a relatively larger change in pressure for a given change in lung volume, and hence a lower compliance. The lower part of the lung is better perfused as a result of gravity.

When an individual is supine, ventilation and perfusion become more uniform and the effects of gravity less marked. The differences between base and apex are then replaced by differences between dependent and non-dependent parts of the lung. Stroke volume and cardiac output may increase as a result of the increase in central venous pressure. Baroreceptors sense an increase in arterial pressure, leading to a fall in heart rate and systemic vascular resistance.

The physiological effects of a change of posture when anaesthetized depend on additional factors:

- pharmacological effects
- circulating blood volume
- method of ventilation.

The functional residual capacity (FRC) decreases by about 20% following induction, though closing capacity remains unchanged. Anaesthetized patients are vasodilated and have diminished compensatory cardiovascular reflexes. Therefore, all positioning movements must be made slowly. The basic supine position is generally well tolerated and has no additional physiological effects in healthy patients.

Pregnant patients may suffer from the supine hypotensive syndrome, where the weight of the gravid uterus reduces venous return by compression of the inferior vena cava (IVC). This can be avoided by a lateral tilt of the operating table, usually to the left side.

Direct pressure complications: the eyes should be taped closed to prevent corneal drying or injury from scratching. Limbs must be fully supported and moved with care to prevent joint dislocation or even fracture. The arms can be secured in the drawsheet, or by the use of padded arm supports.

Skin overlying all bony points is prone to pressure damage, especially the occiput, elbows, knees, greater trochanter of the femur and sacrum. As little as 2 hours of unrelieved pressure may result in a pressure sore; the duration of pressure is considered to be more important than its intensity. The ankles should be placed in soft foam-rubber boots to avoid pressure necrosis of the heel skin.

Injury to peripheral nerves (Figure 1) is often a consequence of the way in which the patient is positioned during surgery. Nerve injury is most likely to occur with the combination of muscle relaxation, an extreme position and prolonged surgery. Peripheral nerves are damaged by local ischaemia caused by compression or stretching. This produces segmental demyelination. Complete clinical recovery usually occurs within 6–8 weeks, but may take several months. Severe damage may be associated with permanent injury. Electromyography studies may aid the prognosis.

Supine position – nerve injuries

Nerve injury	Comments
• Supraorbital	Compression by catheter mount, trachael tube connectors
• Nerves to the eye	Compression from face mask
• Facial (VIIth)	Compression by anaesthetist's fingers against ramus of mandible, face mask harness
• Brachial plexus	Stretching injury, especially when arm is abducted > 90°, externally rotated, elbow extended and forearm supinated
• Ulnar	Most common nerve injury occurring during anaesthesia. Compression between the medial epicondyle of the humerus and the edge of the operating table. Pronation of the forearm may place the nerve more at risk than supination
• Radial	Compression between the edge of the operating table or armboard and the shaft of the humerus, compression from a head-screen support
• Pudendal	Compression from the post of an orthopaedic fracture table may cause pudendal nerve injury or genital trauma
• Sciatic	Direct compression in thin patients undergoing prolonged surgery on a hard table

1

Lateral ('lateral decubitus') position

Indications:

- thoracic surgery
- lateral approach to the kidney
- surgery to the hip.

Reference to the right or left lateral position indicates the side on which the patient is lying.

Physiological consequences: when lying awake in the lateral position, ventilation to the upper and lower lungs behaves in a similar fashion to the ventilation of lung apex and base when upright. The lower lung lies on the steeper, more compliant part of the intrapleural pressure–volume curve (see Figure 2, page 12). The weight of the abdominal contents pushes the lower lung diaphragm higher than the diaphragm of the upper lung, so that it is also able to generate a higher force of contraction. The lower lung is therefore better ventilated than the upper lung. Perfusion of the lower lung is also greater as a result of gravity.

Following anaesthesia, the distribution of blood flow remains unchanged but there are significant changes to the distribution of ventilation. Muscle tone is greatly reduced or absent and the FRC of each lung falls, especially in the lower lung as a result of the weight of the mediastinum pushing down from above and the weight of the abdominal contents below. This has the effect of moving the upper lung down to a more favourable (i.e. steeper and more compliant) part of the intrapleural pressure–volume curve. The lower lung moves down to a flatter, less compliant part of the curve. Therefore the upper lung becomes the better ventilated, but because it receives less of the pulmonary blood flow, ventilation–perfusion mismatch increases.

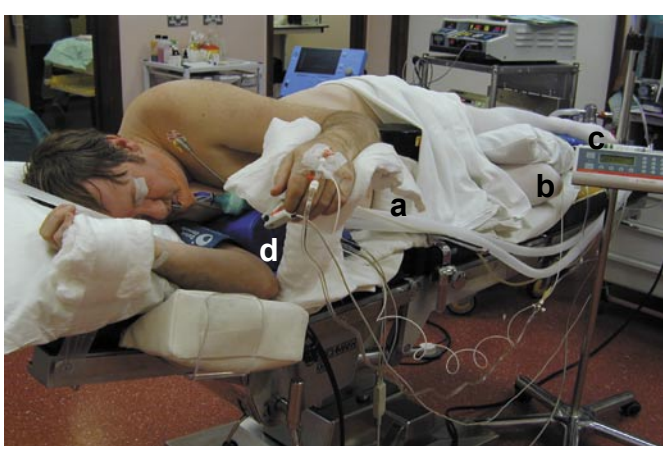
To expose the flank during the lateral approach to the kidney, the lateral flexed position over a support ('kidney position') may be necessary. Significant hypotension may result when the patient is positioned on the right side for a left kidney operation. Reduced venous return occurs as a result of partial obstruction of the IVC from the support. Hepatic encroachment on the IVC may also contribute. This problem is less common when the patient is in the left lateral position.

Direct pressure complications: the pelvis and shoulders must be well supported to prevent the patient from rolling backwards off the table, or forwards into the recovery position. The lower leg should be flexed and the upper leg extended, with a pillow between the two (Figure 2).

An axillary roll places the weight of the chest on to the ribcage and prevents direct compression injury to the shoulder and axilla, thus avoiding deltoid muscle ischaemia or neurovascular damage to the lower arm.

The lower leg is at risk from pressure damage, especially in obese patients. Compartment syndrome, myoglobinuria and acute renal failure have been reported.

Nerve injuries that may result from the lateral position are listed in Figure 3.



2 The lateral position.
a Padded supports to prevent patient rolling over – anteriorly next to iliac crests; posteriorly next to lumbar spine.
b Lower leg flexed and pillow between knees.
c Heel supported.
d An axillary roll places the weight of the chest on to the ribcage.

Lateral position – nerve injuries

Nerve injury	Comments
• Cervical spine	Lateral flexion may stretch cervical spinal nerves and make arthritic joint pain worse. May cause Horner's syndrome
• Brachial plexus	Stretching injury when the neck is extended and in lateral flexion. May occur when the arm is suspended from a bar or gutter and is inadequately supported
• Common peroneal	Compression between the operating table and the head of the fibula

3

Trendelenburg ('head-down') position

Indications:

- pelvic surgery
- insertion of central venous lines.

Friedrich Trendelenburg first described the 45° supine head-down position in 1890. This position facilitates access to the pelvis. Most head-down positions are now about 20° or less with acceptable results. The steep head-down position is now avoided because it is unnecessary and has too many disadvantages. A corrugated or non-slip mattress helps prevent patient movement.

Physiological consequences: there is a greater reduction in FRC than in the basic supine position as a result of pressure of the abdominal contents on the diaphragm. Usually ventilation is little impaired, especially in fit patients and for short periods. For longer operations and in obese patients, there is increased work of breathing against the weight of the abdominal contents, therefore controlled ventilation is preferable.

Central venous pressure rises, and cardiac output may increase. This may precipitate acute heart failure in patients with poor cardiac reserve. The position is not generally effective in improving the circulation during shock and can increase venous pooling in the upper half of the body. A prolonged head-down position will cause venous congestion and oedema in the head and neck.

Barrier pressure is the difference in intraluminal pressures either side of the gastro-oesophageal junction. The pressure within the oesophagus is normally 15–25 mm Hg higher than gastric pressure and gastro-oesophageal reflux is prevented. Barrier pressure is maintained by the action of the smooth muscle cells of the lower oesophageal sphincter and the skeletal muscle of the surrounding crural diaphragm. The head-down position may raise intragastric pressure, reduce barrier pressure and encourage reflux to occur.

There is an increase in intracranial and intraocular pressure. While inserting central venous lines in patients with head injury, care should be taken to limit the head-down tilt to the minimum necessary so as not to worsen cerebral perfusion pressure.

Direct pressure complications: injury to the brachial plexus was common when the steep 45° head-down position was used and patient movement was prevented by shoulder supports or wrist straps. Patient movement is prevented by the non-slip mattress when lesser degrees of head-down tilt are used (e.g. 20°). Brachial plexus injury is now uncommon.

Reverse Trendelenburg ('head-up') position

Indications:
- operations on the head and neck; this position reduces venous pressure and helps reduce bleeding
- surgical access to the gall bladder and proximal gastrointestinal tract, especially during laparoscopic surgery
- operations on the shoulder joint.

Usually, 15–20° head-up tilt is sufficient.

Physiological consequences: there is a small decrease in arterial pressure; but less of a decrease in FRC than in the basic supine position because less pressure is exerted on the diaphragm by the abdominal contents. There is a reduction in intraocular and intracranial pressure, mainly as a result of improved venous drainage.

Any open vein or sinus above the level of the right atrium can cause venous air embolism.

Direct pressure complications: injury to the brachial plexus may be caused by excessive rotation and lateral flexion of the neck away from the operative site.

Lithotomy position

Indications:
- urological procedures
- operations on the perineum, anus and rectum.

The patient is positioned in the supine position, with both hips and knees flexed and the thighs abducted. The ankles and feet may be supported by lithotomy poles using stirrups or calf supports, or by strapping into padded boots. The position is usually combined with some head-down tilt to aid surgical access.

Physiological consequences: the lithotomy position is generally well tolerated. There is a reduction in vital capacity and FRC as a result of diaphragmatic splinting from upward displacement of abdominal contents. This may cause difficulty with spontaneous ventilation in obese patients and controlled ventilation may be preferable. Care should be taken when the legs are lowered because this may reveal previously unrecognized hypovolaemia and cause sudden hypotension.

Direct pressure complications: backache is common and may be reduced by providing a support to maintain the normal lumbar lordosis. The sacrum must be supported and should not hang free over the end of the table. Marked flexion of the hips and knees may cause sacroiliac strain, and the legs must be moved together to avoid pelvic asymmetry. Slippage of the lithotomy poles once the legs are positioned can cause hip dislocation. Moving the thighs too far apart may strain the adductor muscles.

Compartment syndrome in the lower leg may be initiated by pressure of the calf muscles on the stirrup pole. 'Breaking' or raising the lower end of the table when the fingers have been inadvertently trapped in the gap has caused crush injury.

Anaesthesia should not be induced with the legs elevated because raised intra-abdominal pressure may predispose to regurgitation, and turning the patient will be difficult.

Nerve injuries that may occur with the lithotomy position are shown in Figure 4.

Lithotomy position – nerve injuries

Nerve injury	Comments
• Sciatic	Stretching as a result of maximum external rotation of the flexed thigh
• Common peroneal	Compression between lithotomy pole and the head of the fibula
• Tibial	Compression if the legs are supported by stirrups behind the knees
• Femoral	Compression beneath the inguinal ligament when the thighs are fully flexed on the abdomen
• Obturator	Compression at the obturator foramen when the thighs are fully flexed on the abdomen
• Saphenous	Compression between the medial condyle of the tibia and lithotomy post or stirrup

Prone position

Indications:
- operations on the spine and posterior cranial fossa
- operations on the buttocks and natal cleft
- percutaneous extraction of renal calculi.

Physiological consequences: there is often an improvement in gas exchange in the prone position. This may be as a result of the greater inspiratory pressures required to maintain the tidal volume, which decreases atelectasis, increases FRC and improves oxygenation. Pulmonary barotrauma caused by excessive inspiratory pressures should be avoided by correct positioning of the pelvis and upper chest.

The pelvis and the upper chest must be supported so that the abdomen is not compressed and the diaphragm can descend freely during respiration. This may be particularly difficult to achieve in obese patients. Patients may be positioned by using pillows, supporting the iliac crests with cushioned props, or by the use of a specialized hollowed mattress. Controlled ventilation is preferable in most patients.

There are no significant cardiovascular changes. Pulmonary blood flow is essentially unchanged from the supine position. Poor positioning and high inspiratory pressures may decrease venous return. Patients with previous coronary artery bypass grafting may be at risk from graft occlusion.

Direct pressure complications: turning the supine patient prone requires a team of four people. Great care must be taken with the head and neck to avoid twisting or hyperextension injury to the cervical spine. The face should rest on a cushioned horseshoe with the weight of the head evenly distributed. The eyes are naturally protected within their bony sockets, but exophthalmos or a flattened nasal bridge may allow transmission of pressure to the globe. Prolonged compression may result in central retinal vein thrombosis and blindness.

The tracheal tube must be securely fixed and its position checked after the turn. Some experienced anaesthetists may use the laryngeal mask for airway maintenance in prone patients, though the use of a reinforced tracheal tube is likely to be safer for the trainee. Excessive pressure on the breasts may cause ischaemic damage to the nipples, interstitial bleeding or rupture of breast implants. In men, the penis or scrotum may become trapped and compressed.

Possible nerve injuries are shown in Figure 5.

Prone position – nerve injuries

Nerve injury	Comments
• Cervical spinal cord	Stretching injury caused by overextensio plane
• Nerves to the eye	Compression from face support
• Facial (VIIth)	Compression from face support
• Brachial plexus	Stretching injury caused by extreme abduction of the arms. Limit abduction to 90°
• Ulnar	Compression between the medial epicondyle of the humerus and the mattress
• Lateral cutaneous nerve	Compression between iliac crest of the thigh and the positioning prop. If used, props should be angulated and positioned so that the patient is unable to slip sideways
• Anterior tibial	Stretching injury caused by forced plantar flexion of the foot

The sitting position

Indications:
- operations on the posterior cranial fossa and cervical spine
- dental chair anaesthesia.

The sitting position enables the surgeon to gain clear access, with optimal venous drainage, low arterial pressure and reduced bleeding. CSF drainage is good and brain swelling is minimized.

Dental chair anaesthesia in the sitting position is now uncommon.

Physiological consequences: the patient is anaesthetized in the standard supine position and the neurosurgical pins and head frame are applied. On the operating table, the patient is progressively sat upright with the neck flexed; the knees are slightly flexed and the legs are lowered. The arms rest in the lap on a pillow, with the elbows flexed.

A small fall in systolic blood pressure of 20 mm Hg usually occurs; this can be offset by prior volume loading with 500 ml of colloid solution. Occasionally, persistent instability of blood pressure can occur that may cause the position to be abandoned despite the use of vasopressors. Controlled ventilation is the method of choice, to enable control of Pa_{CO_2} and intracranial pressure. It maintains a higher mean intrathoracic pressure and reduces the likelihood of air embolus.

Air embolus is the major complication. All patients must be considered to be at risk throughout the procedure. For this reason, many neurosurgeons seldom use this position. It is still used when insufficient access is provided by the alternative prone or semi-prone positions.

Dysrhythmias, especially bradycardia, and blood pressure instability may occur following surgical manipulation in the region of the brain stem. This is a result of direct pressure effects on the autonomic control centres of the medulla.

Direct pressure complications: nerve injuries that may result from the sitting position are shown in Figure 6.

The sitting position – nerve injuries

Nerve injury	Comments
• Cervical spinal cord	Stretching injury and spinal cord ischaemia following excessive neck flexion. A two-finger breadth gap between chin and chest is recommended
• Brachial plexus	Stretching injury if the arms are unsupported
• Ulnar	Compression between the medial epicondyle of the humerus and the arm supports
• Sciatic	Stretching injury if thighs are flexed and knees extended. Maintain adequate knee flexion

Premedication

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Premedication involves the prescription of drugs before the induction of anaesthesia in order to alleviate the apprehension associated with surgery, to counteract the side-effects of anaesthetic agents or to reduce the risks of pre-existing pathology (Figure 1). When choosing a premedicant drug the anaesthetist must consider which of its properties are appropriate for the individual patient, the possible side-effects and its potential effect on the proposed anaesthetic technique. The ideal premedicant is:

- painless to administer
- highly reliable and specific
- of rapid onset and rapidly cleared
- free of side-effects and interactions with other drugs.

Premedicant drugs entered anaesthetic practice in the late 19th century. Early anaesthetic agents were delivered by open systems and induced unconsciousness slowly. Ether caused an increase in pharyngeal and bronchial secretions, which interfered with smooth gaseous induction. Chloroform caused marked vagal stimulation of the heart leading to bradycardia. Atropine was first used in premedication in 1890. Hyoscine, which combined anticholinergic effects with antiemesis and sedation, was often combined with an opioid (e.g. papaveretum) to produce ‘twilight sleep’. Opioids were prescribed to aid the induction of anaesthesia before the development of more potent anaesthetic induction agents.

The routine use of drugs for premedication is now in decline. There are several reasons for this.

- Modern anaesthetic agents are potent and have a rapid, smooth onset.
- The increased use of day-care surgery requires rapid patient recovery.
- In-patients are often admitted on the day of surgery and the time available between preoperative assessment and induction of anaesthesia is short.
- Pressures of high patient turnover and staffing constraints can make premedication difficult to deliver in practice.

Rationale of premedication

- Reduction of anxiety and fear
- Sedation
- Amnesia
- Antiemesis
- Reduction in volume and acidity of gastric secretions
- Attenuation of autonomic reflexes
- Maintenance of cardiovascular stability
- Reduction of airway secretions
- Provision of analgesia

1

Anxiolysis, sedation and amnesia

The preoperative visit: anxiety is common in preoperative patients. As well as being unpleasant, this anxiety is part of a stress response that may worsen coexisting pathology such as hypertension or angina. A preoperative visit by the anaesthetist is the most effective way to allay the fears and anxieties of forthcoming surgery. This visit can be used to establish rapport with the patient, to discuss the proposed anaesthetic technique in terms that they can understand and to address their worries in a sympathetic manner. Older children will benefit from inclusion in preoperative discussions and it is becoming usual for parents to stay with children during induction of anaesthesia.

For some patients, the preoperative visit alone is insufficient to allay anxiety and pharmacological methods are required. The nature of the surgical procedure, coexisting pathology or the need for a rapid recovery from anaesthesia may dictate extreme caution before the prescription of sedating premedication (Figure 2). Co-administration of an opioid and a benzodiazepine has a potent respiratory depressant effect.

Relative contraindications to sedative premedication

- Airway obstruction or airway surgery
- Poor ventilatory reserve
- Sleep apnoea
- Intracranial pathology
- Severe hepatic or renal disease
- Rapid-sequence induction
- Obstetric anaesthesia
- Day-case anaesthesia (delayed discharge)
- Extremes of age

2

Benzodiazepines
Benzodiazepines are the most commonly used premedication. They are safe and have a broad therapeutic index though they can cause unpredictable psychological effects at the extremes of age. Those that are suitable premedicants can usually be given by mouth about 1 hour before induction, have a short duration of action and produce inactive metabolites (Figure 3).

Benzodiazepines are agonists of γ-aminobutyric acid (GABA) receptors within the CNS. GABA is an important inhibitory neurotransmitter, which hyperpolarizes the neuron by causing an influx of chloride ion. Benzodiazepines also produce sedation and amnesia by their action on the limbic system. Both these effects are variable and depend on the drug used and the dose given.

Temazepam is an effective anxiolytic and is available in elixir or tablet form. It has a sufficiently short duration of action to allow its use in day-case surgery. Midazolam is presented in 2 mg/ml or 5 mg/ml glass vials. Unlike the other benzodiazepines it is water soluble at acid pH but becomes highly lipophilic at physiological pH. It can be given orally or nasally, which makes it an attractive premedicant for children in doses of 0.2–0.5 mg/kg. Lorazepam, 0.05 mg/kg (max. 4 mg), produces intense anterograde amnesia within 30 minutes, often lasting over 3 hours. Amnesia may be viewed as an advantageous property of a premedicant but some patients find the sensation unpleasant.

Benzodiazepines commonly used as premedication

Drug	Usual adult dose	Half-life of parent drug (hours)	Half-life of active metabolites (hours)
• Diazepam	5–10 mg p.o.	24–48	4–10
• Temazepam	10–30 mg p.o.	4–10	None
• Lorazepam	2–4 mg p.o.	10–20	None
• Midazolam	5–10 mg i.m. 0.5 mg/kg (maximum 20 mg) p.o. in children	1–3	None

3

Other anxiolytics and sedatives
Phenothiazines are major tranquillizers that have sedative and anticholinergic actions. They are histamine antagonists (via H_1-receptors) and have antidopaminergic and α-adrenoceptor blocking properties. They may cause pallor and restlessness in the presence of pain and hypotension. Trimeprazine elixir is sedating and is used for children in doses of 1.5–2 mg/kg, up to 2 hours before surgery. It is not licensed for use in children less than 2 years of age.

Droperidol is the only commonly used butyrophenone in current anaesthetic practice. It has antiemetic and sedating properties. Antidopaminergic side-effects such as dystonic reactions and agitation limit its routine use at sedating doses (e.g. 10 mg orally for adults).

Antiemesis

Postoperative nausea and vomiting (PONV) is a common problem, which is distressing for the patient. There are several risk factors:

- gender (incidence is three times higher in women than in men)
- patients undergoing operations on the ear, squint surgery, gynaecological procedures and laparoscopy
- previous history of PONV or motion sickness
- use of morphine
- anaesthetic technique (volatile anaesthetic maintenance is more emetic than intravenous propofol maintenance).

The vomiting reflex is coordinated by the vomiting centre within the dorsolateral reticular formation of the medulla. It receives multiple afferent pathways from peripheral and central chemoreceptors, nociceptors, the vestibular system and the cerebral cortex. The synapses in these pathways are predominantly muscarinic. The vomiting centre also receives stimuli from the chemoreceptor trigger zone in the area postrema on the floor of the fourth ventricle, but outside the blood–brain barrier. This structure is rich in dopamine (D_2) and serotonin (5-HT_3) receptors. The antiemetics commonly used in anaesthetic practice involve inhibition at one or more of these receptor sites.

Muscarinic antagonists: hyoscine (adults, 300 µg; children 4–10 years, 75–150 µg orally) is a more effective antiemetic and is more sedating than atropine. Antihistamines, including cyclizine, 50 mg orally, i.v. or i.m., and promethazine, children 2–5 years, 5–15 mg, 5–10 years, 10–25 mg orally; adults, 25–50 mg orally or intramuscularly, also have antiemetic properties, largely as a result of their antimuscarinic activity. Antimuscarinics cause dry mouth, blurred vision, and bowel and bladder dysfunction.

Dopamine antagonists are powerful antiemetics but extra-pyramidal side-effects, such as dystonia, dyskinesia, tremor and oculogyric crisis are not uncommon.

Prochlorperazine, 12.5 mg i.m., is the most widely used phenothiazine because it is less sedating and has fewer antidopaminergic and α-blockade side-effects than others of the same group.

Droperidol is an effective antiemetic at low dose, 0.625–1.25 mg, reducing the risk of unpleasant dopaminergic or psychological effects. It is usually given intravenously at induction.

Metoclopramide, 0.1 mg/kg i.v., i.m. or orally, is a dopamine antagonist with peripheral as well as central effects. Its prokinetic effects are more marked than its antiemetic properties and comparative studies have raised doubt about its effectiveness as a prophylactic antiemetic.

5-HT antagonists are powerful new antiemetics that are relatively free of side-effects. The most widely used agent is ondansetron, 4 mg i.v., given immediately before or at the end of surgery. Their relative expense has resulted in the cost-effectiveness of their prophylactic use being questioned.

Non-pharmacological measures including acupunture and acupressure have been explored. There is some evidence that these techniques are weakly effective.

Reduction in volume and acidity of gastric secretions

The potential for lung damage from the aspiration of gastric contents increases with the volume and the acidity of the aspirate. Risk of aspiration accompanies late pregnancy, emergency or trauma surgery, symptomatic oesophageal reflux, and obesity.

Acid secretion by gastric parietal cells can be reduced by the use of H_2-histamine antagonists such as ranitidine, 150 mg p.o. Proton pump inhibitors such as omeprazole, 20 mg p.o., are more powerful in reducing acid secretion but inhibit the metabolism of other drugs such as warfarin, phenytoin and diazepam.

A 0.3 molar solution of sodium citrate, 30 ml, will raise gastric pH and is less irritant to the airway should aspiration occur. The routine use of the prokinetic agent metoclopramide, 10 mg, is common practice but of no proven value in the prevention of gastric aspiration.

Attenuation of autonomic reflexes

Parasympathetic stimulation can lead to hypotension, bradycardia or even asystole mediated via the vagus nerve. Triggers include:

- traction on the extraocular muscles during squint surgery
- surgical dilatation of the cervix or of the anal sphincter
- repeated doses of suxamethonium
- laryngoscopy in children (especially on lifting the epiglottis with a straight-bladed laryngoscope)
- opioid analgesics, propofol and halothane.

Glycopyrronium, 0.2 mg i.v. at induction, provides prophylaxis without the discomfort of a dry mouth before surgery. It does not penetrate the blood–brain barrier and lacks the central side-effects of atropine.

An increase in circulating catecholamines may be caused by several factors:

- laryngoscopy and tracheal intubation
- surgical stimulation and pain
- drugs such as ketamine, cocaine and adrenaline (epinephrine) in local anaesthetics.

This increase may cause hypertension and increased myocardial oxygen demand. It may result in myocardial ischaemia in susceptible patients. A balanced anaesthetic technique reduces these risks, and β-blocker premedication (atenolol, 50 mg p.o.) may be of benefit.

There has been recent interest in the use of α_2-adrenoceptor agonists such as clonidine, 3 µg/kg p.o., as premedicants. They reduce sympathetic activity, cause sedation, a reduction in anaesthetic requirement (decreased minimum alveolar concentration) and reduce pressor responses including that of laryngoscopy. However, there appears to be a narrow therapeutic window with the potential for development of hypotension and bradycardia.

Reduction in airway secretions

Antisialogogues are occasionally prescribed as premedicants though their use in modern-day practice is uncommon. Glycopyrronium, 0.2 mg i.v. or i.m., may be used to improve conditions before fibre-optic intubation.

Analgesia

Opioids (e.g. morphine, 0.1–0.2 mg/kg i.v. or i.m.) should be used to relieve acute preoperative pain. However, in the absence of any preoperative distress and with the development of new potent opioid analgesics with a rapid onset given at induction, such as fentanyl, alfentanil and remifentanil, an opioid premedicant is seldom indicated.

Non-steroidal anti-inflammatory drugs decrease the requirement for opioid analgesia during and after a surgical procedure. Typically, ibuprofen, 400 mg p.o., or diclofenac, 50–100 mg p.o., p.r. or i.v., may be given. They should be avoided in patients with a history of peptic ulceration or renal impairment and used with caution in asthmatic patients. Other simple analgesics such as paracetamol, 1 g, can also be given p.o. or p.r.

The concept of pre-emptive analgesia is that nociception can be modulated at the level of the spinal cord by analgesia given before surgery, thereby reducing total postoperative analgesic requirements. While this concept is attractive and has been demonstrated in animal models, clinical studies have yet to prove its value.

Topical anaesthetics such as eutectic mixture of local anaesthetic (*Emla* cream) or amethocaine gel applied to the site of venepuncture, reduce the fear of intravenous anaesthetic induction in children and many adults.

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Principles of Anaesthetic Vaporizers

Eileen Palayiwa

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Gases, liquids and vapours

Substances can exist in the solid, liquid or gaseous state. Below a certain temperature, known as the critical temperature, it is possible to liquefy gases by compressing them. When a gas is below this critical temperature it is referred to as a vapour.

Vapours consist of molecules that have left the surface of a liquid below the critical temperature. Vapour molecules have had sufficient energy to break away from the attraction of the molecules left behind in the liquid and are therefore the more energetic molecules. Molecules leave the surface of the liquid and return to it randomly. When the vapour is in equilibrium with the liquid, the number of molecules leaving the liquid is equal to the number returning to it, and the vapour is said to be saturated. If there is insufficient liquid for there to be a reservoir from which molecules can evaporate and to which they can return, then the vapour is unsaturated and behaves as a gas.

The pressure of a vapour in equilibrium with a liquid is known as the saturated vapour pressure (SVP).

Variation of SVP with temperature

As the temperature of the liquid increases, more molecules have sufficient energy to escape from the surface and therefore the SVP rises. When the boiling point is reached, all the molecules evaporate and the SVP is equal to atmospheric pressure. Figure 1 shows the variation of SVP with temperature for halothane, enflurane and isoflurane. Unsaturated vapours behave as gases so that the pressure is inversely proportional to the volume (Boyle's law).

Cooling due to vaporization

If molecules that have left the surface of a liquid are not allowed to return to it (e.g. if they are swept away by a stream of fresh gas) then the liquid cools. This is because the evaporating molecules are more energetic than those left behind, therefore there is a net loss of energy from the liquid, which causes a drop in temperature. The latent heat of vaporization is the heat required to convert a unit mass of liquid into its vapour phase at a constant temperature. Cooling may be prevented or reduced if the liquid is in contact with a surface that can supply heat by conduction. The amount of heat that a body can supply at a given temperature depends on its specific heat and its mass, or, in other words, on its thermal capacity. Heat is also supplied by conduction from the surroundings and the rate at which this occurs is determined by the thermal conductivity of the body.

The specific heat of a substance is defined as the amount of heat (or energy) required to raise the temperature of a unit mass of the substance through 1 deg C. The units of specific heat are joules per kilogram per Kelvin change in temperature (J/(kg.K)).

The thermal capacity of a body is the heat required to raise its temperature through 1 deg C (this is also equivalent to the amount of energy the body loses when cooled by 1 deg C). The units of thermal capacity are joules per kilogram (J/kg). The thermal capacity of a body is equal to the product of its mass and specific heat.

The thermal conductivity of a material is the rate of heat transfer per unit area when a temperature difference of 1 deg C is maintained across an insulated block of the material 1 m thick. The units of thermal conductivity are Watts per metre per Kelvin (W/(m.K)).

Values of specific heat, density and thermal conductivity for copper, aluminium, glass and stainless steel are shown in Figure 2. It can be seen from this table that copper has the highest thermal conductivity of these materials so that vaporizers made of copper are the most efficient at conducting heat from the atmosphere to replace the energy that the liquid agent loses due to evaporation. Copper has the lowest specific heat of these substances; however, since it is much denser than aluminium or glass, the thermal capacity of a given volume of copper is higher than that of either of these materials. A given volume of stainless steel has the highest heat capacity of these materials. In practice, most vaporizers are made of stainless steel because it is readily available. However, copper is thermally more suitable because its much higher thermal conductivity more than compensates for the lower heat capacity.

Anaesthetic vaporizers

The SVP of most anaesthetic agents at room temperature is too high for them to be delivered to a patient without dilution (Figure 1). For example, the SVP of isoflurane at 20°C is 236.5 mm Hg (i.e. 31% v/v if atmospheric pressure is 760 mm Hg). In general, concentrations below 2% v/v are required for maintenance of anaesthesia. An anaesthetic vaporizer is a device that dilutes the vapour to give a known concentration of the agent.

Fresh gas enters the vaporizer and is split into two portions (Figure 3). One portion flows through an area known as the vaporizing chamber, where it comes into contact with the anaesthetic vapour; the remainder of the gas bypasses this chamber. The two flows then recombine and the vapour is diluted. By varying the flow rate in the two paths the resultant vapour concentration can be varied. The concentration of agent depends on the flow through the vaporizing chamber, the total fresh gas flow and the saturated vapour pressure of the anaesthetic agent. The way in which the gas flow is split between the bypass and vaporizing chamber depends on the relative resistance of each pathway. If the total fresh gas flow (F) is split into a bypass flow (F_b) and a vaporizing chamber flow (F_v) then:

$F_v + F_b = F$

The flow rate emerging from the vaporizing chamber (F_e) will be greater than that entering it, due to the volume of vapour added:

$F_e = F_v + F_e \times SVP/100$

where SVP is expressed as a percentage.

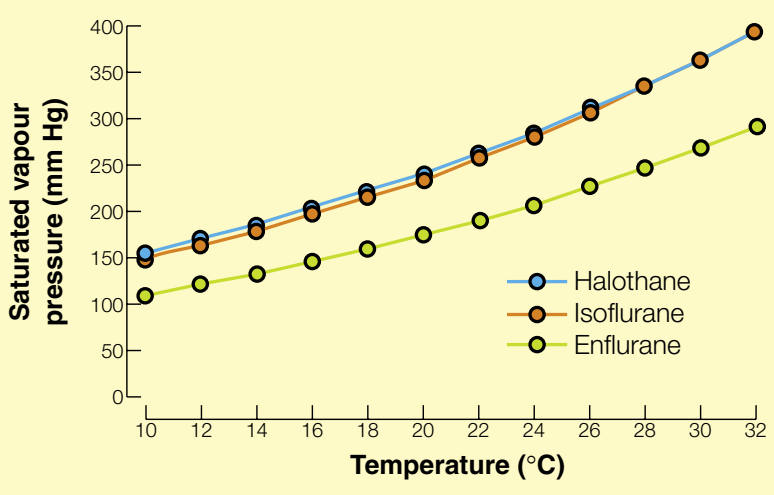
Therefore $F_e = F_v/[1-(SVP/100)]$

The concentration (C) of the vapour in the gas emerging from the vaporizer will be given by:

$C = F_e \times SVP/(F_b + F_e)$

This calculation assumes that the gas emerging from the vaporizing chamber is fully saturated with vapour. To ensure that this is the case, manufacturers increase the surface area of liquid that the gas passes over by introducing wicks made of cloth or metal into the vaporizing chamber. In many cases the gas is forced to take a long pathway through the chamber, which also helps to ensure saturation.

Variation of saturated vapour pressure with temperature



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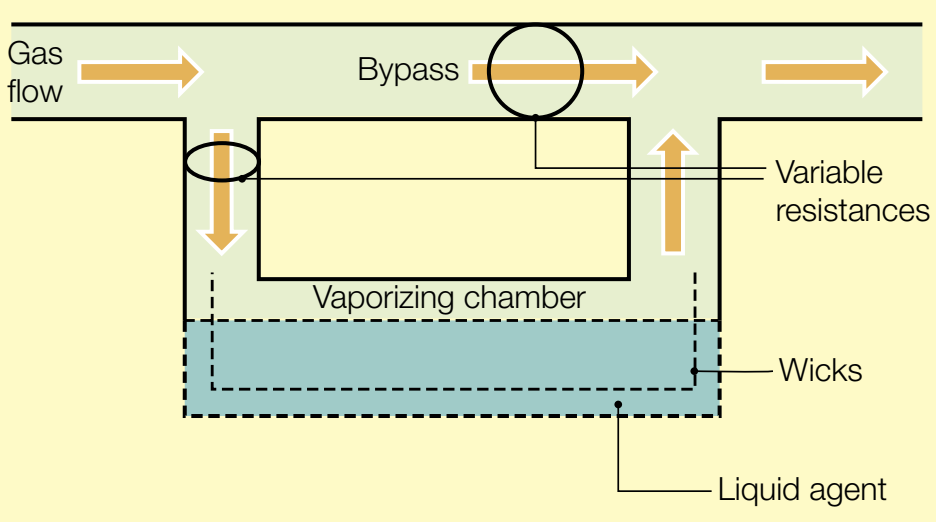
Physical properties of some common materials at 293K

	Specific heat (J/(kg.K))	Thermal conductivity (W/(m.K))	Density (kg/m³)
Copper	385	385	8930
Aluminium	913	201	2710
Glass	670	1	2600
Stainless steel	510	150	7930

2

An anaesthetic vaporizer



3

Temperature compensation

As liquid evaporates from the vaporizing chamber the temperature drops, and unless there is some means of compensating for this, the output of the vaporizer also drops. The temperature drop, and hence the fall in output, is lower if the vaporizer has a large heat capacity and can therefore supply energy to the liquid to compensate for that which it has lost. For this reason most vaporizers contain a large mass of metal that can also conduct heat from the surroundings into the liquid. In addition, most vaporizers incorporate some kind of temperature compensation, which reduces the resistance of the vaporizing chamber relative to that of the bypass as the temperature drops. As a result, more gas flows through the vaporizing chamber so that the vapour concentration is maintained.

Effect of intermittent positive-pressure ventilation (IPPV)

During IPPV, the pressure at the outlet of a vaporizer is not constant. When the pressure is high, flow emerging from the vaporizer reduces and the pressure in the vaporizing chamber builds up. As the pressure drops, the excess of vapour, which has accumulated in the vaporizing chamber at this time, emerges not only from the normal outlet of the vaporizing chamber but also from the inlet. This means that the bypass gas contains vapour and therefore the concentration rises. Manufacturers have compensated for this by introducing a long inlet tube into the vaporizing chamber. When the pressure inside the vaporizing chamber drops, the vapour enters this tube, but its volume is not enough to emerge into the bypass.

Effect of flow rate on vaporizer output

The vaporizer output is dependent on the resistance of the vaporizing chamber relative to that of the bypass. With varying flows the vaporizer output remains constant only if this does not change. In practice, this is difficult to achieve over the wide range of flows used in anaesthetic practice. Only if laminar flow is maintained in each pathway throughout the flow range will this be the case. Another factor influencing the output at high flows is the increased cooling, which occurs as a result of the large amount of evaporation taking place.

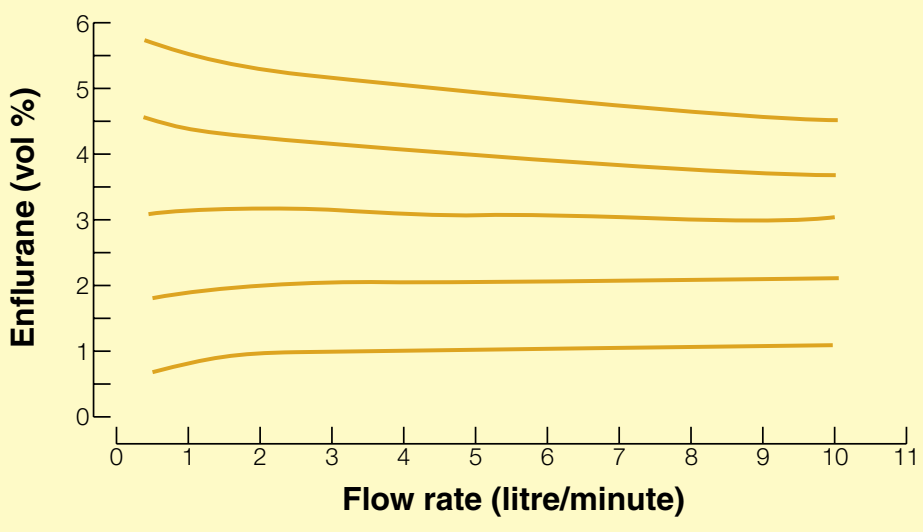
Figure 4 shows the variation of output with flow for a Penlon plenum enflurane vaporizer. It can be seen that the output of this vaporizer at high settings drops as the flow rate increases. However, at the lower settings more commonly in use, the output remains reasonably constant. This indicates that the temperature compensator in the Penlon plenum vaporizer (PPV) can adjust adequately for cooling due to evaporation except at the highest dial settings and flow rates.

Effect of gas composition

The relative flow rates through the bypass and vaporizing chamber at a given dial setting remain constant only if laminar flow is maintained in both pathways. As soon as the flow in one pathway becomes turbulent, its resistance rises causing less gas to flow through it, unless it is matched by a proportional rise in the resistance of the other pathway.

Nitrous oxide has different physical characteristics from oxygen (Figure 5); in particular, the ratio of viscosity to density, which determines the flow rate at which turbulence sets in, is much lower. The effect that this has on the output of the vaporizer depends on its design. In some vaporizers, output drops when the carrier gas contains nitrous oxide whereas in others it increases.

Variation of output with flow for the Penlon plenum vaporizer



Courtesy of Penlon Ltd.

4

Physical properties of oxygen and nitrous oxide

Gas	Density (kg/m^3)	Viscosity ($\mu N.second/m^2$)	Kinematic viscosity ($m^2/second$)
Oxygen	1.43	18.9	10.3×10^{-5}
Nitrous oxide	1.96	13.5	6.9×10^{-5}

5

Types of vaporizer

Vaporizers fall into two broad categories.

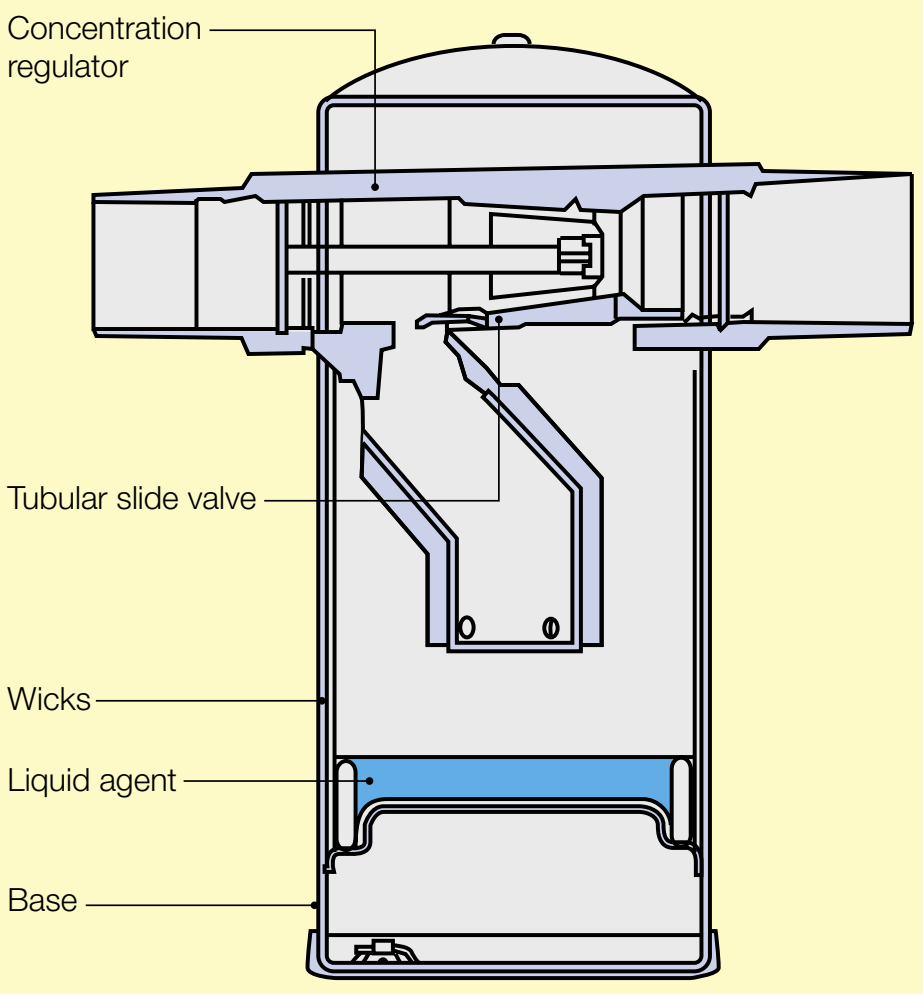
Drawover vaporizers – in a drawover vaporizer, gas is pulled through as the patient inspires (expiration is to atmosphere via a non-rebreathing valve). The flow rate of gas through the vaporizer is therefore not constant and it is necessary for the vaporizer to have a low resistance.

Plenum vaporizers – in a plenum vaporizer, gas is driven through under positive pressure. The term plenum is derived from the plenum system of ventilation where gas is forced into the system. Plenum vaporizers may have a higher resistance than drawover vaporizers though some vaporizers are designed to be used in either mode (e.g. the Oxford miniature vaporizer).

Oxford miniature vaporizer

The Oxford miniature vaporizer (Figure 6) is designed as a low resistance drawover vaporizer. It does not have any temperature compensation, but it has a water-filled jacket to increase its heat capacity.

Oxford miniature vaporizer



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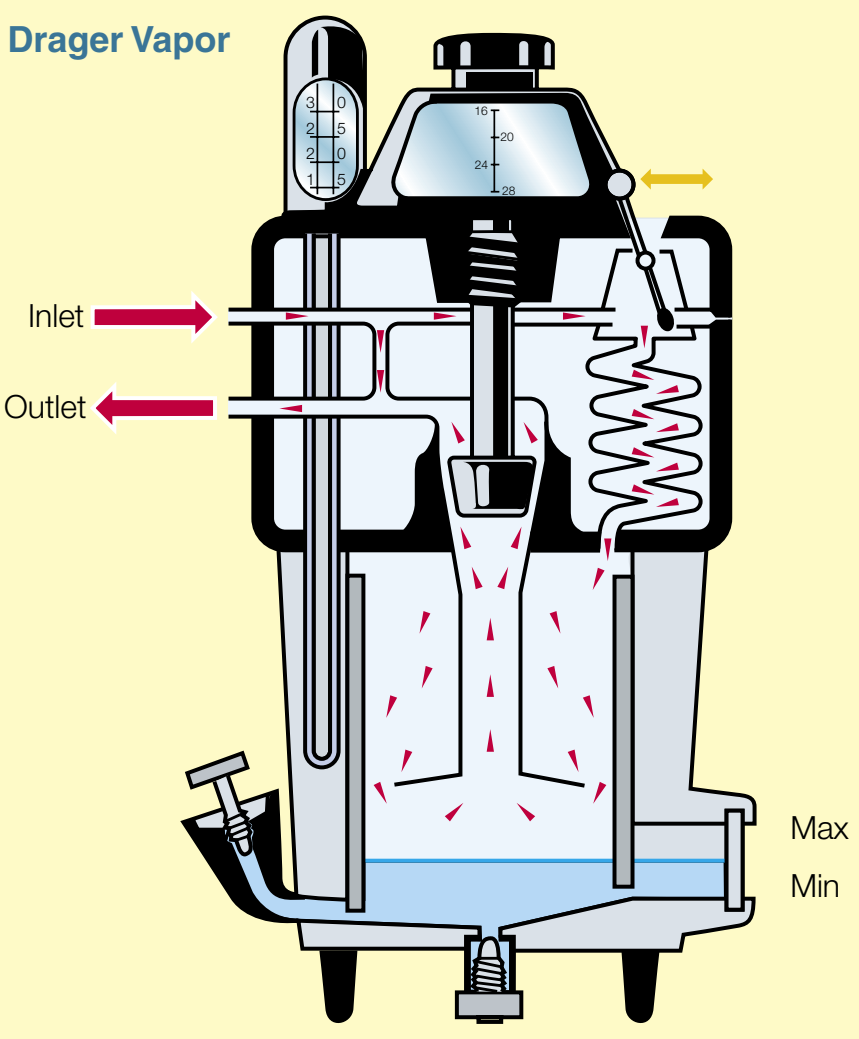
Drager Vapor

The Drager Vapor (Figure 7) is constructed from a large block of copper and is therefore thermally stable. It has a built-in thermometer so that the temperature of the liquid agent may be read and the position of the concentration dial is adjusted according to this temperature. In this vaporizer, the gas flow through the bypass and the vaporizing chamber is controlled by a pair of needle valves, which are carefully manufactured to ensure that gas flow is laminar in both pathways over a large range of flow rates. There is therefore little variation of output with flow rate for this vaporizer.

Drager Vapor



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PPV

In the PPV (Figure 8), when the control dial is in the zero position the vaporizing chamber is isolated by means of a spring-loaded valve attached to the push rod, which is aligned with the control knob. When the control knob zero lock button is pressed the push rod opens the valve and as the control knob is rotated the vapour control orifice opens to allow more gas to flow through the vaporizing chamber.

Temperature compensation is achieved by a moving needle valve within the bypass orifice, which increases the bypass resistance as the temperature drops, thus forcing more gas to flow through the vaporizing chamber. The movement of the valve is controlled by a push rod attached to an ether-filled metal bellows unit. As the liquid agent changes temperature, the ether in the bellows expands or contracts causing the bellows to expand or contract linearly. Compensation for fluctuating back pressure is achieved by the inclusion of a long narrow tube in the vaporizing chamber.

Penlon plenum vaporizer

8

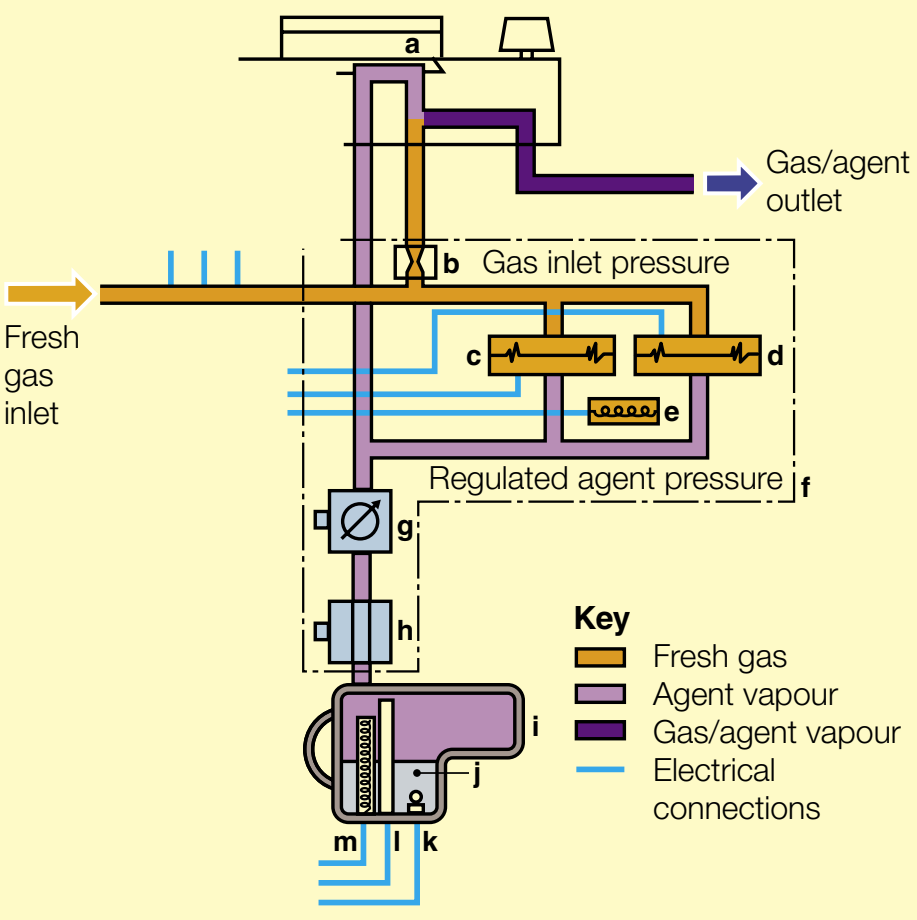
Tec 6 vaporizer

The Tec 6 vaporizer (Figure 9) varies from most other conventional vaporizers because it incorporates a heater element. This is necessary because desflurane concentrations up to 18% v/v may be required. The concentration knob has an interlock system, which means that it cannot be turned until the liquid agent has been heated to the correct temperature. When the control dial is turned, an electronic signal opens the shut-off valve. The pressure transducer measures the difference between the gas inlet pressure and the regulated agent pressure. The agent pressure is controlled electronically by opening or closing the pressure-regulating valve to balance the pressures. When the pressures are correctly balanced the vaporizer functions correctly.

Calibration of vaporizers

Anaesthetic vaporizers are calibrated in the factory using a refractometer (an accurate optical device) in a temperature-controlled room. In general, either oxygen or air at a medium flow rate is used for the carrier gas. The output of a vaporizer may vary under different conditions of temperature, flow or carrier gas – this is not surprising, considering the wide range of flow rates and concentrations over which a vaporizer is used. It has been said that one should expect vaporizers to produce concentrations only within 20% of their dial settings. While this is a wide margin, it is not at all unusual for concentrations to differ by 10% of the dial setting and as conditions become more extreme this difference may approach 20%. It is important that anaesthetists recognize the problems faced by manufacturers when designing vaporizers and that they do not always expect vapour concentration and dial setting to coincide.

Tec 6 vaporizer



a Dial and rotary valve, **b** fixed restrictor, **c** pressure control transducer, **d** pressure monitor transducer, **e** heater in vapour control manifold, **f** vapour control manifold assembly, **g** pressure-regulating valve, **h** shut-off valve, **i** sump assembly, **j** agent, **k** level switch, **l** level sensor, **m** sump heaters

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Recognition and Management of Anaphylactic and Anaphylactoid Reactions

Andrew McIndoe

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The term anaphylaxis was coined by Charles Richet in 1902 to describe the reaction of dogs to a second, and often fatal, injection of foreign protein (sea anemone toxin). The term was introduced to distinguish this later injection from the first 'prophylactic' injection that induced sensitization.

Anaphylaxis is now recognized to be an immediate hypersensitivity or type I immune reaction mediated by immunoglobulin E (IgE) and resulting in mast cell degranulation and basophil activation. It is not dose related and can occur in response to minute exposure to an allergen. Typically, the severity of the response worsens on re-exposure owing to progressive sensitization of the subject. The true incidence of anaphylaxis is unknown but is estimated to be 1/6000–20,000 anaesthetics or 1/10,000 of the general population/year. Women are more likely to suffer an anaphylactic reaction than men, with a quoted increase in risk of 3–10:1. Intravenous administration of the antigen is more likely to precipitate a severe generalized reaction. Cross-sensitivities with non-steroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants makes previous exposure unnecessary. Up to 80% of neuromuscular blocking agent reactions are not associated with known prior exposure.

Anaphylactoid reactions may present with a similar clinical picture, but do not result from hypersensitivity and are not mediated by IgE. Drugs such as opioids can directly stimulate mast cell degranulation with histamine release causing pruritus, rash and hypotension. They should be managed as potential anaphylactic reactions because confusion over the diagnosis merely delays effective treatment.

Pathophysiology

Primary exposure to an antigen results in the synthesis of specific IgE antibodies by lymphocytes and plasma cells. The Fc portions of these antibodies are able to fix themselves to the surface of tissue mast cells and circulating basophils. The antigen binding sites are thus presented externally. Subsequent contact with antigen causes IgE antibody:antigen cross-binding and triggers immediate degranulation of the host mast cell or basophil. Release of histamine and serotonin results in an acute inflammatory reaction, smooth muscle constriction, vasodilatation and increased capillary permeability. The clinical picture depends on the mode of exposure.

- Skin – urticaria, flare and weal reaction (hence the use of skin prick testing).
- Eyes – conjunctivitis.
- Mouth/airway – perioral and laryngeal oedema, broncho-spasm.
- Parenteral – generalized cardiovascular collapse.
- Eosinophils are mobilized by chemotaxis, attracted by histamine and other substances, they produce histaminase, helping to terminate the reaction.

History and examination

Anaphylaxis may present with a spectrum of clinical signs including hypotension, tachycardia, dysrhythmias, dyspnoea, laryngeal oedema, bronchospasm, angio-oedema, flushing, urticaria, conjunctivitis, rhinitis, abdominal pain and diarrhoea. It can therefore mimic a variety of other conditions. Diagnosis is further complicated by a variable time for exposure until symptoms develop, varying from a few seconds to several hours. 5% of patients show a biphasic response with symptoms recurring from 1–72 hours after the initial attack. Many patients do not develop all the classic signs (Figure 1).

Differential diagnoses are vasovagal faint with hypotension, bradycardia and pale, sweaty skin and panic attack with hyperventilation, tachycardia and an erythematous rash.

Percentage of patients presenting with classic signs of anaphylaxis

Signs	Patients (%)
• Cardiovascular collapse	88
• Erythema	45
• Bronchospasm	36
• Angio-oedema	24
• Rash	13
• Urticaria	8.5

1

Management

The management of anaphylaxis is summarized in Figure 2.

Management of anaphylaxis

Condition
IgE mediated immediate hypersensitivity reaction to an antigen resulting in histamine and serotonin release from mast cells and basophils

Presentation
- Cardiovascular collapse
- Erythema
- Bronchospasm
- Oedema
- Rash

Immediate action
- Remove trigger
- 100% oxygen
- Elevate legs
- Adrenaline (epinephrine) 500 μg i.m. or 50 μg increments i.v. titrated to effect
- 20 ml/kg i.v. fluid challenge

Follow-up action
- Chlorphenamine (chlorpheniramine), 10–20 mg i.v.
- Hydrocortisone, 100–300 mg i.v.
- Arterial blood gases

Investigations
- Plasma tryptase
- Urinary methylhistamine

Also consider
- Primary myocardial/cardiovascular problem
- Latex sensitivity
- Airway obstruction
- Asthma
- Tension pneumothorax
- Panic attack

2

Immediate management
- Check the airway, breathing and circulation. Stop the administration of or exposure to any potential triggers, particularly intravenous agents. Muscle relaxants, antibiotics and NSAIDs (and increasingly latex) are the most common triggers in an anaesthetic environment. Outside the operating theatre, foods (especially nuts, fish, shellfish, eggs and milk), insect venom, drugs (antibiotics, NSAIDs, contrast media, opioids) and latex are the most common precipitants.
- Call for help.
- Maintain the airway and give 100% oxygen. Reassess airway patency frequently and regularly, especially in known asthmatics and in those exposed to the allergen via the airway or mouth. If in doubt and the reaction is severe, intubate early because it may be impossible to do so later in the presence of increased oedema.
- Cardiovascular collapse is most likely following parenteral exposure to the allergen. Lay the patient flat with the legs elevated to increase central venous return.
- If the patient has a continuous ECG monitor attached, give adrenaline (epinephrine) in 50 μg i.v. increments (0.5 ml of a 1:10,000 solution) at a rate of 100 μg/minute until the blood pressure or bronchospasm improves. Alternatively, give adrenaline (epinephrine) 0.5–1 mg i.m. as 0.5–1.0 ml of a 1:1000 solution (repeated after 10 minutes if necessary). Adrenaline (epinephrine) stabilizes mast cell membranes, increases myocardial contractility, causes bronchodilatation and reverses vasodilatation; it therefore treats both cause and effect.
- Give intravenous fluid (colloid or suitable crystalloid), 20 ml/kg.
- Latex allergy may take up to 30 minutes to manifest itself. Removal of all latex triggers can then be a complex process. Allergen is more readily absorbed across mucous membranes (e.g. from surgical gloves or a urinary catheter, which should be removed immediately and hands should be re-washed to remove latex-impregnated starch granules). Inhalation of aerosolized particles within the breathing circuit is minimized by the use of an airway filter. Ensure that rubber 'corings' are not introduced intravenously (e.g. ampoule bungs and injection sets). Laryngeal mask airways are made of silicone and do not contain latex. *Diprivan* syringe bungs are also latex free.

Subsequent management
- Give an antihistamine (H_1-blocker) such as chlorphenamine (chlorpheniramine, *Piriton*), 10–20 mg by slow i.v. or i.m. injection. Consider H_2-antagonists, such as ranitidine, 50 mg slow i.v. injection.
- Give corticosteroids such as hydrocortisone, 100–300 mg by slow i.v. or i.m. injection, to inhibit later relapses.
- Give a catecholamine infusion because cardiovascular instability may last for several hours. Consider adrenaline (epinephrine) 0.05–0.1 μg/kg/minute (e.g. 4 ml/hour of 1:10,000 for a 70 kg adult) or noradrenaline (norepinephrine) 0.05–0.1 μg/kg/minute (e.g. 4 ml/hour of a solution of 4 mg made up to 40 ml in 5% dextrose for a 70 kg adult).
- Check arterial blood gases for acidosis and consider giving bicarbonate, 0.5–1.0 mmol/kg (8.4% solution = 1 mmol/ml).
- Check for the presence of airway oedema by letting down the tracheal cuff and confirming a leak before extubation.
- Consider bronchodilators for persistent bronchospasm (e.g. salbutamol, 5 mg by nebulizer or 250 μg slow i.v. injection, aminophylline 250–500 mg slow i.v. injection).

Complications

Hospital mortality to anaesthetic drug-induced anaphylaxis is 4%, despite the presence of good resuscitation facilities. Over half of those who die of anaphylaxis do so within the first hour. The deaths are related to asphyxia, from severe bronchospasm or upper airway obstruction, and from refractory hypotension.

The early use of adrenaline (epinephrine) is advisable but advice differs over the safest and most appropriate mode of administration. Adrenaline (epinephrine) is best administered by intramuscular injection (0.5 mg – usually 0.5 ml of 1:1000 solution) by first responders because it is a reliable means of achieving therapeutic plasma concentrations quickly and safely. The subcutaneous route is slow and unpredictable and is inappropriate during an acute life-threatening reaction. Anaesthetists often opt for intravenous administration of a 1:10,000 solution in incremental doses (of 50–100 μg). The intravenous route, while rapidly effective, can result in tachydysrhythmias. Cardiac complications are more common in the presence of hypoxia, hypercapnoea, and in patients taking tricyclic antidepressants or cocaine.

Patients taking β-blockers are likely to suffer more severe reactions and may be resistant to treatment with adrenaline (epinephrine). However, β-blockers are competitive antagonists and careful but continued titration of adrenaline (by sequential doubling of the initial dose in severe cases) should achieve a clinical effect.

Late diagnosis may be complicated by severe compromise of the airway and difficulty intubating the trachea.

Investigations

Investigations should be carried out when the patient has been stabilized.

Plasma tryptase: at least one 10 ml clotted blood sample should be taken 1–6 hours after the start of the reaction to perform a tryptase assay. The specimen must be spun down as soon as possible and the serum stored at –20°C, to stabilize the protein for later analysis. Tryptase is the main protein released during mast cell degranulation and is a specific marker of histamine release due to anaphylaxis or anaphylactoid reaction. Normal basal levels of serum tryptase are less than 1 ng/ml. However, unlike histamine, which is rapidly eliminated, tryptase levels remain elevated for up to 6 hours after an anaphylactic reaction. It is not a protein that is produced by RBCs or WBCs and is therefore not raised by haemolysis. Levels over 20 ng/ml may accompany an anaphylactic reaction.

Elevated metabolites in the form of urinary methylhistamine may also be measured. The value measured has to be corrected for urinary creatinine but levels in excess of 15–20 ng/ml/mmol creatinine/litre are considered higher than normal, and may indicate anaphylaxis.

Radio allergosorbent testing (RAST) is a means of searching for antigen-specific IgE in the serum. Tests are limited to specific allergens. At present only a few anaesthetic RASTs are available (e.g. suxamethonium). Fluoroimmunoassay is an alternative (*CAP System*, Pharmacia).

Follow-up and prognosis

The anaesthetist should follow up the investigation, report reactions to the Committee on Safety of Medicines via the 'yellow card' reporting scheme, and arrange skin prick testing in consultation with an immunologist. Having identified allergens, the patient should be advised to wear an alert bracelet at all times. Those who have suffered a severe reaction, especially anaphylaxis to allergens that are commonly encountered in everyday life, may be advised on how to carry and when to administer their own adrenaline (epinephrine). The *Epipen* syringe is preloaded with adrenaline (epinephrine) and will deliver a fixed intramuscular injection of 300 µg (0.3 ml of 1:1000) for adults or 150 µg for children.

Desensitization is a process that attempts to stimulate the production of IgG or IgA antibodies that competitively bind to the antigen and help block the IgE antibody–antigen hypersensitivity reaction that precipitates anaphylaxis. It is not without risk because it involves repeated inoculation with small doses of antigen.

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Recognition of Correct Placement of Tracheal Tubes

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The technique of tracheal intubation is fundamental to anaesthetic practice. Critical incident reporting indicates that oesophageal intubation is a relatively common problem. Misplacement of a tracheal tube is not in itself harmful if the diagnosis is made promptly and corrective action taken. However, tracheal tube misplacement still accounts for a large proportion of anaesthetic deaths. It should be considered in any hypoxic intubated patient. Failure to detect incorrect tube placement is equally common for trainees and consultants. It is as likely with routine as with difficult intubation.

Methods of confirming correct tube placement

Clinical signs are often unhelpful in detecting tube misplacement and intubation should be confirmed by:

- direct visualization of the tube passing through the vocal cords
- auscultation over both axillae, lung bases and the epi-gastrium
- capnography
- oesophageal detector device or colorimetric detector if capnography is not readily available.

Visualization of larynx

The larynx is usually visualized and the tracheal tube is observed passing between the vocal cords into the trachea. However, a view of the larynx is not always possible. In routine laryngoscopy, an anaesthetist may become distracted at the moment of intubation, allowing the tube to slide past into the oesophagus. Occasionally the oesophagus may be mistakenly identified as the trachea or the tube may become displaced during fixation. Direct visualization is thus not totally reliable and may even delay a diagnosis of tube misplacement by promoting a false sense of security.

Repeat laryngoscopy is essential if a tube problem is suspected; oesophageal intubation, extubation or a kinked tube can all be identified and remedial action taken.

Chest movement

Bilateral symmetrical chest wall expansion should occur coincident with inspiration. It may be difficult to discern in the obese patient, in those with a rigid chest wall, or in chronic lung disease (e.g. emphysema). Oesophageal ventilation may imitate chest movement by expansion of the mediastinum, while gastric distension can simulate diaphragmatic and lower chest wall ventilation, especially in infants.

Auscultation

The combination of auscultation over each axilla, lung base and epigastrium achieves the most reliable results. Direct auscultation over the trachea may be of additional benefit; more obvious breath sounds can be heard, which are less likely to be confused with oesophageal ventilation.

Breath sounds over the chest wall do not always exclude oesophageal intubation. Air ventilating the oesophagus can be transmitted through the lungs to resemble convincing breath sounds. Conversely, breath sounds may be inaudible in the obese patient.

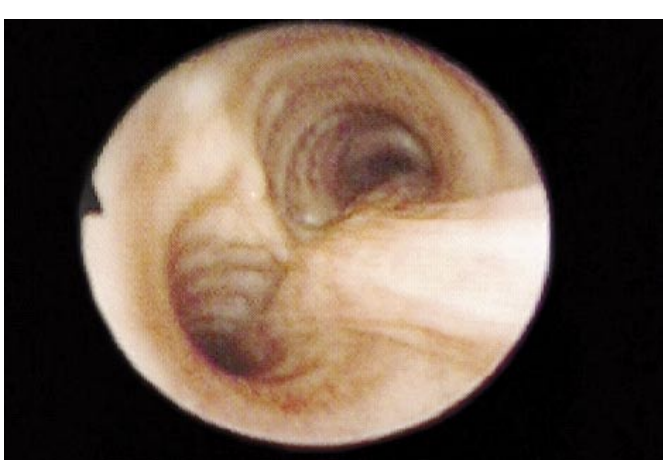
Breathing circuit

The ability to ventilate the lungs via the reservoir bag together with its typical compliance characteristics is a useful sign for the anaesthetist. In a spontaneously breathing patient the bag should empty and refill synchronously with the patient's breathing pattern. However, small movements (cardiac oscillations) can be demonstrated with oesophageal tube placement.

In contrast, it may be difficult to ventilate a morbidly obese patient via the reservoir bag or to differentiate between oesophageal intubation and partial or complete bronchospasm.

Fibre-optic laryngoscopy

The fibre-optic bronchoscope or laryngoscope can reliably confirm tracheal tube placement by identification of the tracheal rings and carina under direct vision (Figure 1). The technique requires operator experience and the equipment must be readily available.



1 View of the carina via a fibrescope, confirming the correct placement of the tracheal tube.

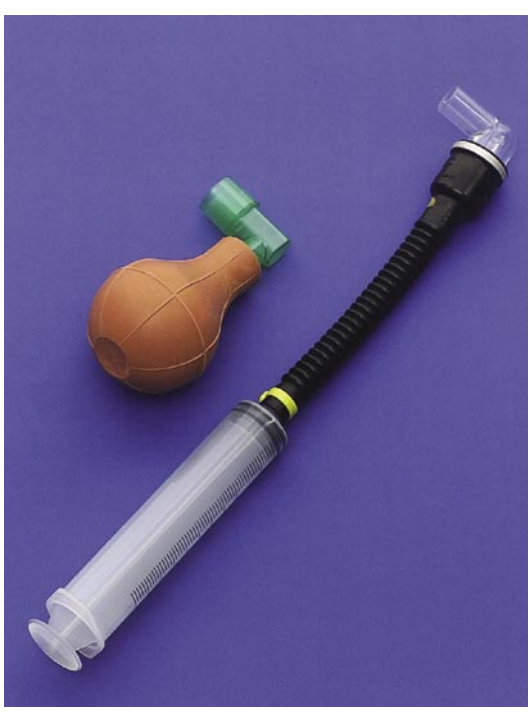
Oesophageal detector device

The Wee oesophageal detector device (ODD) consists of a 60 ml bladder syringe connected to a catheter mount. This is attached to the tracheal tube following intubation. The syringe freely aspirates gas from the patient's lungs if the tube is in the trachea (negative result). However, if this negative pressure is applied to a tube within the oesophagus, the oesophageal wall collapses and no air can be aspirated (positive result).

As a modification, the syringe has been replaced by a large rubber bulb (Ellick's evacuator) to enable the device to be used one-handed (Figure 2). In this case the bulb is first emptied and then failure to refill indicates oesophageal intubation.

The ODD is cheap, simple to construct, easy to use and reliable. It has been validated in several studies with only a small incidence of false-positive results, possibly related to endobronchial intubation or secretions blocking the lumen of the tracheal tube; there are no reported false-negative results.

It has been used successfully with uncuffed tubes in older children but is unreliable in those under 2 years of age.



2 Oesophageal detector device with Ellick's evacuator modification.

Capnography

Capnography is the real-time detection of carbon dioxide in the breathing gases and its display as a waveform that plots concentration versus time. Carbon dioxide is detected by infrared spectroscopy. It is the gold standard for verifying tracheal intubation. The guidelines of the Association of Anaesthetists state that during induction of anaesthesia, capnography is 'essential to the safe conduct of anaesthesia'.

For carbon dioxide to be detected, it must be produced in the tissues, then transported to the lungs, and finally exhaled in the expiratory gas. The capnograph is therefore an important monitor that gives information about:

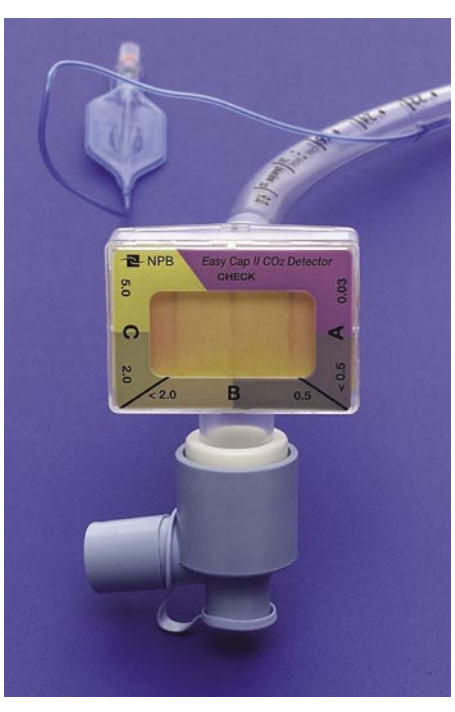
- metabolic rate
- pulmonary perfusion
- alveolar ventilation.

If metabolic rate and pulmonary perfusion (or cardiac output) are constant, then changes in the capnograph trace reflect the adequacy of alveolar ventilation.

Deceptively low values may result from a large leak around the tube. Gas arising from the stomach and oesophagus usually contains only a trace of carbon dioxide, but false-positive results occur if expired alveolar gas is introduced into the stomach from mask ventilation. Significant concentrations of carbon dioxide have been reported following ingestion of carbonated drinks ('cola complication'). In these circumstances, capnography following oesophageal intubation initially resembles the normal waveform for end-tidal carbon dioxide. This initial value rapidly diminishes towards zero as the carbon dioxide is washed out. It has been suggested that the waveform should be observed for a minimum of six breaths.

Colorimetric carbon dioxide detector

This small disposable device contains a pH-sensitive indicator that displays a colour change (e.g. from purple to yellow) when exposed to carbon dioxide (Figure 3). The colour change is rapid and the detector can be left in the breathing circuit for several hours allowing continuous ventilatory monitoring. The device is about the same size and weight as a heat/moisture exchange filter and requires no power source for operation. This portability makes it useful during cardiopulmonary resuscitation or in emergency situations when capnography may not be available. Reduced carbon dioxide concentrations often present in these clinical situations, which may reduce its sensitivity.



3 Colorimetric carbon dioxide detector.

Complications of oesophageal and endobronchial tube placement

Oesophageal intubation

Undetected oesophageal intubation is a major anaesthetic cause of permanent neurological damage and death. There should be a high index of suspicion in any situation in which hypoxia develops following intubation; the onset may be delayed if preoxygenation has occurred. Difficulty in ventilation, poor or absent chest movement, inaudible breath sounds and increasing abdominal distension should all alert the anaesthetist to the possibility of tube misplacement. In practice, clinical signs are not always obvious.

Progressive gastric distension may cause regurgitation and subsequent aspiration. Splinting of the diaphragm impairs ventilation even after the patient has been correctly intubated unless the stomach is actively decompressed using a nasogastric or orogastric tube.

If there is any doubt as to correct tube placement, it is essential to remove the tube and recommence mask ventilation.

Endobronchial intubation

Endobronchial intubation is more common in children owing to the smaller length of the trachea. Flexion or extension of the neck can move the tube a significant amount within the trachea (up to 5 cm in adults), leading to endobronchial intubation or inadvertent extubation. The right main bronchus is more commonly intubated than the left side because it arises at a straighter angle from the trachea.

One-lung ventilation causes hypoxaemia due to the shunt effect that failure to ventilate the opposite lung produces. Progressive lung collapse of this unventilated side occurs. There is a reduced uptake of volatile anaesthetic agent and bronchospasm is a common occurrence, probably as a result of vagal stimulation from irritation of the carina.

The diagnosis may be obvious with asymmetric chest movement and absent breath sounds on one side of the chest, but clinical signs are often unreliable. With an uncuffed tube, breath sounds can easily be transmitted to the non-ventilated lung. A chest radiograph confirms the diagnosis and provides an estimate of the distance that the tube needs to be withdrawn. Fibre-optic bronchoscopy can also be useful.

The chances of endobronchial intubation can be lessened by cutting tracheal tubes to an appropriate size (e.g. 22–24 cm in the adult) preceding intubation. The black marker line present at the distal end of some tracheal tubes can also serve as a guide to the length of the tube to be passed through the vocal cords.

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Regurgitation, Vomiting and Aspiration

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Regurgitation is the passive movement of gastric contents into the pharynx. The lower oesophageal sphincter normally prevents regurgitation. The sphincter is a physiological, rather than a distinct anatomical structure. Reflux is prevented because the lower oesophageal pressure is greater than the gastric pressure. This is referred to as the barrier pressure.

Vomiting is an active reflex usually occurring in the lighter planes of anaesthesia (i.e. induction and emergence). It is the forceful ejection of the contents of the upper gastrointestinal tract through the mouth. It is often secondary to stimulation from inappropriate airway manipulation.

The afferent limb of the reflex arc is composed of fibres from the gastrointestinal tract, the vestibular system, or from the chemoreceptor trigger zone in the brain stem. The vomiting centre' in the brain stem coordinates the reflex. The efferent limb involves autonomic outflow to the gastro-intestinal tract and also produces widespread effects such as pupillary dilation, sweating, salivation, vasoconstriction and tachycardia.

Pulmonary aspiration of gastric contents into the lungs is a serious, though infrequent, complication of modern anaesthesia. Mendleson first described it in detail in 1946 in 66 obstetric patients. Aspiration occurs following gastro-oesophageal regurgitation or vomiting when protective laryngeal reflexes are depressed or absent. Prevention of pulmonary aspiration is by measures aimed at reducing the incidence of regurgitation and vomiting.

Although silent regurgitation is thought to occur in up to 25% of patients under anaesthesia, the incidence of significant pulmonary aspiration in the general surgical population is much less at 1–6/10,000. For obstetric general anaesthesia the incidence is doubled. The mortality following aspiration is about 5%.

Pathophysiology

The adverse effects of pulmonary aspiration occur by three mechanisms.

Particle related – this could result in acute airway obstruction.

Acid related – the traditional view is that patients are 'at risk' if the gastric contents consist of a critical volume of more than 25 ml and have a pH of less than 2.5; there is little clinical evidence to support this. pH is the more critical factor for lung injury sustained following aspiration though there may not be an exact cut-off value. Significant morbidity can occur following inhalation of material with a very low pH even in small volumes due to chemical pneumonitis, and following large volumes of neutral fluid due to a 'near drowning' effect.

Bacterial related – aspirated fluid is not sterile and lung infection may result. Damaged lung is also more prone to secondary infection.

Risk factors

Predisposing factors for pulmonary aspiration are shown in Figure 1. Vomiting and regurgitation during induction of anaesthesia occur most often in emergency cases with acute abdominal pathology or following trauma. Pain, fear, anxiety and opioid administration all delay gastric emptying. These patients should be regarded as at high risk and appropriate precautions taken. The interval between last oral intake and time of injury in trauma patients is said to give a better guide to gastric emptying than the duration of fasting. In practice this is unreliable and it is often best to assume patients have a full stomach.

Risk factors for aspiration

Condition	Examples
Full stomach	Inadequate preoperative fasting Gastrointestinal obstruction, bleeding or ileus Trauma, burns, pain, anxiety Pregnancy Drugs (e.g. opioids)
Reduced lower oesophageal sphincter function	Hiatus hernia Drugs (e.g. opioids, atropine) Pregnancy Raised intra-abdominal pressure Obesity Lithotomy position
Material in oesophagus/ pharynx	Achalasia, scleroderma Strictures, carcinoma Pharyngeal pouch
Depressed laryngeal reflexes	Reduced consciousness (e.g. general anaesthesia, drug or alcohol intoxication, cerebrovascular accident, head injury, seizures or postictal state) Topical anaesthesia Neurological disease (e.g. myasthenia, multiple sclerosis, Parkinson's disease, Guillain–Barré syndrome) Muscular dystrophies
Others	Inexperienced anaesthetist Night-time surgery Emergency surgery Extremes of age

Obstetrics
In the third trimester, the enlarged uterus increases intra-abdominal pressure and therefore intra-gastric pressure. Before this, there is an increased risk of aspiration due to the production of:

- gastrin from the placenta, which increases gastric acid secretion
- progesterone, which relaxes smooth muscle and reduces gastrointestinal motility.

Anatomical changes in late pregnancy may increase the incidence of airway difficulties and thus of aspiration (e.g. increased body weight, large breasts, upper airway oedema). Surgery often occurs 'out of hours' as an emergency. Risks may be increased further during labour from the effects of pain, anxiety and opioid administration. Pregnant patients should be assumed to have a full stomach from the end of the first trimester until at least 18 hours post-partum. Regional anaesthesia should be used whenever possible to reduce the aspiration risks.

Prevention

Methods to prevent pulmonary aspiration are directed towards reducing the volume and increasing the pH of the stomach contents. The technique of cricoid pressure and induction of anaesthesia in the patient with a full stomach is elsewhere.

Fasting requirements
Traditionally, patients were fasted overnight before elective surgery. More recently it has been shown that the administration of clear fluids (e.g. water, non-particulate juice) up to 2–3 hours preoperatively does not increase residual gastric volume or alter pH. This increases patient comfort and reduces dehydration and hypoglycaemia in infants. An example of current fasting guidelines for elective, nonobstetric patients is shown in Figure 2.

Fasting requirements are less straightforward for emergency surgery. It is often necessary to provide anaesthesia to patients suspected of having a full stomach. Delaying urgent surgery to reduce the possibility of aspiration is usually of no benefit and may be detrimental. Patients requiring emergency surgery should be assumed to have a full stomach, irrespective of the duration of fasting, because gastric emptying is likely to be delayed. Following painful trauma, a significant gastric residue can be present after 24 hours. It is not currently recommended that emergency patients be allowed to drink clear fluids before surgery. Intravenous therapy should be used to prevent dehydration. At present there is no consensus regarding fasting during labour.

Preoperative fasting guidelines for patients undergoing elective surgery

	Length of fast (hours)
Adults	
• Solid food	6
• Clear fluid	2–3
Children	
• Solid food	6
• Formula milk	4
• Breast milk	3
• Clear fluid	2

Regional anaesthesia
Avoiding general anaesthesia reduces the risk of pulmonary aspiration. Both the proposed surgery and the patient must be amenable to the technique. The patient should be fasted because an inadequate or failed regional block, or adverse reaction, may make general anaesthesia necessary.

Gastric decompression
The insertion of a nasogastric tube to decompress the stomach may be useful. Liquid, but not solid, gastric contents can be aspirated via the tube. It is not usually possible to empty the stomach completely by this means, so the possibility of aspiration remains. If a nasogastric tube has been passed before surgery, it should be aspirated before induction. Effective cricoid pressure can be performed with the tube *in situ*.

Pharmacotherapy
Antacids: prophylactic administration of antacids to high-risk patients is recommended. These drugs neutralize gastric acid and raise gastric luminal pH. Neutral pH aspirate causes less lung damage than fluid of acidic pH. Antacids should be non-particulate to reduce the potential for lung damage if inhaled. 0.3 M sodium citrate, 30 ml, is effective in elevating the pH of gastric contents if given 15–20 minutes preoperatively; it remains effective for 1–3 hours. Antacids are used routinely in elective and emergency obstetric anaesthesia, but less often in the general surgical population.

H_2-receptor antagonists reduce the volume and acidity of gastric contents by the inhibition of hydrochloric acid secretion from gastric parietal cells. Cimetidine, 400 mg orally 90–120 minutes before induction, and ranitidine, 150 mg orally 120 minutes before induction, 50 mg intramuscularly or slow intravenous administration 45 minutes before induction, are commonly used H_2-antagonists. Ranitidine has a duration of action of at least 8 hours; about twice as long as cimetidine. It is also associated with fewer side-effects. Side-effects with cimetidine, though infrequent, include sedation and confusion, and the potentiation of other drugs through inhibition of hepatic enzymes. Hypotension, bradycardia and even cardiac arrest can follow rapid intravenous injection of cimetidine, and also of ranitidine, though ranitidine has a much lower incidence.

Prokinetics: metoclopramide, 10 mg orally 1–4 hours before surgery or intravenously shortly before induction, acts centrally and peripherally to stimulate gastric emptying, increases lower oesophageal sphincter pressure and is anti-emetic. Its central action is due to its antidopaminergic properties whereas peripherally it stimulates acetylcholine release, resulting in increased gastrointestinal motility.

Proton pump inhibitors: omeprazole, 40 mg orally at night and on the morning of surgery, inhibits the proton pump in the parietal cells of the gastric mucosa, resulting in prolonged suppression of acid secretion. It elevates gastric pH. Combining omeprazole with metoclopramide reduces gastric volume. It is seldom used in the UK despite proven effectiveness.

Anticholinergics (e.g. atropine, glycopyrollate) can decrease gastric acid secretion, but have an adverse effect on barrier pressure by decreasing lower oesophageal pressure. They are not used for aspiration prophylaxis.

Induction of anaesthesia
If general anaesthesia is chosen, a cuffed tube in the trachea should secure the patient's airway. The airway should be assessed to predict whether this is likely to be difficult. The laryngeal mask airway has become popular in modern anaesthetic practice, however, it does not protect the airway from aspiration of gastric contents as efficiently as a cuffed tube and should not be used routinely in patients at high risk.

Uncuffed tubes are used in children because the paediatric airway narrows at the cricoid ring. Uncuffed tubes prevent tracheal mucosal damage by excessive cuff pressure, and may allow passage of a slightly larger tube size permitting improved gas flow. There is no precise age or size at which cuffed tubes are chosen, but use of uncuffed tubes in children below 8–10 years is usual. The absence of a cuff may imply the theoretical risk that aspiration can still occur, although satisfactory airway protection still occurs in clinical practice.

Position:there is controversy regarding the optimum position for induction of anaesthesia in the patient at risk of pulmonary aspiration. Some anaesthetists argue in favour of a head-up (reverse Trendelenburg) or semi-sitting position, because this may reduce the incidence of reflux in patients prone to passive regurgitation. Others favour a head-down (Trendelenburg) position with the patient on their side, because this may decrease the likelihood of aspiration should regurgitation occur.

Patient safety is paramount and therefore clinicians should induce anaesthesia in the position in which they have the most experience and confidence. This will usually be a rapid sequence induction in the supine position.

Rapid sequence induction: if the anaesthetist is confident that tracheal intubation will be straightforward then an intravenous rapid sequence induction performed with cricoid pressure is indicated. Aspiration is most likely to occur in the time from loss of consciousness to intubation with a cuffed tracheal tube. Rapid sequence induction reduces this time to a minimum.

Awake intubation: if a difficult intubation is anticipated consideration should be given to securing the airway before induction. In modern practice this involves topical local anaesthesia to the airway, and intubation via a flexible fibre-optic laryngoscope. A 'blind nasal' technique used to be popular, but the arrival of modern fibre-optic instruments has allowed awake intubation to be performed under direct vision.

Inhalational (gaseous) induction may be indicated in a patient considered at risk from aspiration, in whom conventional laryngoscopy and intubation is predicted to be difficult and where awake intubation attempts may be hazardous (e.g. acute stridor, maxillofacial trauma). There is a trade-off between taking steps to prevent aspiration during induction, and maintaining and securing the airway. A senior anaesthetist should manage these cases and patient safety is paramount.

Extubation should be performed with the patient awake and following the return of upper airway protective reflexes. It is often safest to position the patient on their side with head-down tilt to facilitate clearance of the upper airway using suction, should regurgitation occur.

Diagnosis

Clinical signs and symptoms of aspiration are variable (Figure 3) and it is sometimes difficult to make a definitive diagnosis. 'Silent' aspiration may occur, and may not be diagnosed until after surgery when the patient has returned to the ward. The initial and most reliable sign of aspiration is hypoxia, which occurs following even mild cases. Wheezing is also common. In severe cases an acute respiratory distress syndrome can result. In such patients there is increased intrapulmonary shunting, ventilation–perfusion (V/Q) mismatch, increased lung water, increased airway resistance and reduced lung compliance. Although aspiration classically affects the posterior aspect of the right lower lobe, radiographic changes are variable, nonspecific and may be absent, particularly in the first few hours. The most usual findings are irregular fluffy den-sities, frequently bilaterally, collapse or pulmonary oedema (Figure 4).

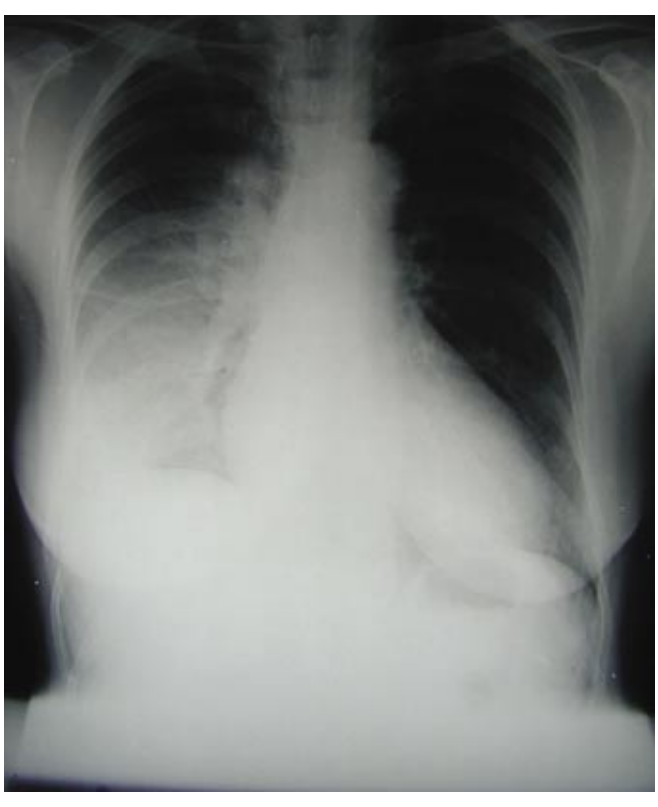
Differential diagnoses include anaphylaxis, cardiac failure, pulmonary embolism, fat embolism, sepsis and, in obstetric patients, amniotic fluid embolism.

Signs and symptoms of pulmonary aspiration

Symptoms
- Cough
- Breathlessness

Signs
- Stomach contents in oropharynx
- Tachypnoea
- Wheeze, crackles (mainly coarse)
- Cyanosis
- Tachycardia
- Pulmonary oedema
- Increased airway pressure
- Radiographic changes

3



4 Typical radiographic appearance of the chest in a patient with aspiration.

Management

If acute aspiration occurs the following procedure should be carried out.
- Place the patient in a head-down position, with head turned to one side.
- Suction material from the oropharynx.
- Administer 100% oxygen.
- Intubate the trachea if:

– adequate oxygenation cannot be maintained with spontaneous ventilation
– further tracheobronchial suction is required
– the patient is unable to protect their own airway.

The decision to continue with surgery depends on the severity of the aspiration and the urgency of surgery.

The management of established aspiration is largely supportive. Treatment is described in Figure 5.

Management of established aspiration

Oxygen therapy
- Guided by blood gas estimations or pulse oximetry

Ventilatory support
- Spontaneous ventilation may be adequate in mild cases
- Continuous positive airway pressure can be used for more severe cases, but requires alert, cooperative patient at no further risk of aspiration
- For severe cases, or those who cannot maintain a patent airway, mechanical ventilation via a tracheal tube is indicated
- Positive end-expiratory pressure is applied to increase functional residual capacity of the lung and minimize intrapulmonary shunting

Removal of aspirate
- Regular suctioning and physiotherapy are needed
- Bronchoscopy is required in more severe cases

Bronchodilators
- Given regularly by nebulizer

Antibiotics
- No proven benefit from prophylactic use
- Antibiotics often prescribed before identification of any pathogens

Fluid balance
- Shifts of fluid from the circulation to the lungs can result in pulmonary oedema
- Central venous pressure and urine output monitoring help guide fluid management
- A positive fluid balance worsens gas exchange and should be avoided

Corticosteroid therapy
- Routine use of corticosteroids is not indicated – no current evidence has shown benefit from their use

5

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Surgical Diathermy: Mechanisms, Use and Abuse

Andrew D Farmery

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The application of heat to wounds is evident in unearthed Neolithic skulls. Thermal cautery to ulcers and tumours of the breast was described in a papyrus from about 3000 BC, and later described by Hippocrates in 300 BC. Electrical diathermy is at least 250 years old, predating the practice of anaesthesia by a century.

Diathermy (*dia*, through; *thermy*, heat) strictly applies to the uniform heating of tissues by radiofrequency current or radiation. As a surgical tool, uniform heating is not required, but rather discrete and destructive heating in a specific area. This application is called 'electrosurgery' in the USA, and 'surgical diathermy' in the UK, but the term diathermy has remained.

Basic electrical principles

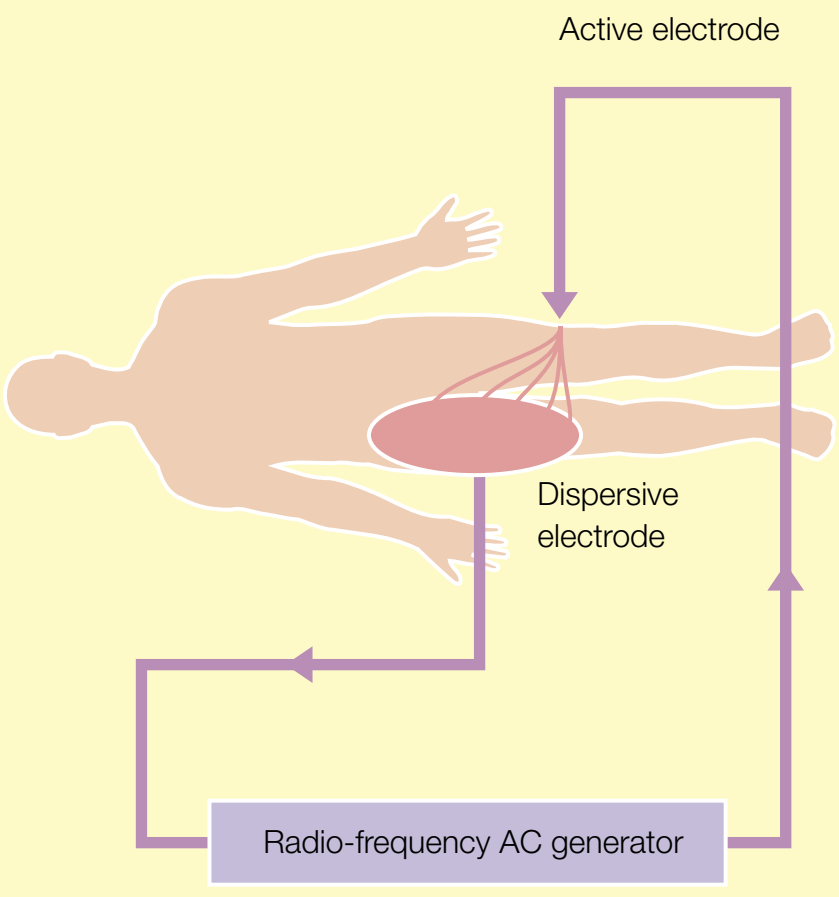
Forcing current through a resistance liberates heat

The power to heat, cut or vaporize tissues is derived from passing an electrical current through it. At any point in an electric circuit, the power dissipated is given by the formula:

$$\text{Power} = \text{Current}^2 \times \text{Resistance} \qquad (P = I^2 \times R) \quad 1$$

Current forced through regions of high resistance produces more heat than the same current passed through regions of low resistance. Figure 1 shows how the current density (and resistance) at the tip of a diathermy probe is many orders of magnitude higher than the current density elsewhere in the circuit, namely the patient's body and the large 'dispersive' electrode. This is analogous to a large crowd of people moving along a wide walkway to gain access to a football stadium. The flow is ordered and comfortable at the rear of the walkway, but when the same 'flow' is forced through a narrow turnstile, the 'power' of the crowd will be liberated (destructively) at this high resistance, high flow-density point.

Current density



The tiny active electrode/tissue contact has a high resistance, therefore a high power is liberated ($P = I^2 \times R$). Because this power is delivered to a small area, the power density, and ability to heat the tissue, is great. By contrast, the dispersive electrode, with its larger area of contact, has a low resistance and thus little power is liberated and it is distributed over a wide area, therefore the heating effect is negligible.

1

Using high-frequency alternating current prevents 'electrocution'

In Equation 1, both direct current (DC; e.g from a large battery) or alternating current (AC; e.g. from the mains supply) produce the same amount of heat for the same mean current. However, DC polarizes a tissue such that tissue connected to the anode becomes 'positive', and that connected to the cathode, 'negative'. This triggers ion channel opening and depolarizes important excitable tissues such as nerves, striated muscle and myocardium. The same is true of moderately low-frequency AC (e.g. 50 Hz), in which the tissue is alternately polarized and depolarized because the polarity of the applied voltage changes sinusoidally. This can result in convulsions, tetanic muscle twitch and ventricular fibrillation (i.e. electrocution).

High-frequency current is less prone to causing these phenomena because voltage-sensitive ion channels in excitable tissues do not respond instantly to an applied depolarizing voltage, but have a finite response time. An analogy is when the rudder of a tanker is turned suddenly, there is a delay before it slowly starts to change direction. If the rudder is turned from left to right with a low frequency, the tanker steers a course veering from left to right sinusoidally. However, if the rudder is oscillated from left to right with a high frequency, the ship steers a straight course because it does not have enough time to respond to a rudder movement in one direction before being directed to move in the opposite direction.

In the same way, a high-frequency AC voltage applied to the myocardium will neither polarize nor depolarize the membrane, because the ion channels will not have time to open or close before the polarity of the applied voltage is reversed and so the tissue will continue to function normally. Electrosurgical generators typically operate at frequencies of 0.5–4 MHz.

Surgical effects of diathermy

There are three main diathermy modes: desiccation, cutting and coagulation.

Desiccation

To cause desiccation (drying out), a low power current is passed through the tissues, as in Figure 1. The aim is to increase tissue temperature at the site of contact with the active electrode. Intracellular water is slowly driven off as steam and the tissue is dried out. This produces a blanching of tissue. Because the current is of low power, it is effective only in delicate tissues and small vessels (e.g. it is often used to blanch the fallopian tube before surgical division in laparoscopic sterilization). When tissue has been desiccated, its resistance to current flow becomes very high and current flow effectively ceases, thus terminating the heating process. It is impossible to 'cut' tissue in this mode. The current waveform is not important in this application.

Cutting

In the cutting mode, the aim is to make a discrete cut through the tissue. Initial contact with the electrode heats the tissue rapidly so that cells explode and their contents are instantly vaporized. Heat is not conducted very far from the site of contact because most of the liberated power is used to vaporize water (i.e. is consumed as latent heat of vaporization). The heating effect is therefore concentrated and neighbouring tissue is undamaged. Unlike desiccation, 'sparking' is a key feature.

The vaporized desiccated tissue is a poor electrical conductor and therefore breaks the circuit so that current flow ceases through this pathway. However, if the voltage (the driving force for current) is high enough, air around the electrode is ionized. Ionized air is a better conductor than desiccated tissue, and so current will now flow as a spark jumps to the nearest region of moist tissue. Tissue heating is produced by:

- current delivered by the spark ($I^2 \times R$)
- radiant heat from the spark
- collision of electrons bombarding the tissue.

This causes intense local heating, vaporization and thermal destruction. Cells are torn apart. The current waveform used is a continuous radiofrequency sinewave (Figure 2a).

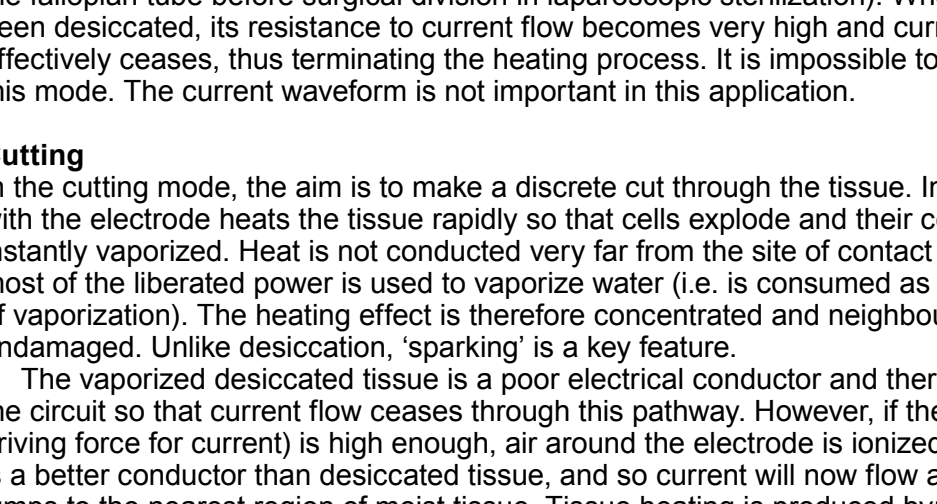
Coagulation

In coagulation mode (Figure 2b), the current waveform comprises short bursts of radiofrequency sinewaves (about 1 MHz), with bursts occurring about 20,000 times per second (burst frequency 20 kHz). The coagulation waveform can cause sparking to tissues. However, the radiofrequency current is delivered in intermittent bursts and therefore the ion cloud generated at each spark has a chance to disappear between bursts. Therefore, with each current burst, ionization occurs afresh, and because this is a random process sparking occurs more randomly and over a wider area than it does in cutting mode. This reduces the concentration of the sparking power and allows effective coagulation of vessels without tissue cutting. Peak voltages are much higher in the coagulation mode than in the cut mode because the current is zero for most of the time and so in order to deliver the same average power, the coagulation waveform generator has to deliver more power in the short periods when current is switched on.

Waveforms

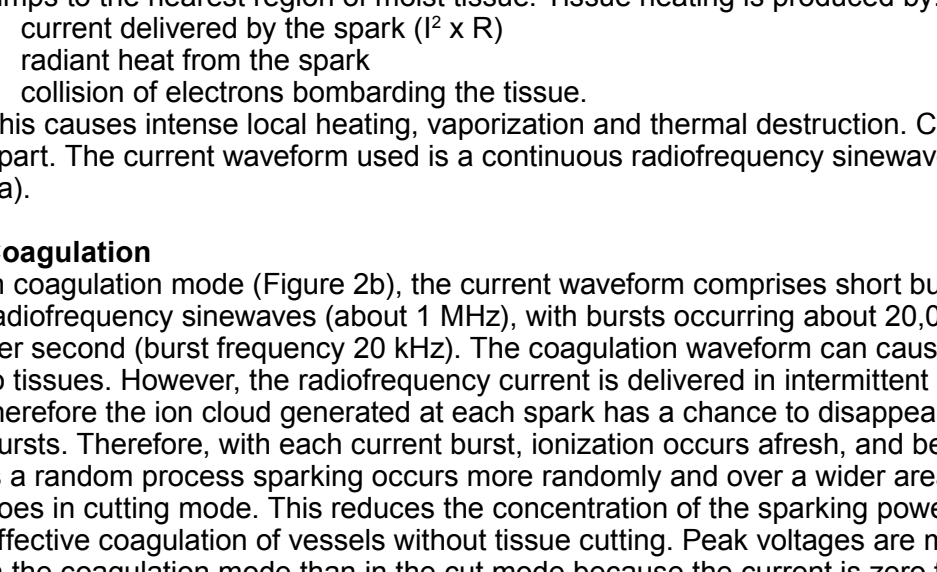
a Cutting waveform

A continuous radiofrequency sinewave of about 1 MHz



b Coagulation waveform

A 1 MHz sinewave delivered in bursts (20,000/second)



2

Monopolar and bipolar systems

Monopolar

The system described in Figure 1 is monopolar. Current is delivered via a pinpoint active electrode, which then passes through the patient (in a low-density path) to return via the dispersive electrode. This is the most widely used system because it is most effective in producing cutting as well as coagulation.

Bipolar
In a bipolar system, current is delivered via one arm of a pair of insulated forceps. It passes through any tissue grasped between the arms of the forceps and returns via the opposite arm. With a bipolar system, only desiccation can be achieved. The system is of limited power, and sparking does not occur. If the arms of the forceps are allowed to make contact with each other directly, despite there being some tissue in the path, current will be 'shorted-out', and diathermy will be less effective. Bipolar diathermy is indicated where it is undesirable to pass current through the patient's body to a distant dispersive electrode; some examples are given below.

Narrow current conduits to extremities (e.g. testicle surgery) – if a monopolar system were used, with the dispersive electrode placed on the abdominal wall, current would be forced to pass from the testicle along the vas deferens (the path of least resistance) to the trunk. Because the vas deferens is a narrow tube, current density would be high within it, and thermal injury might result.

Metal prostheses – if a metal prosthesis lies between the dispersive and active electrode, current preferentially passes through this low resistance route, producing a high current density and heating in narrow points such as a cortical screw. This may necrose bone or conduct heat to neighbouring soft tissue or vessels, sufficient to perforate an artery.

Cardiac pacemakers – the cable connecting a pacemaker generator box (implanted in the anterior chest) to the electrode in the right ventricle and/or atrium constitutes a low impedance pathway for radiofrequency current if it lies between the active and dispersive diathermy electrodes. This may result in a high current density at the point of pacemaker electrode insertion into the myocardium. Tissue desiccation may occur at this point, increasing the resistance of the contact. The 'threshold' potential may increase, such that the pacing pulse fails to trigger the heart.

More sophisticated pacemakers are capable of detecting intrinsic cardiac activity and withholding activation of the pacemaker. It is possible that stray radiofrequency current may be detected by the pacemaker, and interpreted as intrinsic cardiac activity, resulting in inappropriate inactivation of the pacemaker. For this reason, it is advisable, if possible, to have the pacemaker programmed so that this function is disabled. The safest precaution, however, is to avoid monopolar diathermy.

Patient safety

The principal issues are:
- avoidance of inadvertent thermal burns from stray diathermy current
- avoidance of inadvertent electrocution from stray 50 Hz mains current.

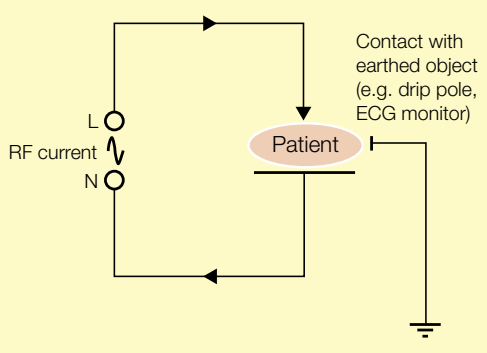
Isolated (unearthed) dispersive electrode system
Figure 3a shows a simple circuit in which neither live nor neutral terminals of the radiofrequency current generator are connected to earth.

A fundamental law of electricity is that all the current leaving the live terminal is returned to the neutral terminal. Therefore, if the patient makes contact with an earthed object (e.g. lithotomy pole, drip stand or faulty low impedance ECG electrode) none of the radiofrequency diathermy current should pass via this contact to earth because such a stray current would not be able to return to the neutral terminal. All the current should pass to the neutral terminal via the large dispersive electrode, thereby eliminating the potential for burns. This might seem a safe system but it is possible to burn patients inadvertently with isolated systems because of the phenomenon of 'capacitive coupling'. It is difficult to confine very high-frequency currents to wires, and currents tend to pass out of the cables like a radio transmitter because a wire and another conductor (e.g. earth) can behave like the two plates of a capacitor. Capacitors can conduct high-frequency current, even though insulation and a few feet of air separate the wire and earth. Radiofrequency leakage current flows only if there is a route for it to return to the neutral terminal; Figure 3b shows how this might happen. A certain amount of current from the active lead is leaked to earth via this capacitive coupling. This can return to the patient via any small, grounded contact point and potentially cause a burn at this site. From this point, the leakage current joins the main current and returns to the neutral terminal via the dispersive electrode.

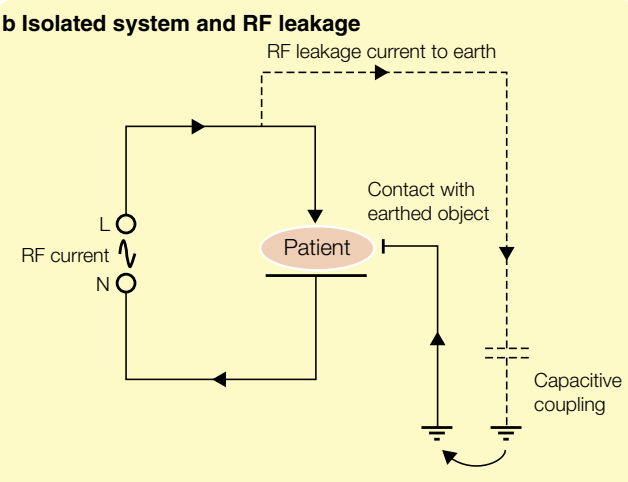
Early electrosurgical generators were not truly isolated. There was usually some connection of the neutral terminal and dispersive electrode cable to earth because of capacitive coupling between them, in a similar way to that described above. Figure 3c shows how this allows current to flow to earth through grounded contact points and complete the circuit to the neutral terminal via the 'virtual' earth connection. The amount of stray current passing through the grounded contact points depends on the relative impedance of the pathways. Given that one cannot avoid some current passing to ground, the best way to prevent this passing through unwanted pathways is to provide a route to ground via the dispersive electrode which is more 'attractive' than the alternative routes. This is done by physically earthing the dispersive plate and making the impedance of this connection as low as possible.

Isolated and earthed systems

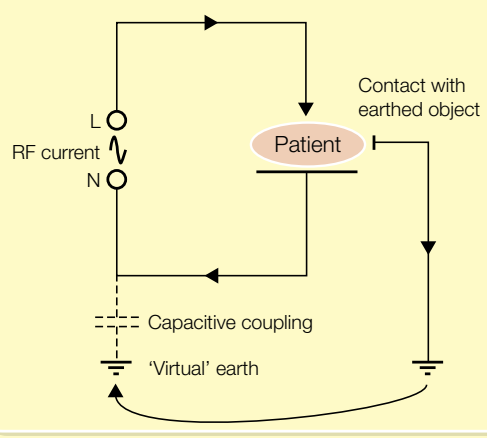
a Isolated system



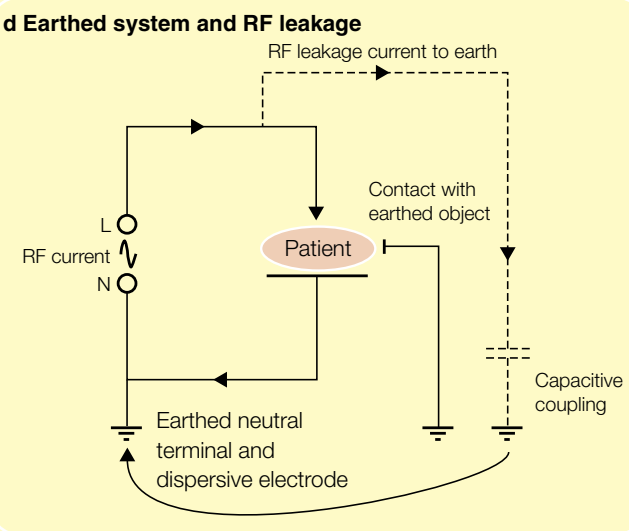
b Isolated system and RF leakage



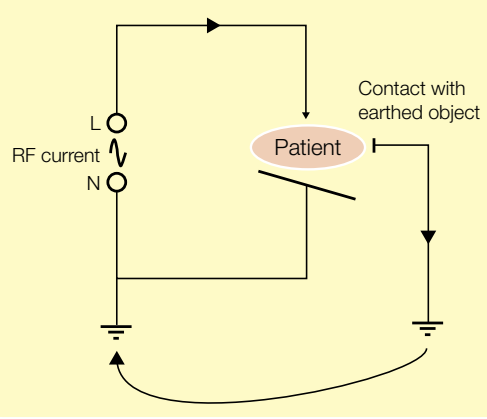
c Isolated system and 'virtual' earthing of dispersive electrode



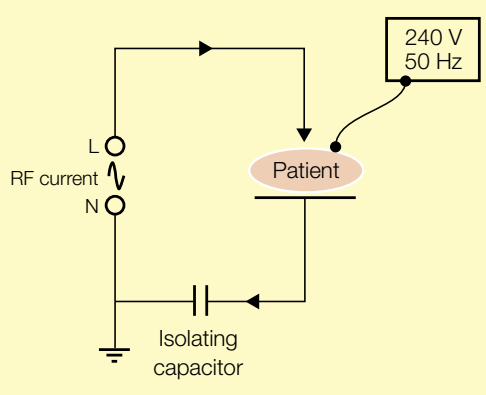
d Earthed system and RF leakage



e Earthed system and poor dispersive electrode contact



f Earthed system and isolating capacitor



L, live; N, neutral; RF, radiofrequency

Earthed dispersive electrode system
Earthing the dispersive electrode overcomes both the 'virtual' earth problem (Figure 3c) and the radiofrequency leakage problem (Figure 3b). Figure 3d shows how if the dispersive electrode and neutral terminal are earthed, any radiofrequency leakage current can return to the neutral terminal via a direct low impedance earth route that bypasses the patient. However, earthing poses other problems.

Dispersive electrode detachment: the dispersive electrode is an attractive route for ground-seeking radiofrequency current only if its impedance is many orders of magnitude lower than unwanted stray routes. If the dispersive electrode becomes detached or makes poor contact, all of the radiofrequency current can pass to earth (and hence return to the neutral terminal) via unwanted grounded contact point, as shown in Figure 3e, thus causing burns.

Mains electrocution: if the patient is exposed to a live mains voltage (e.g. via a faulty monitor lead) the earthed dispersive electrode provides a low impedance pathway for this dangerous 50 Hz current to pass through the patient to earth, thus causing electrocution. This is because mains voltage is ground seeking. This problem can be overcome by placing a capacitor in the circuit as in Figure 3f. This is capable of passing radio-frequency current, but does not conduct low frequency (50 Hz) current. Even though the patient is exposed to a live mains cable, no 50 Hz current will flow through the patient to the ground.

Techniques of Cricoid Pressure

Richard Vanner

Richard Vanner is Consultant Anaesthetist and Clinical Director in a large District General Hospital in the UK. He is a generalist with a specific interest in obstetric anaesthesia.

In 1956, the Association of Anaesthetists had collected 1000 reports of anaesthetic deaths; 110 from pulmonary aspiration of stomach contents. This often occurred during induction of general anaesthesia especially when muscle-relaxant drugs were used. Anaesthetic techniques were developed to prevent aspiration in patients at risk and included:

- emptying the stomach before induction
- intravenous induction with head-up tilt position
- inhalational induction in the lateral and head-down position.

In 1961, Sellick described cricoid pressure as a technique used to prevent regurgitation of stomach contents during the induction of general anaesthesia. It was brought into widespread practice in the UK by 1970 and largely replaced the other techniques, despite no randomized controlled trials demonstrating its benefit. It has become a routine part of anaesthetic practice for patients at risk of aspiration in combination with pre-oxygenation, an intravenous induction and tracheal intubation. All UK maternity units routinely apply cricoid pressure during induction of general anaesthesia.

Before the introduction of cricoid pressure, the incidence of aspiration pneumonitis in obstetric general anaesthetics was about 0.15%. If cricoid pressure prevents aspiration, the number needed to treat to prevent one case of aspiration would be 666. A controlled trial would be difficult because of the large numbers of patients needed and the difficulty of obtaining ethical approval.

Indications

In a patient who has been prepared for elective surgery and has not eaten for 6 hours or drunk for 2 hours, regurgitation of stomach contents during the induction of anaesthesia is unusual even when muscle-relaxant drugs are used, which relax the upper oesophageal sphincter. In these patients, cricoid pressure is unnecessary, because its benefits have to outweigh the risk of complications. However, cricoid pressure is indicated if:

- surgery is necessary before the patient is fasted
- gastric emptying is delayed
- the lower oesophageal sphincter is incompetent (e.g. in the last half of pregnancy or in reflux oesophagitis). With a full stomach from any cause, distention of the fundus causes reflex relaxation of the lower oesophageal sphincter.

Mechanism of action

Regurgitation is the flow of fluid from the oesophagus into the pharynx and is a passive process. When patients are awake the upper oesophageal sphincter prevents regurgitation. The pressure that this sphincter exerts is about 40 mm Hg and it relaxes during swallowing and during sudden distension of the oesophagus (e.g. belching, vomiting). The sphincter is mainly the cricopharyngeus muscle, a skeletal muscle, which is attached to the lateral aspects of the cricoid cartilage and is positioned behind it like a sling. The lumen of the hypopharynx within the cricopharyngeus is therefore crescent shaped. The oesophagus begins below the level of the cricoid cartilage.

The upper oesophageal sphincter relaxes during intravenous induction with thiopental (thiopentone), with heavy sedation, during deep sleep or following muscle-relaxant drugs. In all of these situations the sphincter pressure is reduced to less than 10 mm Hg, which is low enough to allow regurgitation. Following thiopental (thiopentone) the sphincter starts to relax just before loss of consciousness but is not fully relaxed until 30 seconds later. Ketamine does not relax the upper oesophageal sphincter, nor does an inhalational induction. Coughing during an inhalational induction increases upper oesophageal sphincter pressure to over 100 mm Hg.

Cricoid pressure prevents regurgitation by replacing the function of the upper oesophageal sphincter by compressing the hypopharynx against the prevertebral fascia muscles and vertebrae behind. The convex cricoid is pressed against the convex body of either the 5th or 6th cervical vertebrae. Inevitably the cricoid cartilage is deviated slightly laterally (Figures 1 and 2). Part of the crescent-shaped lumen is compressed against the vertebral body and the rest of it is less well compressed against the longus colli muscle to one side. A nasogastric tube is squeezed laterally towards the less well compressed part of the lumen and makes the occlusion of the hypopharynx more complete and therefore cricoid pressure more efficient.

A study of women undergoing emergency caesarean section under general anaesthesia with muscle relaxation showed that gastric pressure is likely to be less than 25 mm Hg in 99%. Oesophageal pressure can rise to equal gastric pressure during gastro-oesophageal reflux as the lower oesophageal sphincter relaxes to create a common cavity. A study of ten cadavers showed that 20 Newtons (N) of force applied to the cricoid cartilage prevented the regurgitation of oesophageal fluid at a pressure of 25 mm Hg in all cases and 30 N prevented regurgitation at a pressure of 40 mm Hg in all cases. Therefore, 20 N of cricoid pressure is probably sufficient and 30 N is more than enough to prevent regurgitation into the pharynx. Anaesthetic assistants can be trained to apply the correct force by practising on weighing scales and by doing this they can apply a range of forces between 5 N above or below the target force. A reasonable recommendation is to apply 30 N (3 kg).

Correct technique

Although cricoid pressure is apparently a simple technique there is growing evidence that incorrect application can cause serious problems during induction of anaesthesia. The anaesthetic assistant should practise the correct forces on weighing scales. The anaesthetist should be confident that the anaesthetic assistant knows the anatomical landmarks of the cricoid cartilage. Although Sellick suggested that the patient's head should be extended, the author recommends that it should rest on a pillow because intubation is easier and cricoid pressure is just as effective in this position. After pre-oxygenation, but before intravenous induction, lightly applied cricoid pressure should be started with a force of 10 N (1 kg), after loss of consciousness the force is increased to 30 N (3 kg). Forces of 20 N or more are not tolerated by awake patients and may cause them to retch and vomit. Normally the assistant applies cricoid pressure with their dominant hand because this can be maintained more accurately and for longer (3–5 minutes). There is no evidence that a bimanual technique, with the assistant's other hand supporting the patient's neck, improves the view at laryngoscopy when the correct forces are applied. The assistant's other hand is best kept free to assist with a difficult intubation if necessary.

Patients with small bowel obstruction should have a nasogastric tube inserted preoperatively. This should be aspirated before induction and left in place during induction. This does not make cricoid pressure less efficient and may improve it. As the tube is not compressed, it is possible, by leaving it open to atmospheric pressure, to vent liquid and gas remaining in the stomach, minimizing any increase in gastric pressure.

Sellick described the application of cricoid pressure with three fingers, thumb and middle finger on each side of the cartilage with the pressure applied with the forefinger. However, with the head on a pillow it is more comfortable to apply it with two fingers, forefinger and thumb on each side of the cartilage. This gives flexibility to apply upward and backward cricoid pressure, which improves the view at laryngoscopy if this becomes necessary. As the cricoid inevitably moves slightly laterally during cricoid pressure, it is better to ensure that it moves to the patient's right rather than to the left because this also makes intubation easier with a Macintosh laryngoscope.

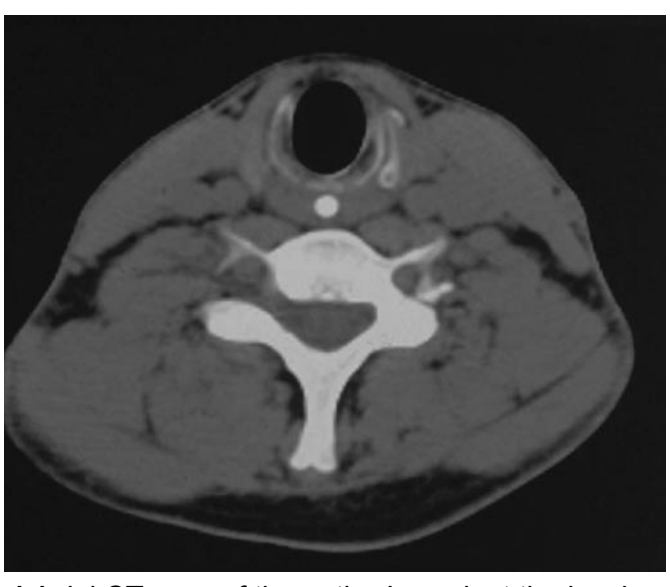
Complications

Excess force applied to the awake patient has caused retching and death from aspiration and ruptured oesophagus.

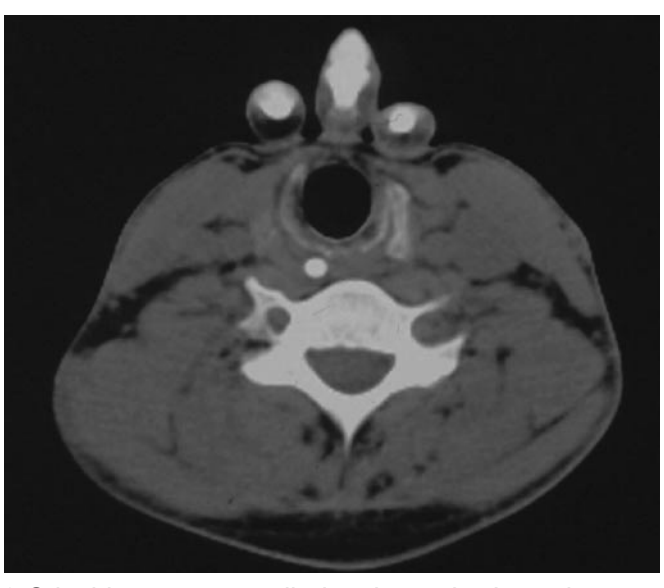
Difficult intubation can be caused by cricoid pressure if the force is applied to the thyroid cartilage or if the larynx is pushed laterally to the left or if too much force is used, which compresses the airway. When cricoid pressure is applied properly with a force of 30 N (3 kg) the view at laryngoscopy is improved compared with the situation when no cricoid pressure is used. However, if only the epiglottis can be seen, then the slight lateral displacement of the larynx, which is inevitable, will make the passage of a gum elastic bougie more difficult because this is normally passed in the midline.

The so-called 'cricoid yoke', a force transducer applied to the neck, is not ideal, because it may not be applied accurately to the cricoid cartilage and may cause tracheal compression or extreme lateral displacement of the larynx, resulting in difficulty with tracheal intubation.

Difficult ventilation – cricoid pressure can obstruct the airway and prevent ventilation of the lungs with a face mask and Guedel airway. This is proportional to the force applied; 30 N causes complete obstruction in 2% of patients and 40 N does in 35%. Upward and backward cricoid pressure at a force of 30 N causes airway obstruction in 56% possibly because it tilts the cricoid cartilage and opposes the vocal cords. Following a failed intubation in a patient with a full stomach when the lungs cannot be ventilated, the force of cricoid pressure should be reduced by half. If this does not allow ventilation, cricoid pressure should be released completely to allow ventilation, with laryngoscope and suction immediately available. Further airways that may then be necessary (e.g. laryngeal mask, *Combitube*, cricothyrotomy cannula) are all better placed without cricoid pressure applied.



1 Axial CT scan of the author's neck at the level of the cricoid cartilage showing a nasogastric tube filled with radio-opaque contrast media.



2 Cricoid pressure applied to the author's neck showing the slight lateral displacement of the cricoid and the lateral position of the nasogastric tube.

FURTHER READING

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Sellick B A. Cricoid Pressure to Control Regurgitation of Stomach Contents during Induction of Anaesthesia. *Lancet* 1961; **2:** 404–6.
Vanner R G, Pryle B J, O'Dwyer J P, Reynolds F. Upper Oesophageal Sphincter Pressure and the Intravenous Induction of Anaesthesia. *Anaesthesia* 1992; **47:** 371–5.

Tracheal Intubation: Management of Difficult and Failed Intubation

Stuart W Benham

Stuart W Benham is Consultant in Anaesthetics and Intensive Care Medicine at the John Radcliffe Hospital, Oxford, UK. He qualified from Glasgow University and trained in anaesthetics and general medicine in the west of Scotland before finishing his training in intensive care in Oxford. His research interests include acute renal failure on the ICU and difficult airway training and research.

Securing the airway with a tracheal tube is a core skill for anaesthetists. The technique may be required during anaesthesia, resuscitation or intensive care. The ability to manage patients when laryngoscopy is predicted to be difficult, or when intubation has previously failed, requires a methodical approach and a workable back-up plan. Indications for tracheal intubation are given in Figure 1.

Patients with depressed conscious levels (e.g. following head injury, self-poisoning, vascular accident, infections) need careful assessment. If there is any concern that airway reflexes are diminished, the airway must be secured with a tracheal tube. A low Glasgow Coma Score (e.g. GCS < 9) should not be relied on as the sole indication of airway compromise.

Intermittent positive-pressure ventilation can be achieved by non-invasive means without tracheal intubation. In the operating theatre this is often performed with the laryngeal mask airway (LMA), and in the ICU with a secure fitting face mask with head strapping.

Indications for tracheal intubation

Surgical indications
- Shared airway surgery
- Requirement for one lung ventilation
- Prone or sitting position for surgery
- Open abdominal or thoracic surgical procedures
- Major head and neck surgery
- Prolonged surgery

Emergency indications
- Prevention of aspiration in unfasted patients requiring general anaesthesia
- Impending airway obstruction (e.g. epiglottitis, airway burns)
- Maxillofacial trauma (blood in the airway)
- Depressed conscious level with poor airway reflexes

Ventilatory failure indications
- For intermittent positive-pressure ventilation
- Prevent aspiration of gastric contents
- Advanced ventilation strategies (e.g. partial liquid ventilation, high frequency jet ventilation)
- Prone ventilation strategies
- Ventilatory failure unresponsive to non-invasive positive- pressure ventilation

1

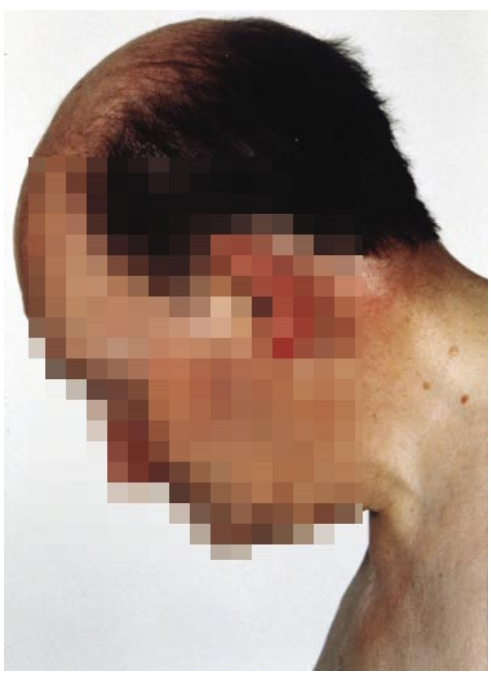
Management of difficult airway and failed intubation

The maintenance of alveolar ventilation is the most important aspect of difficult airway management. Patients in whom intubation is difficult or has failed, and in whom mask ventilation is also difficult are uncommon (about 1:10,000 routine anaesthetics). The anaesthetic plan must not render an awake patient who can maintain a patent airway into an unconscious patient with an unsafe and obstructed one. Preoperative assessment aims to identify patients in whom laryngoscopy and/or airway maintenance are likely to be difficult when consciousness is lost. Patients generally fall into one of three categories:
- anticipated difficult laryngoscopy
- elective unanticipated difficult laryngoscopy
- emergency unanticipated difficult laryngoscopy or failed intubation.

Anticipated difficult laryngoscopy
A comprehensive plan is required involving a primary plan and a secondary plan to be used if the primary plan fails. Two common pitfalls are:
- the operator is inexperienced in the technique chosen (e.g. flexible fibre-optic laryngoscopy – FFL)
- the back-up plan involves staff, skills and equipment that are not readily available at the time of induction (e.g. tracheostomy).

Anaesthetists have to develop plans with their own skill levels in mind, incorporating available equipment and supporting staff. Patient safety is of paramount importance. Generally, less invasive, atraumatic techniques should be preferred to surgical airway control, especially in elective patients. However, the emergency anticipated difficult airway (e.g. patients with severe maxillofacial trauma, or enlarging wound haematoma and stridor following head and neck surgery) may require a surgical airway as the primary plan.

Patients with bony abnormalities may have restricted mouth opening due to temporo-mandibular joint disease, or a cervical spine with limited neck flexion or extension (Figure 2). There is an expectation that the oropharynx and periglottic regions will be normal. In these patients, direct laryngoscopy may be impossible, but the normal oropharyngeal anatomy allows the passage of an FFL under general anaesthesia and assisted ventilation should be possible. If the primary plan fails during this elective surgery, the patient may be woken before implementing the secondary plan.



2 Restricted neck extension in ankylosing spondylitis.

Patients with obstruction in the supraglottic region include those with previous major oral surgery or radiotherapy. If there is evidence of stridor, the patient should be treated with extreme caution and one of the plans outlined below for periglottic or infraglottic obstruction should be considered. Stridor implies 50% airway narrowing. These patients may develop complete airway obstruction when anaesthetized and a surgical airway should be included in the management plan. Depending on the anaesthetist's skill, two options for the non-stridulous patient are:
- an awake fibre-optic endoscopy and intubation, before any relaxant or induction agent is given
- an inhalational induction and direct laryngoscopy to define the anatomical situation, and the feasibility of passing a tracheal tube.

Patients with obstruction in the periglottic region (including obstructing laryngeal tumours) require a thorough preoperative evaluation (e.g. CT, MRI) to assess the degree of obstruction and clinical assessment of the degree of stridor. Indirect laryngoscopy and flexible fibre-optic nasendoscopy are necessary to determine the extent of the obstruction and the feasibility of passing a tracheal tube, which should be performed by an experienced ENT surgeon. Non-stridulous lesions can be managed similarly to lesions causing supraglottic obstruction. Stridulous lesions are the most difficult to manage because neither awake fibre-optic endoscopy nor inhalational induction guarantees success. The choice of technique depends on the degree of stridor, the general condition of the patient and the experience of the anaesthetist. Severe cases may best be managed by awake tracheostomy under local anaesthesia. Depending on the level of the lesion, particularly with infraglottic obstruction, even emergency tracheostomy may not be realistic. For the most severe lesions it may be necessary to consider extracorporeal oxygenation as part of the secondary plan.

Elective unanticipated difficult laryngoscopy
Elective unanticipated difficult laryngoscopy is best managed using a stepwise approach.
- Reconfirm that assisted bag and mask ventilation is possible.
- Consider repositioning the head and neck and the use of a bougie.
- Avoid prolonged attempts at direct laryngoscopy. Change the length of laryngoscope blade once and the type of blade once to achieve the optimum view.
- Call for help and for the FFL if competent in its use.
- Consider the use of the LMA or the intubating LMA (ILMA) for ventilation.
- Consider using the LMA/ILMA as a conduit for intubation (see below).
- Consider abandoning anaesthesia, and performing an awake intubation.

Emergency unanticipated difficult laryngoscopy and failed intubation
This is a failure to secure the airway with a tracheal tube following a rapid sequence induction. Remember that it is failure of oxygenation, rather than a failure of intubation, that accounts for morbidity and mortality. The same stepwise approach as that for the elective unanticipated difficult laryngoscopy should be followed. All departments of anaesthesia should have a failed intubation drill for these circumstances, and clinicians should be familiar with their local protocols (see *Anaesthesia and Intensive Care Medicine* **2:6:** 221). It should be noted that in these situations the removal of cricoid pressure may help ventilation attempts, especially through the LMA. The risks of aspiration are small in comparison to the potential for morbidity and mortality caused by hypoxia from failed ventilation.

Techniques to overcome difficult intubation

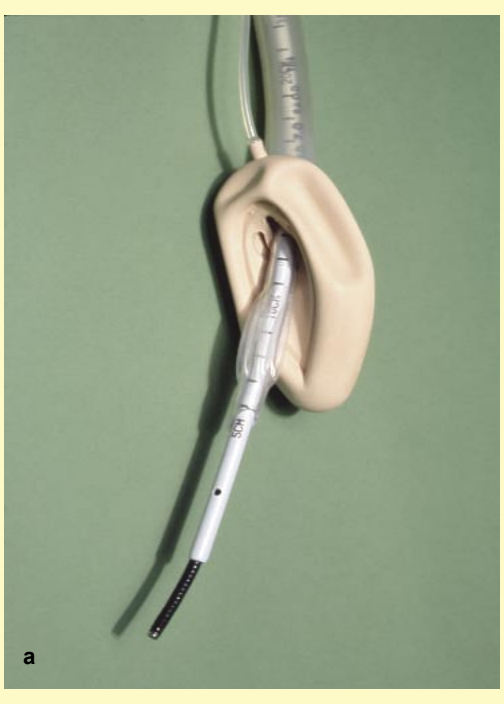
Many devices have been developed to improve the chances of securing the airway with a tracheal tube. Some of those used by practising clinicians are described below.

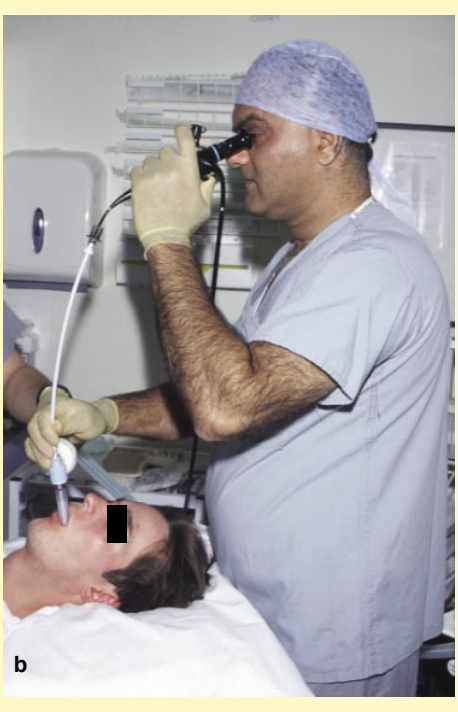
Position and simple manoeuvres
Optimizing the patient's position (flexion of the cervical spine and head extension at the atlanto-occipital joint – the 'sniffing the morning air' position) is the first step to improve the view at direct laryngoscopy. Simple manoeuvres such as external laryngeal manipulation, especially backwards, upwards and rightwards pressure on the larynx can improve the view by more closely aligning the visual axis with the laryngeal inlet.

Laryngoscopes
There is a range of curved and straight blades, as well as blades with movable hinged tips (McCoy), that may improve the view at direct laryngoscopy (see *Anaesthesia and Intensive Care Medicine* **1:1** 34). Many experienced anaesthetists, however, tend to use the same type of laryngoscope blade for all their patients. Skills in the use of different blades are best acquired during routine intubations. The McCoy, or the angled Belscope laryngoscope, may be able to convert a Cormack/Lehane grade 3 view to a grade 2 view, though familiarization with the technique is required.

Simple props and aids
Gum elastic bougies should be used when:
- direct laryngoscopy allows visualization of the epiglottis but not the larynx (a grade 3 view)
- visualization of the larynx is possible but direct passage of the tracheal tube is prevented by awkward oral anatomy or teeth
- a reinforced or flexible tracheal tube cannot be directed into the visualized larynx.

Aintree intubation catheter (Cook©) (Figure 3) can be used like a gum elastic bougie, or in combination with other airway and intubating devices such as the LMA or FFL. It is sufficiently long and thin to allow a tracheal tube to be railroaded over it. It is hollow and has a detachable tube connector/adaptor that allows ventilation during the intubation process. An FFL can also be passed through it if required.





a Flexible fibre-optic laryngoscope and Aintree intubation catheter passed through the laryngeal mask airway (LMA).
b Fibre-optic endoscopy through the LMA with the Aintree exchange catheter.

3

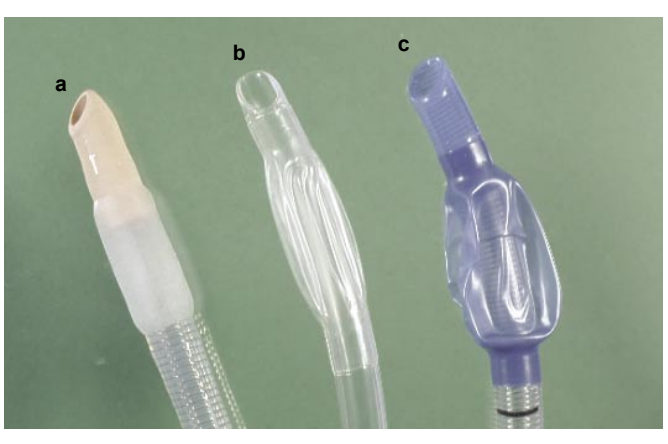
LMA and ILMA
Most anaesthetists use the LMA regularly for patients not requiring intubation. The ability to insert an LMA to allow spontaneous or assisted ventilation is a core skill for anaesthetists. It also provides a route guide for intubation, either blind or guided by an FFL. The LMA may help to achieve ventilation in patients who are otherwise difficult to intubate and ventilate.

The ILMA is modified to improve the chances of passing a tube blindly through the mask into the trachea. There is an initial short learning curve for the operator, and the clinician should practise using the ILMA in patients with normal airways before it is used in those with difficult or abnormal ones.

The main limitation on both devices is that there has to be enough mouth opening to permit inserting the device. Intubation can be blind, but both devices can be used with an FFL to visualize laryngeal anatomy and aid intubation.

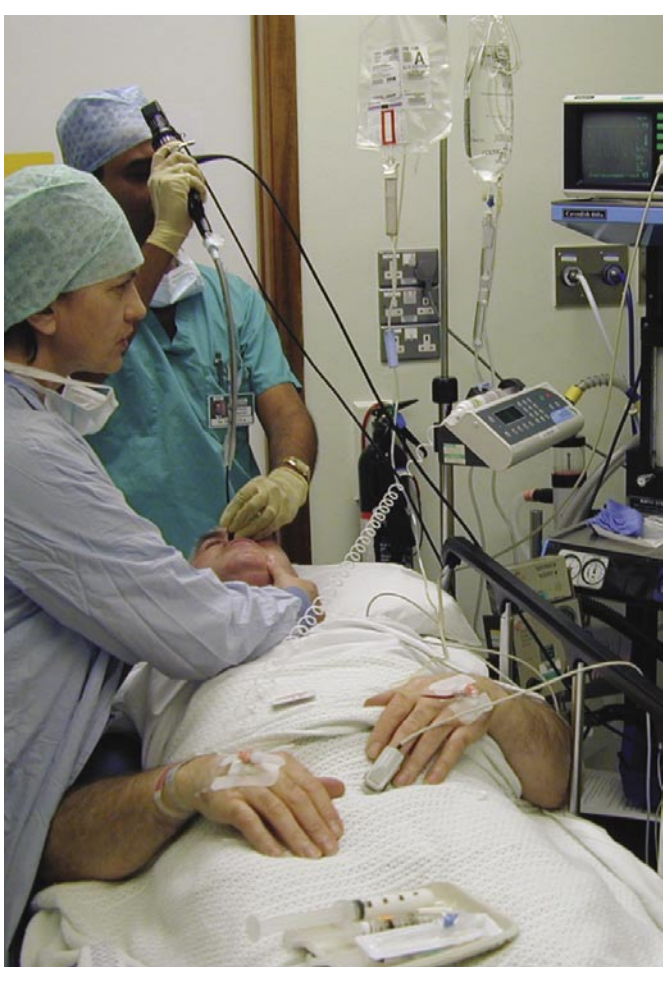
Railroading the tracheal tube
The need to railroad the tracheal tube over the guide is the final step in intubation. Two manoeuvres to increase its success rate and minimize laryngeal trauma are choice of tracheal tube and bevel direction.

- The ILMA tube (softer tip) or reinforced tracheal tube (less acute bevel and softer tip) has a higher chance of passing through the vocal cords (Figure 4).
- The bevel of the standard tracheal tube is directed to lie in the right or left lateral position as it reaches the vocal cords. It is then rotated 90° as it is pushed gently through the cords. If this is unsuccessful, the tube is rotated through 360° continuously with gentle pressure to slip through the cords. If still unsuccessful, direct laryngoscopy can be performed to check the position of the route guide, and to lift the epiglottis to facilitate tube railroading.



4 Tracheal tube tips. **a** The intubating laryngeal mask airway tube, **b** standard tube, and **c** the flexometallic tube

FFL and intubation
FFL and intubation can be performed with the patient awake or anaesthetized. Awake fibre-optic intubation performed by a competent endoscopist is safe (Figure 5). The patient remains awake and self-ventilating with maintained pharyngeal muscle tone.



5 Awake fibre-optic intubation. Note the use of propofol sedation and jaw thrust.

Suggested procedure for awake fibre-optic intubation
1 Premedication of morphine, 0.1–0.15 mg/kg i.m., and hyoscine (scopolamine), 200 µg i.m., 1 hour before procedure.
2 The patient should lie semi-reclined on a trolley in the anaesthetic room, facing the anaesthetist.
3 Intravenous sedation should be administered cautiously. Target-controlled infusion with propofol (plasma concentration 0.5–1.5 µg/ml) is well tolerated.
4 Topical anaesthesia of the upper airway should be provided:

- Nasal mucosa; mixture of 5% cocaine, 2 ml, and 8.4% bicarbonate, 2 ml, as topical spray, with the patient taking deep breaths in with each spray. If the patient requires orotracheal intubation the oropharynx can be anaesthetized with lidocaine (lignocaine) spray or gel. Oropharyngeal route guides (e.g. *Ovassapian* or *Berman* airway) can be used to aid orotracheal intubation. These allow the operator to pass the FFL and tracheal tube through them. They prevent soft tissue collapse and are sized to guide the FFL through the mouth, and emerge at the epiglottis, where it can be directed into the larynx.
- Spray as you go (SAYGO) with 4% lidocaine (lignocaine) through the working channel of the FFL. Insertion of an epidural catheter through the working channel to the tip of the scope, with the catheter end trimmed to produce one end-hole, can facilitate accurate delivery of the local anaesthetic injection. Inject 1 ml solution with 4–5 ml air to help disperse the anaesthetic. Before the first attempt to pass the FFL, and before each subsequent attempt, oropharyngeal suctioning with a Yankaur sucker may be required.
- Administer supplemental oxygen. This can be delivered conveniently via a flexible suction catheter passed into the opposite nostril.

5 Allow adequate time (at least 30 seconds) after topicalization before the FFL is advanced. Avoid passing the FFL blindly. If the view ahead becomes obscured, gently withdraw the insertion cord until airway anatomy is again identified. Ask the patient to take deep breaths when advancing towards the laryngeal inlet. This opens the airway and abducts the vocal cords. If visualization of the larynx is difficult, performing a gentle jaw thrust manoeuvre on the patient can help.
6 Once the scope has been advanced through the cords it should be advanced to just proximal to the carina. A common error is to allow the FFL to withdraw, or even become displaced from the trachea while the tube is railroaded into place. This happens more often if the patient coughs at this time. The operator should attempt to keep the FFL in the centre of the airspace at all times. This minimizes trauma to the delicate tracheal mucosa and reduces the amount of blood in the airway.
7 Railroading the tracheal tube is described above. It is helpful for the assistant to hold the FFL stationary allowing the operator to railroad the tube into place using both hands.
8 A final useful check to estimate the distance from the end of the tracheal tube to carina can be performed as follows. Once intubation has been performed, the FFL is passed down just proximal to the carina. The assistant lightly pinches the FFL as it enters the proximal end of the tracheal tube. The FFL is then withdrawn slowly until the distal end of the tracheal tube comes into view. As soon as this is seen, the distance from the assistant's fingers to the tube connector of the tracheal tube is noted. This is the distance from tip of tube to carina.
9 The breathing system with capnograph is connected. The patient may then be anaesthetized and laid flat. Satisfactory ventilation is confirmed, and muscle relaxant can be given if required.

Problems with flexible fibre-optic intubation: the FFL is an intubating tool, not a ventilation device. Oxygenation and ventilation must be maintained throughout the intubation procedure.

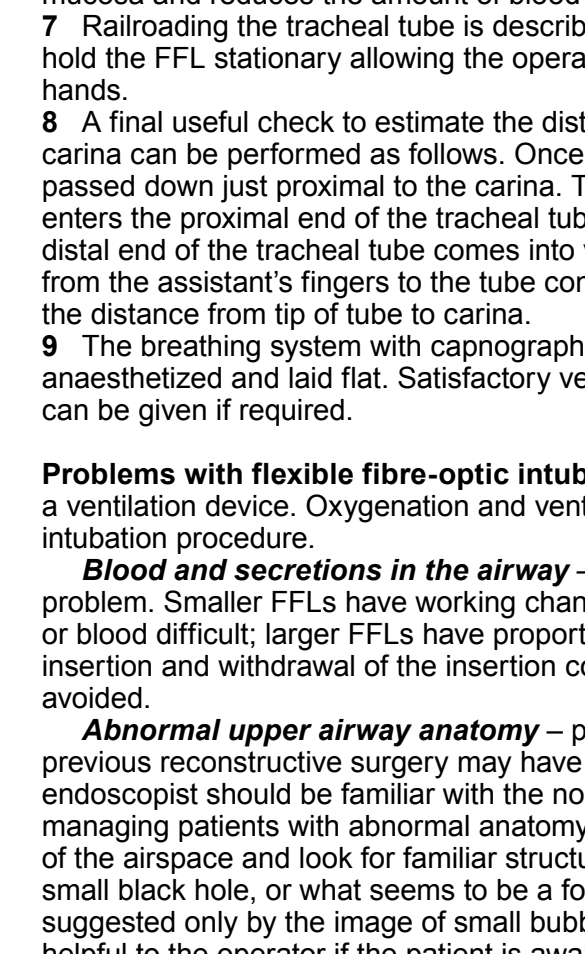
Blood and secretions in the airway – a poor view is the endoscopist's main problem. Smaller FFLs have working channels that make suctioning of sticky secretions or blood difficult; larger FFLs have proportionally larger suction channels. Repeated insertion and withdrawal of the insertion cord may precipitate bleeding and should be avoided.

Abnormal upper airway anatomy – patients with oro-pharyngeal lesions or previous reconstructive surgery may have abnormal upper airway anatomy. The endoscopist should be familiar with the normal appearances through the FFL before managing patients with abnormal anatomy. In all patients, keep the FFL in the centre of the airspace and look for familiar structures. Often the larynx is identified only as a small black hole, or what seems to be a fold in the mucosa. Identification is sometimes suggested only by the image of small bubbles appearing from a dark crevice. It is helpful to the operator if the patient is awake, semi-recumbent, and cooperating by taking deep breaths.

Equipment problems – the FFL should be checked and cleaned before use.

- The tracheal tube should be loaded on the FFL before endoscopy; forgetting to do this is a common mistake.
- Ensure that the light is on and working with white balance and focus optimal before commencing endoscopy.
- Lubricating jelly should be applied to the outside of the scope, and the tracheal tube, to facilitate easy nasal passage and tracheal intubation.
- Difficulties in railroading the tracheal tube can sometimes result from a large difference in the external diameter of the scope and internal diameter of the tracheal tube. This may be overcome by use of the Aintree intubation catheter. The intubation catheter can be railroaded over the scope, and then the tracheal tube railroaded over this.

Lack of hand–eye coordination can be remedied by practice on simulators, manikins and learning models such as an artificial bronchial tree or the Oxford 'hit-the-hole' box (Figure 6). It is indefensible to acquire these basic skills at the expense of the patient's mucosa.



6 The Oxford 'hit-the-hole' training box.

An inability to recognize anatomy is easily addressed by experience gained from instructional videos, clinical teaching and supervision. The case for using an FFL to aid routine nasal intubation is robust. In addition to the excellent learning opportunity afforded by routine use of the FFL, it assists in the selection of the best nostril and largest airspace, and identifies vulnerable nasal pathology such as polyps.

Transtracheal access

The final route for rescuing an obstructed airway is direct transtracheal access. This can be through the cricothyroid membrane, or through the upper trachea. Most anaesthetists never need to resort to this. Elective procedures, such as cricothyroid puncture used to inject local anaesthetic, or performing percutaneous tracheostomies in the ICU, provide valuable experience in tracheal access. The ability to identify the cricothyroid membrane and to insert a cricothyroid airway catheter rapidly may be a life-saving procedure. See Anaesthesia and Intensive Care Medicine issue 2:7: 268 for discussion of emergency tracheal access.

FURTHER READING

Latto I P, Vaughan R S, eds. *Difficulties in Tracheal Intubation.* 2nd ed. Philadelphia: WB Saunders, 1997.

Popat M. *Practical Fibreoptic Intubation. Oxford:* Butterworth-Heinemann, 2001.

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Airway Control

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Securing control of the airway is one of the most important skills required of the anaesthetist. Whether for elective or emergency surgery, and whether the need for airway control has been predicted or not, the safety of the patient depends on the anaesthetist's ability to intervene to ensure adequate oxygenation and ventilation should the need arise. The anaesthetist must:

- develop the skills of airway assessment and management
- be familiar with the equipment and techniques available for control of the airway
- be able to choose the appropriate measures for the individual patient.

This contribution focuses on these basic principles.

Assessment of the airway

The anaesthetist must assess the airway before undertaking any anaesthesia. When general anaesthesia is contemplated, assessment facilitates a planned approach to anticipated difficulties with laryngoscopy and intubation. When a regional or local technique is contemplated, the need for airway intervention may also arise, for example, following respiratory embarrassment as a result of a high spinal or epidural blockade level, over-zealous sedation, or more rarely, following an allergic reaction to a drug.

The patient's previous anaesthetic notes should be consulted if available. It is important to realize, however, that the patient's circumstances may have changed, and a previously easy intubation may have become difficult (e.g. as a result of pregnancy). A number of anatomical factors are associated with difficulty in laryngoscopy and intubation:

- obesity, pregnancy
- large protruding incisor teeth
- short neck, especially in a heavy patient
- reduced mobility of the neck (e.g. rheumatoid arthritis)
- instability of the neck
- reduced mouth opening
- intraoral masses
- large goitre.

Anatomical assessment

Whether laryngoscopy and intubation would be possible with reasonable ease should be assessed using a reliable and reproducible bedside method of airway assessment that has minimal false-positive and false-negative rates. No single test provides this information, but the modified Mallampati test in conjunction with an assessment of thyromental distance combines ease with reasonable accuracy.

The modified Mallampati test assesses the size of the base of the tongue in relation to the size of the oropharynx. The patient sits upright with the head in the neutral position. The assessor sits in front of the patient at the patient's eye level. The patient opens their mouth as wide as possible. Without phonating, the tongue is protruded as far as possible. The assessor inspects the pharyngeal structures visible and a score is allocated according to which structures are visible (Figure 1).

Modified Mallampati test

Class	Pharyngeal structures visible
1	Fauces, faucial pillars (the palatoglossal and palatopharyngeal arches), uvula, soft palate
2	Faucial pillars are obscured leaving the fauces, uvula and soft palate visible (i.e. posterior pharyngeal wall visible below soft palate)
3	Only the soft palate and the base of the uvula seen (i.e posterior pharyngeal wall not visible below soft palate)
4	Even the soft palate obscured

1

The measurement of thyromental distance as recommended by Frerk is obtained by maximally extending the head on the neck and measuring from the prominence of the thyroid cartilage to the bony point of the chin.

A modified Mallampati grade of 3 or 4 combined with a thyromental distance of 7 cm or less gives a bedside assessment system with a sensitivity of 81% and a specificity of 98% for difficulty with intubation.

The view of the laryngeal structures obtained at direct laryngoscopy is often classified according to the system described by Cormack and Lehane (Figure 2). In this system, grades 3 and 4 constitute difficult laryngoscopies. Fairly severe difficulty with intubation may occur with grade 3, and the use of a bougie/introducer, posterior to, but held up against the epiglottis may permit blind intubation. With a grade 4 view, intubation by standard methods is virtually impossible despite optimal positioning.

Cormack and Lehane classification system

Grade	Laryngeal structures visible
1	Most of the glottis visible
2	Only the posterior part of the glottis (posterior commissure, arytenoid cartilages) visible
3	Only the epiglottis visible, no part of the glottis seen
4	Not even the epiglottis seen

2

Airway patency

Partial obstruction of the airway in the awake patient may be caused by masses in the upper airway (e.g. tonsils, adenoids, tumour), foreign bodies, or epiglottitis. In the sedated or unconscious patient, laxity of the muscles that normally keep the tongue anterior to the posterior pharyngeal wall allows the tongue to fall back and obstruct the airway. Partial obstruction is recognized by noisy inspiration (stridor), tracheal tug, and dyssynchronous movements of the thorax and abdomen on inspiration.

In normal, unobstructed breathing, the abdomen expands as the diaphragm descends in inspiration and the thorax expands as indrawn gas fills the lungs. With obstruction, the abdomen still expands, but if inspired gas cannot be inhaled at a sufficiently fast rate, the sternum is drawn inwards by the increasing, unrelieved negative intrathoracic pressure. Partial obstruction and its cause (and therefore ease of reversal) must be recognized before embarking on anaesthesia. The technique of airway management is highly modified in the presence of partial obstruction.

Aspiration risk

For elective anaesthesia, the patient is fasted. Solid food, non-clear liquids (especially those containing milk) and chewing gum should not be consumed in the 6 hours before anaesthesia. Clear liquids are permissible up to 2 hours before induction.

For emergency anaesthesia, the interval between last food or drink and the injury or onset of illness is assessed. Gastrointestinal obstruction or other abnormal motility state (e.g. ileus, diabetes mellitus, renal failure, acute pain) all increase the risk of aspiration on induction of anaesthesia.

Equipment and techniques for routine airway management

Before embarking on general anaesthesia, the equipment required should be to hand and its correct function checked. A preoperative checklist such as that proposed by the Association of Anaesthetists of Great Britain and Ireland is particularly useful (see *Anaesthesia and Intensive Care Medicine* **1:2:** 65). The minimum equipment required includes:

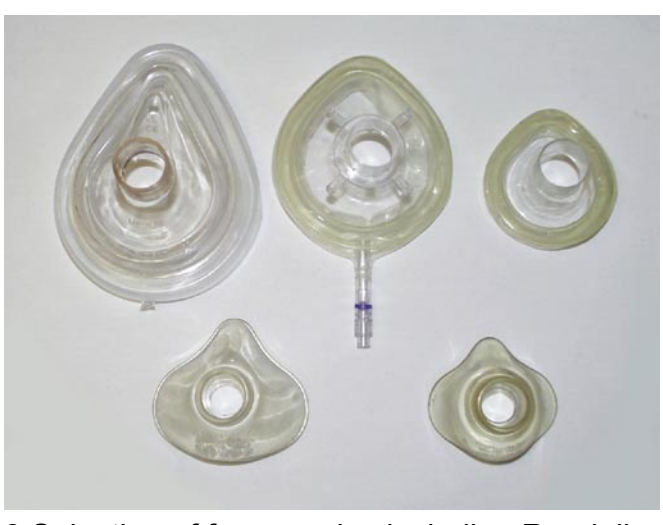
- source of pressurized oxygen (plus bag-valve-mask or anaesthesia circuit)
- selection of face masks
- selection of oropharyngeal and nasopharyngeal airways
- high-flow suction
- Yankauer suction catheter, and selection of narrow-bore suction catheters
- two laryngoscopes
- selection of tracheal tubes
- selection of laryngeal mask airways
- Magill's forceps
- sterile lubricating gel
- ties and padding to secure tracheal tube
- gum-elastic or other suitable bougie.

For non-emergency anaesthesia, several interventions to control the airway are available. These range from oxygen administration through a face mask, delivery of inhalational anaesthesia via an anaesthetic face mask or laryngeal mask airway, through to tracheal intubation.

Non-relaxant anaesthesia

If relaxant anaesthesia is not required (e.g. for body-surface surgery in the patient not at risk for aspiration) then inhalational anaesthesia via a face mask is appropriate. In the absence of flammable anaesthetic agents, the mask is usually clear plastic with an inflatable rim that provides a good seal in contact with the face. The size of the mask is determined by the patient's size and physical features, but a range of sizes (Figure 3) should be available. For paediatric anaesthesia, the mask should have as little dead space as possible (e.g. the Rendell-Baker–Souchet mask). Nasal masks are indicated for anaesthesia in the dental chair.

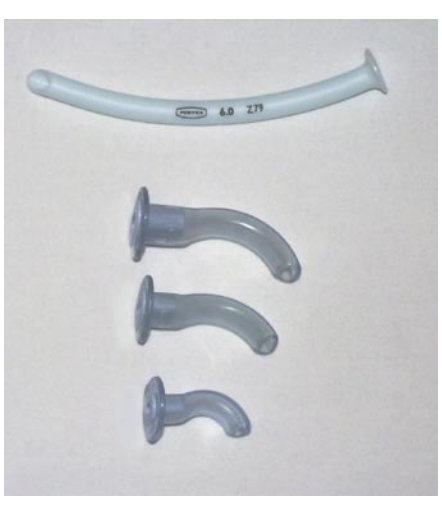
Induction in the absence of airway obstruction may be inhalational or by intravenous injection of a suitable induction agent. If there is any suggestion of airway obstruction then inhalational induction or another approach (e.g. awake fibre-optic intubation) is required.



3 Selection of face masks, including Rendell-Baker–Souchet paediatric masks (lower row).

Supporting the airway

Whatever the means of induction, once the patient is unconscious it is necessary to support the airway. There is a tendency for the airway to become partially obstructed at this stage because the tongue falls back against the posterior wall of the pharynx. Induction will normally have occurred with the patient supine, head resting on a pillow. This allows the anaesthetist to extend the head on the neck at the same time as applying a jaw thrust and opening the mouth. To achieve this triple manoeuvre, the mask is secured on to the face using one or both hands, with the thumbs on the upper part of the mask, index fingers on the lower part and the rest of the fingers effectively pulling the patient's mandible forward into the mask. It is crucial that unopposed downward pressure on the mask is not used to obtain a seal between mask and face because this will close the airway. Likewise, the third, fourth and fifth fingers must stay on the mandible and must not press on the floor of the mouth, which also tends to cause obstruction. If it is impossible to open the airway using these techniques, an artificial airway is required. Two methods are available: the oropharyngeal and the nasopharyngeal airway (Figure 4).



4a Nasopharyngeal airway.
b Selection of smaller oropharyngeal airways.

The oropharyngeal (Guedel) airway is a curved tube that has a flanged and reinforced oral end. The flange enables correct positioning at the incisor teeth, and the reinforcement prevents the patient from obstructing or severing the device by biting down. This airway is available in a range of sizes (size 3–4 is usually required for an adult, Figure 4b), and it is vital that the appropriate size is used for the patient. An easy way to determine size is to choose the airway in which the length is equal to the distance between the corner of the patient's mouth and the angle of the jaw. If the airway is too short it tends to push the tongue backwards and cause increased obstruction. If too long, the device tends to stimulate the larynx, provoking spasm, and it fails to sit securely with the flange at the front incisors. The Guedel airway is usually inserted upside-down (the pharyngeal opening facing the roof of the mouth, then rotated 180° as it passes the back of the tongue). A lightly anaesthetized patient may gag or cough with this intervention. It may also provoke laryngeal spasm.

The nasopharyngeal airway is a less stimulating intervention. It is a soft curved tube with a flanged nasal end and a bevelled pharyngeal end (Figure 4a). It is also available in a range of sizes. Sizes 6–8 mm (measured as internal diameter) are suitable for adults, the usual measure is the diameter of the patient's little finger. Before inserting the airway, a safety pin is inserted eccentrically at the flanged end, to prevent inhalation of the device. The airway should be coated with lubricating gel, and inserted into either nostril. It is advanced along the floor of the nose in a posterior direction, and should come to lie with the bevelled end in the oropharynx, behind the tongue and above the glottis. The eccentric positioning of the pin permits access of a catheter for suctioning secretions from the pharynx and airway.

Face mask: for brief procedures, anaesthesia can be maintained using a face mask, with or without airway adjuncts. For longer procedures, when it is desirable for the anaesthetist to have both hands free, the standard mask can be supported by a harness. It is now more common to insert a laryngeal mask airway for such procedures. This has the advantage of maintaining the airway without additional instrumentation, in addition to providing a more secure airway and providing hands-free operation.

The laryngeal mask airway (LMA) was designed to provide a connection between the artificial and anatomical airways in a less invasive way than with a tracheal tube, and yet with greater convenience and reliability than a conventional face mask. The standard LMA is made from silicone and is designed for multiple patient (up to 40) uses. It consists of a silicone bowl surrounded by a thin-walled elliptical ring that can be deflated to form a thin wedge shape, and which when inflated in the space posterior to the pharynx creates a seal around the laryngeal aperture. This seal permits ventilation of the airway under positive pressure. It also prevents insufflation of gas into the oesophagus and stomach, unless high inflation pressures (20–30 cm H_2O) are used. The device has a central aperture, with vertical bars, designed to prevent prolapse of the epiglottis into the tube that connects the mask to the anaesthetic circuit.

The LMA is available in a variety of sizes (Figure 5).

Correct placement is important to ensure a high-performance seal without overinflation of the cuff, and the appropriate size is chosen for the size of the patient (Figure 6).

The LMA is also available with a flexible, reinforced, non-kinking tube instead of the standard tube. This type is particularly useful for situations in which the head may be moved during surgery and for oral and ENT surgery. The intubating LMA is a development of the standard airway designed to act as a conduit permitting blind intubation of the trachea using a specially designed silicone tube.

A full description of the recommended technique for inserting the LMA is beyond the scope of this contribution. Briefly, the device is completely deflated (preferably using a cuff deflation tool, which will ensure deflation to the correct shape). The patient's head is supported on a pillow, in the classic intubating position. Extension of the head and flexion of the neck on the thorax is achieved by the non-dominant hand. The posterior surface of the LMA is lubricated with water-soluble gel. The LMA is held between index finger and thumb, with the index finger of the operator's gloved dominant hand at the junction of the mask and the tube. The aperture of the device faces caudally. An assistant holds the patient's mouth open, and the device is inserted under direct vision, with its posterior, lubricated surface firmly against the hard palate. The LMA is pushed, keeping it firmly against the palate at all times following the palate posteriorly and down into the hypopharynx. Resistance to insertion is met when the tip of the device is in the hypopharynx, with the tip resting at the upper oesophageal sphincter. It may be necessary to push the device using the non-dominant hand, if the inserting finger is not long enough. The device is released. The cuff is inflated with the recommended volume of air, at which point the tube may rise from the mouth as the device seats itself around the larynx. The tube of the LMA is connected to the anaesthetic circuit, if necessary using a swivel connector.

The LMA may be used to ventilate the anaesthetized muscle-relaxed patient, provided that the inflation pressures do not exceed about 20 cm H_2O. Above this pressure, the risk of gradual insufflation of the stomach with anaesthetic gas increases. This increases the risk of regurgitation and aspiration of gastric contents.

5a Standard laryngeal mask airways, sizes 2½, 3, 4. **b** Reinforced laryngeal mask airway, size 4.

Relaxant anaesthesia

Anaesthesia requiring a muscle-relaxant technique most commonly requires tracheal intubation. Indications for relaxant techniques and/or intubation are:

- provision of clear airway
- airway protection from blood, oral or gastric secretions
- facilitation of suctioning of airway
- prone or sitting patient, airway inaccessible
- abdominal, thoracic anaesthesia
- likelihood of postoperative respiratory support
- administration of positive end-expiratory pressure.

Tracheal intubation

Equipment: in addition to the equipment for inhalational anaesthesia using a face mask, a suitable laryngoscope, with a spare available, and a range of suitable tracheal tubes are necessary.

The laryngoscope consists of a handle (which houses the batteries) and a detachable blade, which has a screw-in bulb. Alternatively, the bulb may be in the handle, and a fibre-optic bundle transmits the light to the blade. Two basic types of laryngoscope are available (Figure 7):

- curved-blade (usually Macintosh)
- straight-blade (e.g. Wisconsin, Seward, Magill).

The curved-blade instruments are most commonly used for adults and larger children: the tip is placed in the vallecula, anterior to the epiglottis. Forward traction elevates the epiglottis without touching the posterior surface of the epiglottis. By contrast, straight-blade laryngoscopes are inserted posterior to the epiglottis and lift it from behind. These instruments are most often used for smaller children, because the epiglottis is longer and more floppy in this age group. The blades are available in a number of sizes, with the Macintosh 3 being suitable for most adults.

Tracheal tubes – an extensive range of tracheal tubes is available (Figure 8). They are most commonly made from polyvinylchloride or polyurethane and are bevel-ended. They may be plain or have a high-volume low-pressure cuff, which provides a seal enabling positive-pressure ventilation and preventing aspiration of secretions into the airway. Uncuffed (plain) tubes are used in children. This avoids the potential for ischaemic damage on the tracheal lining from high cuff pressure and maximizes tube size available. The presence of an air leak around the plain tube ensures that the fit is not too tight.

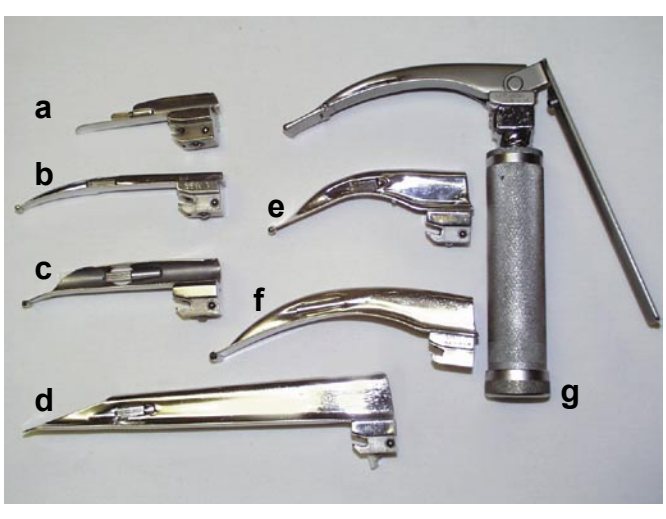
Tracheal tubes are usually inserted via the mouth, or if necessary via the nose (e.g. for intraoral surgery). Tube size is measured by the internal diameter, ranging from 2.5 mm to about 10 mm in 0.5 mm increments. The tube is usually cut to the appropriate length for the patient. Adult males usually require size 8–9 mm and adult females 7–8 mm, cut to 21–23 cm for oral intubation. For children, the tube size can be estimated from the formula (age/4 + 4 mm), and length (age/2 + 12 cm), with age being in years. This is an approximate size, and tubes 0.5 mm greater than and less than the estimated size should be available.

The tube is connected to the anaesthetic circuit at the proximal end with a tapered connector of suitable size (see *Anaesthesia and Intensive Care Medicine* **1:2:** 68). The distal end may have, in addition to the end hole, a side opening (Murphy eye) to allow passage of gas should the bevelled end be occluded by abutting on the tracheal wall.

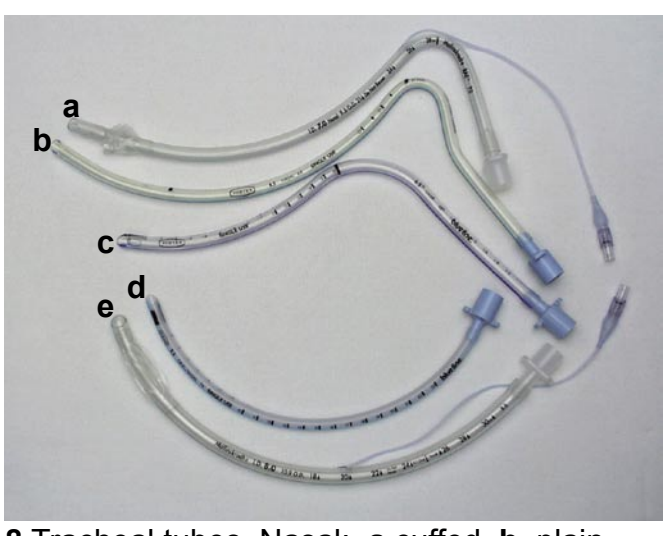
Sizes of laryngeal mask airway

Size	Patient	Cuff volume (ml)
1	Neonates up to 6.5 kg	4
2	Patients 6.5–20 kg	10
2½	Patients 20–30 kg	14
3	Children and small adults	20
4	Normal adults	30
5	Large adults	40

6



7 Selection of straight- and curved-blade laryngoscopes. **a** Wisconsin, **b** Seward, **c** Oxford, **d** Soper, **e** Macintosh size 2, **f** Macintosh size 3 **g** McCoy laryngoscope.



8 Tracheal tubes. Nasal: **a** cuffed, **b** plain. Oral: **c** North-facing plain polar. Magill pattern oral tubes: **d** plain, **e** cuffed.

Anaesthetic management

Positioning the patient correctly before intubation is crucial. Tracheal intubation requires approximate collinearity between the axes of the mouth, oropharynx and larynx. True collinearity of these structures is impossible, but appropriate positioning can make the difference between a relatively easy laryngoscopy and intubation, and failure to visualize the larynx at laryngoscopy. The classic intubating position is the sniffing position: the head is extended on the neck (atlantoaxial extension) and the neck is flexed on the thorax. For most adults this is easily achieved by having the patient lie supine on the trolley or bed and placing a pillow under the occiput. If the pillow is too caudad (elevating the shoulders) then extension of the neck on the thorax occurs. This almost always makes laryngoscopy more difficult. In small children, the relatively large head provides the correct position without the use of a pillow.

Induction – if the patient is not at risk of aspiration of gastric content, difficulty with laryngoscopy is not anticipated, and the airway is unobstructed, induction of anaesthesia is as for the mask techniques outlined above. Following induction, it is possible, providing the patient is deeply anaesthetized, to perform laryngoscopy and intubation. This practice is relatively uncommon. More usually, the anaesthetist confirms that it is possible to ventilate the patient using the mask (with an artificial airway if needed). Then an intubating dose of a muscle relaxant is given (e.g. suxamethonium, 1–1.5mg/kg). While the advantages of the speed of onset and quality of relaxation

obtained with suxamethonium are significant, its side-effects include myalgia (which can be quite severe), occasional profound bradycardia (especially in children, and particularly likely with second doses of the drug given shortly after a first dose), hyperkalaemia, and precipitation of malignant hyperthermia in susceptible individuals. To overcome these disadvantages, an intermediate-duration non-depolarizing drug such as vecuronium, 0.1 mg/kg, atracurium, 0.5 mg/kg, or rocuronium, 0.6 mg/kg, can be used. However, they commit the anaesthetist to providing ventilation by mask for a prolonged period if intubation proves more difficult than anticipated, or is impossible. With the exception of rocuronium they also take a longer time to achieve good intubating conditions, which makes them much less suitable for the patient at risk of aspiration of gastric content. The lungs are usually manually ventilated while awaiting the onset of muscle relaxation. A mixture of oxygen and the volatile agent chosen to maintain anaesthesia is used, together with nitrous oxide, if desired. The use of nitrous oxide reduces the interval allowable for laryngoscopy and intubation. The patient will become hypoxaemic more rapidly following cessation of ventilation if this gas is used, because available oxygen stores will be reduced. A peripheral nerve stimulator may be used to confirm the presence of adequate paralysis, as demonstrated by the absence of twitch response to a supramaximal stimulus.

Laryngoscopy is then performed. The right hand opens the patient's mouth and the assistant separates the patient's lips to expose the teeth. Using a curved-blade laryngoscope, held in the left hand, the blade is inserted into the right-hand side of the mouth, and advanced as far as the tonsillar bed. Sweeping the blade into the midline at this point should displace the tongue to the left, and give a view of the tip of the epiglottis. The blade is advanced, with force applied along the shaft of the laryngoscope directed upwards and outwards (at about 30–45° to the horizontal). The patient's upper incisors or gum must not be used as a fulcrum. The tip of the blade should enter the vallecula in front of the epiglottis, and the applied force elevates the epiglottis, exposing the larynx. The tracheal tube is picked up in the right hand and advanced from the right-hand side of the mouth, using the natural curvature of the tube to place the tip in the larynx under direct vision. Once the cuff of the tube is safely past the cords, the laryngoscope is carefully removed. The anaesthetic circuit is connected to the tube using a swivel connector and a catheter mount (if desired). The lungs are ventilated and the cuff of the tube inflated with just sufficient air (or gas mixture) to abolish the audible leak of gas on inflation of the lungs. Bilateral breath sounds and absence of sounds of gastric insufflation help confirm placement, however monitoring for appropriate and continuous concentration of carbon dioxide in the exhaled gas is mandatory.

Extubation – anaesthesia is maintained with inhalational agents, and the patient is ventilated using intermittent positive-pressure ventilation throughout the operation. At the end of the operation, residual neuromuscular blockade is reversed using a combination of a cholinesterase inhibitor and a muscarinic blocking drug (to prevent bradycardia). The drugs most commonly used are neostigmine, 0.05 mg/kg, with either atropine, 0.02 mg/kg, or glycopyrrolate, 0.01 mg/kg. Secretions and occasionally gastric content will have accumulated in the pharynx during the procedure. To prevent aspiration of these secretions and severe laryngeal spasm on removal of the tracheal tube, these are removed using a Yankauer sucker or equivalent, under direct vision (with a laryngoscope). The patient is ventilated with 100% oxygen. As the patient starts to breathe, the circuit is changed to permit spontaneous ventilation, with the reservoir bag providing visible confirmation of ventilatory effort and volume.

The tracheal tube is removed when the patient is breathing adequately and has regained protective airway reflexes (the patient is actively resisting the presence of the tube). The patient may be extubated in the supine position if the anaesthetist is satisfied that a clear airway can be maintained and the patient is not at risk for aspiration. If the patient is at risk, then extubation should take place in the lateral position, with the patient as fully awake as possible. Extubation should be performed during inspiration. Having deflated the cuff of the tracheal tube, the bag on the anaesthetic circuit is squeezed to expel secretions above the cuff into the oropharynx, away from the vocal cords. The tube is removed in a smooth movement, the breathing circuit rapidly reconnected to an anaesthetic mask, and the mask closely applied to the face.

Partial obstruction of the airway may occur at this stage if the tongue falls back into the pharynx, or more often because of mild laryngeal spasm. It may respond to the application of positive end-expiratory pressure. This may be achieved by partially closing the exhaust valve on the anaesthetic circuit, but the airway pressure must be monitored. If the airway is obstructed by the tongue, then an oral or nasopharyngeal airway may be required to relieve the obstruction. When the patient is breathing adequately, he is transferred to the recovery room, ensuring that he breathes supplementary oxygen during the transfer.

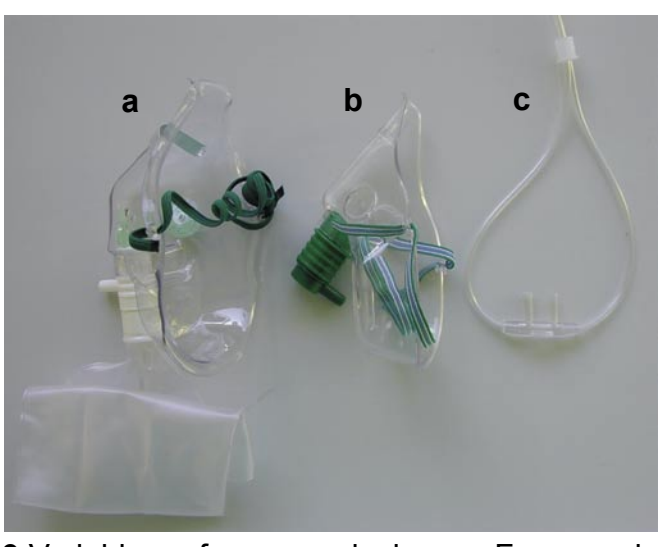
Recovery

Supplementary oxygen should be administered to all patients in the immediate recovery period. This is to prevent hypoxaemia that may otherwise occur from the ventilation–perfusion mismatch induced by surgery and anaesthesia, and the hypoventilation that may ensue from respiratory depressant drugs. Hypoxaemia may also be caused by dilutional hypoxia following cessation of nitrous oxide.

The duration of oxygen therapy may be limited to 15 minutes for young healthy patients undergoing minor day- case procedures, but extended for many hours or days for those with more serious pathology or complicated surgery. Therapy is guided by pulse oximetry or blood gas estimation, and oxygen therapy is usually titrated to achieve oxygen saturation greater than 95%.

Oxygen therapy devices may deliver either a variable or fixed concentration of supplementary oxygen to the inspired gas.

Variable performance devices include nasal prongs and simple 'Hudson'-type face masks with or without an oxygen reservoir (Figure 9). The oxygen flow delivered to the device is typically 2–4 litres/minute, which will be diluted by the air entrained during inspiration. The concentration of inspired oxygen depends on the oxygen flow rate, the patient's respiratory rate and peak inspiratory flow. Typically, 30–40% inspired oxygen is achieved when 4 litres/minute is delivered to a patient via a Hudson mask, and this concentration reduces as respiratory rate and inspiratory flows increase, due to increased air entrainment. The oxygen concentration delivered cannot be predicted accurately. This is usually of no consequence to a patient on the recovery ward, who simply needs supplemental oxygen, though the precise concentration is not critical. The inspired oxygen percentage can be increased further if an oxygen reservoir is used with the mask, and 80% inspired oxygen may then be achieved using a 12–15 litres/minute oxygen flow rate.

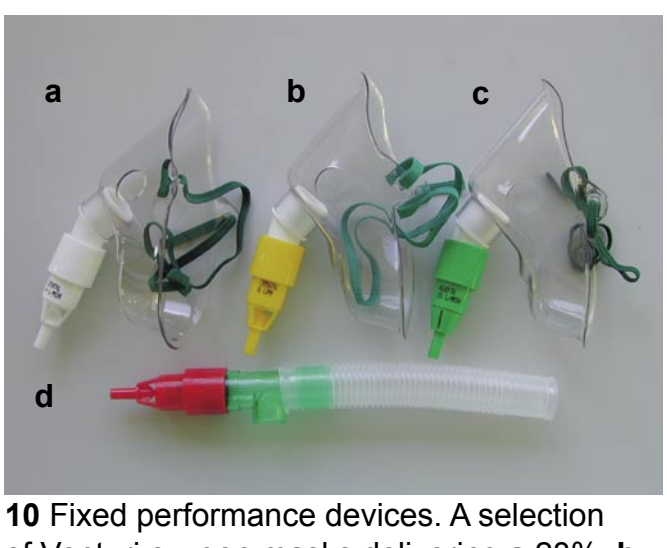


9 Variable performance devices. **a** Face mask with oxygen reservoir bag (folded); **b** simple Hudson-type oxygen face mask; **c** nasal prongs.

Fixed performance devices include face masks with Venturi-type injectors (Figure 10). They achieve a fixed inspired oxygen concentration by ensuring that a high flow rate of oxygen and entrained air is delivered, in excess of the patient's maximum peak inspiratory flow rate.

The use of a Venturi injector face mask delivers about 60 litres/minute of gas and so the inspired oxygen concentration is independent of the characteristics of inspiratory flow. Venturi devices are available to deliver fixed oxygen concentrations between 24% and 60%. The correct oxygen flow rate must be selected for the correct Venturi injector, and used with the correct mask. Details are printed on each Venturi, but typically 2 litres/minute delivers 24% oxygen, and 8 litres/minute delivers 35% oxygen. Venturi injector devices are not interchangeable with masks from different manufacturers, because the mask volume allows for adequate mixing of driving and entrained gases.

Fixed performance devices are often used in the high-dependency setting to enable accurate assessment of oxygenation, in patients with chronic lung disease who depend on a hypoxic respiratory drive, and on the general wards.



10 Fixed performance devices. A selection of Venturi oxygen masks delivering **a** 28%, **b** 35%, **c** 60% oxgen. **d** Venturi T-piece delivering 40% oxygen for use with laryngeal mask airway, tracheal tube or tracheostomy tube.

Anaesthesia for Laparoscopic Surgery

Michael W Platt

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Laparoscopic surgery is a revolution in modern surgical techniques and has reduced postoperative pain, respiratory complications and hospital stay considerably. However, it produces extra stresses on the heart and lungs, therefore patients should be screened carefully and the risks explained fully as part of obtaining consent for the procedure. Anaesthetists should consult their surgical colleagues about the relative risks in those with cardiac and respiratory disease and should be prepared to cope with complications as they arise.

History

The earliest recorded references to endoscopy are from Hippocrates in Greece (460–375 BC), who made reference to a rectal speculum. It was only in the 1970s that the problems of transmitting light, insufflation technology and optical technology were surmounted sufficiently for gynaecologists to embrace laparoscopic surgery. Laparoscopic techniques were not supported whole-heartedly by general surgeons until after 1987, when Mouret performed the first laparoscopic cholecystectomy in France. Following this, the rapid development of solid state video camera technology has further broadened the field of laparoscopic surgery.

The advantages of minimally invasive surgery are less ileus, the greatly reduced stress response to surgery and trauma, reduced acute phase reaction, reduced pain, reduced post-operative pulmonary dysfunction and reduced hospital stay. These also have economic advantages.

More procedures are being developed for laparoscopic surgery, including extraperitoneal inguinal hernia repair and retro-peritoneal nephrectomy and adrenalectomy. Routine general surgical laparoscopic procedures now include: oesophagectomy, Nissen's fundoplication, gastric banding, oversewing of peptic ulcer, intestinal resections, including hemicolectomy and col-ectomy, rectopexy and hernia repair.

Pathophysiology and complications of laparoscopy

The complications of laparoscopy include: haemorrhage, hypotension, decreased cardiac output, acidosis, pneumothorax, pneumomediastinum, subcutaneous emphysema, retroperitoneal carbon dioxide (CO_2), venous stasis, bradycardia, increased vagal tone, cardiac arrest, fatal venous CO_2 embolism, regurgitation and aspiration. Many of these complications are the result of peritoneal insufflation (pneumoperitoneum).

Pneumoperitoneum, the insufflation of the peritoneal cavity, is required to enable a gas milieu for visualization through the laparoscope (the operating telescope). CO_2 is used for laparoscopy because it is highly soluble in blood. Blood can carry large quantities of CO_2 as bicarbonate, carboxyhaemoglobin, and in plasma proteins. Carbon dioxide is eliminated rapidly and the lethal dose as an embolus is five times that of air. Usually a CO_2 gas embolism resolves rapidly, but if it is large, it can be fatal.

Pneumoperitoneum is achieved by insufflating the peritoneal cavity with CO_2 to a pressure of 10–18 mm Hg. The intra-peritoneal insufflation of CO_2 to these pressures causes respir-atory and haemodynamic changes.

Respiratory changes that occur as a result of pneumoperitoneum consist of a reduction of chest compliance by 30–50%. Airway pressures to maintain tidal volume rise to counter the reduction of chest compliance and the elevation of the diaphragm. Functional residual capacity of the lungs decreases and there is an increase in physiological dead space and shunt because of basal compression by the diaphragm and increased ventilation/perfusion mis-matching, which may result in a reduced arterial partial pressure of oxygen. Basal atelectasis may persist into the postoperative period. If minute volume is kept constant, end-tidal CO_2 increases due to absorption of CO_2 from the peritoneal cavity. The latter changes are usually countered by increasing the tidal volume and applying positive end-expiratory pressure (PEEP).

Haemodynamic changes also occur as a result of the pneumo-peritoneum. Compression of the inferior vena cava leads to a reduction in venous return, potentially followed by a fall in cardiac output. However, a reflex tachycardia and a massive increase in peripheral vascular resistance tends to maintain cardiac output at near-normal levels, by pulling blood centrally from the periphery, but with a concomitant increase in mean arterial blood pressure. This increase in myocardial work can result in myocardial ischaemia in those at risk and can lead to infarction, which may not occur until the postoperative period. Active vasodilatation and β blockade are often required to counter these effects.

Compression of the inferior vena cava causes reduced venous flow from the legs, resulting in venous stasis and an increased risk of venous thrombosis. Prophylactic anticoagulation and elastic stockings or pneumatic calf compressors should be used, especially in the elderly.

Respiratory and haemodynamic changes are affected by the patient's position. For example, head-up tilt, used for upper abdominal operations (e.g. cholecystectomy, Nissen's fundoplication) further inhibits venous return. Head-down tilt, used for colonic and pelvic surgery, promotes venous return, but aggravates respiratory changes, further reducing chest compliance and functional residual capacity and increasing basal compression.

Other complications of pneumoperitoneum include surgical emphysema, which can affect most tissues, including the conjunctivae and the scrotal sack. Cardiac arrhythmias can be secondary to vagal stimulation (bradycardia) or to hypercarbia (tachyarrythmias). Pneumothorax (including tension pneumo-thorax) may occur, particularly with upper abdominal procedures such as Nissen's fundoplication. Gastric reflux can occur because of increased intraperitoneal pressure, although retained gas in the stomach may obstruct the surgeon's view for upper abdominal operations. Pressure on the renal veins and arteries may cause a temporary reduction in renal function, due to reduced renal blood flow. Major CO_2 gas embolus seldom occurs and is usually the result of accidental direct injection of gas into a major vessel (e.g. the inferior vena cava). This may cause an obstruction to cardiac output when it reaches the heart. The treatment is to turn the patient onto the right side immediately and position them head down, causing the gas embolus to occupy the apex of the right ventricle, relieving the obstruction to ventricular outflow.

Anaesthetic technique

Preoperative assessment

Patients should be assessed carefully preoperatively, focussing on their cardiac function and reserve, because of the amount of extra cardiac work required during pneumoperitoneum. Patients with significant cardiac disease and limited cardiac reserve should be assessed by a cardiologist. It may be that an open procedure or even cancelling the procedure would be best for the patient. Patients with added risks of venous thrombosis should be treated prophylactically with fractionated heparin, elastic stockings and calf compressors during surgery. Surgery for patients with previously untreated hypertension should be postponed until treatment has stabilized. Respiratory function should also be assessed. Pulmonary function tests should be performed in those with significant pulmonary disease. Liver and renal function need to be ascertained because these organs may also be affected by pneumoperitoneum. Intercurrent medications (especially antihypertensives) should be given as normal on the morning of operation. A light sedative, such as a short-acting benzodiazepine, may be given before surgery.

Perioperative management

A routine intravenous induction is appropriate. It is preferable to intubate and ventilate patients undergoing laparoscopic surgery. This ensures a secure airway while ventilating with higher airway pressures and reducing the inherently small risk of aspiration from gastric regurgitation. A large-bore intravenous cannula should be placed to allow ready access for the management of major complications. In upper abdominal procedures a 12–16 FG oro- or nasogastric tube is passed to allow egress of gas from the stomach to facilitate the surgeon's view.

Maintenance may be by total intravenous or inhalational anaesthesia. Intermittent positive-pressure ventilation is preferable, to ensure adequate ventilation in the presence of the reduced compliance and elevated diaphragm caused by the pneumo-peritoneum.

Opioid supplementation aids analgesia and improves post-operative analgesia. This may be as intermittent morphine and diamorphine or as an infusion of a short-acting agent such as alfentanil or remifentanil.

Monitoring should be the minimum standard of non-invasive blood pressure, electrocardiograph, end-tidal CO_2, anaesthetic gases and pulse oximetry. For patients who require laparoscopic surgery, but who have very borderline cardiac function, invasive blood pressure and central venous pressure may be necessary, to allow closer control of cardiac function, in particular myocardial work. A pulmonary artery flotation catheter may be considered if there is concern regarding left heart function.

When peritoneal insufflation begins, there is often a reflex tachycardia and significant increase in blood pressure, even at deep levels of anaesthesia. To avoid hypertensive crises, with diastolic blood pressures above 120 mm Hg, it is advisable to have a vasodilator and β blocker available. Carefully titrated doses of labetalol can be effective, with its combined α and β effects. Occasionally, vagally-mediated bradycardia, even to the point of sinus arrest, may be seen. In this case, insufflation should cease immediately, while an appropriate vagolytic (e.g. atropine) is given. Ventilation should be adjusted to increase tidal volume and PEEP applied to counter the reduced compliance, elevated diaphragm and increased CO_2 load.

At the end of the procedure, it is preferable for the surgeon to infiltrate the small port wounds with long-acting local anaesthetic to reduce postoperative pain. The raw areas of tissue that occur after cholecystectomy can contribute to pain, due to carbonic acid formation by CO_2. Spraying the peritoneal cavity with bupivacaine may be effective in these cases.

Recovery

Pain in the immediate postoperative period can be severe, presumably due mainly to stretching of the tissues. Shoulder-tip pain is common, secondary to diaphragmatic irritation. Sitting the patient up and giving systemic analgesia should help this to settle. Occasionally, large doses of intravenous opioid are required for adequate relief. However, once the pain is controlled, recovery is rapid and the patient usually goes home in 2–3 days.

Postoperative complications

Surgical emphysema is occasionally alarming because it involves much of the trunk. It is advisable to deflate the scrotal sack before recovery. More generalized emphysema settles rapidly with time, but a pneumothorax should be excluded. The main problem with surgical emphysema is pain, which should be controlled systemically. Basal atelectasis with secondary pulmonary infection may also occur. It is more common in those with pre-existing pulmonary disease, and should be treated with antibiotics and physiotherapy. Aspiration may manifest as pleural effusions or rarely as Mendelson's syndrome. These may require the input of a respiratory physician, but are not usually a major problem in fasted patients.

The most serious complications are usually haemodynamic. Postoperative myocardial infarction can occur as a result of the increase in myocardial work during the procedure.

Deep venous thrombosis may occur due to venous stasis in the legs during surgery. This occasionally presents postoperatively with pulmonary embolus. ◆

FURTHER READING

Chui P T, Gin T, Oh T E. Anaesth Intens Care 1993; 21(2): 163–71.

Anaesthesia for Reconstructive Free Flap Surgery

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Reconstructive free flap surgery is a complex method of wound closure for large wounds not amenable to linear (primary) closure. It involves the transfer of free tissue (skin, muscle, bone, bowel or a combination) to a site of tissue loss where its circulation is restored via microvascular anastomoses. A muscle flap produces a more even contour and better aesthetic appearance than that achieved by a simple skin graft and provides a better defence against infection. The defect may be caused by trauma, infection or extensive surgery (e.g. mastectomy, head and neck cancer). The site and size of the defect determines which flap is used. The most commonly used flaps are the gracilis muscle for lower leg trauma; latissimus dorsi and rectus abdominis for breast reconstruction; and pectoralis major and radial forearm flap for head and neck reconstruction.

In patients with lower third tibulofibular defects, free tissue transfer is typically required. The bony injury should be repaired and adequate debridement achieved before skin and muscle coverage begins. This should occur within the first 6 days after injury before colonization of the wound and the risk of complications increases. In patients with multiple trauma, any life-threatening injuries must be addressed first and the patient's haemodynamic status stabilized before reconstructive surgery is contemplated.

Flap transfer

The free flap is transferred with its accompanying artery and vein, which are then reattached to vessels at the donor site using microvascular techniques. The stages of flap transfer are:

- flap elevation and clamping of vessels
- primary ischaemia as blood flow ceases and intracellular metabolism becomes anaerobic (this is dependent on surgical time and lasts 60–90 minutes)
- reperfusion as the arterial and venous anastomoses are completed and the clamps released
- secondary ischaemia is subsequent to hypoperfusion of the flap (minimized by appropriate anaesthetic management).

Primary ischaemia

With cessation of blood flow, the flap becomes anoxic. In the presence of anaerobic metabolism, lactate accumulates, intra-cellular pH drops, ATP decreases, calcium levels rise and pro-inflammatory mediators accumulate. The severity of the damage caused by primary ischaemia is proportional to the duration of ischaemia. Tissues with a high metabolic rate are more susceptible to ischaemia, therefore skeletal muscle in a flap is more sensitive to ischaemic injury than skin. At the conclusion of primary ischaemia, the changes in the flap tissue include:

- narrowed capillaries due to endothelial swelling, vasoconstriction and oedema
- sequestration of leucocytes ready to release proteolytic enzymes and reactive oxygen intermediates
- diminished ability of endothelial cells to release vasodilators and degrade ambient vasoconstrictors
- end-organ cell membrane dysfunction and accumulation of intracellular and extracellular toxins
- up-regulation of enzyme systems to produce inflammatory mediators.

Reperfusion begins with the release of the vascular clamps. Normally, the re-establishment of blood flow reverses the transient physiological derangement produced by primary ischaemia. The flap recovers with minimal injury and normal cellular metabolism is restored. However, an ischaemia/reperfusion injury may result if factors in the flap are unfavourable. Prolonged ischaemia time or poor perfusion pressure make this more likely. Reperfusion injury occurs when the restored blood flow allows the influx of inflammatory substrates that may ultimately destroy the flap.

Secondary ischaemia occurs after a free flap has been transplanted and reperfused. This period of ischaemia is more damaging to the flap than primary ischaemia. Flaps affected by secondary ischaemia have massive intravascular thrombosis and significant interstitial oedema. Fibrinogen and platelet concentrations are increased in the venous effluent. Although skin flaps can tolerate 10–12 hours of ischaemia, irreversible histopathological changes in muscle can be seen after 4 hours.

Causes of flap failure: the general causes of poor flap perfusion may be classified as arterial, venous or resulting from oedema. The arterial anastomosis may be inadequate, in spasm or thrombosed. The venous anastomosis may similarly be defective, in spasm or compressed (e.g. by tight dressings or poor positioning). Oedema reduces flow to the flap and may be a result of excessive crystalloids, extreme haemodilution, trauma from handling or a prolonged ischaemia time. Flap tissue has no lymphatic drainage and is therefore susceptible to oedema.

Microcirculation: the blood flow through the microcirculation is crucial to the viability of a free flap. The microcirculation is a series of successive branchings of arterioles and venules from the central vessels. Regulation of blood flow and oxygen delivery is accomplished by three functionally distinct portions of the microcirculation: the resistance vessels, the exchange vessels and the capacitance vessels.

The resistance vessels are the muscular arterioles that control regional blood flow. Arterioles range in diameter from 20 μm to 50 μm and contain a relatively large amount of vascular smooth muscle in their walls. Alterations in vascular smooth muscle tone are responsible for active constriction and dilation in arterioles and thus control resistance to blood flow.

The capillaries constitute the network of vessels primarily responsible for the exchange function in the circulation. Small bands of vascular smooth muscle, the precapillary sphincters, are located at the arterial end of many capillaries and are responsible for the control of blood flow within the capillaries.

The venules act as the capacitance vessels, which collect blood from the capillary network and function as a reservoir for blood in the circulation.

The vascular bed of skeletal muscle has rich adrenergic in-nervation and therefore has a marked vasoconstrictor response to neural stimulation, primarily through the resistance vessels. Precapillary sphincters also constrict in response to sympathetic stimulation, but are sensitive to local factors such as hypoxia, hypercapnia, and increases in potassium, osmolality and mag-nesium, which may cause relaxation. Other vasoactive hormones (e.g. renin, vasopressin, prostaglandins, kinins) also have a role in microvascular control.

Transplanted vessels in a free flap have no sympathetic innervation but are still able to respond to local and humoral factors, including circulating catecholamines.

The flow behaviour (rheology) of blood in the microcirculation is determined by the red cell concentration, plasma viscosity, red cell aggregation and red cell deformability. Following all surgery under general anaesthesia, the changes in blood rheology include:

- increased platelet aggregation and adhesion
- an impairment of red cell deformability
- an increase in whole blood viscosity
- increased clotting factors
- increased plasma fibrinogen and red cell aggregation
- disturbance of fibrinolysis.

Normal levels of 2,3-diphosphoglycerate (2,3-DPG) are required for optimal red cell deformability. After blood transfusion, this deformability is impaired owing to the negligible amount of 2,3-DPG in stored blood.

Physiology

The physiological status of the patient has a major influence on the viability of the transferred tissues, so the conduct of anaesthesia and postoperative management have a direct effect on outcome. Surgery is long (often 6–8 hours) with multiple sites for tissue trauma, resulting in extensive blood and fluid losses as well as heat loss. The resulting hypovolaemic vasoconstriction and hypothermia, if not corrected, compromise blood flow to the flap and result in flap failure.

Even with good fluid management, blood flow to a flap may decrease by 50% for 6–12 hours postoperatively. The guiding principle of anaesthesia for free flap surgery is the maintenance of optimum blood flow. The determinants of flow are summarized by the Hagen–Poiseuille equation:

$$\text{Laminar flow} = \frac{\Delta P \times r^4 \times \pi}{8 \times \eta \times l}$$

where: ΔP is the pressure difference across the tube, r is the radius of the vessel, η is viscosity and l is the length of the tube.

From this we may deduce that the goals of anaesthesia for free flap surgery are vasodilatation, good perfusion pressure and low viscosity.

Vasodilatation

Vessel radius is the most important determinant of flow, for the vessels supplying the flap as well as those in the flap.

Temperature – the patient should be kept warm in theatre, the recovery room and the ward for the first 24–48 hours. This is best achieved by raising the ambient temperature in theatre and by using a warm air blanket. Active warming should begin before the start of anaesthesia because patient cooling occurs rapidly after induction of anaesthesia. In an awake patient, the central core temperature is higher than that of the peripheral tissue and skin temperature. After the induction of anaesthesia, vasodilatation modifies the thermal balance between compartments. The volume of the central compartment enlarges leading to a decrease in its mean temperature, while the temperature of the peripheral and skin compartments increases. At thermoregulation, the size of the central compartment becomes smaller owing to vasoconstriction, which leads to an increase in the mean temperature, although the peripheral and skin temperatures fall.

In addition to vasoconstriction, hypothermia also produces a rise in haematocrit and plasma viscosity, the aggregation of red blood cells into rouleaux, and platelet aggregation. These effects may reduce the microcirculatory blood flow in the flap.

Fluid – peripheral vasoconstriction due to an underestimation of fluid losses is common. There are two operating sites in free flap transfer: the donor site and the recipient site. Both have insensible fluid losses and both may have blood losses. A warm theatre environment also increases fluid loss. Modest hypervolaemia reduces sympathetic vascular tone and dilates the supply vessels to the flap. An increase in central venous pressure of 2 cm H_2O above the control measurement can double the cardiac output and produce skin and muscle vasodilatation. Figure 1 gives a guide to fluid management.

Guide to fluid management

Crystalloids
- 10–20 ml/kg to replace preoperative deficit
- 4–8 ml/kg/hour to replace insensible losses

Colloids
- 10–15 ml/kg for haemodilution
- To replace blood loss

Blood
- To maintain haematocrit at 30%

Dextran
- Often given postoperatively

1

Anaesthesia – isoflurane has the advantage over other volatile anaesthetics and propofol that it causes vasodilatation with minimal myocardial depression. Propofol inhibits platelet aggregation which could reduce the risk of thrombosis. This may be due to an effect of intralipid on the platelet–erythrocyte interaction, and by the increased synthesis of nitric oxide by leucocytes.

Vasospasm of the transplanted vessels may occur after surgical handling or after damage to the intima of the vessels, and can occur during surgery or postoperatively. The surgeons may use topical vasodilators such as papaverine, lidocaine (lignocaine) or verapamil during the operation to relieve the vasospasm.

Sympathetic blockade – epidural, brachial plexus or interpleural local anaesthetic infusions, used intraoperatively and postoperatively, provide sympathetic blockade to further dilate vessels. Concerns have been raised that the sympathetically-denervated transplanted vessels would be unable to dilate after lumbar epidural blockade, resulting in a 'steal' effect reducing flap blood flow. In fact, provided any hypotension due to the sympathetic block is treated appropriately, blood flow to the flap improves as a result of the increased flow through the feeding recipient artery. Other advantages of epidural analgesia include a reduction in intraoperative and postoperative blood loss and vessel spasm; a lower incidence of deep venous thrombosis; improved diaphragmatic function and more rapid post-operative recovery. Good analgesia reduces the level of circulating catecholamines and avoids the vasoconstrictor response to pain.

Perfusion pressure

The preservation of a good perfusion pressure with wide pulse pressure is essential to flap survival. Appropriate anaesthetic depth and aggressive fluid management are usually all that is needed. Most inotropes are contraindicated owing to their vasoconstrictive effects, but if required, dobutamine and low-dose dopamine could be used.

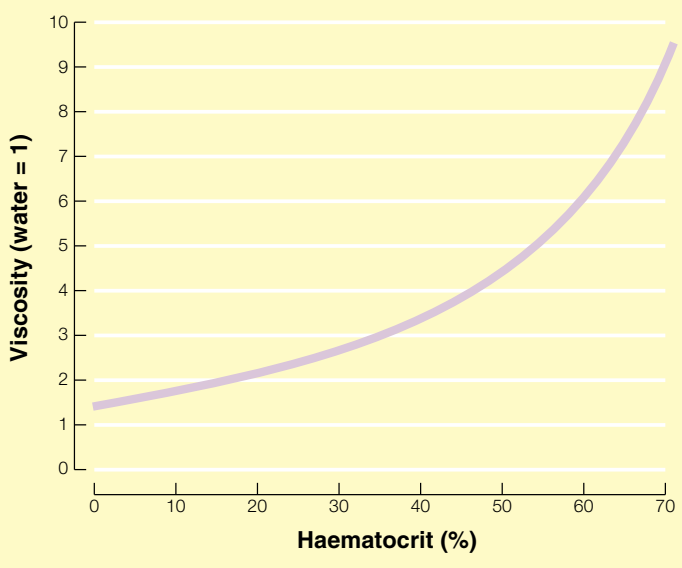
Viscosity

Isovolaemic haemodilution to a haematocrit of 30% improves flow by reducing viscosity, reducing reperfusion injury in muscle and increasing the number of patent capillaries, which decrease tissue necrosis. Further reductions in haematocrit do not provide much more advantage because the curve of viscosity versus haematocrit flattens off markedly (Figure 2). If the haematocrit falls further, the marginally improved flow characteristics from a lower viscosity may then be offset by a reduction in oxygen delivery:

$$DO_2 = CO \times [(Hb \times sat \times 1.34) + (PaO_2 \times 0.003)]$$

A low haematocrit also increases myocardial work, therefore care should be taken in patients with poor cardiac reserve.

Viscosity versus haematocrit



Source: MacDonald D J F. *Br J Anaesth* 1985; **57:** 904–21.

Practical conduct of anaesthesia

Monitoring

In addition to basic monitoring, these patients require invasive blood pressure monitoring to enable safe manipulation of the perfusion pressure. Direct measurement of arterial pressure gives a continuous record of the pressure and is more accurate than non-invasive indirect techniques. An arterial cannula also provides access to blood gas analysis and haematocrit estimations.

Central venous pressure reflects cardiac filling pressures and can be manipulated to increase cardiac output.

Core temperature measurement is essential when active warming is instituted. A nasopharyngeal or rectal probe is used intraoperatively for a continuous reading, while intermittent tympanic or axillary measurements are used in the recovery and ward areas.

Peripheral temperature is also measured because a fall in skin temperature can reflect hypovolaemia and vasoconstriction. A difference of less than 2°C between core and peripheral temp-eratures indicates a warm, well-filled patient. The temperature of the skin flap is sometimes monitored postoperatively because a drop in temperature may herald flap failure. However, this is not a sensitive test, because by the time the temperature has fallen the flap will have suffered sufficient vascular damage to render it virtually unsalvageable.

Urine output is another indicator of volume status. A urine output of 1–2 ml/kg/hour should be maintained intraoperatively and postoperatively with appropriate fluid management. Diuretics are contraindicated in these operations because volume depletion compromises flap survival.

Induction

Active warming starts before the patient is asleep. The ambient temperature in theatre is raised to about 22–24°C, a level high enough to reduce patient heat loss, but not too hot to be uncomfortable for the theatre staff. The patient is covered in a hot air blanket before induction of anaesthesia and this remains in place while the patient is prepared for theatre. Once in theatre, the blanket is moved to enable surgical access, but with as much surface area coverage as possible.

If appropriate, a regional block is inserted, preferably to cover the free flap recipient site (rather than the donor site) for the full benefit of the sympathetic block. The patient is intubated and ventilated; and a large gauge peripheral line, central line, arterial line, urinary catheter and core temperature and skin temperature probes are positioned.

Nitrous oxide diffusion into air in the stomach combined with gastric stasis results in gastric distension, with associated post-
operative nausea and vomiting. A nasogastric tube is therefore sited at intubation, left on free drainage, then aspirated and removed at the end of the operation.

Fluid, administered through a fluid warmer, is started in the anaesthetic room to compensate for preoperative dehydration.

Maintenance

Careful positioning of the patient is imperative for such a long operation. Limbs are positioned and supported to avoid neuro-logical damage or vascular compression. Eyes are taped and lightly padded to reduce the incidence of corneal abrasion and prevent drying of the cornea.

Prophylaxis against deep venous thrombosis is necessary for all patients. Subcutaneous heparin or low-molecular-weight heparin is given preoperatively, while anti-embolism (TED) stockings and compression boots are used intraoperatively.

The patient is ventilated to normocapnia. Hypocapnia increases peripheral vascular resistance and reduces cardiac output, while hypercapnia causes sympathetic stimulation. If the surgeon uses the microscope for vessel preparation or anastomosis on the chest or abdomen, the tidal volume is reduced to minimize movement in and out of the surgeon's field of vision. The respiratory rate is then increased to maintain minute ventilation.

Controlled hypotension is useful during the initial dissection and is most easily achieved using epidural local anaesthetic and/or isoflurane. An infusion of glyceryl trinitrate may be added if needed.

Crystalloids are used to replace the preoperative fluid deficit from starvation and to cover intraoperative insensible losses. The latter are high because the warm theatre increases evaporative losses from the two operating sites. Excessive use of crystalloid may precipitate oedema in the flap.

Hypervolaemic haemodilution is achieved using colloids.

Blood gas analysis and haematocrit measurement should be carried out at the start of the operation and repeated every 2 hours.

By the time the flap is reperfused, the patient should be warm, well-filled and sympathetically blocked with a high cardiac output.

Emergence and recovery

The patient should wake up pain-free. Analgesia is maintained postoperatively with local anaesthetic infusions for regional blocks, intravenous patient-controlled analgesia, or both. Coughing and vomiting increase venous pressure and reduce flap flow, so smooth emergence and extubation are needed. The principles of perioperative and postoperative care are listed in Figure 3. ◆

Principles of perioperative and postoperative care

- Maintain high cardiac output
- Normal arterial blood pressure (systolic >100 mm Hg)
- Low systemic vascular resistance
- Normothermia
- High urine output (> 1 ml/kg/hour)
- Effective analgesia
- Haematocrit 30–35%
- Monitoring of blood flow in flap (Doppler postoperatively)

FURTHER READING

MacDonald D J F. Anaesthesia for Microvascular Surgery. *Br J Anaesth* 1985; **57:** 904–21.

Sigurdsson G H, Thomson D. Anaesthesia and Microvascular Surgery: Clinical Practice and Research. *Eur J Anaesthesiol* 1995; **12:** 101–22.

The Anaesthetic Machine

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Many anaesthetic machines incorporate patient monitoring; conventionally this is considered separately and will not be discussed here.

Types of anaesthetic machine

Demand and intermittent flow machines
The patient's inspiration controls the flow of fresh gases. Such machines have been used for dental anaesthesia (e.g. the McKesson anaesthetic machine) and for military field anaesthesia (the Triservice apparatus).

Continuous flow machines (Boyle's machine)
Continuous flow machines are encountered in day-to-day hospital practice in the UK. The driving force for gas flow is compressed gases. This contribution discusses continuous flow machines.

Pressures in the anaesthetic machine

Units of pressure
To understand the anaesthetic machine, it is important to be able to relate the various different units that are used to describe pressure; 1 atmosphere pressure is approximately:

- 101 kPa
- 760 mm Hg
- 1035 cm H_2O
- 1 bar
- 15 psi.

Absolute and gauge pressure

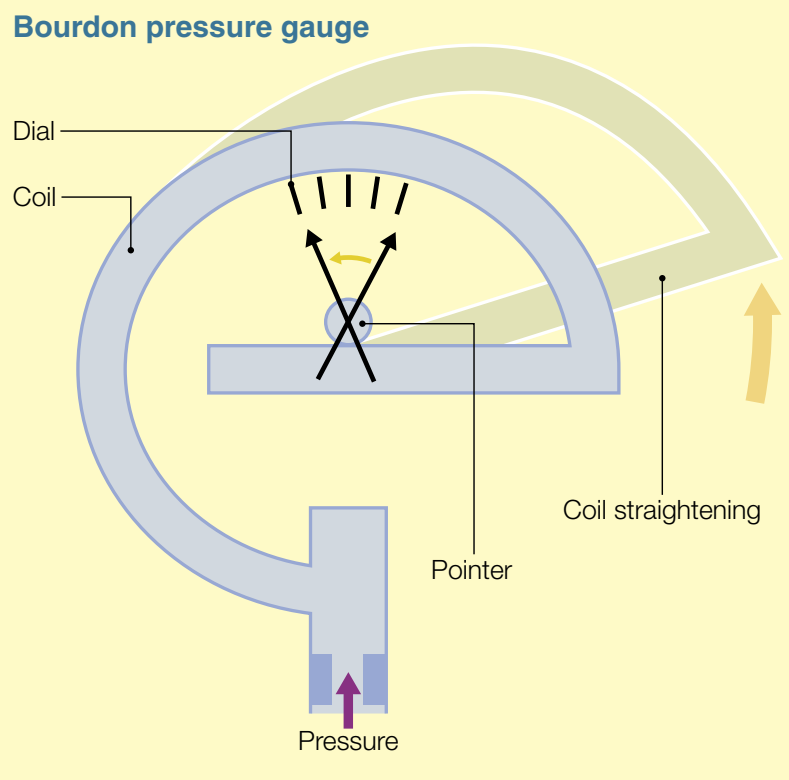
- Absolute pressure is pressure above that in a vacuum.
- Gauge pressure is pressure above atmospheric. Pressures in the anaesthetic machine are always quoted as gauge pressures.

All pipeline pressures are 400 kPa except for pressure in the air pipeline used to drive equipment such as orthopaedic drills, which is 700 kPa. Cylinder pressures are reduced to a machine working pressure of 400 kPa by pressure regulators (see below, page 66).

Pressure downstream of the flowmeters can range between zero (i.e. 1 atmosphere pressure), when the common gas outlet is open to the atmosphere, and about 33 kPa if the common gas outlet is completely obstructed and the safety valve in the back bar vents to the atmosphere.

Measurement of pressure
Cylinder and pipeline pressures are measured by a Bourdon pressure gauge (Figure 1). This is an aneroid (i.e. without liquid) gauge consisting of a coiled tube attached at one end to the gas supply and at the other to a pointer. The pressure of the gas causes straightening of the coil and thus movement of the pointer over the colour-coded, labelled and calibrated dial (Figure 2). The gauge is faced with heavy glass and designed such that leaks vent from the back of the valve casing and do not blow out the glass.

Bourdon pressure gauge



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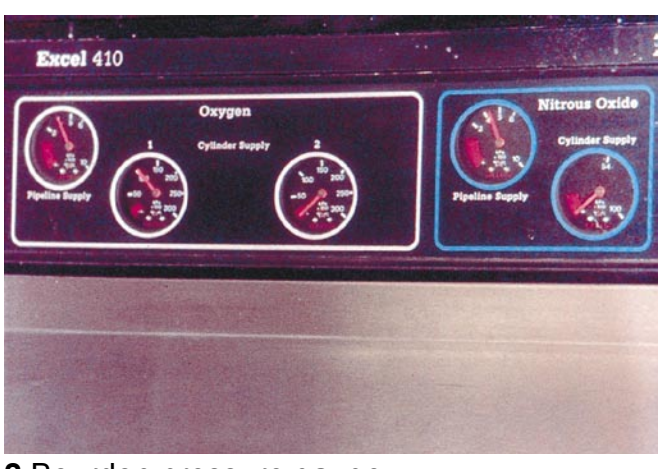
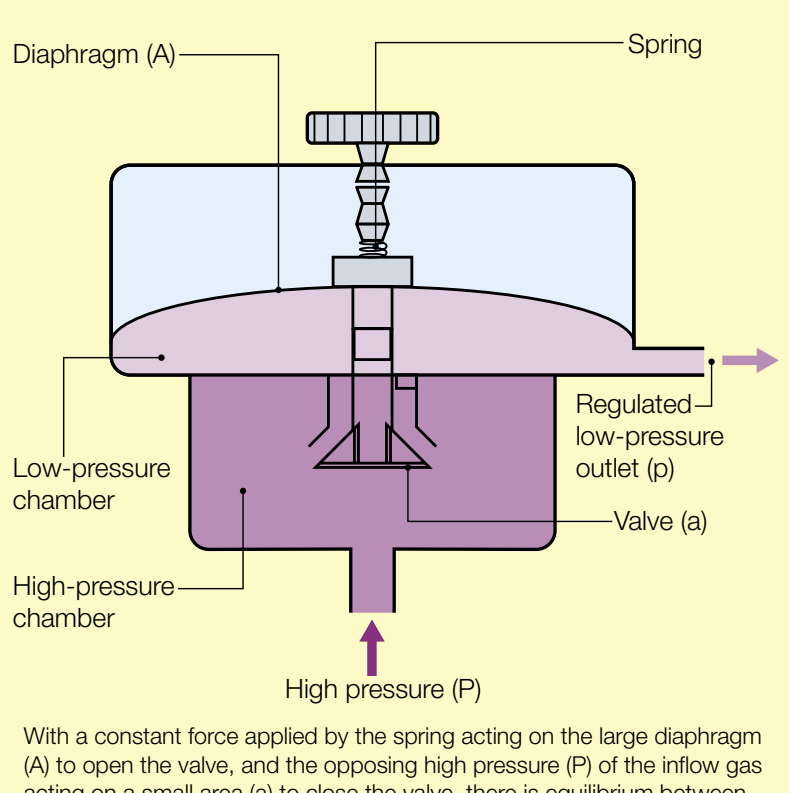


2 Bourdon pressure gauge.

Pressure regulators
Although sometimes referred to as pressure-reducing valves, the term pressure regulators is preferred because their function is not simply to reduce pressure, but in doing so to allow more accurate control of flow and to make up for the fall in cylinder pressures as they empty.

Figure 3 demonstrates the function of a pressure regulator. The principle is similar to that of the pressure-relief valve (see *Anaesthesia and Intensive Care Medicine* **1:3:** 107) except that there are two chambers, one of high pressure and the other of low, and two discs of different areas.

Pressure regulator



With a constant force applied by the spring acting on the large diaphragm (A) to open the valve, and the opposing high pressure (P) of the inflow gas acting on a small area (a) to close the valve, there is equilibrium between the high- and low-pressure chambers. To balance the equilibrium and keep the valve open, the pressure in the second chamber is thus reduced. Thus: P x a = p x A, where P = pressure in the high-pressure chamber; p = pressure in the low-pressure chamber; A = area of large diaphragm; a = area of small diaphragm.

Adjustment of the tension in the spring and thus the force it applies to the discs, regulates the pressure at the outlet to produce a constant operating pressure. As the inlet pressure falls during use of the cylinder, the force from the spring opens the valve wider, allowing more gas to flow into the second chamber and maintaining pressure at the outlet. The opposite happens if the inlet pressure rises, resulting in valve closure and thus less flow into the second chamber.

3

Flowmeters

Rotameters
Flow in most anaesthetic machines is measured by a variable orifice flowmeter known as a rotameter. A rotameter consists of a bobbin that floats in a glass tube with a diameter that increases with height up the tube. The pressure drop across the bobbin remains constant, and as flow increases it rises up the tube.

The two important properties of the gas flowing through a rotameter that influence its calibration are:

- viscosity
- density.

Gas flows in the annulus between the bobbin and the tube. At the lower end of the tube the annulus is long with respect to its cross-sectional area, and flow is laminar and dependent on the viscosity of the gas. Higher up the tube, the cross-sectional area of the annulus is greater, the gas is effectively flowing through an orifice, and flow is turbulent and dependent on the density of the gas (Figure 4).

Flowmeter

Laminar flow around the bobbin at the bottom of the tube, turbulent flow at the top. NB Pitch of the rotameter tube has been greatly exaggerated

4

Features of rotameters

- For any given gas, the flow through a rotameter depends on both its viscosity and its density. Rotameters therefore have to be calibrated individually for the gas they will be measuring.
- The bore may be varied to measure low flows accurately.
- The back plate may be luminous.
- Calibration is from the lowest accurate point, not zero.
- Accuracy is ± 2%.
- In many machines there is a constant low flow of oxygen.

Potential sources of inaccuracy in rotameters

- If the tube is not truly vertical, the annulus between the tube and the bobbin is altered.
- Static electricity can cause inaccuracies. To minimize this, glass is conductive and sprayed with antistatic material.
- Dust can collect on the bobbin or within the tube.
- Tubes may be damaged. In the UK, the oxygen rotameter tube is on the left (said to be because Boyle was left-handed). This can mean that any damage to the tubes would preferentially leak oxygen and result in the delivery of a hypoxic mixture. Many manufacturers now arrange the order in which the gases finally mix so that oxygen is the last gas added to the mixture.
- The top-sealing washer may be defective.
- The carbon dioxide bobbin may become stuck at the top of the tube.
- Back pressure from a minute volume divider such as a Manley ventilator increases the density of the gas and may cause the rotameter to under-read by about 7%.
- Atmospheric pressure affects density. Low pressure gives over-reading.
- Temperature affects density and viscosity. Increased temperature causes decreased density and increased viscosity.

Vaporizers

Vaporizers are discussed elsewhere.

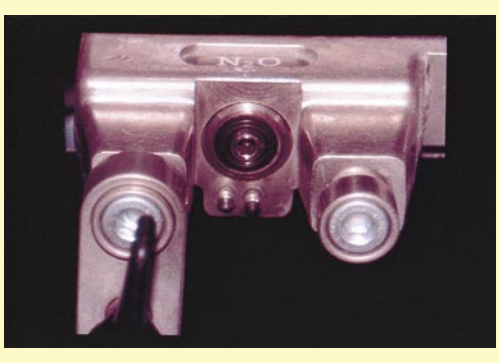
Safety

The anaesthetic machine has several in-built safety features that vary from machine to machine. The commonly found features that are of importance to anaesthetists are listed in Figure 5.

Perhaps the most important safety feature is that the machine should always be checked in a systematic fashion before use. The Association of Anaesthetists of Great Britain and Ireland has published a useful checklist, part of which is reproduced in Figure 6. These checks must be performed at the beginning of each theatre session.

Anaesthetic machine – safety features

- Non-interchangeable pipeline outlets (often referred to as Schrader connectors, though this is really a trade name)
- Pipelines are coloured and marked with the name of the gas
- Non-interchangeable screw thread connectors connect the pipeline to the anaesthetic machine
- The pin index system prevents accidental connection of the wrong cylinder to the wrong yoke
- Cylinders are coloured and marked with the name of the contents
- Grease can be flammable or explosive in contact with gases at high pressure. A Bodok seal (see below) makes a gas-tight connection between cylinder and yoke
- There are pressure gauges for pipelines and cylinders
- Rotameter knobs are identified by the oxygen knob being a distinctive colour and shape and more prominent
- The oxygen rotameter outlet may be diverted to enter the gas flow last
- Oxygen and nitrous oxide rotameters may be linked to prevent delivery of a hypoxic mixture
- The oxygen bypass can provide oxygen at high flow (> 30 litres/minute) directly to the common gas outlet
- There is an oxygen failure warning device triggered by a dropin the oxygen pressure, which also vents the flow of anaesthetic gases to the atmosphere to prevent delivery of a hypoxic mixture
- Vaporizer fillers are keyed to prevent a vaporizer being accidentally filled with the wrong agent
- Vaporizers may be arranged so that only one can be turned on at a time
- There is a machine pressure-relief valve in the back bar that prevents the pressure rising above about 33 kPa
- The machine is serviced regularly by a qualified engineer



Bodok seal.

Anaesthesic machine – safety checks

Anaesthetic machine

- Check that the anaesthetic machine and relevant ancillary equipment are connected to the mains electrical supply (where appropriate) and switched on
- Careful note should be taken of any information or labelling on the anaesthetic machine that might refer to its current status

Oxygen analyser

- The oxygen analyser should be placed where it can monitor the composition of the gases leaving the common gas outlet
- The analyser should be switched on, checked and calibrated according to the manufacturer's instructions

Medical gas supplies

- Identify and take note of the gases that are being supplied by the pipeline, confirming with a 'tug test' that each pipeline is correctly inserted into the appropriate gas supply terminal
- Check that the anaesthetic apparatus is connected to a supply of oxygen and that an adequate reserve supply of oxygen is available from a spare cylinder
- Check that adequate supplies of any other gases intended for use are available and connected as appropriate. All cylinders should be securely seated and turned ***Off*** after checking their contents. Carbon dioxide cylinders should not normally be present on the anaesthetic machine. A blanking plug should be fitted to any empty cylinder yoke
- All pressure gauges for pipelines connected to the anaesthetic machine should indicate 400 kPa
- Check the operation of flowmeters, ensuring that each control valve operates smoothly and that the bobbin moves freely through its range without sticking. With only the oxygen flow control valve open and a flow of about 5 litres/minute, check that the oxygen analyser display approaches 100%.

Turn off all flow control valves

- Operate the emergency oxygen bypass control and ensure that flow occurs without significant decrease in the pipeline supply pressure. Confirm that the oxygen analyser display approaches 100% during this test. Ensure that the emergency oxygen bypass control ceases to operate when released

Vaporizers

- Check that the vaporizer(s) for the required volatile agent(s) are fitted correctly to the anaesthetic machine, that any back bar locking mechanism is fully engaged and that the control knobs rotate fully through the full range(s). Ensure that the vaporizer is not tilted.

Turn off the vaporizers

- Check that the vaporizer(s) are adequately filled and that the filling port is tightly closed
- Set a flow of oxygen of 5 litres/minute and, with the vaporizer turned off, temporarily occlude the common gas outlet. There should be no leak from any of the vaporizer fitments and the flowmeter bobbin should dip.

Turn each vaporizer on in turn and repeat this test. There should be no leak of liquid from the filling port.

After this test, ensure that the vaporizers and flowmeters are turned off

Should it be necessary to change a vaporizer at any stage, it is essential to repeat the leak test.

Failure to do so is one of the most common causes of critical incidents

Removal of a vaporizer from a machine in order to refill it is not considered necessary

Source: Association of Anaesthetists of Great Britain and Ireland. *Checklist for Anaesthetic Apparatus, 1997.*

FURTHER READING

Association of Anaesthetists of Great Britain and Ireland. *Checklist for Anaesthetic Apparatus, 1997.*

Moyle J T B, Davey A. *Ward's Anaesthetic Equipment.* 4th ed. Philadelphia: Saunders, 1998.

Artificial Ventilation in the Operating Theatre

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Ventilators are used in two main settings: the operating theatre and the ICU.

- In the operating theatre, ventilators are used to maintain ventilation in anaesthetized, intubated, pharmacologically paralysed patients who have predominantly normal lungs. These ventilators are designed to interface with anaesthetic gas circuits to allow varying concentrations of oxygen, anaesthetic gases and volatile agents to be delivered to the patient. Most theatre ventilators are relatively simple, mechanical or electromechanical devices that do not have patient-sensing capabilities.
- Ventilators are often used in the ICU to ventilate patients with abnormal lungs, who require only air and oxygen as respiratory gases; these patients are seldom paralysed and often require only partial respiratory support. The ventilators used are almost all complex, computer-controlled devices with sensitive mechanisms to detect the patient's respiratory efforts.

This contribution discusses ventilators for theatre use, though many of the basic principles apply to ICU devices.

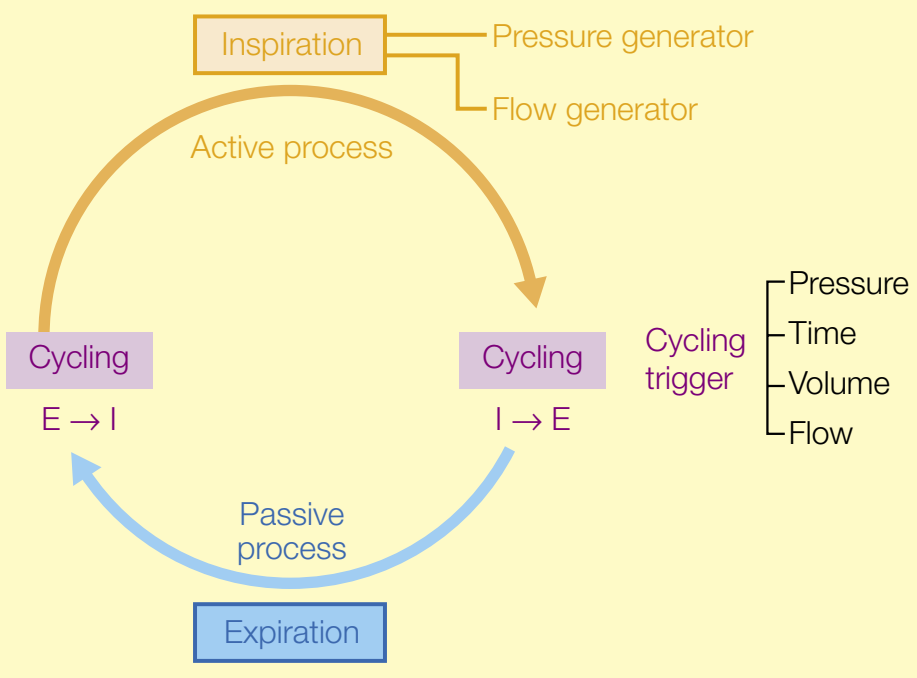
Classification of anaesthetic ventilators

Ventilators can be classified according to their function and operation.

- Functional classification is the most common and clinically useful system. It is based on the pattern of gas that the ventilator generates during inspiration, and the mechanism that cycles between inspiration and expiration (Figure 1).
- Operational classification is based on parameters such as power source or driving mechanism. Operational classification is not covered in this contribution.

Ventilator classifications were devised when most ventilators had only one mode of ventilation. Examples of such ventilators are the Manley ventilator (a time-cycled pressure generator), the Nuffield 200 ventilator (a time-cycled flow generator) and paediatric theatre ventilators (time-cycled pressure generators). Modern theatre ventilators and all ICU ventilators can operate in two or more ventilatory modes and so do not fit neatly into one single category of the traditional functional classification.

Functional classification of the respiratory cycle during intermittent positive-pressure ventilation



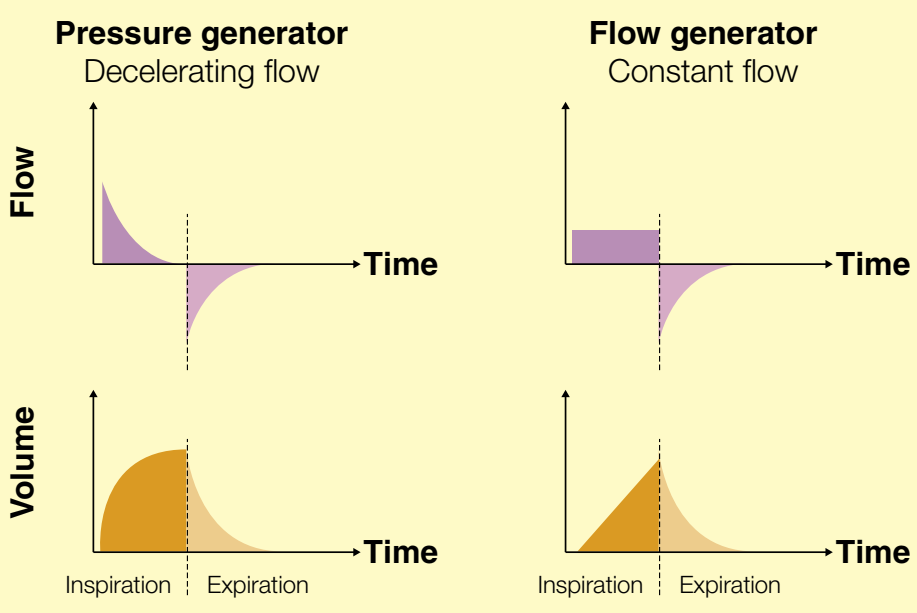
Based on Mapleson classification. I, inspiration; E, expiration

1

Functional classification of ventilators

The important difference between pressure and flow generators is the pattern of gas flow produced during inspiration. This influences the effects of changes in airway resistance, or lung and chest wall compliance, or if there is leak of delivered gases from the system. A summary of the important differences between pressure and flow generators is shown in Figure 2. Knowledge of the basic respiratory mechanics is vital to understanding ventilator–patient interactions.

Pressure generators and flow generators



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Resistance, compliance and time constants: the pressure required to cause gas to flow into the lungs has two components:

- that required to maintain gas flow along the airways, overcoming airways resistance
- that required to overcome the elastic recoil of the respiratory system, determined by compliance.

The interaction of these components determines the time constant (TC).

TC defines the rate of a simple (first-order) exponential process. It is equivalent to the time taken for the exponential process to complete if it were to continue at the same rate as that at which it began. TC describes how fast the lungs fill with a constant applied airway pressure or how fast they empty during expiration. (TC = compliance x resistance.) It increases with increasing resistance (e.g. in asthmatics) and decreases with decreasing compliance (e.g. in pulmonary fibrosis).

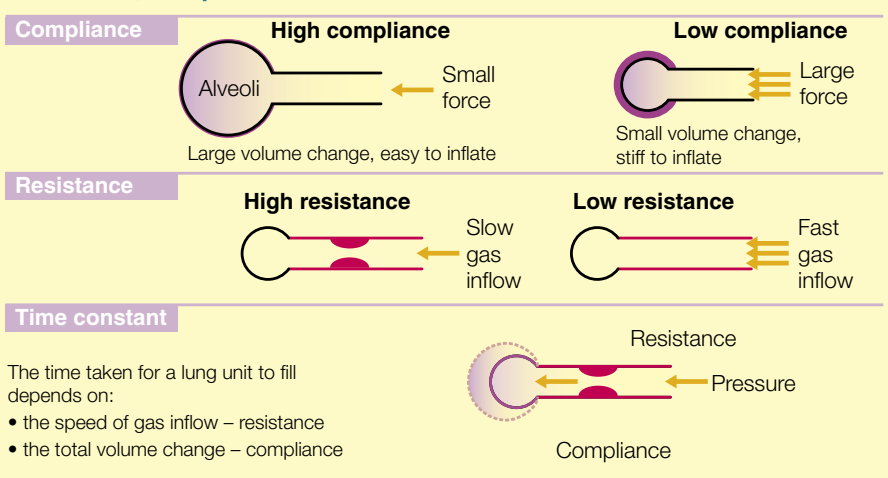
Resistance is a measure of the resistance to gas flow. The major site of respiratory resistance is in the medium-sized bronchi, but total respiratory resistance during positive-pressure ventilation also includes the contribution of the endotracheal tube and to a lesser extent the circuit. In a patient with normal lungs, this increases the total respiratory resistance from 2 to 4–6 cm H_2O/litre/second.

Compliance describes the elasticity of the respiratory system, or the ease with which it inflates, and is measured as the volume change per unit pressure. Total respiratory compliance consists of combined lung and chest wall compliance and is normally 50–70 ml/cm H_2O.

Within the normal working range of the lung compliance is constant though it decreases at extremes of volume. The contribution to compliance from the ventilator circuit is usually small. The exception is during anaesthesia in neonates and infants when the tidal volume is small compared with the circuit volume, and compression of gas within the circuit can make it difficult to ensure that accurate and adequate tidal volumes are delivered (Figure 3).

Effect on artificial ventilation − increased airways resistance and reduced lung and chest wall compliance are the most clinically significant changes in respiratory mechanics affecting artificial ventilation. Some causes are shown in Figure 4.

Resistance, compliance and time constant



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Causes of increased airways resistance and reduced respiratory compliance

Increased airways resistance	Reduced respiratory compliance
• Bronchospasm – asthma, chronic obstructive airway disease (COAD)	• Within lung – pulmonary oedema, adult respiratory distress syndrome, fibrosis, atelectasis
• Mucosal swelling – asthma, COAD	• Around lung – pleural effusion, upward compression from abdominal contents when supine, especially if obese
• Luminal obstruction – excessive secretions	• Chest wall – surgeon compressing chest, expiration retractors, scoliosis, contractures
• Foreign body – tumour	
• Emphysema – dynamic airway compression during	
• Low lung volume	

4

Pressure and flow generators: an understanding of the different types of ventilator and how they function helps predict the behaviour and limitations of each type of machine when resistance and compliance of the lungs change (Figure 5).

Pressure generators - a pressure generator applies a preset positive-pressure waveform to the airway for the duration of inspiration. In its simplest form this pressure is constant (Figure 6).

If the inspiratory time is sufficiently long, the respiratory compliance determines the tidal volume delivered when a given airway pressure is applied. The respiratory compliance decreases linearly with lung size, therefore a pressure generator set at 15−20 cm H_2O delivers an appropriate tidal volume to a small child or an adult with normal lungs.

Pressure generators can maintain the required airway pressure, even in the presence of a leak, within reasonable limits. As a result, the main use for pressure generators in anaesthetic practice is to ventilate children. The cricoid ring is the narrowest point of the airway in children. The insertion of endotracheal tubes can lead to compression of the tracheal mucosa against the cricoid cartilage, resulting in pressure necrosis. This can be avoided by using uncuffed endotracheal tubes; the presence of an air leak during inspiration confirms that the endotracheal tube is not lodged tightly in the cricoid ring.

The pressure generator ensures that adequate tidal volumes are delivered because a consistent pressure is maintained despite the leak. Paediatric patients, particularly neonates, are prone to ventilator-induced lung damage, and constant pressure generators ensure that even when lung dynamics change, the applied pressure remains constant.

Pressure generators are designed for use with normal lungs that remain normal during surgery (delivered tidal volume = pressure x compliance.) The main disadvantage of a pressure generator is that tidal volume is determined by compliance and reductions in compliance may cause significant reductions in delivered tidal volume and minute ventilation. Therefore, pressure generators may not be appropriate when precise control of arterial carbon dioxide tension ($PaCO_2$) is important, for example, during neurosurgery.

Flow generators (Figure 7) are devices that produce a constant gas flow independent of respiratory compliance or resistance. The volume delivered per unit time remains constant even in the presence of high airway pressures. All flow generators need a high-pressure gas source. This can be delivered by compressing bellows or by using proportional control valves, which control gas flow from the pipeline supply.

The delivered tidal volume is determined by control of the inspiratory flow rate and inspiratory time. The peak and mean airway pressure generated depends on the tidal volume, inspiratory flow rate, respiratory compliance and resistance.

The main advantage of a constant flow generator is that a constant tidal volume and minute ventilation are maintained even when the mechanics of the lung are changing. The tidal volume can be set precisely and minute ventilation is predictable and consistent, giving precise control of $PaCO_2$.

The main disadvantage is the potential for high airway pressures and barotrauma if changes in lung mechanics occur. There is also no ability to compensate for leaks. Flow generators are used mainly for adults, particularly where lung mechanics are abnormal, and when precise control of $PaCO_2$ is required.

Cycling parameters - cycling is the process of stopping one phase of ventilation and changing to the next. This occurs twice within each delivered breath. For the purposes of classification, cycling marks the end of inspiration and the beginning of expiration. Ventilators may be:

- time-cycled – cycling occurs after preset time
- volume-cycled – cycling occurs after preset volume delivered
- pressure-cycled – cycling occurs after preset pressure attained
- flow-cycled – cycling occurs when flow falls below a preset value.

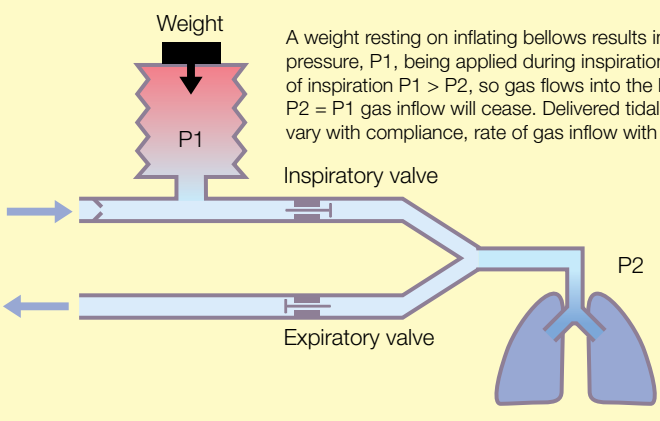
Time cycling is the most common technique. Flow cycling is used in inspiratory pressure support in the ICU but seldom in theatre. Volume and pressure cycling are used infrequently. In most ventilators, cycling from expiration to inspiration is by time.

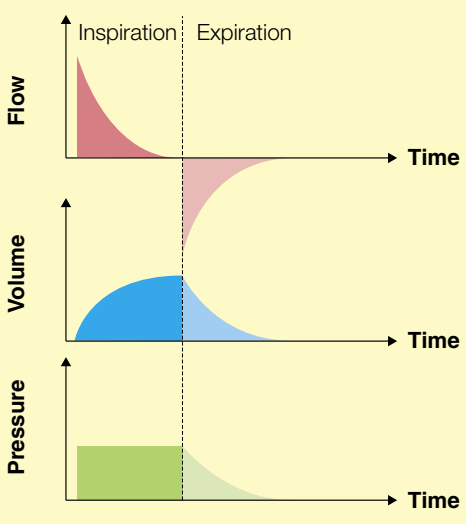
Advantages and disadvantages of pressure and flow generators

	Pressure generators	Flow generators
Advantages	• Protection from high airway pressures and barotrauma • Compensate for leaks	• Ability to maintain a constant tidal volume and minute ventilation even with significant changes in lung mechanics • Precise control of $PaCO_2$
Disadvantages	• Hypoventilation as a result of changes in lung mechanics	• Potential for high airway pressures and barotrauma • Inability to compensate for leaks

5

Constant pressure generator





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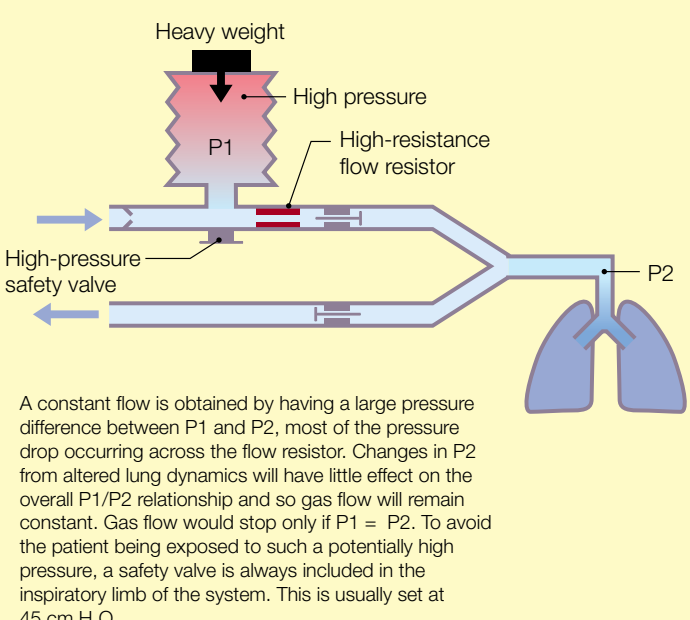
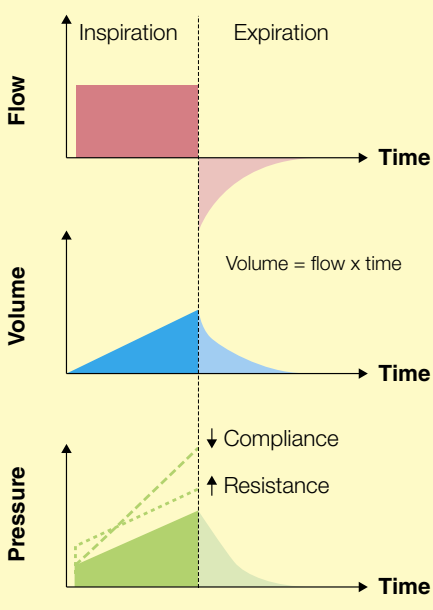
High-pressure, high-resistance flow generator



A constant flow is obtained by having a large pressure difference between P1 and P2, most of the pressure drop occurring across the flow resistor. Changes in P2 from altered lung dynamics will have little effect on the overall P1/P2 relationship and so gas flow will remain constant. Gas flow would stop only if P1 = P2. To avoid the patient being exposed to such a potentially high pressure, a safety valve is always included in the inspiratory limb of the system. This is usually set at 45 cm H_2O.



7

Single- and double-circuit ventilators

In a single-circuit ventilation system the anaesthetic gas is also the driving gas. A well-known example is the Manley ventilator, where the fresh gas flow set on the rotameters is divided into tidal volume (hence the term minute volume divider). The fresh gas flow powers the ventilator and is also delivered to the patient.

In a double-circuit ventilation system the anaesthetic gas and the driving gas are in separate circuits. The clearest example of this is a 'bag in bottle' or bellows ventilator. The anaesthetic gas is contained within the circuit and a set of bellows, which act as a reservoir. After delivering the tidal volume, the bellows refill during expiration. The bellows are contained within an air-tight cylinder and a separate high-pressure driving gas is used to pressurize the cylinder periodically, compressing the bellows and thereby generating inspiratory gas flow. Most modern circle/ventilator systems are double circuits.

Bellows can be of the standing or hanging variety. Standing bellows rise as they refill; hanging bellows are mounted inverted and fall as they refill. The advantage of standing bellows is that a leak of anaesthetic gases will be noticed by a failure of the bellows to rise to the full height. This is especially useful during low-flow circle anaesthesia. Hanging bellows are usually weighted at the base and entrain room air if there is a circuit leak.

The Nuffield 200 series of ventilators are functionally double circuit. Although there is no physical separation of the driving and fresh gas flow, the configuration of these ventilators ensures that fresh (anaesthetic) gases and driving gas do not mix. This is achieved by using a connector hose with an internal volume that is greater than the tidal volume.

Pulmonary physiology and the effects of intermittent positive-pressure ventilation (IPPV)

When a patient breathes spontaneously the expansion of the chest wall creates a negative pressure relative to atmospheric pressure between the visceral and parietal pleura. The transpulmonary pressure gradient created causes the lung to expand and fill. Thus, during inspiration the intrathoracic pressure is negative.

During IPPV the patient makes no respiratory effort and the transpulmonary pressure gradient required to expand the lung is generated by raising the airway pressure. With inspiration, intrathoracic pressure is positive. During artificial ventilation the mean intrathoracic pressure is increased compared with spontaneous ventilation and this has effects on the respiratory, cardiovascular, renal and endocrine systems. The effects of IPPV are wide ranging and must be viewed in the context of the position of the patient on the operating table and the effects of general anaesthesia.

Normal respiratory physiology and the effects of general anaesthesia

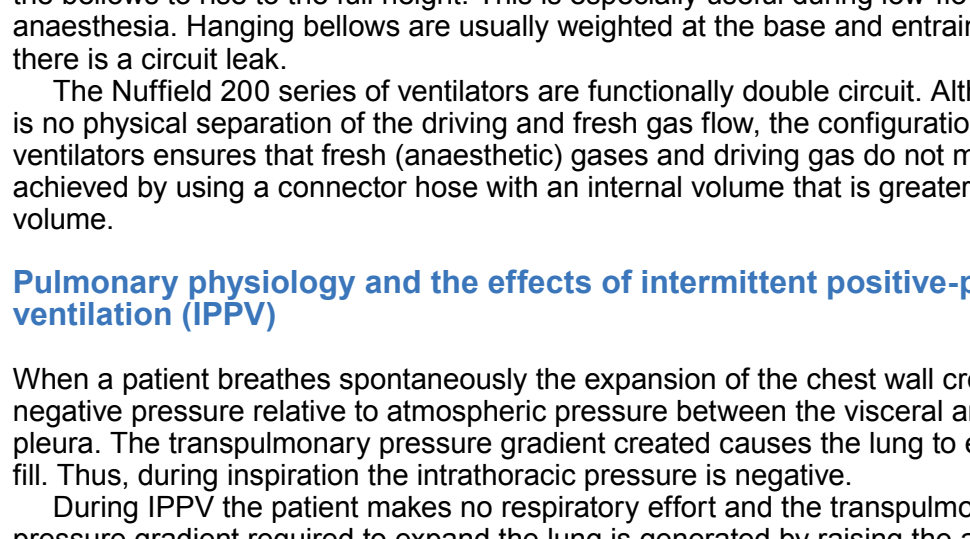
The primary function of ventilation is to move air in and out of the lungs so that carbon dioxide can be eliminated and arterial oxygenation maintained. In healthy individuals it is the requirement to eliminate carbon dioxide that is the prime determinant of minute ventilation. A normal tidal volume is about 500 ml in an adult (8 ml/kg); of this, about 150 ml (2 ml/kg) remains in the conducting airways (anatomical dead space), and the remaining 350 ml enters the alveoli and is available for gas exchange. The respiratory rate depends on the requirement for carbon dioxide elimination, but is usually 10−15 breaths per minute in adults. Effective ventilation maintains a normal arterial $PaCO_2$ of 4.5−5.5 kPa and an arterial oxygen tension (PaO_2) of 13.5 kPa in healthy young adults breathing room air.

Functional residual capacity (FRC): the various subdivisions of lung volume that can be determined by spirometry, whole-body plethysmography or helium dilution are shown in Figure 8. Of these, the most important for anaesthesia and the care of patients in the ICU is FRC. FRC is the end-expiratory volume of the lungs and is determined by the balance between:

- the elastic recoil of the lungs
- the outward recoil of the chest wall
- the respiratory muscle tone
- the position of the diaphragm.

FRC gradually reduces with age and is reduced on lying supine (by 500−800 ml) as a result of upward displacement of the diaphragm by the abdominal contents. This effect is enhanced in patients with abdominal distension or obesity. During general anaesthesia, reduction in diaphragmatic and chest wall tone and function lead to a reduction in FRC of about 20%. The effects of general anaesthesia and the supine position are additive, and can cause a significant reduction in FRC.

Lung volumes (70 kg adult)



Normal values

- Functional residual capacity 2.5 litres
- Inspiratory reserve volume 2.5–3.0 litres
- Tidal volume 0.5–0.6 litres
- Expiratory reserve volume 1.5 litres
- Residual volume 1.5–2 litres
- Vital capacity 3.5–5.5 litres
- Total lung capacity 6 litres

Minute ventilation 7.5 litres/minute
Alveolar ventilation 5 litres/minute
Vd/Vt 0.3

8

Closing capacity (CC) is the lung volume at which small airway closure begins. Closing volume is an alternative term that is equivalent to CC minus residual volume (RV). Normally CC is less than FRC, but they converge with increasing age. When FRC decreases to below CC, airway closure occurs during normal expiration and the resulting decrease in ventilation to areas of the lung distal to the closure worsens the ventilation-perfusion (V/Q) relationship. FRC usually remains greater than CC when supine until about 45 years of age but the additional reduction in FRC that occurs during general anaesthesia makes it more likely that FRC will fall below CC during anaesthesia. The resulting increase in V/Q mismatch leads to a decrease in arterial oxygenation, which is normally countered by increasing the inspired oxygen fraction.

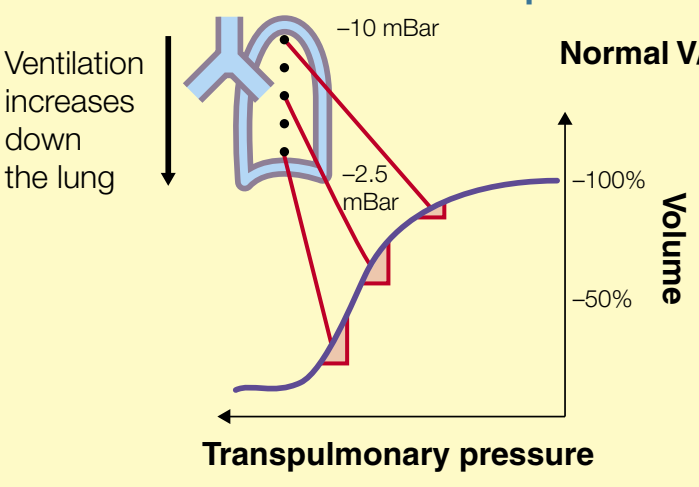
Distribution of ventilation and perfusion: during spontaneous ventilation in an upright position, distribution of ventilation and perfusion are not uniform throughout the lungs. Blood flow increases linearly from the top to the bottom of the lungs as a result of the effects of gravity on the low-pressure pulmonary circulation. The lower zones ventilate better than the upper zones because the dependent parts are on a more compliant (i.e. steeper) part of the pressure-volume curve. During normal inspiration, diaphragmatic contraction is enhanced in the parts of the diaphragm most displaced, aiding increased ventilation of the dependent parts of the lung (Figure 9).

Ideally, ventilation and perfusion at the alveolar level should be matched. Alveolar ventilation should equal perfusion and the V/Q ratio equal 1. In this situation no ventilation or perfusion is 'wasted'. However, the normal V/Q ratio is 0.8. The further the V/Q ratio deviates from 1, the more inefficient the ventilatory process becomes (Figure 10).

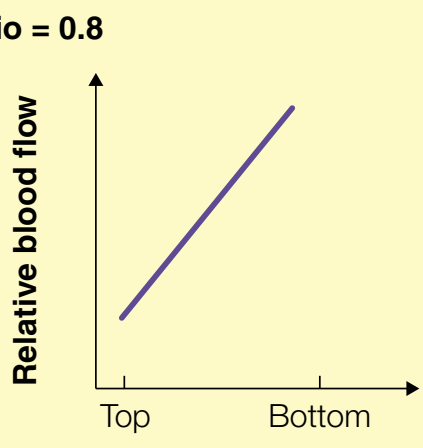
In the supine position, the gravitational effects on the lung are more limited, and perfusion is more homogeneous. However, the reduction of FRC, which is compounded by anaesthesia and the patient's position, leads to uneven ventilation because of airway closure and the tendency of the dependent portions of the lung to reduce in volume more than the superior parts (compression atelectasis).

Therefore, in the supine position (especially under anaesthesia) V/Q relationships worsen. This tends to cause hypoxaemia, which, because it is caused by a V/Q mismatch rather than a true shunt, can be reversed with added inspired oxygen.

Distribution of ventilation and perfusion in the lungs



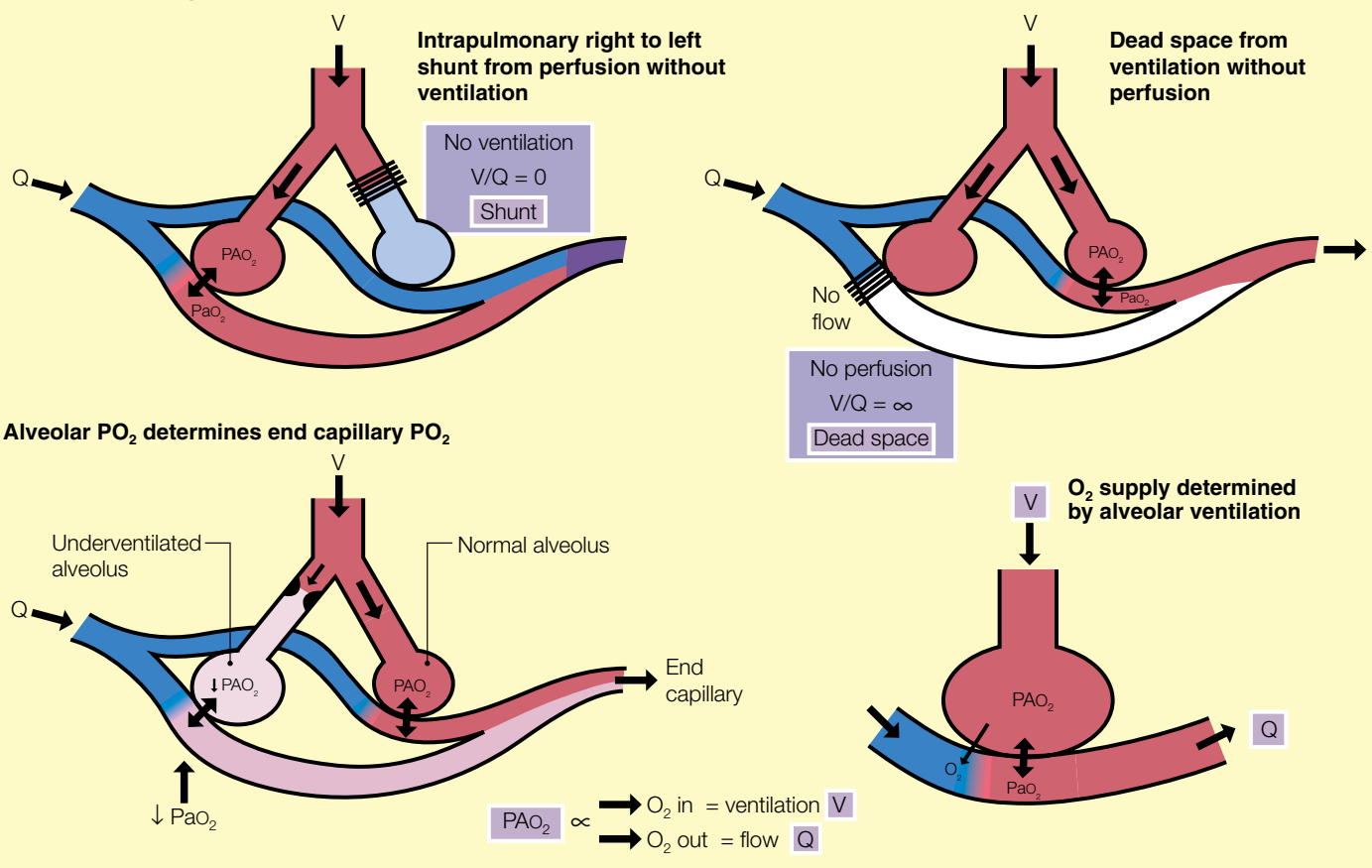
Ventilation increases from the apex to the base. Dependent parts of the lung are on a more compliant part of the pressure–volume curve



Perfusion increases on moving down the lung. The low-pressure pulmonary circulation is affected by gravity

9

Ventilation and perfusion



In an ideal alveolus capillary P_{O_2} (Pa_{O_2}) comes close to alveolar P_{O_2} (PA_{O_2}). PA_{O_2} is determined by the balance between the rate of O_2 uptake by the pulmonary capillaries (Q) and continued supply of O_2 by alveolar ventilation (V). The rate of O_2 removal is determined by the rate of O_2 consumption (metabolic rate). In an under-ventilated alveolus, the supply of O_2 is reduced. If O_2 uptake continues, the result is for PA_{O_2} to fall and so Pa_{O_2} will fall

10

Hypoxic pulmonary vasoconstriction (HPV): when the alveolar PO_2 or, to a lesser extent, the mixed venous PO_2 decreases, smooth muscle contraction occurs in small pulmonary arterioles. This diverts blood from unventilated areas to better-ventilated areas and helps minimize the effects of V/Q imbalance. Volatile anaesthetic agents as well as many vasodilators (e.g. sodium nitroprusside) inhibit HPV, worsening the effects of V/Q mismatching.

Respiratory effects of IPPV

Changes in distribution of ventilation: the preferential ventilation of the non-dependent parts of the lung in the anaesthetized, supine position is increased by IPPV. The non-dependent areas are more compliant than the dependent zones after induction of anaesthesia and muscle relaxation, and so preferentially expand in response to positive pressure. This effect is further exaggerated if the lungs have an increased density, as in the adult respiratory distress syndrome or in patients with cardiogenic pulmonary oedema. It is also compounded by compression of basal areas of the lung as a result of the upward displacement of the paralysed diaphragm.

Changes in distribution of perfusion: normal distribution of perfusion is usually maintained during IPPV. However, in the presence of high intra-alveolar pressures, compression of the alveolar capillaries occurs and flow stops. Capillary pressures are lower in the upper zones because of the effect of gravity on the low-pressure pulmonary circulation, and these zones are particularly vulnerable to increases in airway pressure. These preferentially ventilated upper zones now have much reduced flow and V/Q mismatch is further increased. This is more likely to occur when mean airway pressures are high and with the use of positive end-expiratory pressure (PEEP).

PEEP is the application of a residual positive pressure to the airway at the end of expiration instead of atmospheric pressure. This improves oxygenation by increasing FRC and thus reduces the effects of airway closure and lung volume reduction on V/Q relationships. PEEP may also reopen previously collapsed lung units and maintain their patency (alveolar recruitment).

Barotrauma is the result of excessive pressure gradients between alveoli and the interstitium, with rupture occurring. Air can spread along perivascular spaces into the mediastinum, pericardium, up into the neck, down into the abdomen or into the pleural cavity (pneumothorax). Risk factors include:

- large tidal volumes
- excessive inflation pressures, especially > 40 cm H_2O
- use of PEEP
- non-uniform lung disease
- increased airway resistance.

Recently, the term ‘volutrauma’ has been used in the ICU setting. This refers to overdistension of ‘normal’ areas of the lung by the high pressures required to inflate the diseased areas.

Other respiratory effects of IPPV: during general anaesthesia with intubation and ventilation, there is loss of the ability to cough and so secretions are retained. Inhaled anaesthetics and cold, dry gases inhibit ciliary activity in the bronchial tree, again leading to a tendency to retain secretions. In addition, if the anaesthetic gases are not warmed and humidified, the respiratory tract can be a major source of heat loss.

Cardiovascular effects of IPPV

The major effect of IPPV is to reduce cardiac output via a reduction in venous return. In most patients, this can be counteracted by fluid loading (e.g. 500−1000 ml crystalloid). There are additive effects on the pulmonary circulation and heart, but their relative contribution is thought to be minor, and significant changes occur only with high mean airway pressures.

Cardiac output: a decrease in cardiac output occurs when beginning IPPV, which can cause significant hypotension. The increase in mean intrathoracic pressure during inspiration with positive-pressure ventilation causes the low-pressure veins in the chest to be compressed. Cardiac output falls because of the reduction in venous return to the heart. The decrease in cardiac output and mean arterial blood pressure can be particularly marked in patients who are hypovolaemic or have limited cardiovascular reserve and is further worsened by PEEP. The expected fall in cardiac output can be reduced by prompt infusion of fluids to increase central venous pressure and maintain venous return.

Effects of IPPV on pulmonary vascular resistance and the heart: increased pulmonary vascular resistance occurs when airway pressures are high, from direct compression of alveolar capillaries. As pulmonary vascular resistance increases, there is an increase in right ventricular afterload and right ventricular end-diastolic volume. If end-diastolic volume becomes significantly raised, bulging of the intraventricular septum into the left ventricular cavity can occur, reducing left ventricular compliance and reducing left ventricular stroke volume. In addition, the increased wall tension in the right ventricle, coupled with a reduced arterial pressure, can compromise right ventricular perfusion in compromised patients. The final effect is right heart strain further augmenting a reduction in cardiac output. Paradoxically, in patients with existing heart failure, the increase in transpulmonary pressure transmitted to the thorax can occasionally help to off-load the left heart by reducing venous return from the pulmonary veins, thus reducing left atrial pressures. Left ventricular performance may then improve.

Other effects of IPPV

Renal: mechanical ventilation causes a reduction in urine volume, and thus sodium and water retention. A fall in renal perfusion pressure associated with the reduced cardiac output and a rise in renal venous pressure as a result of impedance of venous return, along with increased levels of antidiuretic hormone associated with IPPV, are thought to be important. An increase in sympathetic stimulation triggered by baroreceptors sensing the changes in pressure and flow may also contribute. The renal effects are persistent and are not fully reversed with fluid infusion or improvement in cardiac output.

Liver: the reduction in cardiac output and increased venous pressure leads to a fall in hepatic blood flow proportional to the drop in cardiac output. Hepatic blood flow may be reduced by up to 50% and hepatic metabolism is reduced. This can be reversed by infusion of fluid. The increased venous pressure caused by the positive intrathoracic pressure can cause hepatic venous congestion, and hypocapnia will lead to vasoconstriction.

Endocrine: antidiuretic hormone levels are increased during IPPV, with corresponding increases in renin and angiotensin levels. This contributes to salt and water retention.

Practical aspects of positive pressure ventilation

Adequate ventilation requires an adequate tidal volume and minute ventilation to be delivered, time for gas distribution and gas exchange to occur, and sufficient time for expiration to be completed. Adequate ventilation results in a normal $PaCO_2$ tension (4.5−5.0 kPa), and in anaesthetic practice this is usually estimated by the end-tidal carbon dioxide tension ($P_{E'}CO_2$). In patients with normal lungs the arterial $PaCO_2$ is about 0.5 kPa greater than the $P_{E'}CO_2$. $P_{E'}CO_2$ is measured from alveolar gases from all ventilating lung units with a spread of V/Q ratios. Units with high V/Q ratios have a reduced alveolar PCO_2 and so ‘dilute’ the gas from units with a V/Q ratio close to unity. This relationship is lost in patients with lung disease; arterial blood gas monitoring may be required in these patients. The minute volume and tidal volumes used should aim for peak airway pressures of 15−20 cm H_2O in most patients.

Arterial oxygenation is determined primarily by the inspired oxygen, which should never be below 30% (FiO_2 0.3) initially. The required inspired oxygen is determined by the saturation recorded by the pulse oximeter; 95% or greater is appropriate. After monitoring the effect of the initial settings in each patient, appropriate alterations can be made to suit the individual.

Initial IPPV settings for routine general surgical cases

Adults:

- flow generator mode of ventilation
- tidal volume 8−10 ml/kg
- respiratory rate 10−12 breaths/minute
- inspiratory/expiratory (I:E) ratio 1:2
- Fi_{O_2} 0.4 (40% oxygen)
- maximum airway pressure 30 cm H_2O.

If a circle absorber system is in use, an initial fresh gas flow of 6 litres/minute should be used.

A tidal volume of 8−10 ml/kg is appropriate for adults. An I:E ratio of 1:2 allows sufficient time for equilibration in inspiration and time for full expiration, in relation to the TC of normal lung. A starting inspired oxygen concentration of 40% helps to prevent a fall in PaO_2 and overcomes the expected increase in V/Q mismatch that occurs during IPPV. Barotrauma is avoided if peak pressures are kept below 30 cm H_2O.

Flow generators are the preferred method of ventilation in adults. A reliable and predictable tidal volume and minute ventilation can be achieved even when there are alterations in lung mechanics from pre-existing lung disease or when temporary peroperative changes occur related to the effects of patient positioning and surgery.

Children:
- pressure generator mode of ventilation
- inspiratory pressure 20 cm H_2O irrespective of weight
- respiratory rate 30−40 breaths/minute for neonates; 20−25 breaths/minute for infants; 15−20 breaths/minute for older children
- I:E ratio 1:2
- Fi_{O_2} 0.5 (50% oxygen).

Owing to their increased basal metabolic rate relative to their weight, neonates and infants have an oxygen requirement (6 ml/kg/minute) twice that of adults. As a result, they have a high carbon dioxide production, hence the need for a high respiratory rate. Young children also have a reduced FRC, high CC and relatively high airways resistance with low respiratory compliance. Their increased metabolic rate and relatively low FRC means they have limited oxygen stores and so their arterial oxygen saturation falls rapidly if ventilation is inadequate. Loss of respiratory gases as an air leak from around their uncuffed endotracheal tube is expected and indeed desirable. It provides evidence that the endotracheal tube is not so tightly fitting as to cause tracheal mucosal compression at the level of the cricoid ring. Pressure generators, which compensate for gas losses and limit peak pressures, are commonly used in paediatric anaesthesia. At puberty, differential growth of the cricoid ring and laryngeal aperture means that the larynx becomes the narrowest part of the airway as in adults, so cuffed tubes may then be used.

Safety issues

Detection of ventilator disconnection

Anaesthetized, paralysed patients are wholly dependent on the ventilator and the anaesthetist to keep them alive. In this respect, a paralysed patient is much more vulnerable than one who is breathing spontaneously. The anaesthetist should be alerted to a disconnection promptly by a disconnect alarm, which may also indicate when inadequate ventilation is occurring.

Disconnections can be sensed by:
- loss of the rhythmic increase in airway pressure
- reduction in expired gas volume
- loss of expired carbon dioxide.

Monitoring of airway pressures and exhaled CO_2 are part of minimum monitoring requirements during mechanical ventilation.

Airway pressure sensors are either aneroid gauges or, more commonly, electronic pressure transducers. The gauge the anaesthetist uses for monitoring and the alarm system are often separate devices. Airway pressure alarms detect an increase above a threshold pressure. If an increasing pressure that exceeds the threshold is not detected in the preset time, an alarm is sounded. This system does not normally detect a blocked endotracheal tube, but an alarm for the excessive inspiratory pressures generated in this scenario is usually incorporated in the same system.

Expired tidal volume or expiratory flow over time can also be measured. A minimum preset volume must be exhaled at a frequency above the preset minimum rate or the alarm will be triggered. Expired tidal volume is usually measured by integrating the expired flow signal.

Capnographs are fitted with limit alarms and often with apnoea detectors, which detect apnoea from the carbon dioxide waveform. In addition, respiratory movements are sometimes sensed via ECG leads and as a very late indicator, pulse oximeters will alarm if significant arterial desaturation occurs.

Ventilator checks

The anaesthetist is responsible for the state of the equipment he or she uses. It is expected that equipment is systematically checked before use. Although on occasion this may be delegated to trained assistants, the final responsibility lies with the anaesthetist. To this end, guidelines for machine checks have been issued by the Associaton of Anaesthetists of Great Britain and Ireland (Figure 11). With the increasing use of sophisticated, electronically controlled anaesthesic machines and ventilators, a ‘generic’ checklist must be used only with reference to the manufacturer’s suggested protocol for each machine.

Ventilator checks

- Ensure that ventilator tubing is correctly configured and securely attached
- Set the controls for use and ensure that an adequate pressure is generated during the inspiratory phase
- Check that the pressure relief valve functions
- Check that the disconnect alarm functions correctly
- Ensure that an alternative means to ventilate the patient’s lungs is available

Source: Association of Anaesthetists of Great Britain and Ireland. *Checklist for Anaesthetist Apparatus*, 1997.

11

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Breathing Systems

Gordon W G French

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A 'breathing system' is the name given to apparatus that delivers and removes gas and vapour to or from a patient. The three main functions of the breathing system are:

- to supply adequate oxygen
- to remove carbon dioxide
- to supply adequate inhalational anaesthetic agent.

The perfect system has yet to be developed but the ideal breathing system should:

- be simple and safe
- deliver the intended mixture
- allow manual and intermittent positive-pressure ventilation (IPPV) in all age groups
- be efficient (able to use low gas flows)
- protect the patient from barotrauma
- be sturdy, lightweight yet compact
- be easy to scavenge
- be cheap.

Essential components of a breathing system

Tubing (hose): originally this was carbon-impregnated rubber (an antistatic design), corrugated to prevent kinking, but it was heavy and prone to perishing. Modern tubing is usually plastic, disposable or designed for single use, and often has a smooth inner bore that reduces resistance to airflow. Early systems had various means of inter-linking tubes, including tapered metal connectors that pushed into each other and screw mountings. These were manufactured in various sizes, with many systems being non-interchangeable, clearly a dangerous situation. The International Standards Organization (ISO.5356, 1987) and British Standard (BS 3849) recommend the following sizes for all breathing systems:

- 30 mm tapered connections for scavenging hose to breathing systems
- 22 mm taper for connections within breathing systems
- 15 mm connections between the breathing system and the endotracheal tube.

An upstream 'male' connector traditionally fits into a downstream 'female' part. The ISO 15 mm standard connector is cumbersome for small paediatric endotracheal tubes (2–6 mm internal diameter). Smaller, lighter 8.5 mm connectors may be used, which have adapters to connect to the 15 mm standard system. Tapered connections between plastic, metal and rubber can be 'locked' by giving them a slight twist after connecting. Systems designed for repeated use can usually be autoclaved, which does not affect their connectors. Single-use systems often distort if heated, making the connectors unsafe.

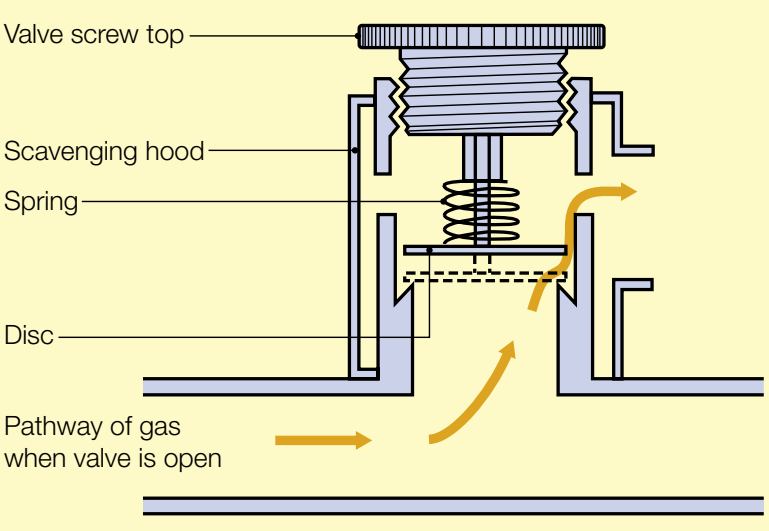
There is controversy among practising anaesthetists as to exactly what 'for single use only' means. Clearly it would be expensive to use a new breathing system for each patient, and almost certainly unnecessary. Many departments employ a cost-effective compromise by using a new disposable antibacterial filter for each patient, but only changing the actual breathing system weekly. It may be changed more often depending on clinical need (e.g. after use in a patient with known lung infection such as tuberculosis).

Reservoir bag: this stores fresh gas when the patient is exhaling and accommodates the high peak inspiratory flow rates during inspiration. Made of rubber or plastic, the common adult size is 2 litres and 0.5 litres for children, but some ventilators use other sizes up to 6 litres. The bag's motion allows observation of ventilatory patterns but does not reflect the tidal volume accurately. As the bag stretches, the pressure in its walls reaches a limit of about 40 cm H_2O (Laplace's law); further distension does not result in greatly increasing pressures. This partly protects the lungs from barotrauma should the breathing system outlet become obstructed, such as when the adjustable pressure-limiting (APL) valve is left fully screwed down. An open-ended reservoir bag is commonly used in paediatric circuits, allowing manual ventilation and assessment of the compliance of a child's lungs (e.g. Mapleson type F).

APL valve: this is a one-way, spring-loaded valve consisting of a thin, lightweight disc (made of hydrophobic material) held by an adjustable spring against knife-edged seating. This arrangement (Figure 1) reduces the area of contact between the disc and the seating, lessening any surface tension that condensed water vapour might create, causing the disc to stick. The disc prevents movement of air into the system when the patient inhales, but opens at low pressure (about 1 cm H_2O) to allow exhaled and surplus gas to be vented during expiration. When fully screwed down, modern valves open at about 60 cm H_2O positive pressure, acting as a safety feature.

Expired gases can be conveniently scavenged by surrounding the valve with a hood. If the valve is sucked open continuously by a faulty scavenging system, a huge increase in the dead space of the apparatus will result. The APL valve should be fully open during spontaneous respiration, partially closed during manual IPPV and fully closed during ventilator IPPV.

Cross-section of an adjustable pressure-limiting valve



1

Classification of breathing systems

The historical development of breathing systems was largely based on the intuition and practical experience of individual anaesthetists. As a result, there are many different systems. One classification based on function is described below.

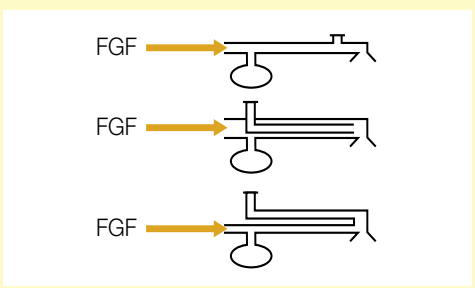
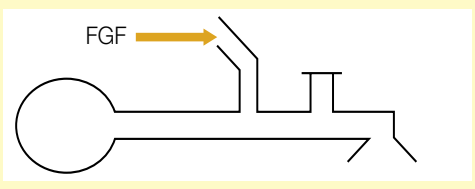
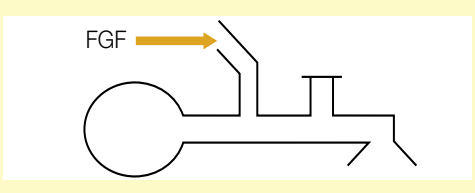
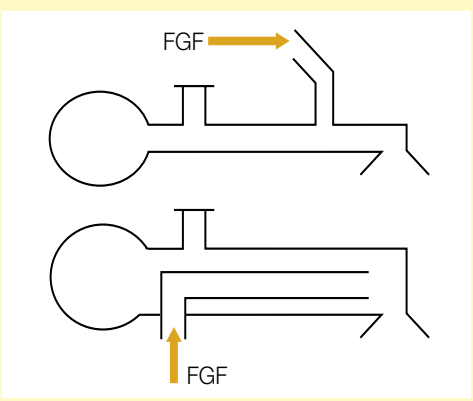
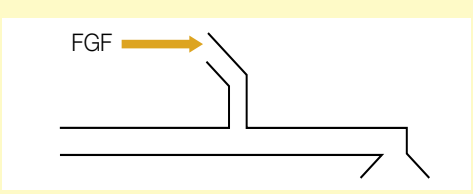
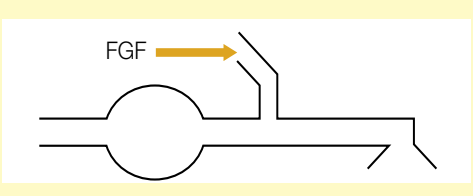
Non-rebreathing systems

Non-rebreathing systems use one-way valves to separate inspired and expired gases. When the patient inspires, the expiratory valve closes and the inspiratory valve opens, allowing inhalation of fresh gas. There is usually a reservoir bag on the inspiratory limb, which provides enough gas for the maximum peak inspiratory flow rate (often > 30 litres/minute), and collects fresh gas when the inspiratory valve is closed in expiration. It may also allow for manual-assisted ventilation. Resuscitation devices commonly include a bag constructed of foam-lined rubber or silicone, which remains inflated in the resting state, in addition to a thin-walled reservoir bag. Manual ventilation is provided by squeezing this bag, which automatically refills from the oxygen inlet and reservoir bag when hand pressure is released. The fresh gas flow (FGF) should at least equal the patient's required minute volume. Examples are resuscitation devices such as the Ambu bag, Laerdal silicone resuscitator, drawover units and the 'Triservice' apparatus.

Rebreathing systems

In rebreathing systems, the inspiratory and expiratory gases can mix in the tubing and re-inhalation of expired gas can occur. Rebreathing refers to inhaling part or all of the previously exhaled tidal volume. In particular, it is the inhaling of previously exhaled carbon dioxide (i.e. alveolar gas) which is of most concern to the anaesthetist. A system is efficient if it can preferentially vent alveolar gas, retaining dead space (non-carbon-dioxide-containing) gas and thus use an FGF that approximates to the patient's alveolar minute ventilation. The extent of carbon dioxide rebreathing thus depends on the FGF flushing the expired gas away before the next inspiration. The normal respiratory cycle consists of an inspiration followed immediately by expiration, but there is then an expiratory pause. It is during this period that the FGF flushes the system. In 1954, Mapleson classified five commonly used systems according to their efficiency at eliminating expired carbon dioxide in spontaneously breathing patients (Mapleson systems A–E). An F system was added in 1975 (Figure 2).

The Mapleson classification of anaesthetic breathing systems and adaptations

Mapleson type		Recommended fresh gas flow	General points
System A **a** Magill **b** Lack **c** Parallel Lack		**Spontaneous** AMV (70 ml/kg/minute) **IPPV** 2–3 x AMV	**a, b, c** Efficient for spontaneous, not for IPPV Heavy, especially at patient end Unsuitable for children < 25 kg because large dead space **b** Lack: coaxial, APL and reservoir bag at machine end Inspiratory gases through outer (30 mm) tube Expiratory via inner (14 mm) **c** Parallel Lack: separate inspiratory and expiratory tubes
System B		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	FGF near patient end. Performs similarly in both modes. Seldom used
System C		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	Similar arrangement to system B. The large-bore tubing to bag is shorter **a** Waters' 'to and fro' circuit: inefficient but small size and simplicity means useful for resuscitation and patient transfers **b** Waters' canister: heavy because incorporates a 1 lb soda lime container between bag and mask or ET tube Channelling occurs if incompletely packed. Nylon pot scourer compresses at bag end. Filter at patient end prevents soda lime dust movement. NB Filter to patient = dead space. Easily sterilized. Now little used. Superseded by circle absorber systems
System D **a** Bain		**Spontaneous** 2–3 x AMV **IPPV** AMV (70 ml/kg/minute)	Inefficient for spontaneous but good for IPPV Manley ventilator on spontaneous ventilation mode is a Mapleson D Safety problems include kinking of inner tube Disconnection of inner tube increases dead space. Both lead to hypoxia and hypercarbia **a** Bain: coaxial D. Length of tube does not affect properties (180–540 cm). FGF through inner tube (opposite to Lack) Ventilate with Penlon 200 replacing bag. Connecting tube long > 500 ml (usually 1 m) to prevent driving gas entering circuit. Lightweight, easy to scavenge. Ga in expiratory limb warm inspiratory gases
System E		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	Used for children up to 30 kg. Low resistance, small dead space, lightweight, no valves. Inefficient but used for spontaneous and IPPV. Expiratory limb is reservoir and should be > V_T to prevent air entraining Ayre's T-piece: developed for neuro/cleft palate surgery
System F		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	Jackson Rees modification. Reservoir bag allows rate and chest compliance to be monitored, ventilation by hand and continuous positive airway pressure application. Barotrauma and humidification a problem

AMV, alveolar minute volume; FGF, fresh gas flow; IPPV, intermittent positive-pressure ventilation; V_T, tidal volume

2

Mapleson A: classically describes the Magill system. The APL valve and any scavenging device make this system cumbersome at the patient's end. Lack solved this problem by creating a co-axial arrangement where the expiratory gases were carried up an inner hose to the APL and scavenging system, both of which were thus distant to the patient. However, this system is bulky, even though it is less weighty at the patient's end. In addition, if the inner tube breaks and this goes unrecognized, the system may become dangerous because carbon dioxide elimination is drastically reduced. It is also difficult to use with a ventilator. A parallel hose breathing arrangement (parallel Lack) eliminates this problem.

The Mapleson A system is an efficient system for spontaneous ventilation because it selectively vents alveolar gas through the APL valve. The first part of the exhaled tidal volume (non-carbon-dioxide-containing dead space gas) is retained in the system and is available for inhalation during the next breath. This efficiency is lost when the system is used for IPPV.

Mapleson B and C: in both systems the FGF, reservoir bag and APL are near the patient, creating a compact and portable system. However, they are both inefficient and only the Waters' 'to and fro' system is commonly used, mainly for patient transport and in postoperative recovery units.

Mapleson D: exhaled gas passes into a reservoir bag along with the fresh gas, so rebreathing occurs unless the FGF is high. The system is efficient for IPPV.

The Bain system is a coaxial version, which is particularly useful for limited-access surgery because of its light weight and the fact that the tubing can be lengthened without affecting the flow characteristics. The system can be connected to a ventilator by replacing the reservoir bag with tubing connected to a ventilator such as the Penlon Nuffield 200. The tubing should be of sufficient length to prevent the ventilator driving gas entering the breathing system (in practice > 500 ml or 1 metre of standard hose). In this system, the FGF is along a narrow internal tube (the opposite of the Lack system), and the expired gas moves along the outer tube, usefully heating up the dry FGF. It is vital that the inner tube is intact because disconnection leads to a huge increase in dead space and possible hypercarbia or hypoxia.

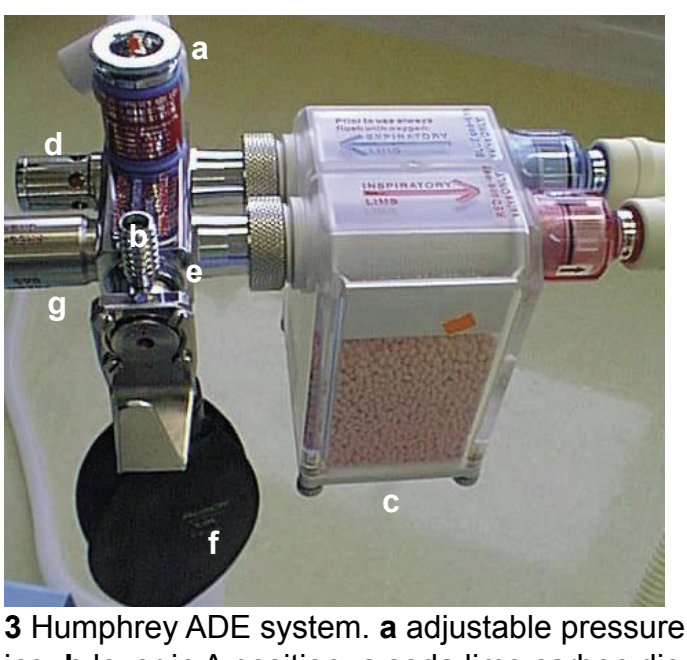
Mapleson E: the Ayre's T-piece is a valveless, lightweight system, with low internal resistance and dead space. In inspiration, gas is inhaled from both the inspiratory and expiratory limb. The volume of the expiratory limb needs to be at least equal to the tidal volume or air may be entrained. If it is too large, then rebreathing can occur because expired gas may not have vented to air before the next inhalation. Occluding the outlet intermittently allows IPPV.

Mapleson F: adding an open-ended reservoir bag to the expiratory limb of the Ayre's T-piece allows manual control of ventilation, observation of breathing and assessment of lung compliance. Some continuous positive airway pressure (CPAP) is also achieved with the system during spontaneous respiration, which, in an infant, may help to increase the functional residual capacity. Scavenging is a problem for both the Mapleson E and F systems. The routine use of capnography allows the FGF to be tailored precisely to achieve normocapnia in individual patients for all these systems.

Humphrey ADE system (Figure 3) is one of a number of hybrid systems that has become popular. It is a low-flow multipurpose system that appears to combine the best of the Magill, Lack and T-piece systems but not their disadvantages. It is cost effective in all modes, being more efficient than the Magill for spontaneous ventilation. The 15 mm, smooth-bore tubing has one-quarter of the resistance to flow of 15 mm corrugated tubing, which allows use in adults and children; 8.5 mm tubing is available for neonates. The reservoir bag, APL, scavenging shroud and a pressure-limiting valve are all located on the 'Humphrey block'. The system tubing connects to the patient via a symmetrical Y-piece, which probably accounts for much of its efficiency as it produces less turbulence than the conventional Magill–patient interface. One lever allows conversion from A mode to E mode, with only a slight increase in FGF being required to eliminate rebreathing. In E mode, the reservoir bag and APL are isolated from the system, and the expiratory tubing acts as the reservoir limb of a T-piece. This is open to the atmosphere via a port on the block to which a bag squeezer ventilator such as the Manley Servovent or Penlon Nuffield 200 or 400 can be attached. The D mode could be engaged by simply attaching a reservoir bag and APL to this port for spontaneous ventilation, but this is much less efficient than the A mode.

The APL valve provides positive end-expiratory pressure of 1 cm H_2O without increasing the airway resistance of the apparatus. The APL valve does not have to be screwed down for IPPV, except if used in the A mode. However, there is a long orange valve seat stem that can be temporarily held down instead. This also moves slightly during spontaneous respiration and gives a visual indication of respiratory movement. A separate 60 cm H_2O pressure-limiting valve lies behind the APL valve on the block. This is always in-line, whatever mode is being used. The system can be fixed on to the anaesthetic machine via a locking nut. A 500 g soda lime canister (lifespan 12 hours), which has a low resistance to flow and is autoclavable, can be fitted in front of the block. This circle system arrangement requires no other alterations in FGF for adults or children.

The entire system is MRI compatible, being made of plastic and brass. In addition, tubing lengths of over 3 m can be used without compromising its function. The main disadvantages are that it protrudes out of the anaesthetic machine, is heavy and can be knocked, which theoretically could fracture old anaesthetic machine outflow pipes.



3 Humphrey ADE system. **a** adjustable pressure limiting valve with scavenging; **b** lever in A position; **c** soda lime carbon dioxide absorber; **d** pressure relief (60 cm H_2O) valve; **e** port for ventilator; **f** reservoir bag; **g** fresh gas flow. Fresh gas flow: A mode (lever up) = 50 ml/kg/minute; E mode (lever down) = 70 ml/kg/minute. Children start at 3 litres/minute.

Systems using carbon dioxide absorbers

The circle system (Figure 4) was first described in the 1920s. It uses soda lime to absorb exhaled carbon dioxide. Partial rebreathing of other exhaled gases can thus be undertaken, depending on the arrangement of the components and the FGF.

Circle systems can be classified as follows:

- semi-open – no rebreathing, very high FGF, APL valve wide open
- semi-closed – rebreathing occurs, low flow, APL valve partly closed
- closed – FGF inflow exactly matches uptake by patient; complete rebreathing of exhaled gases after carbon dioxide uptake and APL valve fully closed.

A circle system consists of:

- FGF source
- inspiratory and expiratory unidirectional valves
- inspiratory and expiratory corrugated tubes
- a Y-piece connector
- an APL valve or pop-off valve
- a reservoir bag
- a canister containing a carbon dioxide absorbent.

Fresh gas enters the circle by a connection from the common gas outlet of the anaesthetic machine. Various arrangements of components are possible, but there are three golden rules to prevent carbon dioxide rebreathing.

- A unidirectional valve must be located between the patient and the reservoir bag on both the inspiratory and expiratory limbs of the circuit. These valves commonly have a clear plastic cover so that their correct movement can be observed during use.
- The FGF cannot enter the circuit between the patient and the expiratory valve.
- The APL valve cannot be located between the patient and the inspiratory valve.

The most efficient circle system has the unidirectional valves near the patient and the APL valve just downstream from the expiratory valve. This arrangement conserves dead space gas and preferentially eliminates alveolar gas. The advantages and disadvantages of a circle system are listed in Figure 5.

Nitrogen washout – at the start of anaesthesia, non-nitrogen-containing gas (unless medical air is being used) is inspired and body nitrogen passes into the lungs. This effectively reduces the oxygen concentration in the alveoli and circle system, producing a potentially hypoxic mixture. The use of high flows of gas at the start of anaesthesia can 'washout' this nitrogen. Pre-oxygenation with 100% oxygen for 7–10 minutes is also effective and can theoretically then allow low circle FGF to be used from the start. Basal metabolic oxygen requirements are about 250 ml/minute, but to allow for leaks in the circle and patient variability, 500 ml/minute oxygen is the minimum recommended flow rate. 'Low flow' anaesthesia is usually regarded as less than 1 litre/minute FGF.

The uptake of volatile agents is highest initially. Fast FGF inflows and large minute volumes produce fast induction of anaesthesia as well as facilitating denitrogenation. As equilibrium is reached, the expired concentration of volatile agent begins to reflect the inspired value, and flows can be reduced. The exhaled gases are added to the fresh gas and have a dilutional effect on the concentration of oxygen and vapour, which will be proportionally greater at low flows. A potentially hypoxic alveolar concentration of oxygen can develop as the FGF reduces. Using an inspired oxygen concentration of 50% to prevent these low oxygen levels in the circle was customary before the advent of in-line gas/vapour analysers. However, this was associated with an increased chance of awareness if the inspired volatile concentration was not increased to compensate for the lower inspired nitrous oxide and volatile concentrations.

Vaporizers can be placed outside (VOC) or inside (VIC) the circle (Figure 6). Most modern vaporizers tend to be outside the circle (e.g. Back bar units such as a TEC vaporizer) and are accurate at low flows. With this set-up, the concentration of volatile gas in the circle is reduced with increased patient uptake and low FGF (due to the dilutional effect of exhaled gas), until uptake reduces and equilibration begins to occur. With a vaporizer in the circle (e.g. Goldman vaporizer), both the fresh and exhaled gas (which already contains vapour) pass through the vaporizer. When the FGF is low and alveolar ventilation high, the concentration of volatile will rise. Thus the concentration of the alveolar and circle vapour is a function of ventilation. In spontaneous ventilation, with deepening anaesthesia and depression of ventilation, the concentration of volatile gas will fall and result in the patient becoming lighter, a useful safety feature. However, low flow controlled ventilation may result in high levels of volatile gas.

Future developments in circle technology may incorporate the VIC arrangement but use a system of vapour injectors instead of the vaporizer. This would be linked to a feedback mechanism incorporating circuit vapour analysis.

Carbon dioxide absorption – closed or semi-closed circle systems require carbon dioxide absorption to make rebreathing possible. Desirable features of a carbon dioxide absorption mechanism are lack of toxicity (intrinsic or with common anaesthetics), low resistance to air flow, low cost, ease of handling and efficiency. Soda lime and baralyme are the two formulations commonly used for carbon dioxide absorption (Figure 7). Both need water but because baralyme contains water as a barium hydroxide octohydrate salt it performs better in dry climates. Soda lime (but not baralyme) is capable of some regeneration after exhaustion. Maximum absorbency of both systems is 26 litres of carbon dioxide per 100 g absorbent.

Dyes (acids or bases) are also added, which change colour as the hydrogen ion concentration changes:

- ethyl violet (colourless to violet; fluorescent light deactivates it)
- phenolphthalein (white to pink)
- Clayton yellow (red to yellow)
- ethyl orange (orange to yellow)
- mimosa z (red to white).

The chemical reaction in soda lime is:

$CO_2 + H_2O \rightleftarrows H_2CO_3$

$H_2CO_3 + 2NaOH\ [KOH] \rightleftarrows Na_2CO_3\ [K_2CO_3] + 2H_2O + heat$

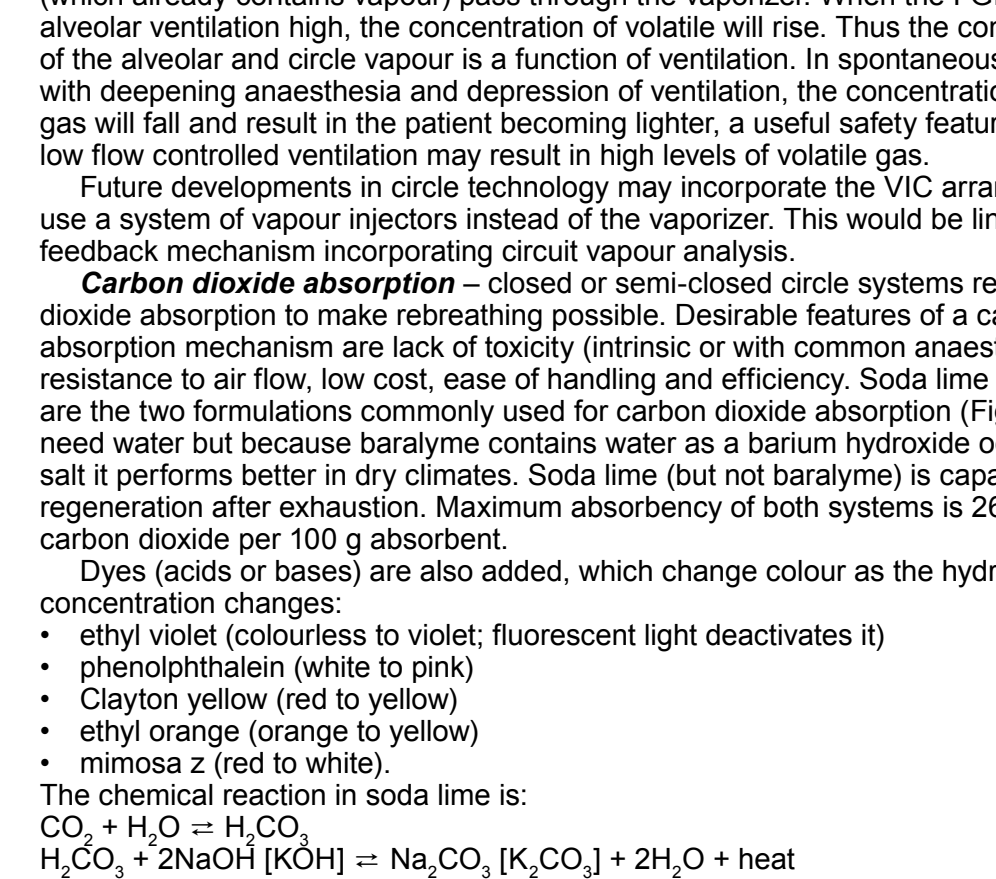
$Na_2CO_3\ [K_2CO_3] + Ca(OH)_2 \rightleftarrows CaCO_3 + 2NaOH\ [KOH]$

Some carbon dioxide reacts directly with calcium hydroxide but this is much slower. In baralyme the carbon dioxide acts directly with barium hydroxide and much more water is released. In the UK, the size of granules is 4–8 mesh (a compromise between surface area for absorption and air flow resistance). Mesh refers to the number of openings per linear inch in a sieve through which the granules pass. A 4-mesh screen indicates four quarter-inch openings per linear inch.

Soda lime and baralyme are not inherently toxic, but at low flows intrinsically produced acetone can accumulate and has been linked to nausea and vomiting. Carbon monoxide can also accumulate at low flows of dry gas (e.g. oxygen running overnight) leading to the formation of carboxyhaemoglobin.

The volatile agent trilene degrades into dichloroacetylene (a neurotoxin causing cranial nerve damage and encephalitis) and phosgene (a potent pulmonary irritant causing adult respiratory distress syndrome).

Sevoflurane and halothane are slightly unstable in soda lime, the rate of degradation increasing with temperature. Sevoflurane degrades into several compounds. Compound A (a vinylether) has been associated with lung haemorrhage and renal tubular necrosis in rats, but neither compound has been shown to cause problems in humans. Many of these problems are resolved by flushing the system regularly.



Properties of a circle system

Advantages	Disadvantages
• Heat/moisture conservation • Easy scavenging • Reduced cost • Small dead space • Good for long cases	• Multiple connections • Valves can stick • Open – leads to rebreathing • Closed – leads to asphyxia • Bulky • Inefficient for short cases • Soda lime changeover a hazard • Gas analyser necessary for accuracy • Potential for infection

5

Properties of vaporizers

Inside the circle	Outside the circle
• Low internal resistance • Low efficiency desirable • Higher concentrations at low fresh gas flow	• High internal resistance (plenum) • High efficiency desirable • Lower concentrations at low fresh gas flow (diluted)

6

Properties of soda lime and baralyme

Soda lime	Baralyme
• Calcium hydroxide (94%) • Sodium hydroxide (the catalyst) (5%) • Potassium hydroxide (1%) • Silica (calcium and sodium silicate harden it and reduce dust formation)	• Calcium hydroxide (80%) • Barium hydroxide (the catalyst) (20%) • More stable so does not contain silica • Denser and 15% less efficient than soda lime

7

System checks

All systems should be checked visually for broken parts and disconnections and a push-and-twist connector test performed. In addition, there are checks specific to individual systems.

- Occluding Mapleson types B and C causes their reservoir bags to fill, testing the air-tightness of the system. Releasing the valve causes the bag to deflate if the valve is functioning normally.
- The Bain system inner tube can be tested in two ways. Occluding the end of the inner tube causes the rotameter bobbin to dip and the pressure alarm/valve to blow if there are no leaks/disconnections up to that point. Occluding the patient end of the system will fill the reservoir bag, testing overall air- tightness. Releasing the occlusion causes the bag to deflate, then continue to empty as a result of the negative pressure caused by the Venturi-effect of the fast FGF leaving the inner tube. The connection of the inner tube can also be visually inspected because the outer corrugated tubing is often made from transparent plastic. This outer tubing may also be temporarily disconnected and a secure inner tube connection confirmed.
- To carry out the low-pressure circle leak test, the end of the system should be occluded and the APL valve closed off. The system is filled using the oxygen flush until the airway pressure gauge registers 30 cm H_2O. The pressure should remain at 30 cm H_2O if no leaks are present.

FURTHER READING

Humphrey D, Brock-Utne J G, Downing J W. Single Lever Humphrey ADE Low Flow Universal Anaesthetic Breathing System. *Can Anaesth Soc J* 1986; **33(6):** 698–718.

Cleaning, Disinfection and Sterilization of Equipment

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Jonathan Warwick

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Hospital-acquired infections have significant implications for the morbidity and mortality of patients as well as for the economics of health care. The protection of patients and medical staff from medical equipment that has come into contact with patients or their body fluids, requires the adoption of various processes enforceable by law. Changes in these laws and guidelines, published by the Department of Health and the Medical Devices Agency, are expected in the near future. One of the reasons for the introduction of new guidelines is the development of new variant Creutzfeldt–Jakob disease, which is resistant to the standard methods of decontamination used in hospital sterile services departments.

Contamination is the soiling or pollution of an inanimate object with harmful, potentially infectious, material. In the clinical setting, this is most likely to be organic material or microorganisms. Contamination may place the patient at risk and may adversely affect equipment.

Decontamination is a method used to remove contamination and prevent microorganisms reaching a susceptible site in large enough numbers to initiate infection or other adverse effects. The three methods of decontamination routinely used are cleaning, disinfection and sterilization. The method of decontamination chosen takes into account the infection risk from the reprocessed piece of equipment. The risk is dependent on:

- the amount of contact the patient has with the piece of equipment (i.e. how invasive)
- the susceptibility of the patient (i.e. immunocompromised, potential hypersensitivity)
- the nature, extent and amount of microbial contamination on the piece of equipment (the bio burden).

The type of equipment and its intended use determine the method of decontamination used (Figure 1). The manufacturer should provide instructions for cleaning, disinfection and sterilization techniques that are effective without affecting the performance of the equipment.

It is essential that records are kept to demonstrate the number of times an item has been decontaminated and the effectiveness of each process. The documentation should allow patients to be traced in the event of any malfunction in the decontamination process.

Risk of contamination for equipment and suggested decontamination process

Risk	Application of equipment	Recommendation
High	• In close contact with a break in the skin or mucous membrane • For introduction into sterile body areas	Sterilization
Intermediate	• In contact with mucous membranes • Contaminated with particularly virulent or easily transmissible organisms • Before use on immunocompromised patients	Sterilization or disinfection (Cleaning may be acceptable in some agreed situations)
Low	• In contact with healthy skin • Not in contact with patient	Cleaning

1

'Single use' equipment

Manufacturers should state in the product literature any restrictions on the number of re-uses. Any device deemed by the manufacturer as unsuitable for reprocessing is labelled 'single use'. Devices labelled 'single patient use' may be used for an extended period of time or intermittently on the same patient. Users who disregard the manufacturer's guidelines, for example by reprocessing single use items or reprocessing more than the recommended number of times may be transferring legal liability for the safe performance of that product from the manufacturer to themselves or the organization for which they work.

Many anaesthetic departments routinely use disposable anaesthetic breathing systems marked as single use for extended periods with multiple patients. The wisdom of this practice is the subject of much controversy. The advantages of these breathing systems include safety (often pre-assembled with fewer opportunities for connection errors by the user), lightweight and low cost if used on several patients. The disadvantage is that this practice may contravene the manufacturer's recommendation for single use only and risk transmission of infection. The responsibility for use of equipment marked single use then lies with the hospital. Departments of anaesthesia should have an operational policy on the management of breathing systems marked for single use. This may include:

- the use of a new bacterial (heat and moisture exchanger type) filter for each patient
- change of all breathing systems weekly
- change of breathing system following use on a patient with known or suspected lung infection
- change of breathing system whenever there is visible contamination from blood or body fluids.

Cleaning

Cleaning physically removes contaminants without necessarily destroying microorganisms. It removes organic material and is required before disinfection or sterilization.

Manual cleaning

Manual cleaning does not disinfect. It should be used only when other mechanical methods are inappropriate or unavailable.

Immersion – wearing appropriate protective clothing, the cleaner should submerge the device in compatible water/detergent solution at the correct dilution and not exceeding 35°C. It is important to ensure that the cleaning solution reaches all surfaces of the device, including lumen surfaces. Endoscopic equipment that may be totally immersed for cleaning is marked with a blue line, usually around the eyepiece adjacent to the focussing ring. The device should be brushed or agitated to remove any visible contaminants. The device should be thoroughly drained and rinsed in clean water. This method is generally satisfactory for the routine cleaning of laryngoscopes between patients. Disinfection with an alcohol spray is then commonly used.

Non-immersion – wearing appropriate protective clothing, the cleaner should immerse a cleaning cloth into the detergent solution and wring it out. The equipment should be cleansed by wiping its surfaces. The surfaces should be hand dried using a cloth, hot air dryer or drying cabinet. This method of cleaning is often used for electrical or electronic equipment which cannot be immersed in water.

Mechanical cleaning

Mechanical cleaning uses automated washers to clean equipment and often combines cleaning with disinfection.

Thermal washer – cleaning occurs by continually spraying the equipment with water and detergent during a timed cycle. During the first process, cleaning occurs at 35°C. The second wash heats the surface of the equipment to a minimum temperature of 71°C for a minimum of 3 minutes, 80°C for 1 minute, or 90°C for 1 second to disinfect it.

Chemical washer – the first part of the cleaning process is the same as the thermal washer. Disinfection occurs by exposing the equipment to an approved disinfectant for a particular period of time at less than 60°C. The residue disinfectant is then removed by a rinse cycle.

Ultrasonic cleaners are often incorporated into washer disinfectors. These work by rapidly forming bubbles in the liquid, which immediately collapse (cavitation). This cavitation agitates the liquid, producing a highly effective cleaning system. The process does not disinfect.

Disinfection

Disinfection is used to reduce the number of viable micro-organisms, but it may not kill all microbial agents such as some viruses and bacterial spores.

Low temperature steam disinfection

Low temperature steam disinfection is also known as pasteur-ization. It kills most vegetative microorganisms and viruses by exposure to moist heat. The equipment is exposed to dry saturated steam at a temperature of 73°C for at least 10 minutes at below atmospheric pressure. The low temperature steam kills vegetative microorganisms and some heat-sensitive viruses. It cannot be used for sealed, oily or greasy pieces of equipment or those with sealed cavities due to the variation in pressure.

The advantages of this system are its broad spectrum of disinfection, it is non-toxic, non-corrosive and the equipment is relatively safe and simple to use. The disadvantages are that it requires a trained operator and that much equipment is unsuitable for disinfection in this way. The capital cost of the disinfector is high and the equipment is fixed and not portable.

Boiling water disinfection

Boiling water is an effective disinfectant against many microorganisms. Immersing a piece of equipment in soft water and boiling at 100°C for at least 5 minutes produces disinfection. Boiling inactivates most non-sporing microorganisms, fungi, viruses and some heat-sensitive spores. This method is not used if a better method is available. It is unsuitable for heat-labile pieces of equipment, hollow or porous items into which the water will not penetrate, or tubing over 1 metre in length.

The advantages are that boiling water has a broad disinfecting effect. The process is non-toxic and inexpensive. The disadvantages are that boiling water is a potential cause of injury. Following disinfection, items are wet and unfit for immediate use and must be allowed to dry and cool, which may allow recontamination. There is also no method of checking the efficacy of the process.

Washer disinfectors

Washer disinfectors are described above. They inactivate all microorganisms except bacterial spores and some heat-resistant viruses. They are unsuitable for equipment that may be heat labile or corroded by chemical disinfectant, and for hollow or porous equipment that does not allow all surfaces to come into contact with the chemical disinfectant or heat.

These methods are safe for the operator. There is minimal handling of the equipment by staff and therefore a low risk of recontamination. Another advantage is that they combine cleaning and disinfection. The disadvantages are the high cost of the equipment and the requirement for trained staff.

Liquid chemical immersion

Liquid chemical immersion relies on good contact between the chemical disinfectant and the equipment. The equipment therefore requires thorough cleaning beforehand. It is then immersed in the chemical disinfectant, ensuring that the disinfectant reaches all surfaces. The equipment is immersed for a predetermined time depending on the chemical disinfectant used. The spectrum of activity also depends on the type of chemical disinfectant used (Figure 2).

The method is unsuitable if the corrosive nature of the chemical disinfection may damage the equipment or if the equipment has areas inaccessible to liquid. It requires trained staff wearing protective clothing. It is potentially toxic, corrosive or volatile. Also, the equipment may have to be hand dried after disinfection allowing possible recontamination.

Equipment disinfectants commonly used and their spectrum of activity and physical properties

Disinfectant	Microbiological activity					Stability	Inactivation by organic matter	Corrosive/ damaging matter	Irritant
	Spores	Mycobacteria	Bacteria	Viruses[1] Enveloped	Viruses[1] Non-enveloped				
• Glutaraldehyde 2%	+++ (slow)	+++	+++	+++	+++	Moderate (fixative)	No	No	Yes
• Peracetic acid 0.2–0.35%	+++	+++	+++	+++	++	Poor (< 1 day)	No	Slight	Slight
• Alcohol (ethyl alcohol) 60–80%	None	++	+++	+++	++	High	Yes (fixative)	Slight	No Flammable
• Peroxygen compounds	None	+	+++	+++	++	Moderate (7 days)	Yes	Slight	No
• Chlorine-releasing agents >1000 ppm average Cl_2	+++	+++	+++	+++	++	Poor (< 1 day)	Yes	Yes	Yes
• Clear soluble phenolics 0.6–2%	None	+++	+++	+	None	Good	No	Slight	Yes
• Quarternary ammonium compounds	None	Variable	Moderate	+	+++	Good	Yes	No	No

[1] Activity varies with concentration of product.

Sterilization

Sterilization is used to produce an object free from viable microbial organisms including viruses and bacterial spores. There are several types of sterilizer (Figure 3).

Steam

When steam is pressurized it reaches a temperature greater than that of boiling water at atmospheric pressure and destroys or renders non-viable, bacteria, viruses and their spores. For this process to be effective, direct contact between the pure dry saturated steam and the object being sterilized is required at the specific temperature and in the absence of air. The temperature reached by the object determines the time required for sterilization. The lowest temperature recommended is 121°C for 15 minutes; the highest temperature of 134°C requires only 3 minutes.

This process is effective against all microorganisms with a significant safety factor. Problems occur with wrapped items because all air must be removed. To overcome this, porous load sterilizers are used, which incorporate a vacuum pump. Air is removed before steam is added. This is the most commonly used method for sterilization in hospitals today (Figure 4). However, it cannot be used for any material that cannot withstand the temperatures or pressures required for sterilization (e.g. thermo-labile plastics, fibre-optic endoscopes).

The advantages of this process are that steam is non-toxic, non-corrosive and a highly effective sterilizing agent. This system can be incorporated into a fully automated process on a large scale, coping with a high turnover of equipment. Disadvantages are that the operator must wear protective clothing to avoid direct contact with the steam.

Different types of hospital sterilizers

Types of sterilizer	Use	Minimum time / temperature
• Steam sterilizer		
Porous load	Wrapped instruments, dressings, utensils	134–138ºC for 3 minutes
Fluid cycle	Fluids in sealed containers	121–124ºC for 15 minutes,
	or 115ºC for 30 minutes	
Unwrapped instruments	Unwrapped instruments and utensils	134–138ºC for 3 minutes
• Hot air sterilizer	Oils, powders, heat-resistant instruments that must be kept dry	160ºC for 2 hours
• Low temperature steam formaldehyde sterilizer	Heat-sensitive equipment	73ºC for 3 hours
• Ethylene oxide	Heat-sensitive equipment	Various temperatures and times

Dry hot air

In this process, sterilization takes place by raising the ambient temperature. Typical processes consist of 160°C for 2 hours, 170°C for 1 hour, 180°C for 30 minutes. If all the items are completely clean and dry before this sterilization process starts, then all microorganisms will be killed. However, it cannot be used for materials that would be damaged by these temperatures (e.g. rubber, plastic).

Dry heat can be used to sterilize stable powders, waxes and non-aqueous liquids. It is also effective for non-stainless metals, hollow needles and glass syringes. However, the sterilization time is long compared with other methods, and items have to cool slowly afterwards. Many pieces of equipment cannot withstand these high temperatures for the allocated time.

Ethylene oxide

Ethylene oxide at ambient pressure and temperature vaporizes easily and thus has good penetrative properties. It is also non-corrosive and has a wide spectrum of activity against bacteria, spores, fungi, viruses and other living cells. Sterilization is usually carried out at 20–60°C for 2–24 hours.

Ethylene oxide is most often used under three different conditions:

- normal atmospheric pressure using undiluted ethylene oxide – the gas is very flammable, and so is often diluted to reduce explosion risk
- ethylene oxide with a diluent gas such as nitrogen at a pressure of 2 bar
- ethylene oxide diluted with carbon dioxide at a pressure of 6 bar.

This process should not be used if heat sterilization is possible. Organic material has a marked protective effect and therefore prior cleaning is essential. Ventilatory or respiratory equipment is contraindicated. Ethylene oxide does not penetrate plastic; therefore items must be wrapped in sterilization paper.

Ethylene oxide is a highly effective sterilizing agent. In particular it is used to sterilize single use medical items that would be damaged by the excessive heat used in other sterilization methods. Disadvantages of ethylene oxide are that it is toxic and long periods of aeration are required after sterilization therefore turn-around time is long. The process is expensive and there are significant health and safety issues concerning ethylene oxide and the equipment required to use it. Because of this, ethylene oxide is not often used in hospitals but is commonly used by industry.

Low temperature steam and formaldehyde

This process uses a combination of dry saturated steam and formaldehyde, which together kill vegetative bacteria, spores, fungi and most viruses. Objects are placed in the sterilizer to allow maximum contact with the steam. Air is actively removed from the container and replaced by dry saturated steam at 73°C at subatmospheric pressure. Formaldehyde is entrained as the steam enters the sterilizer.

The subatmospheric pressure may damage hollow objects. Formaldehyde may be corrosive with certain materials and some fabrics may absorb formaldehyde. This method cannot be used for items contaminated with body fluids, because the proteins in the fluids congeal and produce hard fixed deposits.

Advantages of the process are that it can provide dry, packaged items in a sterile form and the process is fully automated. Disadvantages are that the process is complex and formaldehyde is toxic, irritant and possibly mutagenic. The equipment required is also expensive, with the added problem of toxic waste products.

Irradiation

Irradiation uses γ rays or accelerated electrons. A dose greater than 25,000 Gray produces sterility. Irradiation is often used to sterilize single use items on an industrial scale. It has a broad spectrum of activity. Irradiation can cause significant degradation of materials and is unsuitable for the resterilization of hospital equipment.

The advantages are that it is reliable on an industrial scale for heat-labile pieces of equipment. However, irradiation can damage equipment particularly on re-exposure. Monitoring the process and the required safety equipment is expensive.

Special circumstances

Recent work has identified that the prion strain causing bovine spongiform encephalopathy (BSE) in cattle has infected humans, manifesting itself as a novel human prion disease, new variant Creutzfeldt–Jakob disease (vCJD). The abnormal prion protein is a new class of transmissible agent that demonstrates resistance to the standard methods of sterilization used in hospital sterile services departments.

Affected individuals accumulate prion protein in lympho-reticular tissues (e.g. appendix, tonsils), as well as in the CNS. The number of people incubating the disease is unknown, and there are concerns that prions might be transmitted iatrogenically via contamination of surgical instruments. Such risks remain unquantified, and there have been no identified cases involving vCJD transmission via surgical instruments. All neurosurgical instruments used on patients suspected of carrying vCJD are destroyed. However, there are significant implications for the safety of surgical instruments in ENT and other surgical practice.

The Spongiform Encephalopathy Advisory Committee (SEAC) has recommended that, where feasible, the move to single use instruments is appropriate. From January 2001, the Department of Health requires tonsillectomy and adenoidectomy to be performed using single use instruments in England and Wales. The recommendations are that instruments used to dissect or cut lymphoid tissue are to be disposed of. Anaesthetic equipment may also provide theoretical risk for prion disease transfer. This risk is as yet unquantified and accepted practice is continuing to evolve. It is likely that, in the near future, anaesthetic practice will change to incorporate disposable, single patient use equipment wherever possible (e.g. disposable laryngoscope blades and laryngeal mask airways).

Critical Incidents: The Cardiovascular System

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Hypertension

Hypertension is a common critical incident during anaesthesia. Whether it is harmful depends on its severity, cause and duration, and on the condition of the patient. These factors also determine how actively it needs to be treated. Hypertension is difficult to define because of observer and subject variation, and the arbitrary nature of cut-off values, but definitions include:

- elevation of blood pressure at least 15% above patient's baseline
- systolic blood pressure greater than 160 mm Hg and/or a diastolic blood pressure greater than 95 mm Hg. Figure 1 lists the causes of hypertension during or persisting after anaesthesia.

Causes of hypertension during or persisting after anaesthesia

- Inadequate anaesthesia/analgesia
- Tracheal intubation/extubation
- Inadequate muscle relaxation
- Pre-existing hypertensive disease
- Hypoxaemia
- Hypercapnia
- Aortic clamping
- Raised intracranial pressure, cerebral ischaemia or cerebrovascular accident
- Drugs (e.g. ketamine, adrenaline (epinephrine))
- Metabolic disorders (e.g. malignant hyperpyrexia, thyroid crisis, phaeochromocytoma, carcinoid syndrome)
- Postoperative urinary retention, pain, anxiety

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Complications

Cardiovascular – hypertension may precipitate myocardial ischaemia (especially subendocardial), infarction or failure.

Neurological – cerebral haemorrhage may result, especially in patients with vascular malformations. Cerebral oedema or encephalopathy are less common complications of uncontrolled hypertension.

Haemorrhage at the operation site or from pre-existing vascular malformations.

Renal – severe hypertension may precipitate acute renal failure.

Management

Management of hypertension should be directed towards the underlying cause. The usual cause is inadequate anaesthesia for the level of surgical stimulation being employed and treatment requires an increase in the inhalational or intravenous anaesthetic drug, or an increase in analgesia. Confirmation of the diagnosis may require a trial of therapy. If the cause of the hypertension cannot be diagnosed or removed, an appropriate antihypertensive drug may be used. The following are examples of drugs commonly used.

- Labetalol – combined α- and β-blockade; dose 5–20 mg i.v. over 2 minutes with increments up to 200 mg. Onset 5–30 minutes, duration 50 minutes.
- Metoprolol –β_1 (cardioselective) blockade; 2 mg increments slow i.v., maximum dose 15 mg.
- Esmolol – rapid onset; short half-life of 9 minutes; 500 µg/kg loading dose; 50–200 µg/kg/minute infusion.
- Nifedipine – calcium-channel blocker, sublingual or intranasal; onset 1–5 minutes following a 10 mg dose.
- Phentolamine – α-blockade; 0.5–2 mg i.v., repeated as necessary, rapid onset, short half-life 10–15 minutes.
- Hydralazine – direct-acting arteriolar dilator, peak action after about 20 minutes following 10–20 mg slow i.v. injection over 20 minutes. Onset occurs after 15–20 minutes; duration is 2–6 hours.
- Glyceryl trinitrate – arterial and venous dilator; use 1 mg/ml solution i.v. (preferably a central vein) via syringe driver, dose 10–200 µg/minute, maximum effect after 1–2 minutes.
- Sodium nitroprusside – arteriolar dilator; very rapid response, administered by continuous intravenous infusion via a dedicated vein, 0.5–1.5 µg/kg/minute. Direct arterial blood pressure recording is mandatory. Doses greater than 4 µg/kg/minute may cause cyanide poisoning.

Hypotension

Mild-to-moderate falls in blood pressure are common during anaesthesia, but seldom result in any harm to the patient. It is difficult to determine what is a dangerous level of hypotension; it depends on the duration of hypotension and the patient's preoperative medical condition. Two signs of inadequate myocardial perfusion are the development of ST segment depression and ectopic beats. Increased ventilation–perfusion mismatch secondary to pulmonary hypotension causes a fall in oxygen saturation (SpO_2). In awake patients receiving regional anaesthesia, nausea and dizziness are common symptoms of excessive hypotension. The lower limit of cerebral, renal and hepatic autoregulation occurs at a mean arterial pressure of about 60 mm Hg in otherwise healthy individuals.

Causes

Anaesthesia

- Volatile agents produce a dose-related fall in blood pressure (vasodilatation, myocardial depression, impaired baroreceptor response).
- Induction agents cause a dose-related fall in blood pressure owing to a complex combination of effects involving myocardial depression, vasodilatation, altered baroreceptor reflex and bradycardia (especially propofol).
- Opioids may precipitate histamine release and vasodilatation. Larger doses are associated with bradycardia.
- Non-depolarizing muscle relaxants may produce hypotension secondary to histamine release.
- Positive-pressure ventilation increases intrathoracic pressure and produces a decrease in venous return and cardiac output.
- Spinal and epidural anaesthesia produce sympathetic blockade. This results in vasodilatation, reducing venous return, cardiac output and systemic vascular resistance. Although reflex vasoconstriction occurs above the level of the block, blood pressure usually falls. Higher blocks (T4 or above) obtund the cardiac sympathetics, preventing a compensatory tachycardia.
- In obstetrics, aortocaval compression impairs venous return and in combination with spinal and epidural anaesthesia may produce profound hypotension.

Hypovolaemia, regardless of aetiology, becomes less concealed following induction of anaesthesia owing to impairment of compensatory mechanisms. Hypotension then ensues. Hypovolaemia may occur in patients with:

- trauma or burns
- gastrointestinal disease (e.g. haematemesis, melaena, small bowel obstruction, acute inflammatory bowel disease)
- dehydration from poor fluid intake, vomiting or diarrhoea
- metabolic disorders (e.g. diabetic ketoacidosis, diabetes insipidus, hypercalcaemia).

Surgical causes of hypotension include:

- haemorrhage
- head-up position
- excessive intra-abdominal pressure during laparoscopic surgery may impair venous return causing hypotension
- release of aortic cross-clamping or lower limb tourniquets causes an acute fall in systemic vascular resistance and blood pressure secondary to vasodilatation in the ischaemic tissues.

Cardiovascular disease may lead to hypotension:

- ischaemic heart disease with impaired cardiac contractility (including unstable angina and recent myocardial infarction)
- heart failure
- valvular heart disease (mitral or aortic stenosis and regurg-itation)
- dysrhythmias (fast atrial fibrillation, complete heart block)
- hypertension, especially if poorly controlled
- others (e.g. myocarditis, cardiomyopathy, constrictive pericarditis, myocardial contusion, tamponade, aortic coarctation, congenital cardiac anomalies).

Cardiovascular medication such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, nitrates, α_1-antagonists (prazosin) and centrally acting α_2-agonists (e.g. clonidine, methyldopa) may cause hypotension.

Autonomic neuropathy produces impaired baroreceptor response and may be present in a variety of disease states:

- diabetes mellitus (incidence and severity increase with the duration of the disease)
- Guillain–Barré syndrome
- spinal cord injury and following cerebrovascular accident
- Parkinson's disease
- AIDS.

Other causes

- Anaphylaxis may result in massive histamine-mediated vasodilatation, producing cardiovascular collapse.
- Pulmonary embolus from deep vein thrombosis, or emboli from air, carbon dioxide or fat may reduce cardiac output. Hypotension is accompanied by desaturation and a fall in end-tidal carbon dioxide.

Management

- Identify and remove the precipitating cause.
- Increase fraction of oxygen in inspired air (F_iO_2) to maintain SpO_2.
- Position patient supine, possibly with the legs raised to improve venous return. The head-down position is no longer recommended because it also raises cerebral venous pressure and therefore cerebral perfusion pressure may not be improved.
- Give a rapid intravenous infusion. The type and amount of fluid depends on aetiology and patient factors. A useful guide is to infuse 10 ml/kg of colloid or 20 ml/kg crystalloid initially and assess the response.
- Vasopressors may be considered, particularly if the cause of hypovolaemia is non-haemorrhagic (e.g. ephedrine, 3–6 mg i.v., metaraminol, 0.5–1.0 mg i.v., or phenylephrine, 0.5–1.0 mg i.v.).
- Consider an infusion of a positive inotrope (e.g. adrenaline (epinephrine), dobutamine) or vasoconstrictor (e.g. noradrenaline (norepinephrine)).

Massive haemorrhage

Bleeding is a significant cause of mortality and morbidity because of the loss of blood volume and its constituents and also the effects of infusions of products aimed at compensating for the loss. Massive blood transfusion can be defined as the transfusion of blood, blood products and fluids equivalent to the circulating blood volume in any 24-hour period. The most profound physiological, haematological and biochemical effects occur in those who have the most rapid loss and replacement therapy.

Causes of massive haemorrhage include:

- trauma
- major elective surgery such as orthopaedic or vascular surgery, especially rupture or dissection of the aorta
- during pregnancy and the puerperium (e.g. massive antepartum or post-partum haemorrhage)
- urgent operations and/or procedures in patients with abnormalities of haemostasis or coagulation.

Management

Measuring blood loss: the quantity of blood lost can be estimated by a number of methods.

- Weighing swabs and measurement of blood aspirated into suction apparatus. With major haemorrhage, these methods become less useful because a considerable amount of blood is spilled on to the drapes and floor. In traumatized patients, major blood loss may have occurred before arrival in hospital or may be concealed in the chest or abdomen, or in the limbs and pelvis at the site of fractures.
- Measuring packed cell volume. Blood lactate concentration gives an indication of the adequacy of organ perfusion.
- Clinical observation. The monitoring of cardiovascular variables such as heart rate, arterial pressure, capillary return, central venous pressure, and in some cases pulmonary capillary wedge pressure and cardiac output, allows a clinical impression of the adequacy of volume resuscitation to be made.

Compensatory mechanisms initially maintain the blood supply to vital organs. Unless adequate and appropriate corrective measures are taken, these mechanisms will decompensate. With increasing volumes of blood loss, there is an increase in heart rate, decrease in stroke volume, reduced pulse pressure, increased respiratory rate and a reduction in cerebral blood flow leading to a reduction in conscious level. These compensatory mechanisms are less efficacious in the elderly and very young and may be impaired by disease or medication. Figure 2 shows the relationship between the changes in vital signs and the volume loss from the circulation.

Relationship between the changes in vital signs and the volume loss from the circulation

	Blood loss (ml)			
	≤ 750	**750–1500**	**1500–2000**	**≥ 2000**
Loss as % of blood volume	≤ 15	15–30	30–40	≥ 40
Heart rate	< 100	> 100	> 120	≥ 140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal	Decreased	Decreased	Decreased
Capillary return	Normal	Slowed	Slowed	Slowed
Respiratory rate (breaths/minute)	14–20	20–30	> 30	≥ 35
Urine output (ml/hour)	> 30	20–30	5–15	Negligible
Mental status	Normal	Anxious	Confused	Drowsy
Suggested volume replacement	Crystalloid	Crystalloid/colloid	Blood	Blood

Active management: the rapid and effective restoration of an adequate circulating blood volume is the primary responsibility of the anaesthetist during periods of heavy blood loss.

Establish adequate venous access by siting at least two large-bore cannulae to allow rapid fluid infusion. The most important pre-determinants of the flow rate of fluid are the diameter of the cannula and the ability to apply a continuous pressure of 2–300 mm Hg via a pressurized infusion system. Crystalloids and synthetic colloids may be used initially and should be followed by the administration of blood if bleeding continues.

Commence intravenous fluids – internationally accepted practice is to use Hartmann's solution as the initial resuscitation fluid for trauma and burns. The success of initial resuscitation in an acutely hypovolaemic patient probably depends more on adequacy of repletion than on which fluids are used. For a given blood volume expansion about twice the volume of crystalloid compared with colloid is required. In practice, combined therapy using both crystalloids and colloids is often used.

Fluids should be warmed – a transfusion system should have the ability to transfuse blood at fast flow rates (up to 500 ml/minute) and at temperatures greater than 35°C. Some systems use a constant-pressure infusion device combined with an efficient blood warmer and a purpose-designed blood-warming coil (e.g. *Level One*™). Priming or flushing blood through the system after fluid containing calcium has been used (such as *Haemaccel*) should be avoided, because this may cause blood clot formation in the tubing by reversal of the anticoagulant effect of citrate.

Blood should be taken for grouping and cross-matching, for coagulation studies and for biochemical analysis. Accurate identification of transfusion specimens and of designated units of blood, platelets and fresh frozen plasma (FFP) is particularly important in patients undergoing massive transfusion. It should be noted that most incompatible blood transfusions occur in emergency situations. For operations where significant blood loss is anticipated, replacement therapy should be available in advance of surgery.

Red cell transfusions are given to increase the haemoglobin concentration and thus improve or normalize the delivery of oxygen to the tissues. The haemoglobin concentration at which blood transfusion is commenced depends to a certain extent on the individual patient (e.g. elderly patients are at greater risk of complications from anaemia). A haemoglobin value below 8.5 g/dl would be an indication to transfuse in all apart from the younger fitter patient. A postoperative haemoglobin level of about 10 g/dl is widely accepted as a general guideline in adult surgical patients. However, it is more appropriate to base transfusion decision on a clinical assessment of the patient. If a major surgical procedure is planned, it may be possible to decrease the amount of donor blood transfusions by using an automated cell saver system.

About 80% of patients who have massive haemorrhage develop diffuse ooze from raw or cut surfaces. The causes are multifactorial but include relative hypothermia, abnormal platelet function, dilution of clotting factors, consumption of factors and enhanced fibrinolysis. It is critically important to monitor platelet numbers and the coagulation process during major bleeding and its resuscitation. The platelet count falls steadily with the transfusion of each successive unit of blood. Platelet infusion is indicated if there is:

- a platelet count less than 50 x 10^9/litre and there is impending surgery or an invasive procedure
- diffuse microvascular bleeding and transfusion greater than one blood volume and a platelet count of 50 x 10^9/litre or less, or the result is unavailable
- diffuse microvascular bleeding following cardiopulmonary bypass and the platelet count is 100 x 10^9/litre or less, or the result is unavailable
- bleeding in a patient with a qualitative platelet defect, regardless of platelet count.

Moderate deficiency of coagulation factors is common in massively transfused patients, but does not contribute to microvascular haemorrhage until levels fall below 20% of normal. These levels are reliably reflected by prolongation of the prothrombin (PT) and activated partial thromboplastin times (aPTT) to values of more than 1.5 times the control value. If the PT and aPTT are more than 1.5 times normal, 4 units of FFP should be given. If PT and aPTT are prolonged and fibrinogen is less than 0.8 g/litre, cryoprecipitate is indicated.

Arterial and central venous lines may be sited to allow rapid blood sampling, for acid–base and potassium status, and the direct measurement of arterial and central venous pressures. The central venous catheter also provides access for intermittent bolus administration of drugs or drug infusions.

A urethral catheter should be passed unless contraindicated by pelvic or urethral injury, and urine output monitored.

Core temperature should be measured continuously and every effort made to prevent heat loss. Hypothermia causes platelet dysfunction, reduced metabolism of citrate and lactate and an increased tendency to cardiac arrhythmias. This may result in bleeding diathesis, hypocalcaemia, metabolic acidosis and cardiac arrest.

Arrhythmias

Arrhythmias are one of the most commonly reported critical incidents. About 12% of patients undergoing anaesthesia develop arrhythmias; this increases to 30% in patients with cardiovascular disease. Treatment may not be required; this depends on the nature of the arrhythmia and its effect on cardiac output. Single supraventricular or ventricular ectopic beats, and slow supraventricular rhythms, do not require treatment unless cardiac output is compromised.

Management

Fluid, electrolyte and acid–base disturbances should be corrected preoperatively. Particular attention should be paid to the level of potassium ions in the plasma because they have a vital role in the generation of the resting membrane potential and thus muscle and nerve function. Patients with hypokalaemia may be prone to the development of supraventricular or ventricular extrasystoles and tachycardias. ECG changes of hypokalaemia include a long PR interval, ST depression, T wave flattening and a prominent U wave. Rapid treatment is indicated if arrhythmias are present. Intravenous administration of potassium supplements should not exceed 0.5 mmol/kg/hour.

Continuous intraoperative ECG monitoring is essential. The ECG gives no indication of cardiac output or tissue perfusion, therefore the detection of an abnormal cardiac rhythm should be followed by clinical assessment of the circulation. An absent pulse, severe hypotension or ventricular tachycardia or fibrillation should be treated as a cardiac arrest.

Correcting the precipitating factor is often the only treatment required. Hypoxaemia and inadequate anaesthesia or analgesia must be excluded. Factors associated with the development of arrhythmias are listed in Figure 3.

Intervention with a specific antiarrhythmic agent or cardioversion is indicated if there is:

- a risk of developing ventricular tachycardia or fibrillation (e.g. frequent, multifocal ectopic beats, or 'R on T' complexes)
- a significant decrease in cardiac output (causing dizziness or hypotension)
- evidence of myocardial ischaemia (causing chest pain or ST segment changes).

Factors associated with the development of arrhythmias

Preoperative conditions

- Ischaemic heart disease
- Pre-existing arrhythmias
- Congestive heart failure
- Hypertension
- Valvular heart disease
- Electrolyte disorders
- Medications (theophylline, β_2-agonists, tricyclic antidepressants)
- Others (thyrotoxicosis, myocarditis, cardiomyopathies, trauma, drug and solvent abuse)

Anaesthetic factors

- Hypoxaemia
- Hypo/hypercapnia
- Hypo/hypertension
- Laryngoscopy
- Drugs (e.g. volatile anaesthetic agents, suxamethonium, central venous pressure lines)

Surgical factors

Catecholamines

- Exogenous (e.g. infiltrated adrenaline (epinephrine))
- Endogenous (inadequate analgesia, inadequate anaesthesia)

Autonomic stimulation

- Oculocardiac reflex
- Laryngoscopy, bronchoscopy, oesophagoscopy
- Carotid artery and thyroid surgery
- Peritoneal and visceral traction
- Peritoneal insufflation

Direct stimulation of the heart

- Cardiac and thoracic surgery

Embolism

- Thrombus, fat, air, carbon dioxide, amniotic fluid

Others

- Limb reperfusion
- Aortic cross-clamping

Bradycardia can be treated with an anticholinergic agent such as atropine, 0.6 mg i.v., or glycopyrrolate, 0.2–0.4 mg i.v. If the bradycardia is refractory to treatment, cardiac pacing or an intravenous infusion of isoprenaline, 0.5–10 µg/minute, may be indicated. An anticholinergic drug may be given prophylactically if there is risk of bradycardia (e.g. strabismus surgery or following a second dose of suxamethonium).

Sinus tachycardia associated with myocardial ischaemia may be controlled by administration of a β-blocker such as metoprolol, 2 mg increments slow i.v., maximum dose 15 mg, or esmolol, 500 µg/kg, loading dose followed by 50–200 µg/kg/minute infusion.

Junctional rhythms are usually associated with the use of halothane. A reduction in concentration and/or changing the volatile agent is indicated. An anticholinergic drug may restore sinus rhythm.

Accelerated nodal rhythms may be precipitated by an increase in sympathetic tone in the presence of sensitizing volatile agents. Treatment includes adjusting the depth of anaesthesia and/or changing the anaesthetic agent.

Supraventricular tachycardia (SVT) can occur in susceptible patients, such as Wolff–Parkinson–White or other 'pre-excitation syndromes'. Treatment of SVT consists of:

- carotid sinus massage
- adenosine, 3–12 µg i.v.
- DC cardioversion if haemodynamic decompensation is present
- if there is no decompensation give verapamil, 5–10 mg slow i.v. over 30 seconds; the injection should stop when the SVT is controlled
- in sepsis-related or refractory SVT, volume loading plus amiodarone, 300 mg i.v. by infusion over 20 minutes, then 900 mg over 24 hours
- if the patient is thyrotoxic a β-blocker is useful.

Atrial fibrillation or flutter is often seen as a paroxysmal increase in the ventricular rate in patients with pre-existing atrial fibrillation or flutter. Having corrected any precipitating factors, the therapeutic options include:

- digoxin, 10 µg/kg by slow i.v. injection over 20 minutes, repeat after 4 hours according to response, maintenance dose 125–500 µg/day. Peak effect after 2 hours. Slows the ventricular rate and is a positive inotrope
- amiodarone produces a more rapid ventricular response and may re-establish sinus rhythm, give 300 mg i.v. by infusion over 20 minutes, then 900 mg over 24 hours
- β-blockers, especially in thyrotoxicosis, in combination with digoxin (e.g. propranolol 1 mg slow i.v. repeated every 2 minutes, maximum 5 mg)
- cardioversion is an option if the ventricular rate is fast with a clinically reduced cardiac output.

Premature ventricular contractions are common in healthy patients. Perioperatively they seldom progress to more serious arrhythmias unless there is underlying hypoxaemia or myocardial ischaemia. An underlying cause should be sought before antiarrhythmic agents are considered. If associated with a slow atrial rate, increasing the sinus rate with an anticholinergic drug will abolish them. Halothane lowers the threshold for catecholamine-induced ventricular arrhythmias; this is exacerbated by hypercapnia. Halothane should be used with care in patients receiving sympathomimetic drugs (including local anaesthetics containing adrenaline), and in patients taking tricyclic antidepressants and aminophylline.

Ventricular tachycardia and fibrillation should be treated as a cardiac arrest.

Malignant hyperthermia

Malignant hyperthermia is a rare inherited complication of general anaesthesia triggered by inhalational agents or suxamethonium in susceptible patients. The inheritance is complex and it is a genetically heterogeneous condition. These patients have a defect in intracellular calcium binding within the sarcoplasmic reticulum of skeletal muscle cells. Calcium ions are released on exposure to trigger agents, which initiates widespread skeletal muscle contraction and generalized membrane permeability. There is severe metabolic disturbance and catabolism runs unchecked, because raised levels of myoplasmic calcium ions result in increased production of pyruvate and heat. A successful outcome relies on making an early diagnosis, discontinuation of trigger agents, prompt treatment with intravenous dantrolene and supportive care. The mortality today has decreased to about 25% owing to increased awareness, monitoring and prompt treatment. The mode of presentation is variable and a high index of suspicion is required for early diagnosis.

Signs of malignant hyperthermia include:
- unusual muscle rigidity following suxamethonium (especially masseter spasm)
- unexplained tachycardia and arrhythmias
- rise in end-tidal carbon dioxide
- metabolic acidosis
- fall in oxygen saturation
- hyperkalaemia
- rise in core temperature (about 1–2°C/hour)
- evidence of a coagulation disorder, oozing from wound sites.

Management

Immediate actions
- Discontinue inhalational agents and inform the surgeons. Stop surgery if feasible, make the operating site safe and close wounds.
- Continue sedation or anaesthesia with a total intravenous technique. Hyperventilate with 100% oxygen using a clean breathing system. Change the circle system using fresh soda-lime, or use a non-rebreathing system.
- Immediately instruct staff to prepare dantrolene and commence as soon as available in an intravenous infusion of 1 mg/kg repeated at 10 minute intervals up to 10 mg/kg.
- Remove drapes, fully expose the patient and promote surface cooling with avoidance of vasoconstriction.
- Insert an arterial line to aid monitoring, and allow regular estimation of arterial blood gases, potassium and creatine kinase.
- Monitor the patient's core temperature.

Intermediate actions
- Control life-threatening dysrhythmias (e.g. β-blockers).
- Control hyperkalaemia with intravenous glucose or insulin.
- Control metabolic acidosis by hyperventilation, consider sodium bicarbonate (2–4 mmol/kg) if acidosis is severe (e.g. pH < 7.0).

Later actions
- Send blood for clotting screen (PT, aPTT, fibrinogen).
- Catheterize the patient. Test their urine for myoglobin. Collect samples for vanillylmandelic acid estimation to exclude phaeochromocytoma. Promote diuresis with intravenous fluids and mannitol, 0.5 g/kg over 20 minutes.
- Request a chest radiograph. Send blood for full blood count, biochemistry and thyroid function tests.
- Notify the intensive care unit.
- Repeat the creatine kinase estimation in 24 hours.
- Consider other diagnoses such as recreational drug ingestion (e.g. Ecstasy), neuroleptic malignant syndrome or myopathy.

Future care

The patient and their family should be counselled as to the likely diagnosis and the implications for future anaesthetics. Wearing a Medic-Alert bracelet should be encouraged. The patient and immediate family should be referred for further investigation and muscle biopsy to:

UK MH Investigation Unit, Academic Unit of Anaesthesia
Clinical Sciences Building
St James's University Hospital Trust
Leeds LS9 7TS
Tel: 0113 206 5274
Emergency hotline: 07947 609601

Future anaesthetic care can be provided safely with the avoidance of trigger agents – the volatile anaesthetics and depolarizing muscle relaxants. Prophylactic dantrolene is not recommended. Phenothiazines, antidepressants and haloperidol have been suggested as possible trigger agents, because of the similarity between malignant hyperthermia and the neuroleptic malignant syndrome, but this is unlikely. All other anaesthetic drugs appear to be safe.

Critical Incidents: The Respiratory System

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A critical incident during anaesthesia is any event that may result in actual or potential harm to the patient if uncorrected. It may cause severe morbidity or even mortality. It is often preventable by a change in practice. Incident reporting is the key to preventing future disaster. There is observer bias concerning which incidents are recorded, and the problem for anaesthetists is to distinguish between a critical incident and the normal course of clinical practice.

This contribution deals with life-threatening problems in the management of the respiratory system including the clinical and physiological presentation of some commonly encountered critical incidents and their treatment. All may be a cause of alarming cyanosis under anaesthesia. Not all the problems discussed can be prevented and so some may not meet the precise definition of critical incidents. The recommendations aim to provide the anaesthetist with fast and effective solutions that may be used in clinical, examination or simulation situations. In all cases, the trainee anaesthetist must request senior help at the earliest opportunity.

Aetiology

The 2000 report of the National Confidential Enquiry into Perioperative Deaths (NCEPOD) cites hypotension, hypoxaemia, arrhythmia and cardiac arrest as the most common critical events that occur during or immediately following surgery. It also concludes that modern anaesthetic equipment, when properly checked, is very reliable. Human factors often play a major role in the aetiology of adverse events (Figure 1).

Factors involved in avoidable deaths

- Error of judgement
- Error of clinical expertise
- Lack of experience
- Lack of assistance
- Lack of equipment
- Equipment failure

1

Preparation is an important factor in predicting and treating these events and should involve:

- thorough preoperative patient assessment
- check of all anaesthetic equipment
- appropriate selection of drugs
- appropriate level of clinical expertise.

The Association of Anaesthetists of Great Britain and Ireland (AAGBI) has recently published new recommendations for standards of monitoring during anaesthesia and recovery. The Royal College of Anaesthetists (RCA) has a web page (http://www.rcoa.ac.uk/critincident/ciweb.html) that deals with the processing of critical incidents. The RCA is committed to setting up a national database so that even rare incidents can be reported and acted on. Critical incidents should be discussed locally at regular departmental audit meetings to complement the process of clinical governance.

Respiratory obstruction and increased peak airway pressure

Obstruction to the airway is an immediate threat to life and is the most common critical incident registered. The 'airway' can be considered as the conducting pathway responsible for the delivery of oxygen from anaesthetic machine to the alveolar/blood interface. Thus, obstruction may occur from outside or within the patient. The anaesthetic machine, breathing system and connections must be checked to ensure their patency and correct function before anaesthesia.

Obstruction of the airway within the patient may arise from the upper, supraglottic region, to the lower bronchiolar region. It may be caused by the devices used during anaesthesia or result from airway anatomy, pathology or trauma. Figure 2 shows some of the likely causes of airway obstruction in the perioperative period.

Possible causes of airway obstruction

Supraglottic

- Tongue
- Periglottic abscess, tumour, haematoma
- Regurgitation of solid material
- Blood or secretions
- Laryngeal mask airway (LMA) or tracheal tube luminal occlusion or misplacement

Laryngeal

- Laryngospasm
- Tumour or oedema
- Post-thyroidectomy (laryngeal nerve injury)
- LMA or tracheal tube luminal occlusion or misplacement

Tracheal or bronchial

- Aspiration
- Asthma
- Anaphylaxis
- Pneumothorax
- Pulmonary oedema
- Tracheal obstruction by retrosternal goitre
- LMA or tracheal tube luminal occlusion or misplacement

2

Respiratory obstruction during induction of anaesthesia

Preoperative evaluation of the airway is vital and should include mouth opening, dentition, Mallampati score, jaw movement, thyromental distance and neck movement. The aim is to predict which patients may present difficulty with direct laryngoscopy and intubation and those in whom difficulty may arise with airway maintenance following loss of consciousness, such as those with:

- obesity or a 'bull neck'
- limited mouth opening (e.g. trismus, following infection, trauma)
- restricted head and neck movement (e.g. severe ankylosing spondylitis, rheumatoid arthritis)
- stridor resulting from tumour, trauma, infection or haem-atoma
- upper airway soft tissue swelling (e.g. burns, pre-eclampsia). About 10% of reported critical incidents occur in the anaesthetic room. Patient monitoring during induction of anaesthesia should follow the guidelines established by the AAGBI. The patient must be monitored adequately during this stage of anaesthesia. If the required equipment is unavailable, induction should take place in the operating theatre.

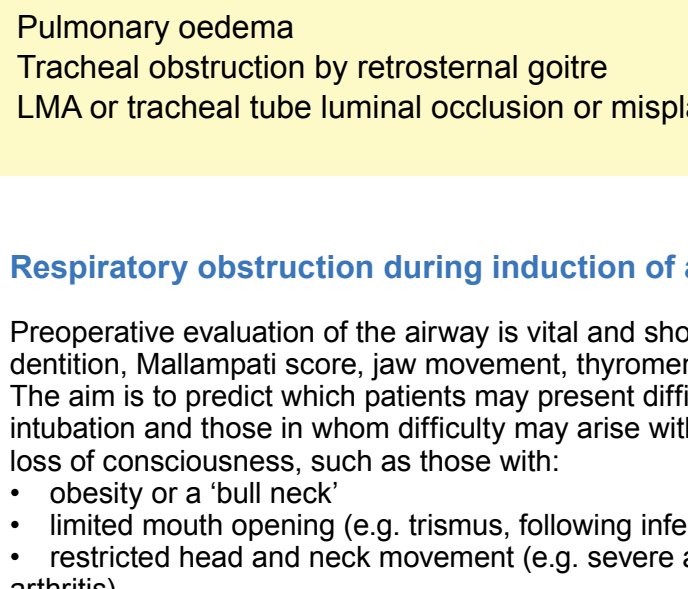
Induction of anaesthesia in patients with upper airway obstruction requires specialized expertise. Management must involve a clear plan of how to proceed in the event of total airway obstruction during induction. These patients are best managed in the operating theatre with surgeons gowned and ready to perform immediate tracheostomy under local anaesthesia if necessary.

In routine practice, airway obstruction that occurs following induction is apparent from:

- paradoxical (see-saw) chest movement (when breathing spontaneously)
- noisy airway
- absent or diminished movement of the reservoir bag
- absent or diminished capnograph trace
- increased airway pressure (when mechanically ventilated)
- progressive oxygen desaturation.

Simple airway manoeuvres such as chin lift and jaw thrust, often combined with the insertion of a correctly sized oropharyngeal or nasal airway are necessary to maintain airway patency following induction. In apnoeic patients or those requiring assisted ventilation, bag and mask ventilation by two operators is more effective than that provided by one operator (Figure 3), allowing more effective face mask application and upper airway management. Manual ventilation with bag and mask is then easier to perform. If management is difficult, it is important to switch to 100% oxygen and call for senior help early on.

Two operators providing bag and mask ventilation



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If airway obstruction persists, a laryngeal mask airway (LMA) often corrects the situation. While tracheal intubation provides a definitive airway, it may be difficult to insert in a patient who has not received muscle relaxants. Neuromuscular blockade should never be administered unless airway patency can be assured. However, if airway maintenance is lost following the administration of muscle relaxants then swift direct laryngoscopy and tracheal intubation should be attempted. Some patients (e.g. those with adenotonsillar hypertrophy, the obese or heavy snorers) are often easy to intubate despite having a difficult airway to maintain with bag and mask. The LMA is also the technique of choice following a failed intubation if subsequent airway management is difficult. Numerous reports testify to the ability of the LMA to provide a clear airway following a failed intubation. The *Combitube* may also be useful, though it is less commonly used in the UK. Both are 'supraglottic' airway devices, therefore it is unlikely that the *Combitube* will provide a clear airway if the LMA does not.

Can't intubate, can't ventilate (CICV)

The inability to intubate or ventilate a patient is rare, with an estimated incidence of 1/10,000 anaesthetics. It occurs when alveolar ventilation cannot be maintained despite best attempts at intubation and bag-mask ventilation (Figure 4).

Analysis of closed-claims in the USA revealed that the most common predisposing factor in the development of CICV was repeated and continued attempts at intubation. With each successive period of re-oxygenation between intubation attempts, bag-mask ventilation became increasingly difficult as laryngeal oedema evolved. The anaesthetist should limit intubation attempts to a maximum of three. The decision must be made early to abandon further attempts at intubation and the anaesthetist must use an alternative airway device, or wake the patient. The main causes of CICV are:

- repeated failed attempts at intubation
- airway or neck trauma
- burns to the head and neck
- pregnancy (especially pre-eclampsia)
- tumour (e.g. larynx)
- infection.

Requirements for optimum best attempts

Optimum best bag-mask ventilation

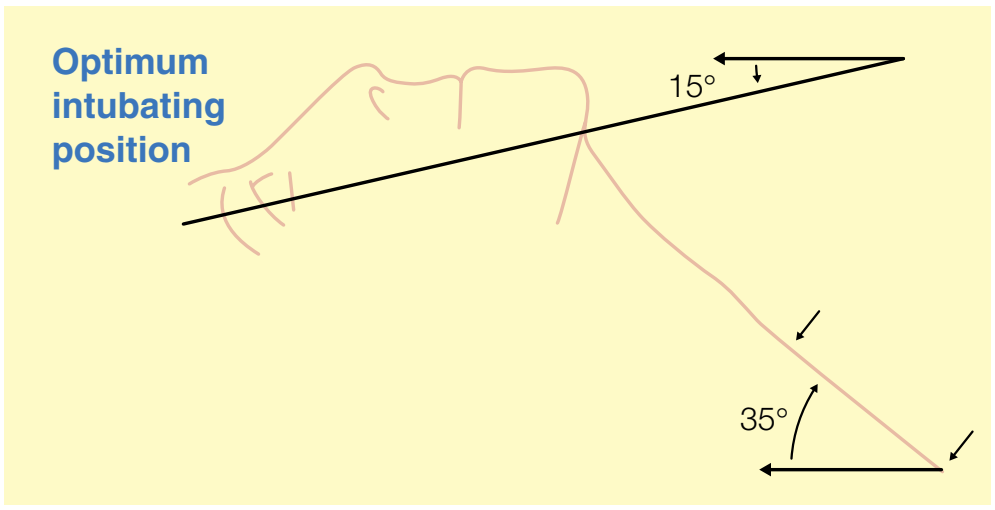
- Correctly sized oral or nasal airway
- Two-operator technique

Optimum best laryngoscopy

- Trained anaesthetist (3 years' training)
- Optimal intubating position
- Optimal external laryngeal manipulation
- Optimal laryngoscope

4

The optimal intubating position is shown in Figure 5. Flexion of the cervical spine, and extension of the head at the atlanto-occipital joint, aligns the glottis with the visual axis. In the obese or pregnant woman at term, this may require at least one pillow under the shoulders and two pillows beneath the head and neck. Anaesthetic induction and tracheal intubation should be avoided when patient positioning is not ideal.



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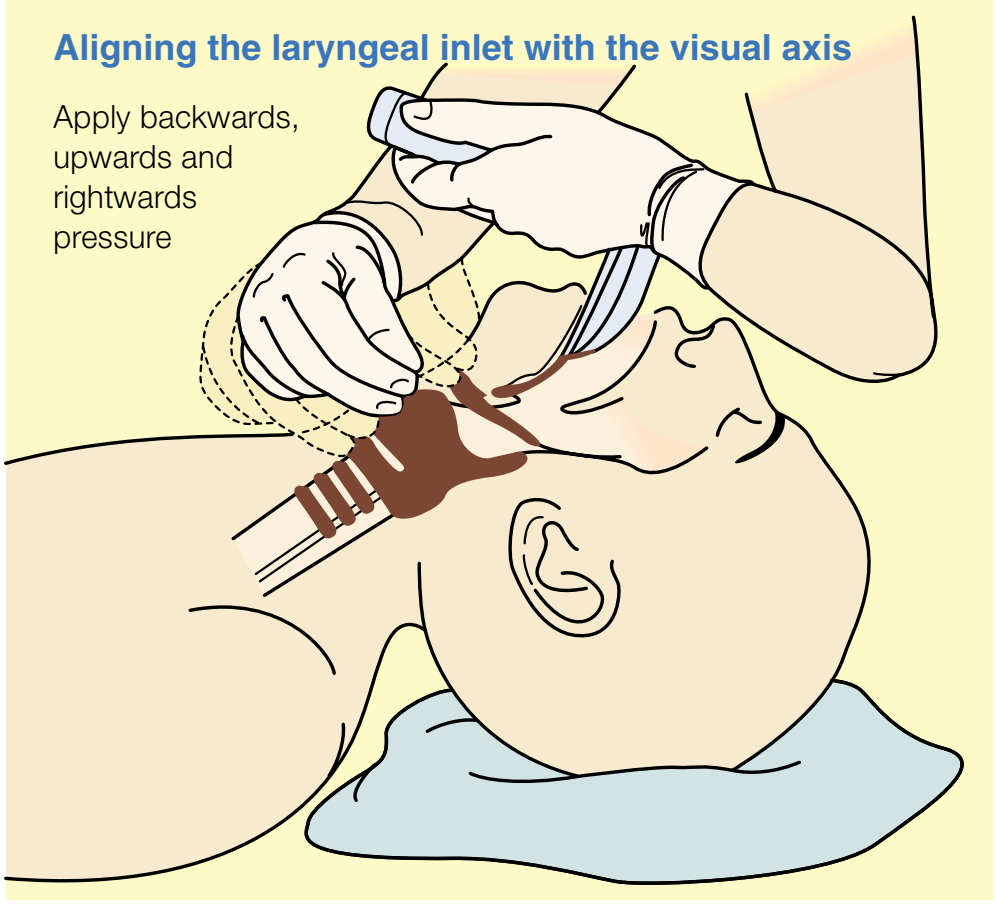
The larynx should be manipulated from the front of the neck by the operator's free hand to help provide the best view. This position is maintained by the anaesthetic assistant while intubation is performed. Optimum external laryngeal manipulation does not mean 'cricoid pressure', which may further distort the view and make direct laryngoscopy more difficult. Optimum manipulation involves direct manipulation of the thyroid cartilage of the larynx. The application of backwards, upwards and rightwards pressure aligns the laryngeal inlet more closely with the visual axis. Correct optimum external laryngeal manipulation is shown in Figure 6.



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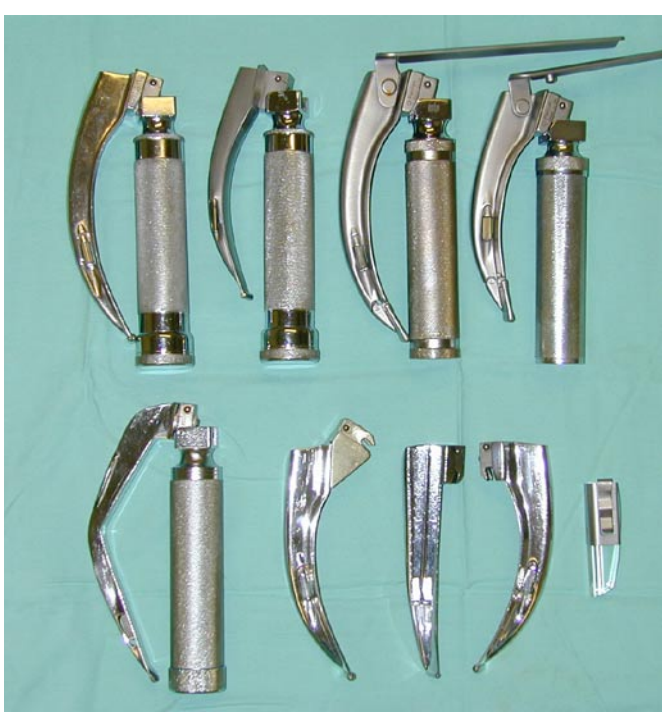
The choice of laryngoscope blade is important. A useful guideline is to change the length of blade once, and the type of blade once, to achieve the best view. A variety of blades is available in clinical practice. The standard Macintosh blade (size 3) may need to be changed to a longer blade (size 4) or to a levering blade such as the McCoy. The McCoy blade can be successful in improving the laryngoscopic view by one grade (Cormack and Lehane grade 3 to 2). The Belscope blade has a 45° angle and a detachable prism, and may similarly improve a grade 3 view. The Polio blade is inclined at an angle greater than 90° to the handle, which may aid insertion into the mouth (Figure 7).



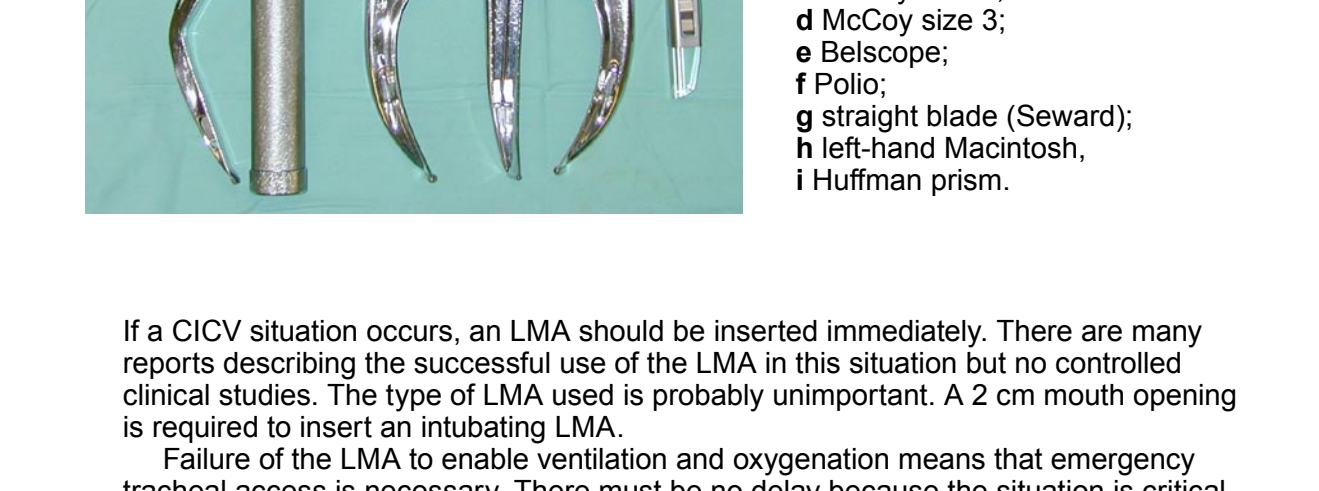
7 Laryngoscope blades:
a Macintosh size 4;
b Macintosh size 3;
c McCoy size 4;
d McCoy size 3;
e Belscope;
f Polio;
g straight blade (Seward);
h left-hand Macintosh,
i Huffman prism.

If a CICV situation occurs, an LMA should be inserted immediately. There are many reports describing the successful use of the LMA in this situation but no controlled clinical studies. The type of LMA used is probably unimportant. A 2 cm mouth opening is required to insert an intubating LMA.

Failure of the LMA to enable ventilation and oxygenation means that emergency tracheal access is necessary. There must be no delay because the situation is critical in a patient with marked hypoxia. Tracheal access is best achieved via the cricothyroid membrane by needle puncture, percutaneous cricothyrotomy or surgical cricothyrotomy. The precise technique depends on: the equipment available; the experience of the anaesthetist; and the nature of the emergency.

It is impossible to give firm recommendations but whatever the means used, the immediate aim is to achieve oxygen delivery to the trachea (and alveoli) via the cricothyroid membrane. This membrane lies subcutaneously between the cricoid and thyroid cartilages of the larynx and in the adult measures 1 x 3 cm. It will accept a tracheal tube of maximum size 7.0 internal diameter (ID). Paired cricothyroid arteries arise from the superior border and pass laterally. The patient's head and neck should be extended to bring the cricothyroid membrane closer to the skin surface to facilitate access. Placing a sandbag or 1 litre fluid bottle between the patient's scapulae may help to achieve this.

Needle cricothyrotomy is minimally invasive but requires a jet ventilator to achieve satisfactory alveolar ventilation. A cannula is inserted via the cricothyroid membrane (Figure 8), free aspiration of air confirms correct placement. Resistance through the cannula is too high to enable conventional bag ventilation. Simple emergency systems can be constructed using green oxygen tubing connected to a flowmeter (e.g. 10-15 litres/minute). A side hole or three-way tap allows for intermittent insufflation by finger occlusion of the hole. The green oxygen tubing is inserted into the barrel of a 2 ml syringe which then allows connection to the cannula. The free end is connected to an oxygen flowmeter or to the anaesthetic machine via a 15 mm connector. Oxygen insufflation techniques provide tracheal oxygen delivery but not satisfactory carbon dioxide elimination. It is recommended that all sites where anaesthesia is administered have access to a jet ventilator. The inspiratory time of about 1 second should be followed by a 3 second expiratory time. It is unlikely that airway obstruction is absolute and passive exhalation will occur via the glottis. If this is deemed inadequate a second cannula should be placed to allow exhalation and prevent overinflation and barotrauma. A needle cricothyrotomy is a temporary measure and preparations should be made for a formal tracheostomy.



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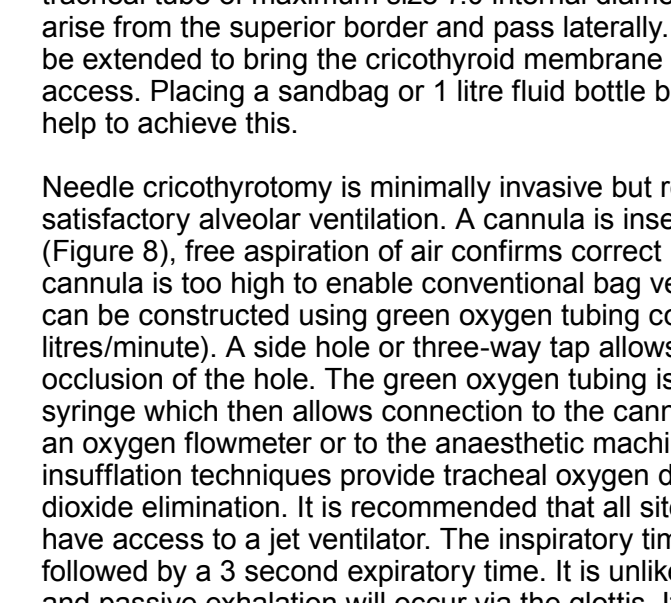
Specific cricothyroid cannulae are available for emergency tracheal access (Figure 9). The Ravussin 13 G jet ventilation catheter (VBM Medical) is flanged to simplify fixation, and has both Luer-lock and 15 mm connections. The Cook 6 F emergency transtracheal catheter is spiral reinforced and kink-resistant; a standard 14 G intravenous catheter is easily kinked and difficult to fix. The main complication of the technique is incorrect needle position and subcutaneous/mediastinal emphysema.



9 Cricothyrotomy needles.
a 13 G Ravussin jet ventilation catheter (VBM Medical);
b 6 F Cook emergency transtracheal catheter;
c 14 G Venflon cannula.

Percutaneous cricothyrotomy allows emergency placement of a tracheal tube to allow more conventional ventilation via bag and mask. Several commercial kits are available, which differ in insertion technique (Seldinger or non-Seldinger), size of tube (3.5-6.0 ID), and time taken for tube placement. There are insufficient data to make recommendations concerning the optimum technique and the anaesthetist should be familiar with the equipment available in their hospital. A non-Seldinger kit (e.g. VBM Quicktrack, 4.0 mm ID) generally allows the most rapid access by direct cricothyroid puncture using a large diameter sharpened stylet. A Seldinger technique (e.g. Cook Melker kit 3.5-6.0 mm ID) may be safer to perform but requires several stages including the use of a dilator. All techniques require familiarization. Complications include bleeding, malposition and subcutaneous emphysema.

Surgical cricothyrotomy rapidly provides a definitive airway, though it requires more surgical experience and bleeding is likely to be considerable. It is ideally suited to the emergency trauma setting in the presence of severe maxillofacial, neck or laryngeal injury. Thorough training is necessary for this seldom performed but life-saving procedure. Practising on the sheep's larynx provides a realistic training model.

With finger and thumb either side, the cricothyroid membrane should be stabilized. A 22 scalpel blade is used to make a 2 cm vertical skin incision to part the skin. The scalpel should then be horizontally inserted into the cricothyroid membrane, perpendicular to the skin. This incision should be enlarged laterally. The scalpel handle should be inserted through the cricothyroid incision and rotated through 90°, then removed. A well-lubricated size 7.0 ID cuffed tracheostomy tube should be inserted. The main complications are bleeding and malposition.

Respiratory obstruction during the intraoperative period

If respiratory obstruction occurs during surgery, the following procedure will help to diagnose the cause of obstruction (Figure 2) and guide appropriate action to correct the situation. Surgery can then recommence.

- 100% oxygen should be commenced.
- The surgeons should be alerted to the problem and advised to stop surgery. The surgical stimulation may have caused the obstruction. Procedures such as dilation of the cervix or anus may precipitate severe stridor especially if anaesthesia is 'light'.
- The anaesthetic delivery circuit should be checked rapidly.

If it is patent, the obstruction must be within the patient.

- Access to the airway may be difficult, especially in head and neck surgery. Extreme circumstances of continued patient deterioration require the complete uncovering of surgical drapes and exposure of the airway.
- The upper airway should be checked for secretions, signs of regurgitation or obvious tube or LMA obstruction. The mouth and trachea should be suctioned if indicated.
- The capnograph confirms alveolar ventilation by displaying a carbon dioxide trace. Absence of a trace is a sign of complete airways obstruction. The normal capnograph trace may change in airways obstruction with a characteristic marked upslope to the alveolar plateau.
- The urgency of the situation is indicated by the oxygen saturation. If there is any doubt about the tracheal tube position, immediate replacement is needed. An LMA will need repositioning or changing to a tracheal tube. Careful observation of the chest wall during manual ventilation may show unilateral or little chest movement. Auscultation of the chest may detect unilateral air entry, wheeze or absent breath sounds. Withdrawing the tracheal tube slightly may alleviate this if the distal end has migrated to the endobronchial position, or is in contact with the carina.
- Fibre-optic bronchoscopy will confirm the position of the tracheal tube and that there is no intraluminal obstruction such as a sputum plug, blood clot or in rare circumstances, an endoluminal tumour.

Bronchospasm during anaesthesia

Bronchospasm is reversible airways obstruction most commonly associated with patients who have asthma or chronic chest disease. The incidence of asthma is 5-10% with a higher prevalence in children. Smokers and patients with upper respiratory tract infection are also at increased risk of bronchospasm. Bronchospasm occurs as a result of smooth muscle constriction within the respiratory subepithelial layers in the bronchioles. It may be accompanied by other pathological effects (e.g. mucosal oedema, cellular infiltrates, mucus secretion, desquamation of surface epithelial cells, goblet cell hyperplasia) which exacerbate smooth muscle contraction. Contraction is stimulated by neural or paracrine effects. Chemical mediators such as histamine and products of arachidonic acid, the leukotrienes, may act locally to initiate bronchoconstriction.

Bronchospasm is not the only cause of intraoperative wheeze (Figure 10). Luminal occlusion from eccentrically inflated tube cuffs (cuff herniation) used to occur with red rubber tracheal tubes, but modern disposable materials have made this complication less common, however the tracheal tube cuff should not be over-distended. The old adage 'if in doubt – take it out' remains true. A monophonic wheeze developing immediately after intubation may indicate tube occlusion, or a distal position next to the carina or within a bronchus.

Bronchospasm is suggested by:

- increased respiratory effort, tachypnoea and intercostal recession (if spontaneously breathing)
- expiratory wheeze (wheeze throughout the respiratory cycle may indicate obstruction within the breathing equipment)
- rise in inspiratory airway pressure (if mechanically ventilated). Management of wheeze while under anaesthesia is as follows.
- The surgeons should be alerted and asked to stop surgery.
- 100% oxygen should be delivered and anaesthesia deepened. Bronchospasm may result from a depth of anaesthesia that is too light for the degree of surgical stimulation. This includes stimulation of the airway by the anaesthetist. All modern inhalational agents are bronchodilators.
- The breath sounds over both lung fields and over the stomach should be listened to. Capnography confirms tracheal intubation. Tracheal tube position should be adjusted if necessary. Signs of pulmonary oedema or tension pneumothorax should be sought.• The position of the tracheal tube should be adjusted if necessary.
- The airway should be checked and the trachea should be suctioned looking for signs of aspiration.
- Full monitoring should be in place. Extreme tachycardia and cardiovascular collapse suggest anaphylaxis.

The treatment of bronchospasm includes the following.

- The inspired concentration of volatile anaesthetic agent should be increased.
- The patient should be treated with continuous inhaled salbutamol nebulizers, 5 mg, and ipratropium, 500 µg, until the wheeze settles. This is best delivered using a separate oxygen cylinder with nebulizer attachment, connected to the tracheal tube on the patient side of any heat/moisture exchange filter.
- If wheeze persists, aminophylline, 250−500 mg (5 mg/kg) i.v.in 500 ml normal saline over 20 minutes can be given (if notalready treated with theophylline or aminophylline preparations); continue with an infusion of 0.5 mg/kg/hour if needed.
- If bronchospasm is severe, salbutamol, 250 µg bolus i.v. over 5−10 minutes may be given, and continued as an infusion of 5 µg/minute, adjusted according to the heart rate and bronchospasm response.
- It may be necessary to adjust ventilator settings. A longer expiratory time may be needed to allow more complete exhalation, though a short inspiratory time will produce higher peak inspiratory pressures. An I:E ratio of 1:2 or 1:1.5 is usual.
- Hydrocortisone, 200 mg i.v., is not immediately effective but provides bronchospasm relief within 6–12 hours.
- Management of anaphylaxis will be covered in **CLINICAL ANAESTHESIA.**

Causes of intraoperative wheeze

- Endobronchial intubation
- Mechanical obstruction of the tracheal tube
- Bronchospasm
- Anaphylaxis
- Pulmonary oedema
- Tension pneumothorax
- Aspiration of gastric contents

Failure to breathe

A delay in the return of spontaneous respiration following anaesthesia is most commonly the result of an imbalance between the:

- patient requirements of anaesthesia and analgesia (differences caused by normal variation and the effects of coadministered drugs or disease)
- doses of drugs used
- timing of their administration.

In all patients, maintain ventilation to ensure satisfactory oxygenation and carbon dioxide removal. The patient is likely to be unconscious and usually all that is required is more time. If there is continued apnoea, inconsistent with the clinical picture, then a careful evaluation of the cause is needed. The patient should be reassured if they are conscious.

Assess neuromuscular block − a train-of-four ratio of 75% is usually adequate for satisfactory ventilation following anaesthesia. The presence of four good twitches with absent fade implies adequate reversal. Modern nerve stimulators (e.g. the train-of-four watch) can provide more accurate assessment of neuromuscular function by measurement of thumb acceleration (and thus force, because the mass of the thumb is constant). The standard 1 ml ampoule of glycopyrrolate, 0.5 mg/neostigmine 2.5 mg, is the correct reversal dose for a 50 kg patient. The ability to sustain a 5-second head lift from the pillow is a useful clinical indicator of neuromuscular recovery. Figure 11 shows factors that prolong the action of a non-depolarizing neuromuscular block.

Factors that may increase duration of non-depolarizing neuromuscular block

- Hypokalaemia
- Hypothermia
- Hypocarbia
- Neuromuscular disease (e.g. myasthenia gravis, Eaton-Lambert syndrome)
- Inhalational anaesthetic agents
- Aminoglycosides
- Calcium antagonists
- Magnesium
- Local anaesthetics
- Lithium
- Frusemide

Partial reversal of neuromuscular block presents as respiratory inadequacy together with jerky, uncoordinated gross muscular movement. Laryngeal muscle weakness can produce airway obstruction and stridor. The best treatment is to:

- reassure the patient (they may be distressed and feel unable to breathe, with tachycardia and hypertension) and administer 100% oxygen
- help allay anxiety by giving midazolam, 2 mg i.v. or reintroduce general anaesthesia for a short period of time
- correct any underlying cause
- administer further neostigmine (with glycopyrrolate) to a total of 70 µg/kg i.v. (maximum dose 5 mg) if necessary.

Plasma cholinesterase activity − if suxamethonium (or mivacurium) has been used and return of adequate neuro-muscular function is delayed, it is likely that plasma cholin-esterase activity is decreased. This may be an inherited abnormality of cholinesterase activity or an acquired reduction in enzyme activity (Figure 12). The genetic variants have autosomal dominant inheritance, and the prevalence of homozygotes for the atypical gene is 1:2500 of the Caucasian population. Only homozygotes display significantly prolonged apnoea. This may produce many hours of continued paralysis. The patient will come to no harm providing ventilation is supported and adequate sedation is continued (e.g. propofol, 4−6 mg/kg/hour). Neuromuscular block should be monitored with a nerve stimulator and eventually wears off. Infusion of fresh frozen plasma containing cholinesterase enzyme speeds recovery of neuro-muscular function. The benefits must be balanced against the cost and infection risk. Acquired conditions (Figure 12) that reduce plasma cholinesterase activity may slightly increase suxamethonium duration.

Factors that may cause decreased plasma cholinesterase activity

Congenital

- Autosomal dominant inheritance of abnormal enzyme Four alleles have been identified: $E1^n$ normal, $E1^a$ atypical, $E1^f$ fluoride-resistant, $E1^s$ silent

Acquired

- Infections
- Malignancy
- Chronic disease
- Liver disease
- Renal failure
- Pregnancy, oral contraceptives
- Hypothyroidism
- Drugs (monoamine oxidase inhibitors, ecothiopate eye drops, organophosphorus compounds, chemotherapy)

Doxapram is a central respiratory stimulant that may reverse the respiratory depression caused by general anaesthetic agents and potent analgesics. It does not reverse the other effects of opioids. It acts by direct stimulation on the carotid body chemoreceptors. A maximum dose of 1.5 mg/kg slow i.v. can be given.

Benzodiazepines − flumazenil can be used to reverse the central sedative effects of benzodiazepines. It has a shorter half-life than midazolam and diazepam, and therefore re-sedation is possible. Flumazenil, 200 µg i.v., should be given followed by 100 µg i.v. every minute as necessary. The maximum total dose is 1 mg. While benzodiazepines may contribute to postoperative sedation, they seldom cause apnoea unless large doses are used or the patient is elderly and frail.

Opioid drugs − if excessive narcotic is suspected, then give naloxone by titrating dose to effect. Dilute 400 µg in 10 ml normal saline and give 1−2 ml every few minutes to achieve the desired effect. It is important not to use excessive naloxone to prevent reversal of the analgesic effect. Pain, hypertension and tachycardia may result. The patient must be observed closely for the next 4−6 hours because the duration of the naloxone effect may be shorter than that of the opioid.

Check end tidal carbon dioxide tension ($P_{E'}CO_2$) – hyperventilation during anaesthesia results in reduced respiratory drive. Spontaneous ventilation is unlikely to occur until the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and $P_{E'}CO_2$ have normalized. The addition of 5% carbon dioxide to the inspiratory gas mixture was common in older anaesthetic practice to stimulate respiratory drive. Hazards associated with carbon dioxide use, in particular the inadvertent use of carbon dioxide from incorrect flowmeter settings, have removed the use of this gas from modern practice.

The $P_{E'}CO_2$ should be allowed to rise by itself by either reducing minute volume, or adding dead space into the breathing system (e.g. disconnection of the absorber from a circle system).

Body temperature – hypothermia delays recovery from anaesthesia, prolongs the duration of neuromuscular blockade and is an important cause of postoperative hypoventilation. The fall in core temperature that occurs with anaesthesia should be anticipated and minimized using passive or active rewarming (see *Anaesthesia and Intensive Care Medicine* **1:3:** 122). Continued ventilation in the recovery area or ICU may be required until rewarming is completed and spontaneous ventilation is satisfactory.

Neurological vital signs − an intracranial bleed during surgery is a rare cause of continued unconsciousness and apnoea. It may occur as a result of an undetected head injury in patients undergoing surgery for trauma, or coincidentally in patients with cerebrovascular disease. A CT scan is required for diagnosis.

Investigations in the patient who fails to breathe following anaesthesia should include:

- blood gases, electrolytes and glucose
- body temperature
- neuromuscular function (nerve stimulator)
- ECG and chest radiograph
- CT head scan
- blood for serum cholinesterase activity if indicated.

Air embolism

If bubbles of gas enter the circulation, they may accumulate in the right ventricle. Unlike liquid, gases are compressible, and therefore adequate ejection of blood is not achieved, reducing stroke volume and cardiac output. This can present clinically as a minor fall in blood pressure, hypoxaemia or complete cardiovascular collapse with electromechanical dissociation. If a patent foramen ovale is present, or any other shunt-causing communication between the right and left sides of the heart, the air could enter the systemic circulation and cause neurological injury or coronary artery embolism and infarction (paradoxical air embolism). The effects of air embolism depend on the:

- volume of air entrained
- rate at which it enters the circulation
- general condition of the patient.

Experiments in dogs suggest that volumes greater than 20 mlare potentially fatal.

Some operations carry an increased risk of air embolus (Figure 13). Air may be entrained into an open vein when the venous pressure is subatmospheric. Air embolism occurs in 25−50% of all craniotomy operations in the sitting position and the incidence has reduced now this position is seldom used. The prone position with head tongs appears to be safer for posterior fossa surgery.

Procedures with increased risk of air embolus

- Posterior cranial fossa neurosurgery (especially in the sitting position)
- Lumbar laminectomy and head and neck surgery when the vertebral column is positioned above the level of the heart
- Hepatic surgery that carries a risk of opening the inferior vena cava
- Any patient with a central venous pressure catheter in situ that may result in accidental entrainment of air
- Varicose vein ligation
- Surgery combined with low venous pressures (e.g. in children)

13

Signs that alert the anaesthetist to the development of air embolism are usually detected by monitoring. Early diagnosis allows prompt institution of preventive measures before the situation becomes critical. The signs of air embolus include:

- sudden fall in $P_{E'}CO_2$ despite unchanged ventilatory settings (if breathing spontaneously the patient may develop respiratory distress)
- turbulent blood flow (monitored by precordial Doppler probe; conventional auscultation may reveal continuous ‘millwheel’ murmur as a late sign)
- fall in oxygen saturation
- pulmonary artery pressure increases during air embolism (it is not often monitored)
- arterial hypotension
- tachycardia, dysrhythmias or cardiac arrest.

Management (Figure 14) comprises prevention of further air entrainment, attempts to remove the air and supportive measures.

Management of air embolus

- Ventilate the patient with 100% oxygen. Stop nitrous oxide administration
- Flood the surgical site with normal saline, wet packs, and apply bone wax to any area of exposed bone cortex. Manually compress the proximal veins to stop further air entrainment
- Attempt to increase venous pressure
  - Position patient head down (or surgical site down)
  - Give rapid fluid bolus (250−500 ml) and observe effects
  - Use vasopressors if the arterial blood pressure is severely affected
  - Compression of the abdomen
  - Activation of antigravity venous compression device (G suit) if fitted
- If a central venous catheter (CVC) is in situ, try to aspirate air from all lumens. Insert a CVC (right internal jugular or subclavian) if one is not present
- The left lateral position may transfer air from the pulmonary artery to the right ventricle, thereby improving pulmonary flow (there is little evidence that this is of benefit)
- Give cardiopulmonary resuscitation if required

14

Pneumothorax

The pleural cavity usually exists only as a potential space between the parietal pleura (attached to the innermost intercostal muscle, the transversus thoracus), and the visceral pleura (continuous with the lung parenchyma). A pneumothorax occurs when this potential cavity is opened, either by breaching the chest wall structures (an open pneumothorax), or by injury to the lung parenchyma (a closed pneumothorax).

- The clinical management is concerned with releasing the accumulation of air from the cavity and correcting the chest wall injury. Understanding the anatomy of the chest cavity allows cause and effect to be identified rapidly.
- The dome of the lung protrudes superiorly above the thoracic inlet to the level of the 6th cervical vertebra. The tip of a needle inserted towards the internal jugular vein could pass more posteriorly where it may cross the pleural space and enter the apices of the lung parenchyma. This is possible even with a relatively high approach.
- The inferior part of the chest cavity extends to the costo-diaphragmatic recess. This reaches to the crura of the diaphragm at the level of the 12th thoracic vertebrae. The cavity can be entered inadvertently in this low position by surgery to the renal bed or lower thoracic and upper lumbar vertebrae.
- The mediastinal pleura lies against the vertebral bodies, oesophagus, aorta, large veins, heart and trachea. Damage to many of these mid-chest structures could allow air or blood to enter the pleural cavity. Trauma from accidents or surgical instrumentation of the oesophagus or trachea may cause this.

The signs and causes of a developing pneumothorax while under general anaesthesia are shown in Figure 15; some or all may be present depending on the nature of the pneumothorax (simple or under tension), its speed of onset, the general health of the patient and whether they are breathing spontaneously or are mechanically ventilated.

Signs and causes of pneumothorax

Signs

- Hypoxaemia
- Wheeze
- Increasing airway pressure
- Unilateral chest wall motion
- Reduced air entry
- Hyperresonance
- Distended neck veins
- Shock
- Shifted trachea away from affected side

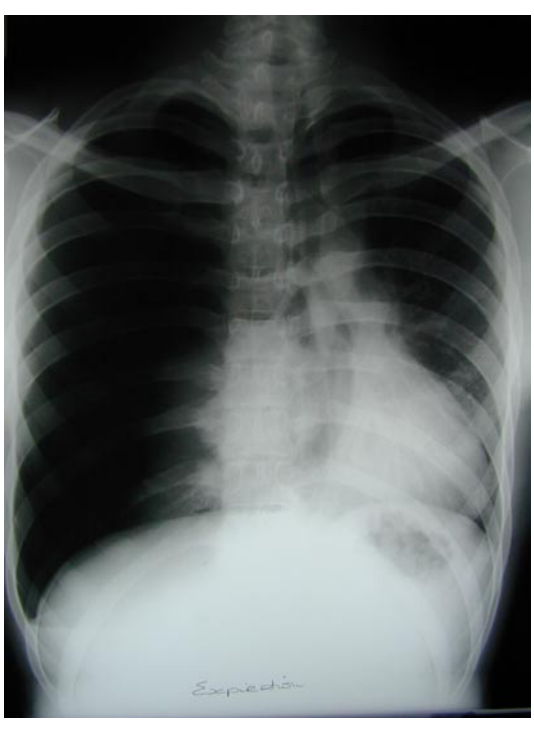
Causes

- Central venous catheter insertion
- Penetrating or blunt chest trauma
- Diaphragmatic, tracheal, oesophageal or cardiac surgery
- Chest drain clamping
- Spontaneous bullae rupture

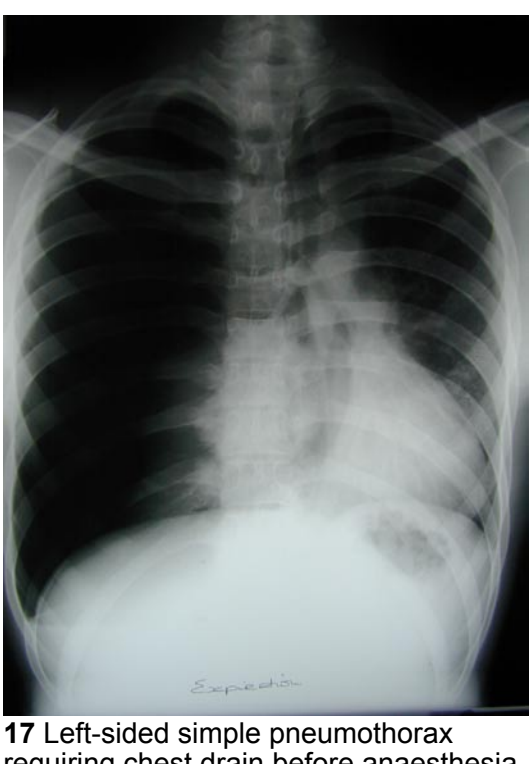
15

In trauma patients, pneumothorax should be identified and treated by chest drain insertion before anaesthesia to avoid the dangers of tension pneumothorax following the start of positive pressure ventilation (Figures 16 and 17). If there is obvious chest injury, but no clinical sign or chest radiograph appearance of pneumothorax, ‘prophylactic’ bilateral chest drains may be indicated. The risks of chest drain insertion must be balanced against the consequences of a tension pneumothorax developing during interhospital or intrahospital transfer or during the perioperative period.

Immediate management of a tension pneumothorax is chest decompression using a 14 G cannula inserted in the midclavicular line and second intercostal space. This should be followed immediately by formal chest drain insertion.



16 Right-sided tension pneumothorax requiring immediate needle decompresion followed by chest drainage. Gross mediastinal deviation is shown to the left.



17 Left-sided simple pneumothorax requiring chest drain before anaesthesia.

Electrical Hazards: Their Causes and Prevention

John Moyle

John Moyle is Consultant in Palliative Medicine in Milton Keynes and a Chartered Engineer. He trained with Philips Electrical Industries. He read medicine at St Bartholomew's Hospital, London and trained in anaesthesia and intensive care at King's College Hospital, London.

Before 1940 there was little electrical equipment in the operating theatre apart from crude radiofrequency diathermy. Since then there has been an invasion of electronic monitoring equipment and many surgical tools are electrically powered. The operating theatre and ICU are unique in electronic engineering because deliberate electrical contact is made with the human body.

The body should be protected from electric current. The body may be considered as an electrolyte solution, which is a good conductor of electricity, contained in a leather bag. Dry leather is a good electrical insulator but conducts electricity easily when damp especially with electrolyte-containing liquids such as sweat.

Electrical injury is caused primarily by the intensity of the current passing through. Current is dependent on the potential difference or 'voltage' across the body and the resistance of the tissues through which it passes (Ohm's law).

$$I = \frac{E}{R}$$

where: E, potential difference (volts); R, resistance (ohms); I, current (amperes)

Severity of injury also depends on the current pathway through the body, environmental factors and the pre-existing health of the patient.

Pathophysiological effects

The pathophysiological effects of electricity range from a mild 'tingling' feeling to ignition in extreme cases. Any electrical current passing through a resistance loses some energy by conversion to heat. The amount of heat generated depends on the current and the value of the resistance; this may be beneficial and forms the basis of coagulation by radiofrequency diathermy. Electricity may stimulate excitable tissues, both nerves and muscles. In a controlled way, this effect may be used medically (e.g. peripheral nerve stimulator, defibrillation). Direct currents, even of low intensity, may cause electrochemical effects. Very high currents, generated by high voltages, cause arcing or sparking and char the tissues. This effect may be harnessed when radiofrequency diathermy is used to cut tissues.

Complications of the inadvertent application of electric currents to the body are:

- cardiopulmonary arrest
- cardiac arrhythmia
- skin and tissue damage
- associated injuries caused by gross muscle contraction.

In the hours after an electric shock there may be further heart rhythm disturbances, hypoxia and electrolyte disturbances, and acute renal failure due to myoglobinuria. It is difficult to predict the effect of electricity on the body because of variables such as body size, proportion and general health. Pre-existing heart problems make the heart more susceptible to arrhythmias.

The current pathway through the body dictates the type of injury. Current passing through the head or across the thorax may cause loss of consciousness and respiratory arrest with or without ventricular fibrillation. Current passing from hand to hand (Figure 1) may cause ventricular fibrillation. Current passing vertically through the body is more likely to cause cardiac muscle damage and injury to other vital organs especially the spinal cord. These injuries depend on the intensity and duration of the current.

The resistance of the human body is not uniform, therefore electricity does not pass evenly through it. Skin resistance is low and allows electricity to pass easily, especially when wet with sweat. Blood has a relatively low resistance, therefore highly vascular areas or inflamed areas of skin have lower resistance. The highest skin resistance is found over heavily calloused areas such as the palm or sole.

The pathway of the current inside the body depends on the resistance of each tissue type. Tissues with the lowest resistance (the best conductance) are nervous tissue, blood, mucous membranes and muscle; the poorest conductors are tendon, bone and fat.

Direct and alternating currents have different effects on the body. Direct current of sufficient intensity causes short duration muscle spasm which may throw the victim from the source. There may be a disturbance of heart rhythm and blunt mechanical trauma. Alternating current, especially at 50 Hz (60 Hz in North America) is approximately three times more dangerous than direct current. Alternating current (40–110 Hz) causes continuous muscle spasm or tetany. As the flexor muscles are more powerful than the extensors, tetany may cause the victim to grip the offending conductor more tightly, thus prolonging the duration of current. Local diaphoresis also reduces skin resistance at the point of contact thus increasing the current.

50 Hz (or 60 Hz) is a bad choice of frequency for the public utility electricity supply because it is the frequency to which the body is most sensitive. At higher frequency the body is progressively less sensitive to the excitable effects of electricity. Radiofrequency surgical diathermy uses frequencies greater than 100 kHz at which comparatively large current may be passed, taking advantage of the heating effects of electricity without affecting excitable tissues.

Effects of hand-to-hand 50 Hz alternating current

1 mA	Tingling sensation
5 mA	Pain
15 mA	Severe pain with local muscle spasm
50 mA	Respiratory muscle spasm
80–100 mA	Dysrhythmias, pump failure, ventricular fibrillation

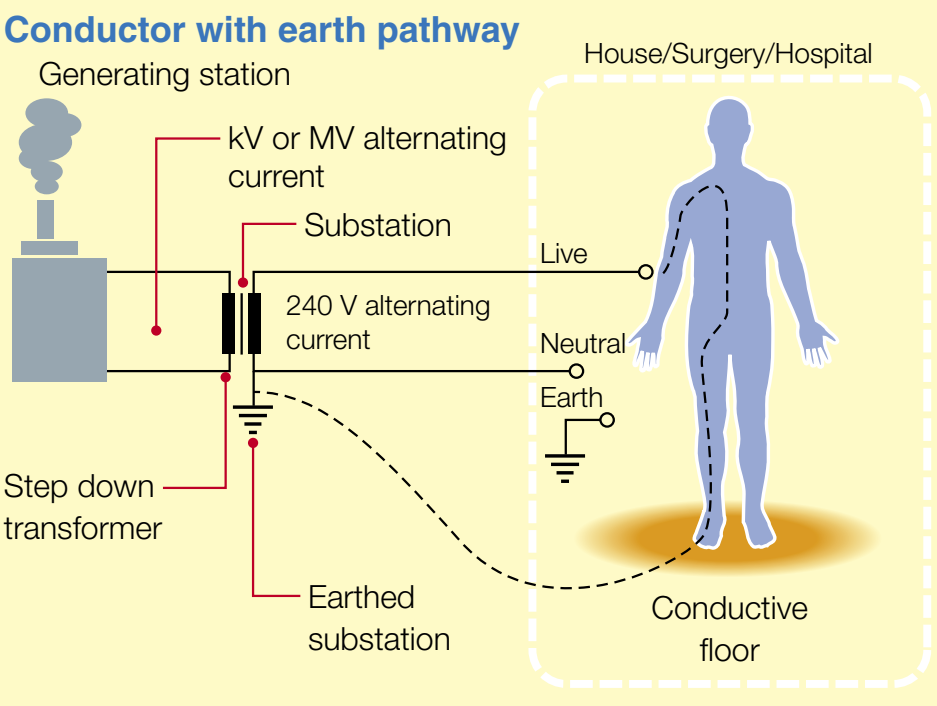
1

Electrical safety

The basic principle of electrical safety is to prevent the body becoming part of an electrical circuit. This requires good design of equipment, cables and connectors. Even with the highest quality of design, the user has the responsibility of using and handling equipment sensibly.

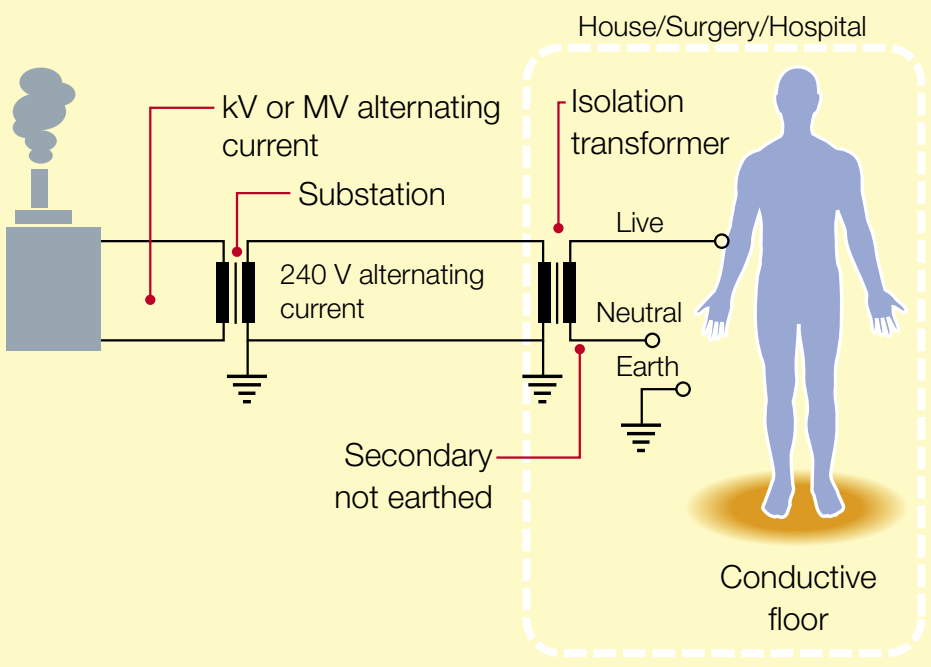
The conventional single-phase mains supply has two conductors: live and neutral. The live conductor is at a voltage dependent on the supply, normally 220–240 volts (110 volts in the USA) with respect to the neutral conductor which is 'tied' to earth at the substation. A safety or earth conductor may also be present which is connected to earth locally and therefore may be at a slightly different potential from the neutral conductor. It is unusual to get an electric shock from the neutral conductor alone but a circuit may be completed between a live conductor or component and either the neutral conductor or, more commonly, an earth pathway (Figure 2). This condition may be eased by the use of an isolation transformer (Figure 3) which will protect against electrocution via earth but not between earth and neutral. Isolation transformers are the most common form of basic protection with medical equipment and are often contained inside the equipment. (Further isolation is required when connection is made directly to the patient, this is described below.)

Conductor with earth pathway



2

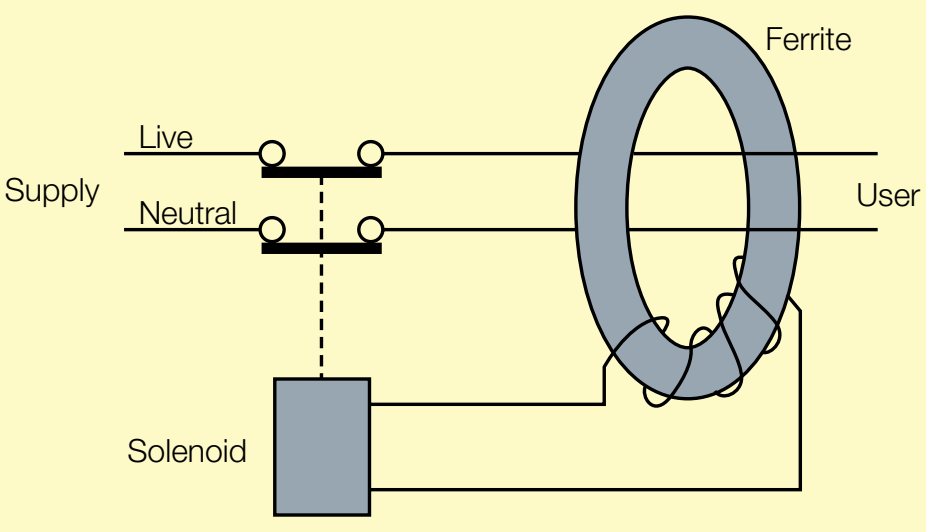
Conductor with isolation transformer



3

Electrocution depends on the duration of exposure and current. The shorter the duration, the higher the current required before damage is done. The earth leakage or residual circuit breaker stops the current passing through the body before any serious damage occurs. This phenomenon is used as the final level of protection from electrocution in the domestic situation and is commonly used commercially for power tools. The principle of the earth leakage circuit breaker (ELCB) is shown in Figure 4. The ferrite ring forms the core of an electrical transformer. The live and neutral conductors pass together through the ring, forming a single-turn primary of the transformer. The secondary of the transformer consists of many turns of much finer wire and is connected to a solenoid. When the solenoid is energized it breaks the supply. In the normal state, current passes down the live conductor, through the appliance and back through the neutral conductor. The current in the neutral is equal and opposite to that in the live and so their magnetic fields are cancelled out and no current is generated in the secondary winding. If some current leaks out of the appliance due to a fault or someone touching a live part, there is an imbalance between the live and neutral and a much amplified current is generated in the secondary, energizing the solenoid and disconnecting the supply.

Earth leakage circuit breaker



4

Microshock: electrocution of the intact human body is commonly referred to as macroshock to distinguish it from microshock in which smaller currents can lead to cardiac dysrhythmia or arrest because one of the points of contact is on or in the heart. 50 Hz mains electricity at a current as low as 50 μA by this route may have serious consequences. Contact may be made with the heart during thoracotomy but a more common and less obvious route is via electrolyte solutions in catheters in or near the heart. Therefore, any equipment that might make connection with the heart must be specially designed to protect against the unintentional passage of these very small currents. Such equipment includes ECG recorders, intravascular pressure monitoring systems, pacemakers and defibrillators.

Leakage current may be defined as electric current that has passed through insulators. It is difficult to design equipment with perfect insulation. The reduction of leakage in medical equipment requires special design features. The designer has to ensure that no electrically live parts are accessible. Any outer metal casing has to be connected to earth; an extra layer of insulation may also be used – the 'double insulation' often used on power tools. These techniques may make a piece of medical equipment safe to be in the patient environment. However, if there is any possibility of connection with the heart, special isolation techniques have to be employed by the equipment designer to ensure that any leakage current is less than 10 μA. This is a stringent limit to achieve.

Safety standards

All medical equipment manufacturers have to comply with published international standards. Each nation also has its own standards organization; in the UK it is the British Standards Institute (BSI). To make standards applicable on a worldwide basis, all national organizations cooperate to write international standards. The International Standards Organization (ISO) deals with everything excluding electricity; the International Electrotechnical Committee (IEC) deals with the standards of anything electrical. Both the ISO and the IEC are based in Geneva.

IEC-60601 is the basic standard for medical equipment. It classifies equipment in two ways; the method of electrical protection and the degree of protection.

- Class I equipment uses a 'protective' earth connection to the outer conductive casing.
- Class II protection is by double insulation. The degree of protection required is classified as B, BF or CF (C, intra cardiac or near cardiac; F, floating) as shown in Figure 5. Figure 6 shows the same symbols, with the indication that the equipment may withstand a defibrillator pulse without damage.

Three types of protection required

Type B applied part

- Maximum leakage current 0.1 mA
- Single fault condition 0.5 mA
- Allowed in patient care area but not in direct contact with patient
- Can be used in X-ray and suction equipment and operating theatre lights

Type BF applied part

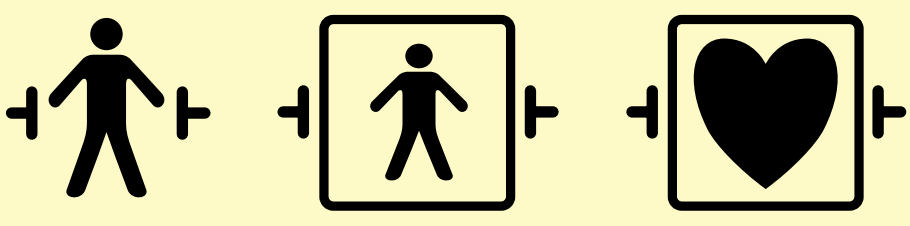
- Maximum leakage current 0.1 mA
- Single fault condition 0.5 mA
- Floating/Isolated
- May be deliberately in contact with patient but not in direct contact with heart
- Can be used in temperature measurement, non-invasive blood pressure measurement, ultrasonography, pulse oximetry, capnography

Type CF applied part

- Maximum leakage current 0.01 mA
- Single fault condition 0.05 mA
- Floating/Isolated
- Suitable for direct cardiac application
- Can be used in ECG, EEG, direct blood pressure measurement, electromagnetic blood flow

5

Symbols indicating equipment is able to withstand a defibrillator pulse



B BF CF

6

Two values of leakage current are given for each category; the lower refers to the equipment in its normal state; the higher value is the maximum allowable leakage current with a single fault condition (SFC). The Standard lists the allowable SFCs for each type of equipment. All medical equipment has to be marked with symbols to show the degree of protection. Figure 7 includes other relevant safety markings that are published in IEC 60601.

Electrical symbols

~	Alternating current
3~	3 Phase alternating current
3N~	3 Phase alternating current with neutral
⎓	Direct current
⏚	Protective earth (ground)
⏚	Earth (ground)
N	Neutral conductor (only on permanently installed equipment)
⏚	Equipotentiality

7

Fires and Explosions

John Moyle

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Less emphasis is placed on the risk of fire and explosion in the operating theatre today than previously mainly because the use of flammable agents has decreased; for example, ether and cyclopropane are no longer used in anaesthesia. This has lead to a false sense of security and little attention to fire safety. It must not be forgotten that alcohol as an antiseptic and dry drapes are flammable and that the microenvironment around a patient may have an increased concentration of oxygen. Nitrous oxide supports combustion better than oxygen. There are also new sources of ignition, such as the intense energy at the end of fibre-optic 'light pipes' and surgical lasers as well as the dangers associated with the use of surgical diathermy.

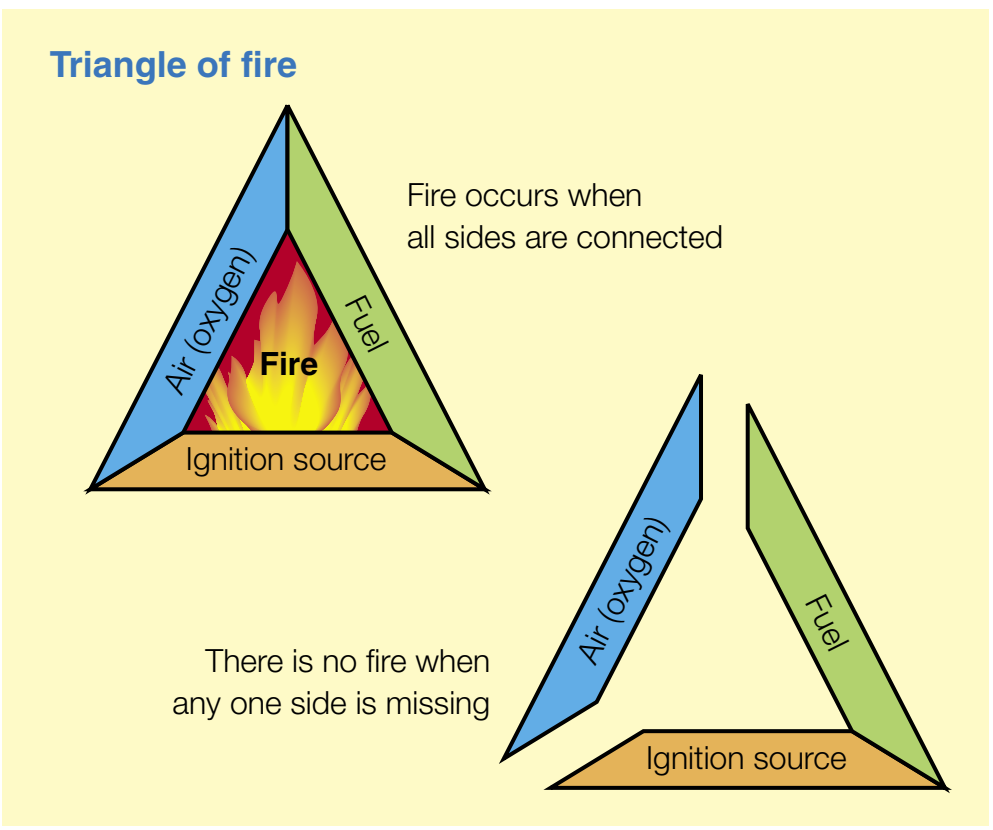
Fire and explosion

Fire or explosion occurs when a substance combines with an oxidizing agent with the release of energy. The reaction requires activation energy to trigger it (Figure 1). If the reaction occurs slowly, heat may be the only obvious evidence, though it usually leads to fire. If the reaction proceeds rapidly, large amounts of heat, light and a rapid increase in pressure occur, making sound; this is an explosion. Fire burns slowly at atmospheric pressure at a temperature of 200–500°C. An explosion is a fast, sudden increase in pressure to a high level at a much higher temperature than fire.

If the rate of liberation of heat is equal to the amount of heat required to maintain the process, the flame will stay still as long as the reactants are made available by convection. If the rate of generation of heat is larger than that required to continue activation, the flame will travel through the mixture. The greater the difference, the greater the likelihood of the reaction travelling so fast that a shock wave occurs; this is an explosion.

On a molecular basis, combustion is a chemical process. In oxidation, the intermolecular bond energy of the end products is less than the bond energy of the reactants and the excess energy is dissipated as heat. To induce the initial deformation of the molecules which allows the rearrangement of these bonds, activation energy has to be added to the system; in the case of fires and explosions this is usually in the form of heat. When the oxidation process begins, positive feedback has to occur to maintain the reaction; if not, the process would cease immediately, before the reaction was complete.

The speed of reaction is greatest for a stochiometric mixture: defined as a mixture in such proportions that none of the reactants is left at the end of the reaction.



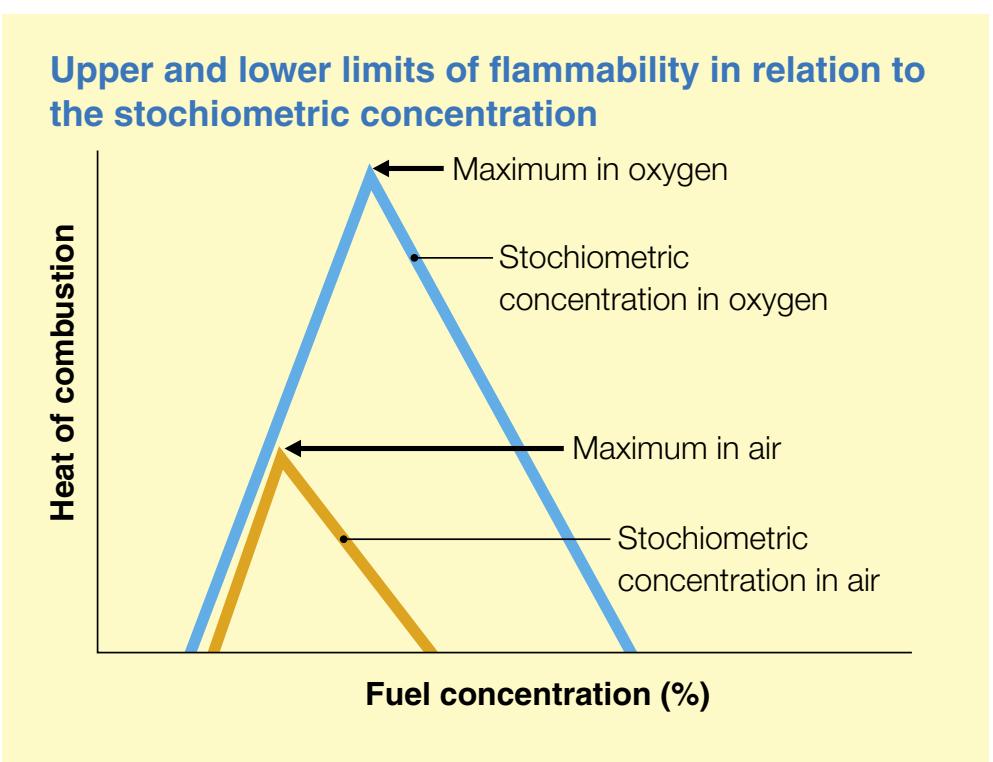
1

Fuel

A gas or vapour may be flammable over a range of concentrations with lower and upper limits of flammability. The stochiometric concentration occurs between these limits. Limits of flammability vary depending on the atmosphere in which the flammable gas or vapour is found (Figure 2).

Anaesthetic gases and vapours are not the only flammable substance that may put the patient at risk.

- Methane and hydrogen are found in bowel gas.
- Alcohol forms the basis of many skin preparation solutions and is in the exhaled gases of the inebriated. Isopropyl alcohol is commonly used to clean the skin before cannulation. Methyl alcohol is used in spirit burners and by down-and-out alcoholics.
- Drapes are often applied to the patient before the alcohol in skin preparation solution has evaporated completely. There may be a high concentration of the vapour, and even some of the liquid alcohol, beneath the drapes.
- Some surgeons use hydrogen peroxide to clean wounds. It rapidly decomposes by enzyme catalysis when poured on to open wounds, producing a froth of hydrogen and oxygen; the gas given off is highly flammable.
- Dry cotton or paper drapes are flammable.
- The plastic compounds used in the manufacture of conventional tracheal tubes may become flammable in high concen-tration of oxygen and high ignition energy levels.



2

Oxygen

Oxygen in the air is the usual source of oxygen involved in a fire. Figure 3 shows that the risk of ignition of any flammable gas or vapour is increased with increased concentration of oxygen above ambient level. Any fire burns more vigorously if the concentration of oxygen is increased.

Nitrous oxide is not combustible but it vigorously supports combustion.

Risks of fire and explosion arise from the strong oxidizing action of nitrous oxide and from its thermodynamic instability. At about 400°C, nitrous oxide breaks down to oxygen and nitrogen and if this comes into contact with combustible material, fire or explosion may result. The concentration of oxygen and nitrous oxide is increased around the mouth and upper airways if a tracheal tube or laryngeal mask does not seal perfectly. There is often an increased concentration of oxygen and nitrous oxide trapped between the patient and the surgical drapes.

Limits of flammability of gases and vapours encountered in the operating theatre[1]

Gas or vapour	Air		Oxygen		Nitrous oxide		30% oxygen 70% nitrous oxide		20% oxygen 80% nitrous oxide	
	L[2]	U	L	U	L	U	L	U	L	U
Diethyl ether	1.9	48	2.0	82	1.5	24				
Cyclopropane	2.4	10	2.5	60	1.6	30				
Ethyl chloride	4.0	15	4.0	67	2.0	33				
Enflurane			4.0				5.75		4.25	
Isoflurane			6.0				7.0		5.25	
Halothane							4.75		3.25	
Methoxyflurane	7.0		5.0	28	4.6					
Trichloroethylene			9.0	65						
Fluoroxene				4.0						
Hydrogen	4.0	74	4.6	94	5.8	86				
Methane	5.3	15	5.4	59	4.0	40				
Sevoflurane			12		11					
Isopropyl alcohol	2.5	12								
Methyl alcohol	6.0	36.5								
Ethyl alcohol	3.3	19								

[1]This is a compilation of information from a number of sources
[2]L, lower limit; U, upper limit.
All values are percentages.

3

Ignition source

Sources of ignition may be sparks generated by static electricity, flames or hot surfaces. Even shaking a bottle containing an organic compound in combination with a peroxide, may cause ignition.

The flash point of a liquid is the lowest temperature at which it gives off enough vapour to form an ignitable mixture with air. At flash point, the vapour will burn, but only briefly because inadequate vapour is produced to maintain combustion. The flash point of a liquid is always quoted but is of less significance to theatre staff than the autoignition temperature.

The autoignition temperature is the minimum temperature above which a flammable mixture is capable of extracting enough energy from the environment to self-ignite. Figure 4 shows the flash points and autoignition temperatures of some compounds in the operating theatre.

If anaesthetic agents that are flammable at clinical concen-trations are used, care must be taken to keep any possible source of ignition outside the zone of risk. There are two zones of risk around the anaesthetic machine, breathing circuit and head and neck of the patient:

- 5 cm if only air is used as the source of oxygen
- 25 cm if nitrous oxide and/or oxygen are used.

Equipment must be marked as AP where air is the only source of oxygen and APG when nitrous oxide or high oxygen concentrations are used.

Possible sources of ignition

Open flames are an obvious source of ignition; they comprise spirit and gas burners, matches and cigarette lighters.

Hot surfaces may cause ignition if the temperature is above the autoignition temperature of the liquid, vapour or solid. In some cases the high temperature of a surface is obvious because it glows or is incandescent.

Hot wire filaments used for cautery may be of high enough temperature to cause ignition. Miniature filament bulbs used in old-fashioned endoscopes may have a surface temperature of 250°C; sufficient to ignite diethyl ether in air.

Light sources – powerful light sources and fibre-optic light-guides have replaced miniature light bulbs but they should always be extinguished when not in use because the energy emitted from the light-guide when not connected to an instrument is intense enough to cause a burn on a surgical drape or the skin. The likelihood of igniting a drape is higher if the concentration of oxygen or nitrous oxide is high in the atmosphere trapped beneath it.

Surgical lasers – see below.

Sparks due to current electricity, as in radiofrequency surgical diathermy and static electricity, are the most obvious sources of ignition in surgical practice. Even sparks that are so small as to be almost invisible may be of sufficient energy to cause ignition.

Sudden increase in gas pressure causes gases to heat. Therefore it is important that no oil, grease or other flammable substance comes into contact with oxygen or nitrous oxide under high pressure.

Lasers

The energy emitted from the tip of a laser applicator is extremely high. The risk of causing ignition is higher than with any other source of emission. Extreme care must be taken to ensure that a laser beam does not come into contact with anything flammable. Any drapes or swabs in the vicinity must be kept wet with water. Care must also be taken to ensure that the beam is not inadvertently reflected on to a flammable surface. If the laser is being used in the mouth, the trachael tube should be of a non-flammable type or be suitably protected. In the case of laser in the bronchi or trachea the oxygen concentration should be 21% or only slightly higher.

Precautions

- Avoid the use of flammable liquids, gases and vapours.
- Keep unsuitable equipment out of zones of risk when flammable anaesthetic agents are in use.
- Observe antistatic precautions.
- Remember bowel gases are flammable.
- Relative humidity should not be less than 50% (a dry atmosphere promotes the generation of static electrical charge).
- At least 15–20 changes of air per hour in the operating theatre will reduce the risk of build-up of flammable vapours.
- High energy light sources must not remain on dry drapes (these sources are of high enough energy to damage tissues).
- Radiofrequency surgical diathermy is a potent source of ignition energy; evaporation of flammable skin preparation solutions must be complete and the atmosphere cleared of the vapour before diathermy is used.

Flash points and autoignition temperatures of flammable liquids encountered in the operating theatre

Compound	Flash point (°C)	Autoignition temperature (°C)
Methyl alcohol	–16	385
Ethyl alcohol	12	363
Diethyl ether	–45	160
Isopropyl alcohol	11.7	455.6

Induction of Anaesthesia

James Austin

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Induction is the process that produces a state of surgical anaesthesia in a patient. The term is used only in the context of general anaesthesia and not with local anaesthesia. It is the first step in the process of anaesthesia whereby the patient is rendered unconscious, preventing both awareness of, and response to, surgical stimuli. Anaesthesia and physiological sleep are different because sleep has structured, specific EEG patterns and endocrine changes, whereas anaesthesia is associated with a diffuse damping-down of EEG function and a stress-type endocrine response.

The process of induction should ensure patient safety, produce a state of unconsciousness, ensure optimal conditions for the surgeon and prepare the patient for waking and recovery.

Before anaesthesia is induced, the anaesthetist must:

- assess the patient as completely as circumstances allow, and institute preoperative preparations (e.g. intravenous fluids, sedative drugs, analgesics)
- discuss the surgery with the surgeon, particularly in complex or unusual cases
- plan the anaesthetic technique
- ensure all necessary equipment and drugs are available, and that the equipment is working.

On arrival in the anaesthetic suite, the anaesthetist must ensure:

- the correct patient has arrived
- the correct operation is planned on the correct side
- consent has been given
- jewellery or prostheses have been removed or declared
- blood for transfusion is available if required.

Anaesthetic room

In the UK, most inductions take place in a dedicated anaesthetic room; however, in many other countries induction takes place on the operating table in theatre. The main advantage of using a dedicated induction room is the quicker change-around as the theatre is cleaned and prepared between patients. If staffing permits, induction may take place while the previous case is being completed. A separate induction room also avoids the psychological stress (for some patients) of seeing the operating theatre. The anaesthetic room must be equipped with the necessary anaesthetic and monitoring equipment for the induction to be completed safely. The duplication of equipment between anaesthetic room and operating theatre may be a financial constraint in some locations. In urgent cases, with potentially unstable patients or with the morbidly obese, theatre is the best place for induction, because it saves the time, physical hazards and period of reduced or absent monitoring associated with transfer.

Equipment checks: successful induction requires planning and attention to detail. Before the procedure begins, checks of the anaesthetic machine must have been completed and the following must be available:

- the patient must be on a tilting bed or trolley
- two working laryngoscopes (in case of bulb failure), including standard and long blades (sizes 3 and 4)
- a selection of laryngoscope blade types (e.g. the Macintosh and the McCoy levering blade)
- a selection of tracheal tube sizes, with their cuffs checked
- suction equipment
- equipment to deal with difficult or failed intubation, including oral and nasal airways, gum-elastic bougie, laryngeal mask
- standard monitoring equipment (e.g. pulse oximeter, ECG, capnometer, blood pressure monitor).

Monitoring

In addition to the clinical observations made by the anaesthetist, the Association of Anaesthetists of Great Britain and Ireland has published recommendation for standards of monitoring equipment during anaesthesia and recovery. Monitoring should be instituted before induction whenever possible and should consist of a pulse oximeter (ideally with continuous display of pulse rate and plethysmography), an ECG and non-invasive arterial blood pressure monitoring. Following unconsciousness, other variables should also be monitored, including:

- carbon dioxide (using a capnometer)
- the anaesthetic vapour concentration
- body temperature
- neuromuscular function if muscle relaxants are used (assessed using a nerve stimulator)
- invasive arterial or central venous pressures and urine output monitoring may be required.

Induction methods

Most anaesthetic inductions are performed using intravenous or inhalational (‘gas’) induction; each has advantages and disadvantages (Figure 1). Less commonly, induction may be carried out by the intramuscular route in uncooperative patients, children or those with difficult venous access. Ketamine,10 mg/kg, provides up to 30 minutes of surgical anaesthesia, but induction times are unpredictable (15–45 minutes) and recovery is slow. Rectal induction with thiopentone, methohexitone, chloral hydrate or benzodiazepines was popular for children at one time, but is seldom used now. Oral induction is effectively a heavy sedative or ‘premedicant’, rather than induction, and recovery time is prolonged.

There are several tasks to be accomplished with any form of induction:

- last-minute preliminary checks (as specified above)
- establish monitoring
- establish intravenous access
- produce unconsciousness
- secure the airway
- establish ventilation
- commence analgesia (systemic or local)
- position the patient
- establish maintenance of anaesthesia.

Intravenous and inhalational induction

Intravenous	Inhalation
Advantages	*Advantages*
• Rapid onset • Patient comfort • Airway protection in rapid-sequence induction	• Does not require IV access • Useful for children • Useful for adults with needle-phobia
Disadvantages	*Disadvantages*
• Contraindicated in patients with a ‘difficult airway’	• Slow induction • ‘Excitement’ phase • Risk of vomiting • Risk of arrhythmias • Volatile agents contraindicated in patients susceptible to malignant hyperpyrexia

1

Intravenous induction

Pulse oximetry and ECG monitoring should be established before intravenous access because occasionally a cardiovascular event (e.g. vasovagal syncope) occurs during cannulation. Intravascular access commonly consists of a simple venous cannula; however, complex cases may require an arterial line, a central venous line and/or a pulmonary artery catheter. These may be sited with local anaesthesia before induction, to provide additional monitoring if haemodynamic instability is expected.

Following intravenous access, preliminary drugs (e.g. analgesics, antibiotics, anti-emetics) may be given. These vary according to the clinical circumstances and a detailed discussion is beyond the scope of this article. A regional analgesic block, if required, may also be given at this stage. Whether to insert the block before or after the patient is anaesthetized is the subject of some controversy (Figure 2).

Advantages of regional nerve blockade performed either before or after induction

Before induction	After induction
• Patient cooperation with correct positioning • Patient may provide feedback to minimize neural damage by needle or injection • Less requirement for anaesthetic monitoring	• Patient preference • Correct positioning may be easier (e.g. patients with painful fractures or skeletal deformity)

2

Pre-oxygenation: some anaesthetists routinely pre-oxygenate their patients before induction. The correct technique is for the patient to breathe 100% oxygen via an anaesthetic circuit and close-fitting mask for about 3 minutes of tidal volume breathing. Alternatively, pre-oxygenation by three vital capacity breaths has been demonstrated to be effective. The aim is to replace nitrogen-containing air in the resting volume of the lungs (the functional residual capacity, FRC) with a high oxygen concentration. The gas within the FRC acts as an important oxygen store, and therefore pre-oxygenation lengthens the time before hypoxaemia occurs following the onset of apnoea. This may provide valuable time in which the airway can be secured if an unexpectedly difficult airway is encountered. Mask phobia and the difficulties in achieving a mask seal in non-compliant patients and children are the only significant contraindications to pre-oxygenation. Pre-oxygenation is mandatory in rapid-sequence induction.

Intravenous drugs: slow, smooth injection of an intravenous anaesthetic agent usually results in loss of consciousness in less than 1 minute. Thiopentone, for example, starts to work in a period of one ‘arm–brain circulation time’. This is the period of time taken for the drug to travel from the site of injection (the arm) to the site of action (the brain) and is about 15 seconds in a healthy patient. The dose is carefully titrated according to patient response. Typical induction doses for healthy individuals are shown in Figure 3, but dose reduction may be required in:

- patients who are less fit
- the elderly or frail
- neonates
- patients with hypotension or poor cardiac reserve
- patients with chronic renal or liver disease
- patients with raised intracranial pressure
- patients who have been premedicated.

It can be difficult to judge when enough induction agent has been given. Care and experience are needed to titrate dose to effect but some indicators include:

- loss of response to verbal command
- loss of eyelash reflex (in which brushing the eyelash produces a blink response)
- relaxation of a motor posture (e.g. a raised arm or a grip on an object)
- cooperation with bag/mask ventilation.

The eyelash reflex has conventionally been regarded as a good end-point for thiopentone induction, but it is less reliable in propofol induction, for which loss of verbal response or motor relaxation is a more useful end-point.

Induction doses of intravenous drugs

Drug	Typical adult induction dose (mg/kg)	Notes
• Propofol	1.5–2.5	Popular and widely used drug associated with rapid and ‘clear-headed' recovery. Rapid metabolism and lack of cumulative effects has made it popular for total intravenous anaesthesia
• Thiopentone	3–5 (2.5% solution)	The ‘gold-standard’ against which all other drugs are judged. Smooth induction in one arm–brain circulation time
• Methohexitone	1–1.5 (1% solution)	Lowers the convulsive threshold, mainly used in anaesthesia for electroconvulsive therapy
• Etomidate	0.2–0.3	Marked cardiovascular stability makes this drug popular for use in unstable patients
• Ketamine	0.5–2	Useful for sedation with profound analgesia. Increases pulse rate and blood pressure and useful for the induction of patients suffering from acute trauma
• Midazolam	0.15–0.5	A benzodiazepine that may provide stable induction for the elderly and frail, in combination with an opioid

3

Further procedures: the induction agent may be followed by a muscle relaxant, particularly if tracheal intubation is planned. It is important to confirm that the patient's lungs can be ventilated via a bag and mask before paralysing. A muscle relaxant should not be given until it has been confirmed that ventilation is possible. Once anaesthesia is adequate, a clear airway is established using a simple face mask (with or without an oral or nasal airway), laryngeal mask airway or tracheal intubation. If the level of anaesthesia proves to be inadequate to allow an airway or tracheal tube to be tolerated, it may be deepened either with supplementary doses of intravenous agent, or by ventilating with volatile anaesthetic. With the airway secure, ventilation can continue by the patient's own effort, by manual 'hand' ventilation, or by mechanical ventilator.

At this stage, further invasive procedures may take place, such as additional vascular access, regional blocks, bladder catheterization, passing of a nasogastric tube or insertion of a temperature probe.

Transfer to theatre: if anaesthesia has been induced in the anaesthetic room, the patient is now transferred to theatre. This is potentially hazardous because for a short time the patient is separated from monitoring equipment and the mechanical ventilator. The patient is also potentially unstable because of the effects of induction drugs and is at risk of injury during the physical transfer. It is the anaesthetist's responsibility to guarantee the patient's safety. It should be ensured that ventilation and anaesthetic maintenance are re-established in good time, that tubes and lines are not dislodged, and that changes in clinical condition are detected promptly, in particular, cardiovascular instability, desaturation or signs of waking from anaesthesia.

Once in theatre, the priorities are:

- prompt transfer on to the operating table
- prompt re-establishment of ventilation
- prompt re-establishment of anaesthetic maintenance if using volatile anaesthetic drugs
- check correct drug delivery if using intravenous maintenance technique
- prompt re-establishment of monitoring equipment
- safe positioning of the patient
- commencement of maintenance fluids and temperature control.

Rapid-sequence induction

Rapid-sequence induction is used to decrease the risk of aspiration if the patient may have a full stomach, for example in an emergency. In patients presenting for elective surgery, a period of starvation of 2 hours for clear fluids, or 6 hours for food, is considered appropriate. Bowel obstruction, incompetent lower oesophageal sphincter, pregnancy and gastroparesis caused by disease, pain or drugs such as opiate analgesics are also causes of a potentially 'full stomach'.

The incidence and severity of aspiration of gastric contents are made worse by the nature, volume and pH of the gastric solution. Mendelson's studies on aspiration pneumonitis showed that aspiration of solid particles produced more damage than purely fluid aspirates. A potential gastric aspirate greater than 25 ml in volume and/or with a pH less than 2.5 is considered dangerous, though there is little direct clinical evidence for this. In these 'at-risk' patients it is sensible to attempt to raise gastric pH, and to try to promote gastric emptying. Pre-medication with ranitidine, 50 mg i.v., to decrease gastric acidity, and metoclopramide, 10 mg i.v., to enhance gastric emptying and increase the tone of the lower oesophageal sphincter is popular with some anaesthetists; both take at least 1 hour to take effect. A non-particulate antacid, such as sodium citrate, 30 ml of 0.3 M solution orally, given on leaving the ward or arriving in the anaesthetic room, further neutralizes residual stomach acid, but at the expense of raising gastric volume further.

Some anaesthetists advise that a nasogastric tube should be passed to drain the stomach, but it is uncomfortable and may induce vomiting. The counter argument is that any vomiting is better done while the patient is fully awake with protective airway reflexes. If a nasogastric tube is already in place it should be aspirated. If the gastric contents are still acidic on litmus test, consideration should be given to instilling sodium citrate. The old practice of inducing vomiting with ipecac or apomorphine is no longer advised.

The 'rapid sequence' of drug administration aims to produce unconsciousness and intubation conditions as rapidly as possible. The airway is swiftly protected by a cuffed tracheal tube without prior inflation of the lungs via bag and mask. This is to prevent possible gastric distension with an increased risk of gastric reflux. It is performed with the help of a trained assistant, competent in the technique of cricoid pressure.

Muscle relaxants are administered before the airway is controlled, and in this way rapid-sequence induction breaks an important rule of anaesthesia. Careful preoperative assessment of potential airway difficulty is therefore vital, and rapid-sequence induction must not be performed if this assessment predicts difficulty with intubation. The trainee anaesthetist must seek further advice, because an awake intubation technique may then be indicated.

Pre-oxygenation is mandatory, though it may be difficult to achieve in children. Pre-oxygenation reduces the need to ventilate the lungs before intubation. The correct technique is described above. Oxygen must be delivered via an anaesthetic breathing system capable of delivering 100% oxygen; standard 'Hudson' type face masks are inadequate.

Drug injection: the chosen drug is rapidly adminstered (Figure 3). Thiopentone is the drug of choice because of its rapid onset of action in one arm–brain circulation time, but propofol or etomidate are alternatives, albeit slightly slower-acting. The use of rapid-acting opioids such as alfentanil, 10 μg/kg, or fentanyl, 1 μg/kg, helps to reduce the pressor response to laryngoscopy.

Cricoid pressure: or Sellick's manoeuvre, is traditionally practised in rapid-sequence induction and is applied by the anaesthetic assistant as the patient starts to lose consciousness. Pressure is applied to the cricoid cartilage to compress it against the oesophagus, preventing passive regurgitation of stomach contents.

If active vomiting occurs, it is recommended that cricoid pressure be removed to prevent oesophageal rupture – suction, head-down tilt and turning the patient's head to one side is then used instead. Otherwise, cricoid pressure is removed only on the instruction of the anaesthetist, once the airway has been secured with a cuffed tube. Occasionally, it may be removed to facilitate an intubation that is being made more difficult by its continued application.

Muscle relaxation: suxamethonium, 1.5 mg/kg, is the drug of choice. Its rapid onset produces ideal intubating conditions, with a peak effect of muscle relaxation within 50 seconds of injection. It is important to allow the drug time to work, and not to begin the intubation sequence before muscle fasciculations have subsided.

The duration of apnoea is usually about 5 minutes in healthy individuals, and thus spontaneous respiration may be re-established early in the event of a failed intubation. Suxamethonium is contraindicated in patients with:

- previous allergy
- susceptibility to malignant hyperpyrexia
- myotonia
- severe burns, muscle damage or paraplegia (of over 1 week's duration)
- known raised serum potassium.

In these patients, rocuronium, 0.6–0.9 mg/kg, may provide relaxation as rapidly as suxamethonium, but with longer duration. Rocuronium is also the drug of choice in patients with reduced or absent plasma cholinesterase activity, in whom suxamethonium has a long and unpredictable duration of action.

Intubation: the trachea is intubated with a cuffed tube following unconsciousness and muscle relaxation. Uncuffed tubes are used in children to avoid local pressure on the tracheal wall and to maximize the internal diameter of tube available. If difficulty is encountered with direct laryngoscopy, then simple steps may be taken to facilitate intubation:

- manipulate the larynx (the assistant providing the cricoid pressure may be distorting the view of the larynx)
- change to a larger blade laryngoscope
- change to a different type of blade (e.g. a McCoy levering blade)
- use the gum-elastic bougie (this thin, flexible stylet may be used to pass through the cords providing a 'track' over which the tracheal tube can be railroaded).

Before the cricoid pressure is released, the correct position of the tube must be checked carefully by auscultation and capnometry. Once the cuff has been inflated and the airway has been secured, a nasogastric tube should be passed and aspirated, if not done previously. The rest of the anaesthetic proceeds as usual; but at the end of the procedure extubation should take place with the patient awake, with their protective airway reflexes re-established, positioned on their side in a head-down tilt, and with suction available.

Failed intubation drill – if the trachea is not successfully intubated, a failed intubation drill must be followed:

- cease further attempts at intubation
- call for help
- maintain cricoid pressure
- insert an oral airway
- hand-ventilate via bag and mask using 100% oxygen
- await return of spontaneous respiration
- once spontaneous ventilation has returned, turn the patient into the lateral position with head tilted down and await return of consciousness.

A decision to abandon further attempts at intubation must be made early and certainly before arterial desaturation supervenes. The prime concern of the anaesthetist is patient safety. The safest option following failed intubation is to wake the patient. Once the effects of the intravenous induction agent and muscle relaxant have worn off, consideration must be given to how to proceed. This requires consultation with a senior anaesthetist and may involve an awake intubation technique.

Inhalational induction

Gas induction, controversially, is often used as a means of inducing anaesthesia (particularly in a child) without having to site an intravenous cannula first. However, in the event of difficulties (e.g. laryngospasm, arrhythmias) instant intravenous access should be available, because otherwise the anaesthetist controlling the airway will be unable to attempt rapid cannulation. For this reason, some anaesthetists seldom perform gas induction; others permit gas induction if a second anaesthetist is present to assist with intravenous cannulation. Gas induction of children and adults has taken place without intravenous access for over 150 years, in most cases safely and without incident.

Indications: gas induction (with intravenous access) is indicated for patients in whom airway difficulties are expected. In these cases, the patient continues to breathe spontaneously throughout and apnoea is avoided, since it may then be impossible to manually ventilate the lungs with bag and mask.

Upper airway obstruction is an important indication for inhalation induction, and in these circumstances fibre-optic techniques for intubating the trachea are contraindicated for fear of producing complete airway obstruction. However, in patients with an unobstructed 'difficult' airway, the increasing availability of fibre-optic intubation equipment and the growing skill of anaesthetists in awake intubation techniques may reduce the need for gas induction. The difficult airway may best be secured even before anaesthesia is induced.

Technique: there is controversy over whether to induce in 100% oxygen or to use nitrous oxide as well.

- Concurrent use of volatile and nitrous oxide exploits the second-gas effect for a cumulatively more rapid induction. The rapid absorption of the second gas (nitrous oxide) has the effect of increasing the alveolar concentration of the first agent. The partial pressure of anaesthetic gas in the alveolus reflects the partial pressure of anaesthetic in the brain and hence the anaesthetic effect.
- 'Pre-induction', with 33% oxygen and 66% nitrous oxide only, may render a child sleepy enough not to resist when the odour of the volatile agent is added. Clearly the more nitrous oxide is used the more anaesthetic effect is achieved; but likewise the less reserve there is against desaturation. A minimum of 30% oxygen should be given.
- Induction in 100% oxygen is least smooth, but should laryngospasm occur, it is an advantage to have as much of the lung FRC filled with oxygen as possible. This maximizes oxygen stores and thus delays the onset of hypoxaemia.

Conventional practice for inhalational induction with halothane is to start with a low inspired concentration of 0.5%, and to increase it by 0.5% every four breaths up to 4%.

Sevoflurane has greatly enhanced gas induction, because it is faster, better tolerated by patients, and is less arrhythmogenic than halothane. It has been suggested that the lower incidence of arrhythmias has contributed to a decrease in dental anaesthetic deaths in recent years. The high blood-gas solubility of sevoflurane accounts for its rapid onset and offset. Because sevoflurane is less pungent it is often used in high concentrations (maximum 8% on most vaporizers) for faster induction.

Enflurane is seldom used for gas inductions because it is slow; isoflurane and desflurane are almost never used because they are pungent and irritating to the airway.

The last-minute checks before inhalational induction are the same as those for the intravenous route. Monitoring should be established; some children make this difficult, but ECG should be the minimum monitoring instituted. Induction should ideally take place via a tight-fitting face mask (even small leaks may significantly delay induction). However, the use of a cupped hand may be less threatening to a small child in the first instance.

'Single-breath induction' has been described with halothane and sevoflurane. A Mapleson A breathing system containing a 4-litre reservoir bag is filled with a maximum concentration of volatile anaesthetic (4% halothane or 8% sevoflurane) in 66% nitrous oxide and 33% oxygen. The patient is asked to exhale to residual volume, then, via a tight-fitting mask, to inhale a full vital-capacity breath of gas, and then to hold their breath for as long as possible. This technique produces a faster induction than conventional tidal volume inhalational induction in cooperative adults. In the case of single-breath 8% sevoflurane, the speed of induction is comparable with induction with intravenous propofol. It may be a useful technique to use in cooperative needle-phobic adults, but it offers few other advantages.

Four main variables determine the speed of inhalational anaesthetic induction.

- The inspired partial pressure of the anaesthetic agent relative to its minimum alveolar concentration (MAC) alters the speed of induction. MAC is the partial pressure of the agent, expressed in volumes %, which at equilibrium prevents gross muscle movement in response to a skin incision in 50% of patients. It is thus the effective dose in 50% of patients and is a measure of anaesthetic potency.
- The faster the patient breathes, or the greater the alveolar ventilation, the faster the alveolar partial pressure of the agent approaches the inspired partial pressure. In a child, crying speeds up gas induction by increasing minute ventilation.
- The higher the cardiac output the more anaesthetic agent is removed from the alveoli and hence the slower the partial pressure rises in the alveoli. Thus, an anxious, hyperdynamic patient is slow to induce, whereas a shocked patient with a low cardiac output is quicker.
- The higher the solubility of an agent (i.e. a high blood-gas solubility coefficient), the more the agent will dissolve in blood and thus a lower partial pressure will be generated. Agents with a low solubility (e.g. sevoflurane) result in more rapid induction.

During a gas induction, most patients pass briefly through a phase of excitability during which they may be agitated and at increased risk of laryngospasm or, more rarely, arrhythmias. If a child is being induced, it is useful to warn the parents of this disinhibition in advance. The disinhibition is not remembered by the patient.

Once the patient is unconscious, anaesthesia should be deepened, assisting the ventilation by hand, using bag and mask if necessary. If not already obtained, intravenous access should be secured, which requires the help of an assistant. Muscle relaxants may then be given intravenously to assist in securing the airway. If the patient is sufficiently deeply anaesthetized, as evidenced by a regular respiratory pattern and a forward gaze in eyes with small pupils, the airway may be secured (even by intubation) purely under inhalational anaesthesia. Nevertheless, it is valuable to have intravenous access before attempting to manipulate the airway, in case any untoward airway reflexes are produced (e.g. arrhythmias, laryngospasm). With the airway secured, the remainder of the induction sequence proceeds as above.

Historical note

In 1937, Arthur Guedel published *'Inhalational Anaesthesia – a Fundamental Guide',* three chapters of which were devoted to his observations of premedicated patients' responses to gas inductions with nitrous oxide, the ethers, chloroform and cyclopropane

Guedel's stages of anaesthesia

Stage	Definition	Features
1 Analgesia	From beginning to loss of consciousness	Sedation Loss of eyelash reflex[1]
2 Delirium	Loss of consciousness to onset of rhythmic breathing	Agitation, vomiting, arrhythmias Eyes deviated
3 Surgical		
• 1st plane	Onset of rhythmic breathing to loss of eyeball movement	Loss of eyelid reflex Loss of conjunctival reflex[1]
• 2nd plane	Loss of eyeball movement to onset of intercostal paralysis	Loss of laryngeal and gag reflexes Loss of corneal reflex[1]
• 3rd plane	Onset to completion of intercostal paralysis	
• 4th plane	Complete intercostal paralysis to respiratory arrest	Dilated pupils Loss of carinal reflex[1]
4 Respiratory paralysis	Respiratory arrest to death	Loss of anal reflex

[1] Not described in Guedel's original monograph

Induction in children

Children from about 3 months of age until the teenage years are generally more anxious, or less able to control their anxiety, than adults. The preoperative visit is important in children because meeting the anaesthetist and having the procedure explained calms the fears of children and parents. If the child is old enough, address your conversation to him or her. Explain in detail what will happen, and invite the parents and child to ask questions. Where possible, bring relevant equipment, particularly a face mask for gas induction, for the child to become familiar with.

Topical local anaesthetic cream such as EMLA (a eutectic mixture of lignocaine and prilocaine) or amethocaine gel is desirable if awake intravenous access is planned. Marking visible veins in advance helps the nurse to cover the right spots. Both preparations are similarly effective in clinical practice though onset and duration of action differ (Figure 4).

It has become common for parents to accompany children to the anaesthetic room, and this is generally helpful. Smaller children may best be anaesthetized on a parent's lap – a well-positioned hug serves to comfort the child and to restrain them during intravenous cannulation or gas induction. Strapping for the cannula, and the induction drugs, should be on hand for swift application once access has been obtained.

- For gas induction, a sideways hug helps to immobilize all the limbs, while the anaesthetist's hands control the head.
- For intravenous cannulation, a 'face-to-face' hug (Figure 5), with the child's arm under the parent's arm, helps to immobilize the arm and restrict the child's view of cannulation.
- The older child may prefer or need to be anaesthetized on the trolley. If the trolley permits, it is useful to raise the back until just before (or even during) induction itself. This more upright position allows the child a better view of their surroundings, and hence a feeling of more control and less anxiety.

Children should be treated with respect at all times. They should be spoken to in non-condescending language they can understand – if something is going to be unpleasant, it should be acknowledged. The alternative is for the child to become suspicious and uncooperative for even the most innocuous procedure. There is no formula that will ensure every paediatric induction is smooth and trouble-free; some children will be understandably fractious despite all efforts to calm them.

Comparison of EMLA cream and amethocaine gel

	EMLA cream	Amethocaine gel
Constituents	Lignocaine 2.5%, prilocaine 2.5% as an oil/water emulsion	Amethocaine 4%
Presentation	White cream, 5 g per tube	Clear gel, 1.5 g per tube
Application	2 g minimum 1 hour before venepuncture, maximum 5 hours	1 g 30–45 minutes before venepuncture. Remove after 45 minutes
Duration	Efficacy declines soon after cream is removed	Efficacy remains 4–6 hours after application
Skin effects	Usually transient paleness May produce redness and oedema	Usually transient redness May produce itching and oedema
Contra-indications	Not for children < 1 year	Not for children < 1 month

4

5 Hugging the child face to face helps to immobilize the arms.

Further Reading

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Induction of Anaesthesia in Special Circumstances

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A full stomach

The pulmonary aspiration of acid gastric contents has long been recognized as a major risk of anaesthesia. Patients are normally asked to fast preoperatively to allow sufficient time for gastric emptying. However, induction of anaesthesia in the presence of a full stomach may be unavoidable when normal gastric emptying is impaired, or when the urgency of surgical intervention overrides the requirement for a patient to have fasted adequately. Gastric stasis, ileus and reverse peristalsis may accompany obstruction or perforation of the gastrointestinal tract. Trauma, pain and its treatment with opioids delays gastric emptying. Gastric motility may also be abnormal in the presence of diabetes mellitus or obesity and in these circumstances no period of fasting may be considered to be safe. The hazards of induction of anaesthesia in these circumstances are listed in Figure 1.

If the patient has a full stomach an attempt to reduce intragastric volume and acidity before anaesthetic induction is desirable. Gastric fluid may be removed through a gastric tube, or if there is time and no contraindications by giving a prokinetic agent (e.g. metoclopramide, 10 mg i.v.). The pH of the gastric contents may be increased by the ingestion before induction of a non-particulate alkali, usually 30 ml of a 0.3 molar solution of sodium bicarbonate.

Induction of anaesthesia in the presence of a full stomach

Hazards	Management
Pulmonary aspiration of gastric contents	Reduce gastric volume Raise intragastric pH with alkali Use of cricoid pressure Rapid sequence induction
Unanticipated failure to intubate	Preoxygenation Rapid sequence induction Failed intubation drill

1

Rapid sequence induction

Rapid sequence induction is the anaesthetic technique indicated in the presence of a full stomach (Figure 2). It aims to reduce to a minimum the period during which the airway is unprotected after induction of anaesthesia and before inflation of the cuff of a correctly placed tracheal tube.

During preparation for rapid sequence induction, a skilled assistant should carefully identify and hold the cricoid cartilage between the thumb and forefinger, ready to apply cricoid pressure as anaesthesia is induced. Cricoid pressure (Sellick's manoeuvre) correctly applied with adequate, but not excessive, force compresses and occludes the upper oesophagus between the flat posterior surface of the cricoid cartilage and the body of the sixth cervical vertebra, preventing reflux of gastric contents without distorting the view at laryngoscopy. If a gastric tube is already in place, it should not be removed but should be allowed to act as a gastric vent.

The main risk of rapid sequence induction is that there is no prior opportunity to ensure that intubation or mask ventilation will be possible after induction. Good preparation for intubation is vital and it is essential that all equipment is checked, suction equipment and aids to oxygenation are ready and the patient is in an optimum intubating position.

The patient's lungs should be preoxygenated. This is achieved by allowing the patient to breathe 100% oxygen through a tightly fitting mask and anaesthetic circuit for about 3 minutes. When apnoea occurs at induction, the lung rests at end tidal volume where there is equilibrium between the elastic recoil of the lungs and the chest wall. Arterial oxygen desaturation follows when the oxygen content within the functional residual capacity (FRC) of the lungs is exhausted. During preoxygenation, the nitrogen in the FRC will be displaced, increasing the oxygen content of this reservoir substantially and delaying the onset of cyanosis after induction of apnoea. Despite these measures, arterial oxygen desaturation is accelerated by the presence of a reduced FRC (e.g. obesity), a raised metabolic oxygen demand (e.g. sepsis) or a combination of the two (e.g. late pregnancy).

Rapid sequence induction requires the use of rapidly acting induction and paralysing agents injected intravenously in quick succession. Most intravenous induction agents cause loss of consciousness within one arm–brain circulation time in the following doses: thiopental (thiopentone), 2–4 mg/kg, etomidate 0.2–0.3 mg/kg, propofol 2–3 mg/kg. In UK practice, suxamethonium, 1.5 mg/kg, remains the neuromuscular blocking agent of choice because it provides optimum intubation conditions in the shortest time.

Once the correct position of the tracheal tube is verified clinically and by capnography and after the cuff has been inflated, cricoid pressure can be released.

In case of failure to intubate, the duration of action of the induction and paralysing agents is critical. Despite the additional time made available by preoxygenation, it may be impossible to see the larynx or intubate the patient. It is then essential to revert to a well-rehearsed failed intubation drill. The effects of the common induction agents wear off in a few minutes and the choice of suxamethonium is reinforced by its short duration of action. The temptation to give a second dose of the drugs and prolong attempts at intubation should be resisted. At this point, resumption of patient oxygenation is the priority.

Rapid sequence induction

- Selection of intubation aids and equipment for cricothyroid puncture
- Skilled assistant applying cricoid pressure
- Patient on surface that can be tipped head down
- Suction switched on with catheter under pillow
- Optimal patient intubating position
- Good quality venous access with running intravenous infusion
- Preoxygenation with 100% oxygen through close fitting face mask
- Single sleep dose of intravenous induction agent
- Single adequate intravenous dose of suxamethonium (e.g. 1.5 mg/kg)
- Failed intubation drill

2

After head injury

Induction of anaesthesia and tracheal intubation after head injury (Figure 3) is indicated when:

- the patient's airway or oxygenation is compromised
- the patient has a depressed level of consciousness (Glasgow Coma Score of 8 or less)
- in the presence of agitation
- before emergency surgery
- in preparation for safe transfer to either CT scanner or to a neurosurgical centre.

It is vital to prevent secondary brain injury due to hypoxia, hypotension, hypercapnia or uncontrolled rises in intracranial pressure. The patient is assumed to have a full stomach so a rapid sequence induction with preoxygenation and cricoid pressure is indicated. In addition, patients presenting with a severe head injury must be assumed to have suffered a cervical spine injury. Cricoid pressure is applied using a two-handed technique, the second hand supporting the back of the cervical spine. Another assistant is required to provide manual in line stabilization of the spine during induction because any cervical collar has to be temporarily removed to facilitate intubation. Coexisting facial injuries need to be assessed carefully because they may affect intubation by displacing, distorting or obstructing the airway.

Careful monitoring of cardiovascular status is required. It may not be practical to monitor blood pressure invasively before induction, but non-invasive measurements should be made frequently. Suppression of the hypertensive response to intubation requires an intravenous induction agent, though the dose may have to be reduced in the presence of depressed consciousness. Lidocaine (lignocaine), 1 mg/kg, may also be given for this purpose. After induction there should be a smooth transition to maintenance sedation, which may include opiates, to avoid fluctuations in blood pressure.

Suxamethonium is associated with a transient rise in intracranial pressure, but this potential for harm is outweighed by its advantage of rapidly producing optimal intubating con-ditions and thereby reducing the risk of hypoxia. A peripheral nerve stimulator will help to ensure adequate neuromuscular blockade before intubation, and that a non-depolarizing agent is given in time to prevent coughing and facilitate controlled ventilation as the effect of suxamethonium wears off.

Tracheal and gastric tubes should not be placed nasally, for fear of breaching a skull base fracture. Constriction or distortion of neck veins that could result in cerebral venous hypertension should be avoided when securing the tracheal tube and applying a cervical collar. Arterial hypotension must be actively investigated and treated, while moderate hypertension should be tolerated because this may be a normal response to intracranial hypertension, preserving cerebral perfusion pressure.

Induction in head injury

Hazards	Management
Full stomach	See Figure 1
Cervical spine injury assumed	In line stabilization of neck Two-handed Sellick manoeuvre
Rising intracranial pressure	Adequate dose of induction agent Adequate neuromuscular blockade Smooth transition to maintenance sedation and paralysis
Reduced cerebral perfusion pressure	Avoid hypotension
Facial injuries	Intubation facilitated or made more difficult
Skull base fracture	Avoid nasal intubation

3

Upper airway obstruction

The management of the patient with obstruction of the upper airway, including the larynx, is a vital skill for anaesthetists (Figure 4). Adequate diagnosis of the airway pathology and the derangement of normal anatomy should precede discussion of the management plan between senior anaesthetic and ENT staff. An alternative strategy must also be agreed so that there is a back-up plan before proceeding. The management plan should be explained clearly to the patient, whose cooperation will be required.

Induction in airway obstruction

Hazards	Management
Potential for airway obstruction in expert hands	Senior help present
Abnormal anatomy	Information from imaging or endoscopy
Loss of muscle tone in upper air-way at induction may precipitate complete obstruction	Inhalation induction or awake tracheostomy
Obstruction during inhalation induction	Back-up plan in place with scrubbed ENT surgeon for surgical airway

4

Assessment of the patient may elicit stridor (inspiratory noise) at rest, which suggests that the airway is more than 50% narrowed. Results of radiographs, CT or MRI scans or nasendoscopy should be available. In their absence it may be appropriate to perform endoscopic examination by fibrescope via a topicalized and vasoconstricted nasal passage. The site of obstruction must not be approached with the fibrescope because attempted fibre-optic intubation may be impossible and may be hazardous, but endoscopy may provide important reconnaissance information. If there is doubt about the feasibility of intubation, then an awake surgical tracheostomy under local anaesthesia should be considered.

If intubation is likely to be possible, an alternative strategy must be in place before embarking on induction of anaesthesia. A scrubbed ENT surgeon must be present ready for immediate intervention and opening of a surgical airway.

The usual technique for induction of anaesthesia in the presence of upper airway obstruction is an inhalation induction. Most experience has been obtained with halothane although use of sevoflurane is growing. Gradual induction of anaesthesia while maintaining spontaneous ventilation and airway muscle tone may allow adequate depth of anaesthesia for intubation without airway closure. Should there be no obstruction, no manipulation of the airway or laryngoscopy is allowed before adequate depth of anaesthesia is achieved as judged by the pupils coming to lie centrally. It is vital that no neuromuscular blockade or intravenous sedation is used before the airway is safely secured.

Obstruction of the airway during inhalation induction prevents further uptake of anaesthetic agent, therefore allowing anaesthetic depth to lighten and the patency of the upper airway to be restored. An awake surgical tracheostomy should then be performed under local anaesthesia.

FURTHER READING

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Maintenance of Anaesthesia

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This contribution is an overview of what is meant, and required, by maintenance of anaesthesia. Many of the topics are covered in greater detail in separate contributions; the aim here is to put these topics in context.

Maintenance of general anaesthesia involves four priorities:

- keeping the patient safe
- keeping the patient comfortable
- presenting the best possible operating conditions for the surgeon
- preparing the patient for the postoperative period.

Keeping the patient safe

There are several aspects involved in keeping the patient safe:

- airway, breathing and circulation
- temperature control
- monitoring
- positioning.

Airway: this will usually have been established at the time of induction. However, it should not be assumed that this remains secure. Airway disconnection or obstruction may occur and the anaesthetist must be able to detect and correct these incidents promptly, assisted by monitors such as the capnograph, pulse oximeter, disconnect alarm and airway pressure monitor. Movement of the tracheal tube (either towards the right main bronchus or withdrawal from the trachea) or dislodgement of the laryngeal mask airway (LMA) are particularly likely to occur when patients are transferred to the operating table or when changes are made to patient position. These periods require increased vigilance by the anaesthetist. The integrity of the airway should be rechecked both clinically and by monitoring after each patient movement.

Tracheostomy, rigid bronchoscopy or 'one-lung' thoracic surgery may require intraoperative changes to the airway. The anaesthetist must be prepared for such changes and, if necessary, should formulate a plan with the surgeon in advance as to how the airway will be managed.

Breathing will often depend on whether muscle relaxants are being employed as part of the anaesthetic technique. Although the use of muscle relaxants is not essential for controlled ventilation, they are usually employed for ventilated patients. Surgical factors often influence the decision to use muscle relaxants. For example, abdominal surgery is greatly facilitated by muscle relaxation. In specialized surgery, such as ophthalmic surgery or neurosurgery, where the slightest move or cough may have disastrous consequences and carbon dioxide must be controlled, paralysis is ideal. Otherwise, anaesthetists have widely differing views as to whether breathing should be controlled. Some anaesthetists use muscle relaxants almost routinely for any operation lasting longer than about 30 minutes, on the basis that carbon dioxide retention is avoided, potent short-acting opioids can be used without fear of respiratory depression, and good lung aeration with avoidance of atelectasis may be easier to achieve. Others control ventilation less often unless indicated for reasons of airway management or the requirements of surgery. Some advantages and disadvantages of paralysis and ventilation are listed in Figure 1.

The technique of 'paralysing and ventilating' may be preferred when a tracheal tube is present. It is likely that a relaxant will already have been given to enable intubation. Also, the presence of a tube within the trachea is a potent stimulus, and unless local anaesthesia has been applied to the respiratory tract, a deeper level of anaesthesia may otherwise be needed for the patient to breathe spontaneously without coughing. Lighter planes can be tolerated when a laryngeal mask or oropharyngeal airway are employed, because these devices are less stimulating to the patient. Paralysing and ventilating may also be used for longer operations, where carbon dioxide control and prevention of atelectasis is important.

However, avoiding relaxants wherever possible can reduce two important complications of general anaesthesia:

- unrecognized awareness – patient movement usually warns of light anaesthesia before the patient becomes aware
- accidental hypoxia – the spontaneously breathing patient may maintain oxygenation even in the event of circuit disconnection.

Use of muscle relaxants and controlled ventilation

Advantages	Disadvantages
• May allow 'lighter' anaesthesia because reflex activity is abolished by neuromuscular blockade	• May allow unrecognized awareness as a result of inadequate anaesthesia
• Facilitates abdominal surgery by relaxation of abdominal muscles	• Reliance on ventilation equipment and circuit integrity to maintain alveolar ventilation
• Intracranial and intraocular pressure control by regulation of $PaCO_2$	• Possible side-effects of muscle relaxant drugs (e.g. histamine release, vagal blockade, malignant hyperpyrexia)
• Allows effective ventilation during, for example, thoracic surgery, prone positioning or long procedures	• Need for reversal of neuromuscular blockade
• Allows use of potent opioids to reduce the surgical stress response in major surgery	• Possible contraindication in patients with a difficult airway. Absence of spontaneous respiration may render ventilation impossible
• May improve surgical conditions by facilitating a hypotensive technique and lowered $PaCO_2$	• When there is requirement to monitor neuromuscular function (e.g. facial nerve during surgery on the parotid gland or acoustic neuroma)
• Decreases intraoperative atelectasis	
• Decreases energy requirements and tissue carbon dioxide production	• Contraindicated in some myopathies

1

Ventilator settings – most anaesthesia ventilators are time-cycled and volume- or flow-driven. A rate, usually with a ratio of inspiratory time to expiratory time (I:E), and a tidal volume or flow need to be set. Most adults have a minute volume of 80–100 ml/kg, therefore a tidal volume of 8 ml/kg (e.g. 500–600 ml) and a rate of 10 breaths/minute is a good starting point; this can be adjusted according to the observed end-tidal partial pressure of carbon dioxide ($P_{E'CO_2}$). For routine surgery, a $P_{E'CO_2}$ of about 4.5 kPa should be aimed for. If metabolic rate and cardiac output (and hence pulmonary perfusion) are assumed to be constant, then $P_{E'CO_2}$ varies inversely with the alveolar ventilation.

In general, an I:E ratio of 1:2 is often the best compromise between maintaining low inflation pressures (e.g. 15–20 cm H_2O), satisfactory oxygenation (Sp_{O_2} > 95%) and adequate carbon dioxide removal ($P_{E'CO_2}$ 4.5 kPa). However, this can be decreased to 1:1.5 or even 1:1 to prolong inspiratory time. This may be useful in some patients to help decrease high airway pressures (e.g. > 25–30 cm H_2O) or improve oxygenation (e.g. in the obese). Some patients with asthma or chronic airway disease may benefit from a longer expiratory time to allow the lungs to empty, and an I:E ratio of 1:3 or 1:4 may be preferable.

Children have a proportionately higher minute ventilation than adults – up to 200 ml/kg in infancy, approaching adult values weight-for-weight by about age 10 years. Given that their tidal volume is slightly less weight-for-weight than adults (7 ml/kg), this increased minute volume must be provided for by an increase in rate. For example, in a 5 kg infant, a minute volume of 1000 ml might be provided by 30 breaths each of about 33 ml/minute.

However, paediatric ventilation is complicated by the obligatory leak around the uncuffed tube. Volume control is unlikely to inflate the lungs to the set volume (especially if a Newton valve is used with T-piece ventilation). This is usually overcome by increasing the tidal volume by titrating against inflation pressure and/or $P_{E'CO_2}$. Some modern anaesthesia ventilators have pressure control capabilities (e.g. the *Draeger Julian*). Specific compliance varies little with age, therefore pressure control mode can be used to deliver an inflation pressure of 15–20 cm H_2O. This provides an adequate tidal volume for any age, despite small to moderate leaks, as long as lung compliance is normal.

Regardless of the mode of ventilation, a fresh gas flow must be selected. This depends on the breathing system in use as well as the size of the patient. A high flow should be used initially (e.g. 6 litres/minute), regardless of the circuit being used. This allows time for denitrogenation and equilibration of inhaled anaesthetic agent during this early period of rapid anaesthetic uptake. After about 10 minutes, flows can be reduced considerably if the system permits. The circle system with carbon dioxide absorber is widely used, and modern lightweight valves and low-resistance tubing make it suitable for paediatric use well below the traditional lower patient weight limit of 20 kg. With appropriate monitoring of gas concentrations within the circle, this permits total fresh gas flows of 1 litre/minute or less. Higher flows are required for T-pieces such as the Bain and Jackson Rees systems. Formulae exist for each of these circuits to predict the flow of fresh gas required per kilogram patient weight to eliminate rebreathing for controlled and spontaneous respiration. However, a more practical approach is to reduce the fresh gas flow gradually, stopping when rebreathing of carbon dioxide begins to appear on the capnograph.

General anaesthesia, particularly when using volatile anaesthetic agents, causes the development of atelectasis in the dependent parts of the lung and impairs the pulmonary vascular response to hypoxia (hypoxic pulmonary vasoconstriction). These two factors produce a small but noticeable degree of shunt, usually about 10%. This can be corrected by giving anaesthetized patients higher inspired oxygen than the 21% present in air; 30% is usually given, though this can be titrated against observed oxygen saturation.

Circulation: appropriate fluid management is an important component of anaesthetic maintenance. Intravenous fluid requirements may range from none in short and relatively non-invasive procedures, to many times the circulating volume in long and traumatic procedures. Fluid requirement consists of:

- replacement of existing deficit – crystalloid or blood
- metabolic maintenance requirements – crystalloid
- replacing additional ongoing losses – crystalloid, colloid or blood.

Existing deficit – in the adult elective surgical patient, who has been starved for at least 4 hours preoperatively (and sometimes much longer), a deficit of 500 ml of crystalloid can be assumed. This deficit is generally well tolerated and does not necessarily need replacing, but it decreases the patient's margin of reserve against any further losses, or against ongoing postoperative dehydration as a result of nausea or vomiting. Many anaesthetists routinely administer 500–1000 ml of crystalloid in all patients except those at risk from fluid overload (e.g. those with renal or cardiac failure). There is evidence to suggest that this may improve the quality of early recovery and help to decrease postoperative nausea.

In the emergency patient, fluid deficit may be considerable, as a result of either trauma-related blood loss, or anorexia, vomiting and/or interstitial (third-space) fluid loss from surgical pathology. In either case, the deficit should be assessed and replaced with the appropriate fluid. The larger the deficit, the more important that it be replaced before induction, whenever circumstances permit. The exception to this rule is during major ongoing blood loss, such as a ruptured aortic aneurysm or major trauma, where the priority is stopping the bleeding rather than prolonging attempts to normalize the circulation preoperatively.

Maintenance – for many patients this is the least important component of intraoperative fluid management – the average adult requirement of about 100 ml/hour is negligible in the context of a short procedure and other fluid losses. However, in small children, maintenance requirements are proportionately larger and more significant. Paediatric maintenance fluid is usually calculated according to: 4 ml/kg/hour for the first 10 kg, plus 2 ml/kg/hour for the next 10 kg, plus 1 ml/kg/hour for the remainder. Thus, a 25 kg child would have a maintenance requirement of 40 + 20 + 5 = 65 ml/hour. The smaller the child, the less reserve there is for managing without ongoing maintenance fluids, and the greater the impact of preoperative starvation.

Infants have small glycogen reserves, and therefore need intravenous dextrose (e.g. as 5% dextrose in 0.18% saline) as maintenance to sustain their blood sugar levels. For longer procedures, careful attention must be paid to electrolyte balance, because infants have less ability to correct excessive salt loads or water loads.

Ongoing losses – the most significant aspect of intraoperative fluid management can be the most difficult to estimate.

Losses from extravascular spaces (e.g. gastrointestinal, evaporative, third-space fluid losses) are usually crystalloid losses. Evaporative losses can be large – an adult may lose in excess of 1 litre/hour from a laparotomy or thoracotomy wound, and even larger amounts from extensive open skin wounds such as burns or large graft sites. There is no way of measuring these losses directly, and measures such as blood pressure, pulse rate or central venous pressure (CVP) provide only an indirect measure of total body water. Urine output may be the most useful clinical measure. Blood tests such as plasma urea, sodium and haematocrit may provide information regarding the hydration state, and plasma electrolytes and haematocrit are now commonly available from blood gas machines.

Losses also occur from the intravascular space (i.e. blood). Losses in suction bottles may be complicated by wash, faeces, urine or amniotic fluid. Visual estimates of blood loss on swabs are often inaccurate – weighing of swabs is more precise, but still neglects losses on drapes, gloves and instruments. A dilutional technique relies on washing all swabs, instruments and gloves in a fixed volume of water, which can then be measured colorimetrically to give an accurate measure of blood loss. Such instruments are not widely available. Intravascular loss may be estimated indirectly from clinical measures such as blood pressure, pulse rate or CVP, though other anaesthetic factors such as the balance between surgical stimulation and depth of anaesthesia complicate these measures. Estimation of haemoglobin is useful only when adequate intravascular volume has been replaced. Blood losses may initially be replaced by colloid solution (e.g. a gelatin solution or hydroxyethyl starch), but larger losses (> 20% blood volume) may require replacement by packed-cell blood. Very large losses (> 1 blood volume) may require supplementation with fresh frozen plasma and/or platelets to maintain clotting function.

In practice, it is likely that fluid losses are under-replaced in many patients. This is offset by the hormonal 'stress response' to surgery: aldosterone, cortisol and antidiuretic hormone levels rise and atrial natriuretic peptide falls; all contribute to postoperative water retention.

Temperature control: there is now good evidence that the maintenance of a physiological body temperature reduces postoperative morbidity. Patients suffering from head injury or undergoing certain neurosurgical procedures are possible exceptions. Shivering increases oxygen consumption, and predisposes to myocardial ischaemia, dysrhythmias, hypotension and acidosis. Hypothermia also increases susceptibility to infection and tends to lengthen hospital stay.

Temperature control is of particular importance in patients at the extremes of age (who have less intrinsic control over body temperature and a larger surface area-to-volume ratio through which to lose heat), in operations involving open body cavities, and in all patients undergoing lengthy procedures. About 20% of trauma patients who arrive at hospital are hypothermic (core temperature < 35°C).

A change in core temperature as a result of general anaesthesia is a three-phase response.

- The first phase is a brisk fall in core temperature as a result of vasodilatation, caused by redistribution of heat to the peripheries. Core temperature may be as low as 35.5°C in some patients after transfer to the operating theatre from the anaesthetic room.
- The second phase is a slower but more sustained fall as a result of accelerated loss of heat to the environment from the warmer peripheries.
- The third phase is a stable equilibrium at a lower core temperature.

It is important to note that the anaesthetic itself brings about these changes, which are independent of the nature of the surgery, though surgery may modify the pattern. The use of spinal or epidural anaesthesia instead of general anaesthesia reduces, but does not abolish, the three-phase response described above.

Passive rewarming is the prevention of heat loss, typically by raising the temperature of the environment. Passive rewarming can serve to modify only the second phase of the heat loss response. Covering with blankets or the use of foil 'space' blankets decreases heat loss by reduced transfer of heat by convection, conduction, evaporation and radiation.

Dry inspired anaesthetic gases need to be humidified, and a heat and moisture exchange filter in the breathing system reduces heat loss by evaporation from the respiratory tract (latent heat). Low flows in a circle system (e.g. 1 litre/minute) further reduce the quantity of dry gas needing to be humidified and help retain heat and moisture within the breathing system.

A 'normal' operating room temperature of 21°C is a compromise between that which is warm enough for the patient, but cool enough for the comfort of theatre personnel. An increase in theatre temperature (e.g. to 25°C) helps to reduce the gradient for heat loss in patients at high risk (e.g. young children, patients with extensive burns).

Active rewarming is the addition of heat into the patient. It may be used to prevent or reverse the first phase of the temperature drop. The local environmental temperature can be raised so much that the transfer of heat is reversed. Warm air convection blankets (e.g. the *Bair Hugger*) are considered as active rewarming.

Intravenous fluid warmers play an increasingly important role the greater the volume of intravenous fluid given. A fluid-warming device should be used in all at-risk patients and especially when stored blood is administered. Ventilatory gases may be warmed using a heated humidifier. Overhead radiant heaters may be used when a large area of the body needs to be exposed, and neonates may undergo surgery on an open incubator such as the *Resuscitaire*.

Cardiopulmonary bypass represents the ultimate in active rewarming, but is practical only in cardiothoracic surgery or in uncommon resuscitation situations.

Care is needed not to overheat the patient and temperature monitoring is necessary when active rewarming methods are used. Monitoring probes are available for a variety of body cavities, including nasopharynx, oesophagus, rectum, bladder and tympanic membrane. In routine clinical practice, core temperature is usually measured by nasopharyngeal or rectal temperature probes. Surface temperature monitors do not reflect core temperature, but the core–peripheral gradient may provide a useful measure of peripheral vasodilatation. A gradient of less than 2°C implies good peripheral perfusion.

Monitoring: the Association of Anaesthetists has published recommendations on standards of monitoring. A summary is given in Figure 2.

Blood sugar should be monitored in infants and diabetic patients. The blood sugar of diabetic patients should be known before anaesthesia is given, and should be estimated every 1–2 hours during routine surgery.

The Association of Anaesthetists summary of standards of monitoring

- The Association of Anaesthetists of Great Britain and Ireland strongly recommends that the standard of monitoring used during general anaesthesia should be uniform in all circumstances irrespective of the duration of anaesthesia or the location of administration
- An anaesthetist must be present throughout the conduct of general anaesthesia
- Monitoring should be commenced before induction and continued until the patient has recovered from the effects of anaesthesia
- These recommendations also apply to the administration of local anaesthesia, regional analgesia or sedation where there is a risk of unconsciousness or cardiovascular or respiratory complications
- The anaesthetist should check all equipment before use. Monitoring of anaesthetic machine function during the administration of anaesthesia should include an oxygen analyser with alarms. During spontaneous ventilation, clinical observation and a capnometer should be used to detect leaks, disconnection, and rebreathing and high pressure in the breathing system. Measurement of airway pressure, expired volume and carbon dioxide concentration is strongly recommended when mechanical ventilation is employed
- A pulse oximeter and capnometer must be available for every patient
- It is strongly recommended that clinical observation of the patient should be supplemented by continuous monitoring devices displaying heart rate, pulse volume or arterial pressure, oxygen saturation, the electrocardiogram and expired carbon dioxide concentration. Devices for measuring intravascular pressures, body temperature and other parameters should be used when appropriate. It is useful to have both waveform and numerical displays
- Intermittent non-invasive arterial pressure measurement must be recorded regularly if invasive monitoring is not indicated. If neuromuscular blocking drugs are used, a means of assessing neuromuscular function should be available
- Additional monitoring may be required in certain situations. These recommendations may be extended at any time on the judgement of the anaesthetist

2

Positioning: an unconscious patient cannot move to relieve an uncomfortable position, and it is the anaesthetist's responsibility to prevent discomfort from becoming damage. The anaesthetist is also responsible for protecting the patient during movement on and off the operating table, and during changes of position. Traditionally, the anaesthetist has particular responsibility for the head and airway. It must be ensured that all members of the team are working to a common agenda and with coordinated timing. It is usually easiest and safest to disconnect as much equipment as possible before moving the patient.

Prophylaxis against venous thromboembolism – the thrombotic process often starts intraoperatively. It is difficult to identify patients at high risk, though coexisting medical illness, major surgery, malignancy, trauma (especially hip and pelvis), obesity, high-dose oestrogen therapy and age greater than 40 years are well-known risk factors. Thromboprophylaxis should commence before anaesthesia; gradated compression stockings and low-dose unfractionated heparin, 5000 IU s.c. twice daily, continued until full mobilization, is popular and effective. When positioning for surgery, raising the heels on foam pads prevents venous stasis in the calves. Intermittent pneumatic compression pumps assist venous return, but it is not known whether this reduces the incidence of postoperative pulmonary embolism.

Keeping the patient comfortable

Traditionally, the main components of anaesthetic maintenance are unconsciousness (hypnosis), analgesia and absence of movement. Some advantages and disadvantages of using muscle relaxants have been discussed. Keeping the patient unconscious and relieving the pain of surgery are now considered.

Maintenance of unconsciousness is usually achieved by anaesthetic drug delivery via the inhalational or intravenous route, or both. The intramuscular route is seldom used in hospital practice owing to the relatively slow onset of drug action, unpredictable duration and delayed recovery. Ketamine, 10 mg/kg, is the only useful intramuscular agent, with an onset of 5–10 minutes producing up to 30 minutes of anaesthesia. It has a role in the provision of emergency anaesthesia in difficult locations.

Inhalational route – this is the most widely used technique, using a volatile anaesthetic agent with or without nitrous oxide. It therefore requires a supply of compressed gas, a vaporizer and a breathing system for drug delivery. Compressed gas may not be required if a 'drawover' type vaporizer is used.

The potency of an inhaled anaesthetic agent may be described in terms of its minimum alveolar concentration (MAC). MAC is defined as the alveolar concentration of the anaesthetic agent which at equilibrium is required to prevent gross reflex muscular movement in response to a standardized skin incision in 50% of healthy, unpremedicated patients. It is therefore a measure of anaesthetic potency, and is the effective dose in 50% of the population (ED_{50}). It should be borne in mind that not all operations are 'a standardized skin incision'. The amount of anaesthetic needed to remove a foreign body from the nose is very different from that needed for an anal stretch. It is important to know the MAC of individual inhalational agents and the factors on which they depend (Figures 3 and 4).

Of any given inhalational anaesthetic, 0.7–1.3 MAC will anaesthetize 95% of the population. MACs are also additive: 0.5 MAC of nitrous oxide (52%) plus 0.5 MAC of isoflurane (0.6%) is equivalent to 1 MAC of any other inhalational agent given alone.

The principle of MAC acts as a useful guide. It allows the anaesthetist to select a vapour concentration that is likely to maintain unconsciousness. The state of anaesthesia is related to the partial pressure of anaesthetic within the brain, which is taken to be equivalent to the alveolar partial pressure. This can be measured by analysis of the end-tidal partial pressure of the anaesthetic agent. What is dialled on the vaporizer or the nitrous flowmeter is not necessarily what is in the patient's alveoli – the fresh gas flow takes time to equilibrate both with the dead space of the circuit and with the uptake by the patient. Observing how the ratio of end-tidal to inspired partial pressure varies with time can assess this rate of uptake (or 'wash-in').

MAC is useful to estimate the amount of anaesthetic required. In clinical practice this must be adjusted against indicators such as pulse rate, blood pressure, respiratory rate, patient movement, pupillary size, lacrimation and sweating. Many of these variables may be abolished by factors other than anaesthetic depth. Tachycardia may be prevented by co-administered β-blockers, hypertension masked by hypovolaemia, respiratory rate and patient movement abolished by paralysing drugs, and pupillary size altered by use of opioids or anti-muscarinic drugs. Thus, lacrimation and sweating, though crude indicators of inadequate anaesthesia, reflect the need for clinical observation in addition to monitoring.

Minimum alveolar concentration (MAC) of inhalational anaesthetic agents

Anaesthetic agent	MAC in oxygen (%)	MAC in 70% nitrous oxide
• Halothane	0.75	0.29
• Enflurane	1.68	0.57
• Isoflurane	1.15	0.50
• Sevoflurane	2.0	0.8
• Desflurane	6–9	2.5–3.5

3

Factors affecting minimum alveolar concentration

Decrease	Increase	No change
• Increasing age	• Decreasing age	• Gender
• Alcohol (acute ingestion)	• Alcohol	• Duration of anaesthesia (chronic ingestion)
• Nitrous oxide	• Hyperthermia	• Time of day
• Analgesics	• Hyperthyroidism	• Hypercarbia
• Sedatives and hypnotics	• Hypocarbia	
• Hypotension		
• Hypothermia		
• Hypothyroidism		
• Hypoxia		

4

Intravenous route – a popular alternative to inhalational anaesthesia is total intravenous anaesthesia (TIVA). Many intravenous anaesthetics have been used for TIVA, including barbiturates, ketamine, etomidate and propofol. The pharmaco-kinetic profile of propofol makes this drug the most commonly used for TIVA. It has a high clearance (1300–1900 ml/minute), short metabolic half-life (60–100 minutes) and inactive metabolites. For short procedures, propofol may be administered following initial intravenous induction by intermittent bolus with no special infusion equipment (e.g. 50 mg as required every 3–5 minutes).

For longer procedures, the advent of reliable electronic syringe pumps, and in particular the development of target-controlled infusion (TCI) software, have contributed to the widespread use of TIVA techniques. Some advantages and disadvantages of inhalational or TIVA maintenance are shown in Figure 5.

Consider a three-compartment model: vascular space, richly perfused organs, and poorly perfused organs plus clearance. A large initial bolus of propofol is needed to fill the vascular compartment, namely the induction dose. Thereafter an initially high rate of infusion is needed to keep up with losses to the richly perfused compartment until it approaches saturation. Then a slower rate is required to keep up with losses to the poorly perfused but difficult to saturate compartment, and with metabolic clearance.

The 'Bristol regimen' reflects these kinetics. This regimen aims to maintain a plasma propofol concentration of about 3 μg/ml by giving patients receiving 67% nitrous oxide an initial bolus of 1 mg/kg, followed immediately by infusion at 10 mg/kg/hour for 10 minutes, then 8 mg/kg/hour for 10 minutes, then 6 mg/kg/hour thereafter. A dose of 10 mg/kg/hour is equal to the patient's weight (in kg) as ml/ hour of 1% propofol – hence a 60 kg patient will initially receive 60 ml/hour of 1% propofol. At the end of the operation, switching off the propofol allows rapid redistribution from the vascular compartment (and therefore from the richly perfused compartment also) to the still unsaturated third compartment. It is this rapid redistribution that allows a prompt wake-up even after a long period of TIVA.

TCI microprocessor-controlled technology (e.g. as incorporated in the Graseby 3500 'Diprifusor' syringe pump) requires manual input of patient age, weight and desired plasma concentration. The pump then administers propofol according to the three-compartment pharmacokinetic model incorporated into its software. Change to a higher propofol concentration is achieved by a rapid zero-order infusion, and the plasma concentration is calculated until the new predicted value is reached. Change to a lower concentration is achieved by temporary cessation of drug infusion until the predicted plasma level falls to the required level, followed by continuation of infusion at a lower rate. The system is used in a similar fashion to adjusting the vaporizer setting during inhalational anaesthesia; the predicted plasma concentration of drug is analogous to the end-tidal concentration of the inhalational agent. Maintenance of satisfactory anaesthesia requires a plasma concentration of propofol of 2–6 mg/ml, depending on patient fitness, coexisting drug therapy and degree of surgical stimulation.

Comparison of inhalational anaesthesia and total intravenous anaesthesia (TIVA) maintenance techniques

Inhalational maintenance

Advantages
- Cost-effective (especially when used with low-flow circle systems)
- Predictable population pharmacokinetics and confidence in anaesthetic depth achieved
- Ease of measurement of end-tidal partial pressure
- Minimal metabolism of modern agents, no accumulation and clearance independent of patient hepatic and renal function

Disadvantages
- Requires conventional tidal ventilation for drug delivery
- Requires specialized equipment (e.g. vaporizer, anaesthetic machine, agent analyser)
- Concern regarding tissue and organ toxicity (especially hepatotoxicity following repeat halothane exposure)
- All volatile anaesthetics are known triggers for malignant hyperpyrexia
- Environmental pollution

TIVA

Advantages
- Independent of airway for drug delivery. May be advantage in, for example, jet ventilation techniques
- No specialized equipment is essential. More suitable technique for patient transport and difficult locations
- Rapid increase in anaesthetic depth possible by administration of intravenous bolus
- Low incidence of postoperative nausea and vomiting and better quality of early recovery (especially for propofol)
- No contraindication in malignant hyperpyrexia

Disadvantages
- Requires patent and dependable intravenous access. Undetected failure may result in awareness
- Drug accumulation with prolonged infusion
- Inability to measure plasma concentration directly has led to concerns about possibility of awareness

5

Analgesia: modern inhalational or intravenous anaesthetic drugs possess little analgesic activity, with the exception of ketamine. For all but the simplest procedures, analgesia must be provided by systemic analgesics (usually opioids) or by local anaesthetics. Analgesia has several effects.

- It reduces the required MAC (or plasma concentration) of co-administered anaesthetic drugs. Analgesia is an important component of the balanced anaesthetic technique.
- It reduces the immediate autonomic activity in response to pain. Sympathetic stimulation otherwise results in cardiovascular and respiratory responses that may lead to myocardial ischaemia and dysrhythmias.
- It reduces the neuroendocrine 'stress response' caused by surgery.

Opioid analgesics such as fentanyl, 15 μg/kg, reduce circulating concentrations of the stress hormones that increase after moderate and major surgery (e.g. noradrenaline, adrenaline, cortisol, growth hormone, glucagon, antidiuretic hormone). The stress response is largely detrimental and leads to increased catabolism, metabolic rate and oxygen consumption. This response is not significant in minor surgery.

The short-acting synthetic opioid drugs such as fentanyl and alfentanil are widely used to provide intraoperative analgesia. Fentanyl, a synthetic opioid structurally related to pethidine, is the most popular (1–2 μg/kg for minor procedures, onset 1–2 minutes, duration 30 minutes). Its potency and minimal effect on pulse and blood pressure make it commonly used for the provision of intense analgesia during surgery. These drugs are unsuitable for routine use in postoperative analgesia because of their short duration of action and their tendency to produce marked respiratory depression. They are commonly substituted by longer-acting analgesics (e.g. morphine 0.1–0.2 mg/kg i.v.) towards the end of the procedure to provide pain relief following surgery.

Pre-emptive analgesia – laboratory work suggests that noxious stimuli produce hypersensitivity in the pain pathways both centrally and peripherally. Larger doses of analgesics are then required to have an effect. If systemic analgesia or local anaesthetics are used to prevent the initial pain, this hypersensitivity is reduced. This is the basis of pre-emptive analgesia, but its clinical significance is disappointing.

Providing the best possible operating conditions

The surgeon hopes for two things from his patient during the operation: not to move, and not to bleed. If the anaesthetist has succeeded in keeping the patient safe and comfortable as described, then the patient is unlikely to move. The anaesthetist can also help to minimize bleeding.

Tourniquets are ideal for extremity surgery. Traditionally, a 90-minute time limit is imposed on upper limb tourniquets (usually at 250 mm Hg), and a 120-minute limit on lower limb tourniquets (usually at 300 mm Hg). This is arbitrary; the longer the tourniquet is on, the greater the potential for damage. The main risk is ischaemic damage to nerves directly under the tourniquet; distal ischaemia is likely to take 4–6 hours to become significant. If antibiotics are necessary, they should be given at least a few minutes before exsanguination.

Sickle-cell disease is an absolute contraindication to tourniquet use, because sickling of haemoglobin S may be induced by the local hypoxia and acidosis.

Positioning – adequate venous drainage from the operative site is ensured by careful attention to patient positioning. Raising the operative site above heart level decreases arterial and venous pressures. Arterial pressure falls by 2 mm Hg for each 2.5 cm vertical height. Head-up tilt is commonly used in head and neck surgery to decrease bleeding, but there is a risk of venous air embolism.

Hypotensive anaesthesia – moderate reduction of systolic blood pressure (e.g. to 70–80 mm Hg) in otherwise fit patients may greatly improve the operative field. It must be used with caution in patients with coronary, cerebral, renal or peripheral vascular diseases who are at risk from ischaemic events. Techniques for deliberate hypotension are outside the scope of this contribution.

Non-steroidal anti-inflammatory drugs used intraoperatively may increase blood loss during surgery.

Blood gases – carbon dioxide is a local vasodilator, and moderate hypocapnia (e.g. P_{CO_2} 4.0–4.5 kPa) contributes to a dry surgical field.

Preparing the patient for the postoperative perio

The maintenance period is often a convenient time to complete the necessary anaesthetic record and drug prescription charts. During anaesthesia, it should be considered what else may be done while the patient is unconscious to enhance his or her postoperative course. This includes the following.

Venous access must be sufficient for postoperative requirements. A central venous line should be sited if access is likely to be difficult or prolonged, or to enable central venous monitoring. A subcutaneous cannula for analgesic administration may avoid the need for injections, especially in children.

A nasogastric tube is more comfortably inserted while the patient is asleep, and its position can be checked during laparotomy.

Analgesia – ideally, the plan for postoperative pain control should be formulated before anaesthesia, and discussed with the patient. 'Balanced analgesia' is the concept of using several analgesics with differing modes of action, thus reducing dose-related side-effects and enhancing overall analgesic effect. Typically this may involve local or regional analgesia in combination with opioids, non-steroidal anti-inflammatory drugs and simple analgesics (e.g. paracetamol).

Antiemetics should be given in particular to patients receiving opioids, and those at high risk of postoperative nausea and vomiting (PONV). High risk includes patients with a history of previous PONV or motion sickness, certain operations (e.g. gynaecological, middle ear or strabismus surgery) and female gender.

Oxygen – all anaesthetics (with the exception of ketamine) induce about 10% shunt. Atelectasis, impaired hypoxic pulmonary vasoconstriction, diffusion hypoxia from nitrous oxide use, opioid-mediated hypoventilation and other factors contribute to making the postoperative patient prone to hypoxia. Added oxygen (e.g. 30–40% via a simple face mask) should be administered in the immediate recovery period to all patients for about 15 minutes, guided by pulse oximetry. Subsequently, the need for added oxygen must be determined for each patient depending on factors such as age, pre-existing disease and the nature of anaesthesia and surgery.

Fluids – there must be clear instructions for postoperative fluid intake. Elective day-surgery patients will drink when ready, but in-patients and those undergoing major procedures require intravenous fluids to replace continuing fluid losses and provide maintenance. How far in advance fluids can be prescribed depends on the accuracy of prediction of future needs.

Thromboprophylaxis – stockings for prevention of thrombo-embolic disease and/or regular heparin should be prescribed where indicated by local policy.

Antibiotics – should be prescribed at the surgeon's discretion.

Monitoring – the anaesthetist should understand the routine standard of monitoring on the postoperative ward and ensure that it meets the needs of the patient. Specific requirements must be clearly communicated, such as hourly urine output, hourly blood pressure, overnight Sp_{O_2} or any other observ-ations in an at-risk patient. Action that should be taken if the observation deviates from the desired targets should be documented.

Medical Gas Storage, Suction Devices and Humidifiers

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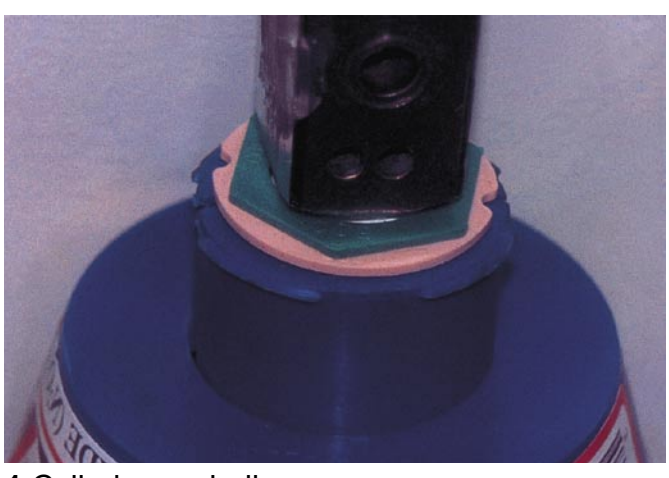
Cylinders

Medical gas cylinders are made of molybdenum steel to ensure they are strong and able to withstand high pressures, but are also relatively light in weight. They are constructed as a seamless tube and consist of a body, shoulder and neck. They are colour coded according to British and International Standards (BS1319C and ISO32) to identify their gas contents (see Figure 7, page 109). Cylinders are manufactured in different sizes from A, the smallest, to J, the largest. Size E cylinders are usually attached to the anaesthetic machine and size J cylinders make up manifolds.

The cylinder valve fits into the cylinder neck by a screw thread mechanism, to permit safe, controlled use of its contents. The junction between the cylinder and valve melts in the presence of intense heat, thus allowing escape of gas and minimizing the risk of explosions. Between the neck and cylinder valve is a plastic disc, the colour and shape of which denotes the year in which the cylinder was last examined (Figure 1).



1 Cylinder neck disc.

Cylinder body
The cylinder body is colour coded and engraved with:
- test pressure
- date of last test performed
- chemical symbol of contents
- tare weight (i.e. weight of empty cylinder).

It is also labelled (Figure 2) with the name and symbol of the gas it contains, its volume, pressure and minimum purity (Figure 3). The label gives additional information relating to storage, use (in conjunction with the Medical Gases Data Sheet) and safety matters. The safety points highlighted are:
- compressed gas
- flammability status
- avoidance of oil or grease because spontaneous combustion can occur with high-pressure gases.

2 Cylinder label.

Cylinder size, volume, pressure and purity of contents

Gas	Cylinder size (litres)	Volume of gas at 15°C	Pressure (kPa)	Purity (%)
Oxygen	E	680	13700	99.5
Nitrous oxide	E	1800	4400	98.0
Air	E	640	13700	21.0 (oxygen)
Carbon dioxide	C	450	5000	99.0

3

Storage
- Cylinders must be stored under cover, in a dry, clean and well-ventilated area, away from extremes of temperature.
- Smoking or the use of a naked flame in the storage area is prohibited.
- Moisture or exposure to chemicals can lead to the corrosion of the cylinder or its valve.
- Cylinders should be kept in the upright position or horizontal on shelves to avoid direct damage to the valves.
- Cylinders should be used in a sequential manner to ensure that no cylinder remains in storage for too long.
- Full and empty cylinders should be kept apart.

Testing
During manufacture, one in every 100 cylinders is cut into strips and tested for tensile strength. Cylinders in circulation are tested on a 5-yearly basis by:
- exposure to hydraulic pressure of about 22,000 kPa (far in excess of the pressures encountered in daily use)
- filling with water under pressure to assess expansion and elastic recoil
- internal endoscopic inspection.

Test date details are recorded on the plastic disc between the cylinder valve and the neck and engraved on to the cylinder body.

Filling
Medical gases are stored either in the gaseous state (oxygen and air) or as a mixture of the liquid and vapour (nitrous oxide and carbon dioxide). Cylinders that contain liquid should be used only in the upright position. Gases and vapours stored in cylinders must be free of water vapour to avoid the formation of ice (secondary to a fall in temperature on cylinder opening), which may block the exit valve. For cylinders containing gas alone, the contents can be assessed directly by measuring the pressure using a Bourdon gauge (see *Anaesthesia and Intensive Care Medicine* **1:2:** 65). In the case of cylinders containing both the liquid and vapour phases the situation is more complex. The contents of these can be determined only by subtraction of the tare weight from the cylinder weight because the pressure within will not fall until the liquid has completely vaporized, assuming the temperature stays constant.

During nitrous oxide use, the liquid within the cylinders cools owing to the uptake of latent heat of vaporization. Condensation or ice may form on the outside of the cylinder. In such circumstances, the cylinder gauge pressure may fall despite there being liquid nitrous oxide in the cylinder owing to the fall in saturated vapour pressure of nitrous oxide following the drop in temperature of the liquid. However, once the gas flow is turned off the temperature returns to that of the atmosphere and the gauge pressure returns to that at the beginning of use. Carbon dioxide is used at low flows so the chances of ice forming are low. Liquid is less compressible than gas, therefore cylinders containing nitrous oxide or carbon dioxide are only partially filled with liquid. Any change in pressure within the cylinder is minimized, thus reducing the chance of cylinder rupture should the temperature rise.

The filling ratio is that between the mass of liquid contained in the cylinder and the mass of water that it could contain if filled to the top. The filling ratios for nitrous oxide and carbon dioxide are both 0.75 in temperate climates and 0.67 in the tropics.

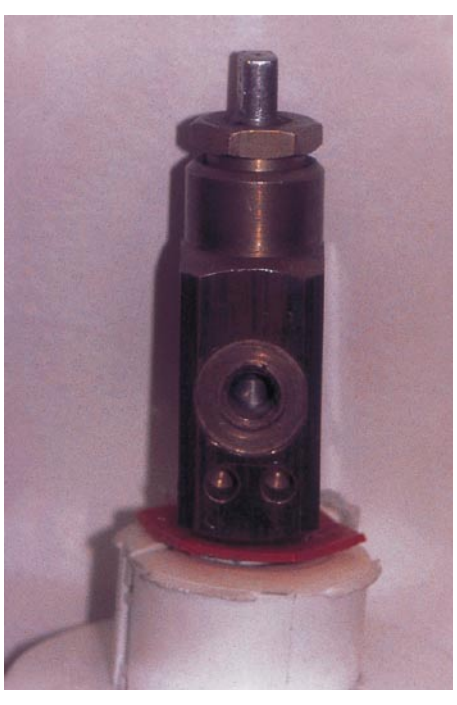
$$\text{Filling ratio} = \frac{\text{Mass of liquid}}{\text{Mass of water}}$$

Cylinder valve
Cylinder valves are made of brass and screw into the cylinder neck. There are four types of valve:
- pin-index valve block
- bull-nose valve
- hand-wheel valve
- star valve.

A pin-index valve is used on all cylinders that are to be attached to an anaesthetic machine. It is an international system (ISO2407) designed to prevent the fitting of the incorrect gas to the yoke and is fully detailed in the British Standard BS1319.

The system is made up of two components.
- Two pins projecting from the yoke, which are arranged in a gas-specific configuration in relation to the valve outlet
- Two holes within the valve block on the cylinder with a corresponding pattern for the designated gas (Figure 4).

This arrangement ensures that it is impossible to fit the incorrect cylinder to the yoke. The pin-index valve block on the cylinder is engraved with:
- tare weight
- chemical symbol for contents
- cylinder owner
- pressure of hydraulic test.



4 Pin-index valve holes on the cylinder.

Cylinder use
New or refilled cylinders are supplied from the manufacturer with a plastic dust cover over the valve to avoid dirt contamination. Before use, this cover should be removed and the valve transiently opened to expel any dirt or grease from the outlet. This reduces the chance of debris entering the anaesthetic machine and is known as 'cracking' the cylinder.

The cylinder is mounted on to the anaesthetic machine by engaging the pins on the yoke with the holes in the valve block. It is secured by tightening the wing nut.

Before use, the cylinder should be opened gently to ensure that there are no leaks, either from the cylinder valve itself or at the point of attachment to the yoke on the anaesthetic machine. A possible reason for gas leakage at the pin-index junction is the absence of the Bodok seal. This is an aluminium-rimmed neoprene washer that sits between the outlet on the valve block and the yoke on the anaesthetic machine. Gentle opening of cylinders minimizes sudden surges of high-pressure gas that may damage the pressure gauge or regulator.

Suction systems

Suction systems form part of the piped medical gases and vacuum systems (see page 107) and must comply with specifications detailed in BS4957. Portable and fixed suction systems are available to accommodate the differing circumstances of use. General operating principles are the same for both systems. Outlets from the central piped vacuum system must have the capability of maintaining a vacuum of at least 53 kPa below atmospheric pressure (101.3 kPa) and supporting a flow of 40 litres/minute.

Suction apparatus and nozzle: suction nozzles are made of either firm plastic (e.g. Yankauer) or metal. They should have a smooth tip to prevent damage to the soft tissues of the oropharynx. The tip often has more than one hole to allow continuation of suction should one hole become blocked. Suction tubing is constructed of semi-rigid plastic to minimize kinking, with a smooth internal surface to limit resistance to flow. The tubing must be of sufficient length to be practical to use, but it should be remembered that the length and width of a tube influences the laminar flow within it, according to the Hagen–Poiseuille equation:

$$\text{laminar flow} = \frac{\Delta P \pi r^4}{8 \eta L}$$

where: ΔP = pressure gradient along tube, r = tube radius, L = tube length, η = viscosity of liquid.

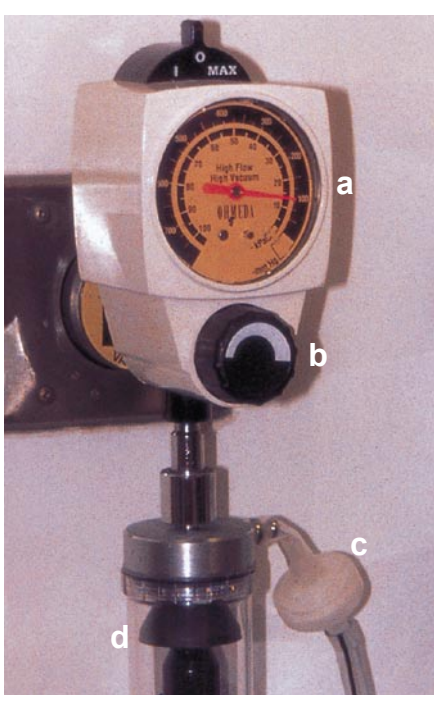
Thus, short, wide tubing maximizes laminar flow.

Reservoir: the reservoir must be of sufficient size to contain the estimated volume of suctioned material, but not so large that it increases the time taken for the vacuum to build up. Most reservoir vessels are constructed of clear material to allow the contents to be visualized and are graduated to permit accurate assessment of aspirate volume. Disposable liners are commonly used to reduce staff exposure to potentially infective material. A floating ball valve within the collection vessel prevents material from entering the control unit and the vacuum source if the container overfills.

Vacuum control regulator unit: this unit is usually situated between the reservoir and the vacuum source (Figure 5). Its function is to allow adjustment of the degree of vacuum applied to the distal suction tubing. The vacuum control adjuster acts as a variable orifice (either directly or by way of a spring acting on a diaphragm) to adjust the force of vacuum, which is indicated on a gauge. Within the unit is a filter and some form of float valve to provide protection from particulate matter.

Distribution pipeline network: between the terminal outlet and the control unit there is a colour-coded (yellow) flexible hose with a specific Schrader probe connection, as for piped medical gases.

Terminal outlet: the terminal outlet of the vacuum pipeline consists of a labelled, self-sealing valve, fronted in yellow, that accepts a probe with indexing collar to prevent misconnection.



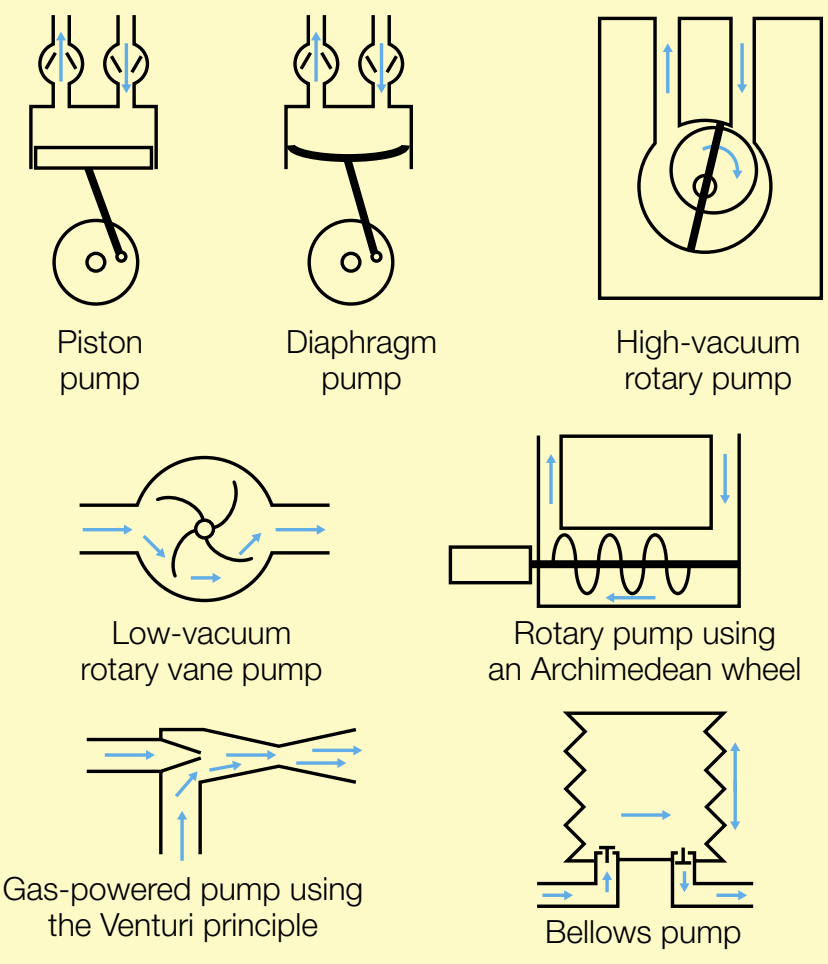
5 Vacuum control regulation unit.
a vacuum gauge, **b** vacuum control, **c** filter, **d** float valve.

Filter unit: filters are sited within the control unit, but also in the case of piped medical gases and vacuum systems between the terminal outlet and the central vacuum source. They remove particulate matter and bacteria from the system to prevent blockage and contamination.

Central pump: the role of the pump is to generate subatmospheric pressure within the system. Pumps are commonly driven by electrical, pneumatic or manual means (Figure 6). The piston, diaphragm and rotary devices shown in Figure 6 all require some form of energy source (usually electricity) to drive mechanical pumps. In contrast to these, the gas-powered pump works on the Venturi principle and the bellows require manual input to generate subatmospheric pressure.

The type of pump is determined by the specific requirements of the suction unit. For example, most portable units use a manual pump, whereas a rotary-driven pump may be used when a large volume of aspirate is anticipated. The pump expels its exhaust gases, via a silencer, to the atmosphere at a suitable site, such that staff and patients are not exposed to the pollution.

Vacuum pumps



Adapted from: Moyle J T B, Davey A. *Ward's Anaesthetic Equipment.* 4th ed. London: WB Saunders, 1998. By courtesy of the publisher.

6

Humidification devices

Humidification strictly refers to the addition of water vapour to air. Humidification of dry, cold anaesthetic gases as they enter the patient's airway is important because dry gases result in drying of the mucosal surfaces, abnormal ciliary function and increase in the viscosity of respiratory tract secretions. Loss of these protective mechanisms can cause mucus plugging, atelectasis, reduction in gas exchange and an increased susceptibility to infection. Also, heat energy due to latent heat of vaporization is lost by the patient in warming and humidifying dry, cold anaesthetic gases.

Aims: under normal circumstances, the upper respiratory tract warms and humidifies the air to an absolute humidity (i.e. mass of water vapour in a given volume of air at specified temperature and pressure) of 34 g/m^3 at 34°C in the trachea and 44 g/m^3 at 37°C in the alveoli. These values equate to fully saturated air whereby the air contains the maximum possible water vapour at specified temperature and pressure. Achievement of these values is the 'gold standard' for humidification. The different efficiencies of various humidifiers are shown in Figure 7.

Approximate efficiency of humidifiers

The exact values depend on the model of humidifier used.

Adapted from: Davis P D, Parbrook G D, Kenny G N C. *Basic Physics and Measurement in Anaesthesia.* 4th ed. Oxford: Butterworth-Heinemann, 1995. By courtesy of the publisher.

7

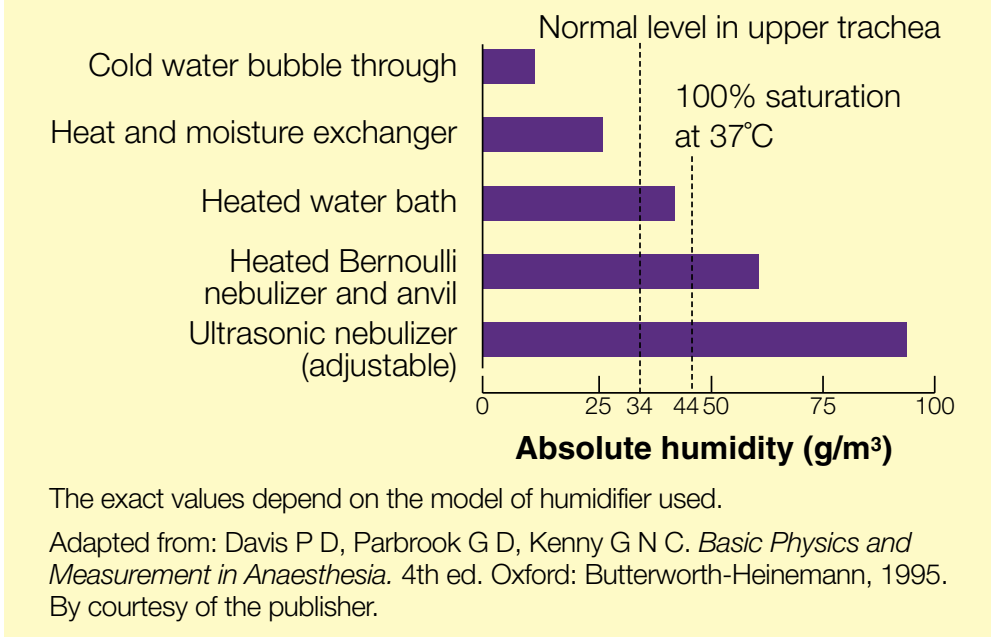
Types of humidifiers

Heat and moisture exchanger (HME) is the most commonly employed humidifier in day-to-day anaesthetic practice (Figure 8). It consists of a sealed unit that is placed within the breathing circuit. The exchanger contains a structure usually of either sponge or mesh, of large surface area, on to which water is absorbed. Absorption is maximized if the mesh is made of a hygroscopic material such as paper coated with calcium chloride or glass fibre. An additional role of some devices is to act as bacterial filters because over 99.99% of bacteria will not pass through pores of less than 0.2 microns. HMEs work on the principle that the moisture from expired gas condenses on to the mesh material within the device as it cools. The mesh is also warmed as the cooling moisture emits latent heat. As gas is inhaled it is warmed and humidified, thus exchanging heat and moisture. The advantages of the system are that it is:

- lightweight
- compact
- disposable
- efficient (60–70% relative humidity at 30–34°C, equating to absolute humidity of about 25–35 g/m^3)
- passive (requires no external power source)
- inexpensive.

The disadvantages are:

- increased dead space
- increased resistance to breathing
- single-patient use.



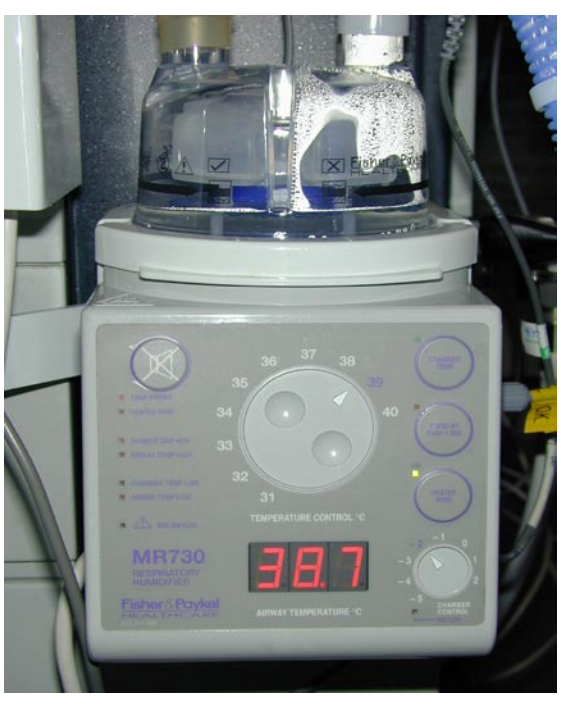
8 Heat and moisture exchanger.

Cold water bath humidifier (Figure 9): this operates by bubbling inspiratory gas through or over a cold water bath. The advantages are it is simple and safe. The disadvantage is that it is inefficient.

Hot water bath humidifier (Figure 10): inspiratory gases are bubbled through, or pass over, a warm water reservoir. The contact surface area is increased in some devices by the use of wicks or multiple bubble holes. The water temperature must be rigidly regulated to attain a balance between maximum humidification, bactericidal activity and heating, with the risk of thermal injury to the patient. This is achieved by the use of a thermostatic control and temperature monitoring within the circuit close to the patient. A water trap must be included on the patient side of the system and the whole apparatus must be below patient level to limit the risk of condensed water in the tubing entering the breathing circuit directly. The system is efficient but the disadvantages are:

- risk of scalding
- bacterial growth if temperature falls below 60°C
- condensation of water within tubing.

9 Cold water bath humidifier.



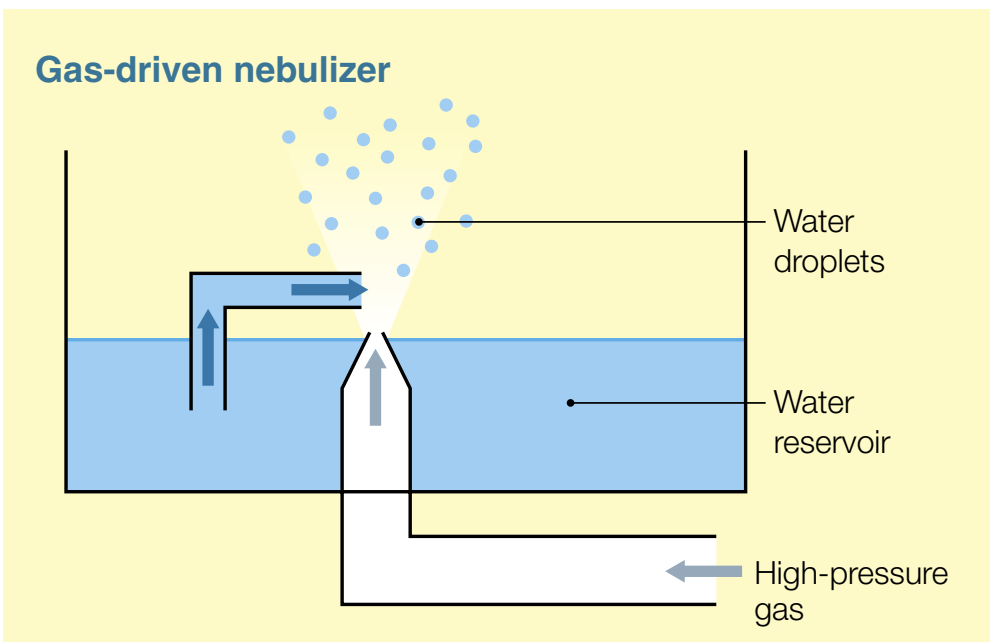
10 Hot water bath humidifier.

Nebulizers: the principle of nebulizers is to add tiny droplets of water to the inspired gas. Strictly speaking nebulizers are not humidifiers because they add water droplets not vapour to the gas. Nebulizers have the potential to produce water droplets of varying sizes. The result of this is that very small droplets pass into the alveoli and thus risk fluid overload, whereas large droplets risk being deposited in the breathing circuit or upper airway. Ideal droplet size is 1–5 microns. Nebulizers are highly efficient but they can be expensive and water overload may occur, especially in ultrasonic devices. There are three commonly encountered methods by which nebulizers produce water droplets.

Venturi principle – water is entrained into a jet of gas that breaks it into droplets (Figure 11). Some systems also contain a solid object (anvil) into which the droplets are propelled, thus further reducing their size. Droplet size averages 2–4 microns. Back pressure from a breathing system can affect the efficiency of the device by reducing water entrainment. Some nebulizers incorporate a heater to increase their efficiency.

Spinning disc – a rapidly rotating disc that throws off tiny water droplets.

Ultrasonic – high-frequency ultrasound waves fragment water into tiny droplets. The water may be dropped on to a vibrating surface or the device may be immersed in a water bath. Droplets 1–2 microns in size are produced.



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Medical Gases and their Delivery

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Medical gas

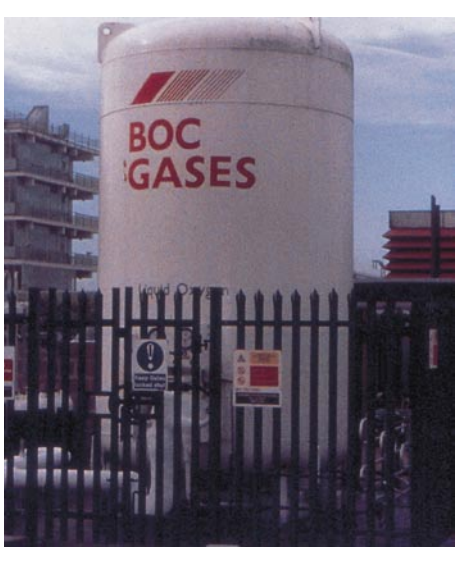
In the UK, most hospitals have piped medical gases and vacuum systems (PMGV) for convenience and economic reasons. The vacuum component of this system is discussed on page 114.

The pipeline network carries medical gases from central bulk storage sites to hose outlets in the walls of anaesthetic rooms, theatres and wards. The responsibility for this section of the PMGV is principally that of the hospital pharmacy, supplies and engineering departments. Anaesthetists have responsibility for the section of pipeline between the terminal outlet and the anaesthetic machine. The bulk store for medical gases is usually a series of cylinder manifolds (Figure 1). In the case of oxygen, the cylinder manifold is often used as a reserve because most hospitals store oxygen in a vacuum-insulated evaporator (VIE) (Figure 2). The cylinder manifold is divided into a primary unit, which is in use, and a secondary unit in reserve. As the pressure in the primary unit falls, the supply is automatically switched to the secondary unit and an alarm sounds to alert the staff to replace the empty cylinders. When there is actual or impending supply failure the alarm usually sounds in the switchboard area of the hospital.

The pipes are constructed of high-grade copper alloy to prevent degradation of gases and are de-greased to reduce the risk of combustion or explosion. They are labelled at regular intervals along their length and are separated from other pipelines within the hospital to avoid confusion. Within the network of pipes there are valves to control the supply to individual theatres or a complete department, in the event of fire or pipeline damage. These are lever-operated, non-lubricated valves housed in clearly accessible units usually behind a breakable glass cover (Figure 3).

The pressure within the pipelines is regulated at about 400 kPa.

1 Cylinder manifolds.



2 Vacuum-insulated evaporator.

3 Pipeline lever safety valve.

Terminal outlet connection

Outlet points (Figure 4) for each of the piped medical gases have specifically labelled, shaped, colour-coded and non-interchangeable Schrader sockets to prevent connection of the incorrect gas supply to the flexible hoses supplying the anaesthetic machine. These must comply with the British Standard codes (BS5682) and be labelled as such. Each terminal outlet is a self-sealing valve unit of specific size to receive the corresponding collar-indexed probe of the flexible hose.

To ensure correct connection and function of the outlet valve, the probe is firmly inserted and a sharp tug applied to ensure full engagement and opening of the valve. This simple procedure is known as the 'tug test'.

4 Terminal gas outlets.

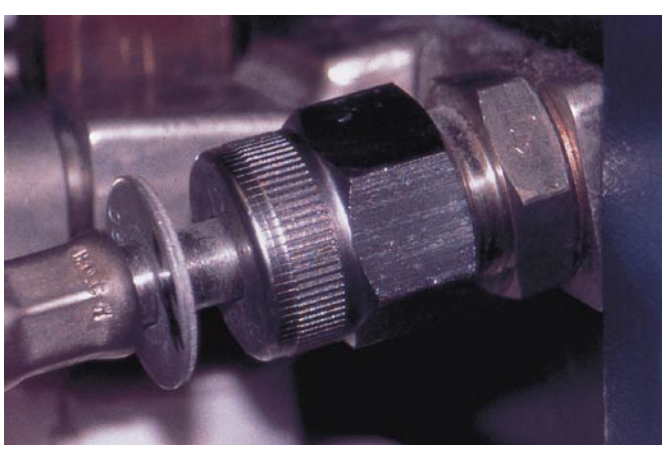
Flexible pipeline

A flexible pipeline carries medical gases from the terminal outlet to the anaesthetic machine. The terminal outlet probe (Schrader probe; Figure 5) is fitted with an indexing collar of a specific diameter for each gas, which will fit only the corresponding gas socket on the terminal outlet valve. In addition, each collar has a notch that fits over a pin within the socket to prevent rotation of the hose once installed. The entire assembly is constructed so that rapid probe insertion or withdrawal can be performed single-handedly and that once withdrawn the terminal outlet unit is self-sealing.

The flexible hose is made of a high-quality copper alloy with antistatic and bacteriostatic properties. It is colour coded and labelled in accordance with the gas it carries.

The hoses are connected to the anaesthetic machine by a non-interchangeable screw thread unit. This unit consists of a probe unique to each gas and a nut to screw the assembly on to the machine. A stainless-steel ferrule is crimped over the whole unit to seal the connection and prevent its removal (Figure 6).

5 Schrader probe.



6 Non-interchangeable screw thread.

Safety

Pipelines and flexible hoses: guidance for manufacturers, installers and maintenance engineers is in accordance with BS5682 (1987) and Health Technical Memorandum 2022 (1994). Pipelines for each of the medical gases are manufactured in different locations within the factory to prevent accidentally mixing up their unique features, for example, connection of the wrong terminal probe, non-interchangeable screw thread fitting or incorrect colour coding.

Pipelines and flexible hoses are steam cleaned, dried and sealed at both ends after internal inspection before being transported to their installation site. This is to prevent contamination and particulate matter from entering the gas supply. In the event of damage to, or technical failure of any part of the pipeline, it must be returned directly to the manufacturer for repair or replacement.

The pharmacy, supplies and engineering departments within each hospital are responsible for the pipeline supply. This includes testing of gases for purity and identity after installation of new pipelines.

The anaesthetist is responsible for ensuring that the flexible hoses are correctly engaged and that the corresponding gas passes into the anaesthetic machine. Correct engagement is checked by using the 'tug test' and the identity of the gas by using the 'single-hose test'. This is done by attaching the oxygen pipeline to the anaesthetic machine, turning on all the flowmeters and ensuring that gas flows only through the oxygen flowmeter and that it is detected by an oxygen analyser fitted at the common gas outlet.

Cylinder gas supply: cylinders and their use in conjunction with the anaesthetic machine are covered elsewhere in *Anaesthesia and intensive care medicine*.

Medical gas pressure

Working pressures within cylinder and piped medical gas supplies are outlined in Figure 7.

Pressure monitoring and display of both pipeline and cylinder gases is performed by Bourdon gauges. The Bourdon gauge is an aneroid (i.e. without liquid) gauge consisting of a coiled tube, attached at one end to the gas supply and at the other end to a pointer. The pressure of the gas causes straightening of the coil and thus causes movement of the pointer over the colour-coded, labelled and calibrated dial. The gauge is faced with heavy glass and designed such that leaks vent from the back of the valve casing and do not blow out the glass.

Cylinder and pipeline colour coding and pressures

	Body colour	Shoulder colour	Pressure (kPa) at 15°C
Cylinder			
• Oxygen	Black	White	13700
• Nitrous oxide	Blue	Blue	4400
• Carbon dioxide	Grey	Grey	5000
• Air	Grey	White/black	13700
Pipeline			
• Oxygen	White		400
• Nitrous oxide	Blue		400
• Air (clinical use)	Black		400
• Air (power tool use)	Black		700

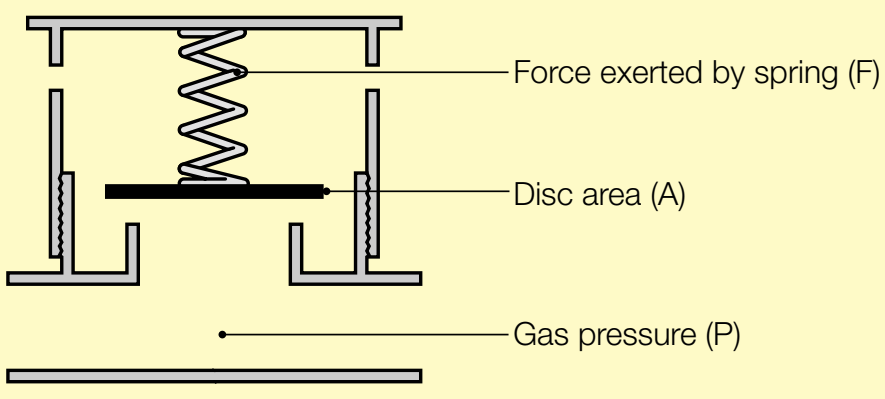
7

Pressure regulators: throughout the medical gas supply network the pressure within the system is closely regulated. This is vital for the protection of both equipment and patient. Measures to maintain a near-constant pressure are found in many sites and usually take the form of a pressure relief valve or a pressure regulator (see *Anaesthesia and Intensive Care Medicine* **1:2:** 66). Both devices are also present within the anaesthetic machine.

Pressure relief valves are designed to allow escape of gas above a certain set pressure. In the case of the VIE this protects the oxygen storage equipment from damage from pressure above 1690 kPa. Similar valves are positioned downstream of pressure regulators within the pipeline supply in case of regulator failure. These are set slightly above 400 kPa.

The principle on which the valve works relates to an equilibrium between two opposing forces: that exerted by the spring and that generated by the gas itself (Figure 8).

Pressure relief valve



$F = P \times A$

As the disc area is constant, and the force exerted by the spring to close the valve is pre-set, once the gas pressure within the system exceeds this closing force, the valve opens and gas escapes

Adapted from: Aitkenhead A R, Smith G, eds. *Textbook of Anaesthesia.* 3rd ed. London: Churchill Livingstone, 1998. By courtesy of the publisher.

8

Medical gases

Oxygen

Manufacture: industrial manufacture is by the fractional distillation of liquid air. This involves the removal of carbon dioxide and then the separation of oxygen and nitrogen by means of their different boiling points.

Oxygen may also be produced by oxygen concentrators, which extract oxygen from air. This process involves the passing of air through a sieve of zeolite (aluminium silicate), which absorbs the nitrogen, leaving oxygen and a trace of argon. The equipment for this process used to be bulky, but recently smaller units suitable for home use have been developed. A maximum concentration of 95% pure oxygen can be produced using these devices.

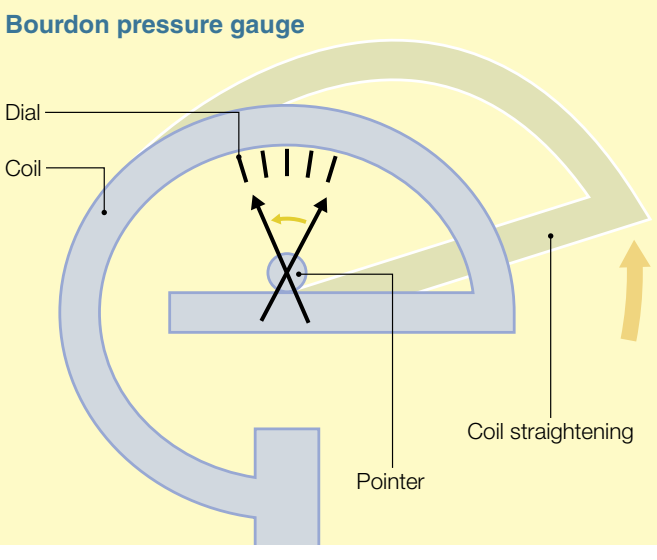
Storage: oxygen is stored either as a gas in cylinders or as a liquid in a VIE. In the UK, cylinders used for oxygen storage are black with a white shoulder (Figure 9); in the USA they are green. The oxygen is stored at a pressure of 13700 kPa at 15°C. Where piped medical gases are used, oxygen is also stored in cylinder manifolds. In cylinders, oxygen is a gas and the volume of oxygen remaining in the cylinder is directly related to the measured pressure, according to Boyle's law.

9 Cylinders. From left: oxygen, nitrous oxide, air, carbon dioxide.

The VIE (Figure 10) is a thermally insulated device similar to a large vacuum flask. Oxygen is stored within this vessel at about –160°C and at a pressure of 5–10 atmospheres (500–1000 kPa). The low temperature is maintained by the vacuum surrounding the main chamber and by heat energy being lost from the liquid oxygen as it evaporates (latent heat of vaporization). Under normal working conditions, oxygen evaporates and passes through the pressure regulator to reduce its pressure to 400 kPa, and then enters the pipeline supply. If demand for oxygen is low, the internal pressure gradually rises until a safety valve opens at 1690 kPa to release gas to the atmosphere. When demand for oxygen is great, the control valve opens allowing liquid oxygen to pass through the pressure-raising superheater and vaporizer, evaporate and enter the pipeline supply. The superheater is a coil of uninsulated copper pipe.

The VIE (Figure 2) can be found outside all hospitals that use piped gases and may be supported by a tripod structure. Two of these legs support the weight of the evaporator, while the third is a weighing device to allow the mass of liquid contained to be measured. Modern designs stand on four legs and the contents are calculated by measuring the pressure difference between the top and bottom of the vessel.

Bourdon pressure gauge



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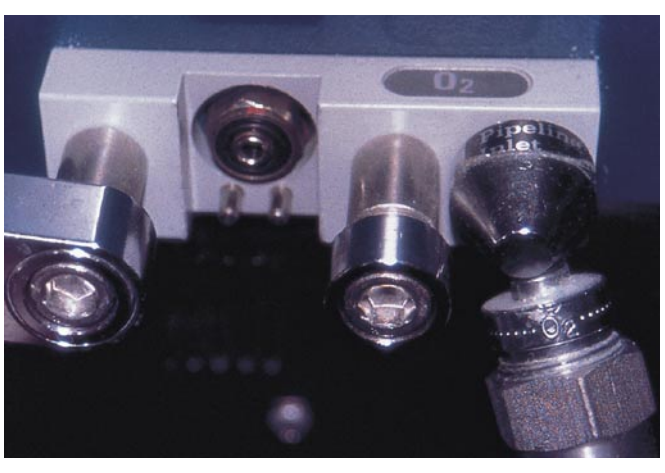

11 Cylinder yoke.

Delivery: oxygen is delivered from a central supply (i.e. a manifold or VIE) or directly from cylinders. Central oxygen supply is via the pipeline system described above. Direct cylinder supply of oxygen to the anaesthetic machine involves the connection of the cylinder valve to the cylinder yoke (Figure 11) on the back of the machine.

Carbon dioxide

Manufacture: carbon dioxide is manufactured by heating calcium or magnesium carbonate in the presence of their oxides. Other sources are as a by-product of the manufacture of hydrogen, fermentation of beer or the combustion of fuel.

Storage: in the UK, carbon dioxide is stored in grey cylinders (Figure 9) at a pressure of 5000 kPa at 15°C, as a liquid in equilibrium with its vapour.

Distribution: unlike the other medical gases, carbon dioxide is not distributed via a central pipeline. The attachment of carbon dioxide cylinders to anaesthetic machines has declined in recent years to minimize the risk of accidental administration during anaesthesia. The present guidelines issued by the Association of Anaesthetists of Great Britain and Ireland state that carbon dioxide cylinders should not be routinely fitted to the anaesthetic machine.

Air

Manufacture: air for medical use is compressed, cleaned and filtered before use.

Storage: compressed air for anaesthetic use is stored in grey cylinders with black and white shoulders (Figure 9) at a pressure of 13,700 kPa at 15°C. In the USA, the cylinders are yellow.

Distribution: pipeline air is sourced from either a manifold (Figure 1) or, more economically, from an air compressor. It is important to know that air for clinical use is regulated to a pressure of 400 kPa, whereas that for the use of surgical power tools is supplied at 700 kPa. The terminal outlet for compressed air is colour coded black and white, labelled and has a non-interchangeable connection (Figure 4).

Cylinders are attached directly to the anaesthetic machine by connection of the cylinder valves to the cylinder yoke. A larger portable cylinder may be attached via a flexible hose.

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Perioperative Fluids

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Any surgery under anaesthesia can upset the patient's normal fluid status through preoperative restriction of oral intake of fluids. The degree of disruption depends on the patient's medical condition, the nature of the surgery and the choice of anaesthetic. Factors to consider when planning perioperative fluid management are listed in Figure 1.

Maintenance requirements: normal values for daily fluid and electrolyte requirements are shown in Figure 2. Dextrose 4% with saline 0.18% contains 30 mmol/litre of sodium and is often used for basal fluid therapy.

Determinants of perioperative fluid requirements

- Maintenance requirements
- Preoperative deficits
- Blood loss
- Third-space losses
- Transcellular fluid losses
- Effects of anaesthetic agents and technique

1

Maintenance fluid and electrolytes

Adults
- 40 ml/kg/day

Children
- 100 ml/kg/day for first 10 kg
- 50 ml/kg/day for second 10 kg
- 25 ml/kg/day for each subsequent kg

Na^+ = 1–1.5 mmol/kg/day
K^+ = 1 mmol/kg/day

2

Preoperative deficits

Preoperative assessment of the fluid status of the patient requires an appropriate history, examination and investigations.

History and examination

The following questions should be asked.
- How long has the patient been starved?
- Do they have an intravenous infusion in progress?
- Have they any reason to expect excessive losses?
- Are they taking diuretics?
- Are they pyrexic?
- Have they been vomiting or do they have a nasogastric tube *in situ*?
- Have they got diarrhoea or had a bowel preparation?
- Could they have third-space losses or occult bleeding?
- Have they any symptoms of fluid overload?

The physical examination includes evaluation of the mucous membranes and skin turgor, and measurement of the vital signs, including orthostatic changes. Ascites, pulmonary oedema and pleural effusions should be sought. Measurement of urine output may be useful.

Investigations

A normal haematocrit value may indicate that the patient has a normal fluid status or it may reflect someone with anaemia who is also dehydrated. A raised serum urea with a normal creatinine level may indicate dehydration. Raised urinary sodium levels, specific gravity and osmolality all reflect the normal homeostatic response to water depletion and can be used to monitor progress with resuscitation. The signs and symptoms of water depletion are described in Figure 3.

Estimation of total body water deficit

Deficit of body weight	For example in a 70 kg man	Signs and symptoms
Up to 5%	3.5 litres	Thirst Dry mouth
5–10%	3.5–7 litres	Decreased skin turgor Decreased intraocular pressure Tachycardia Orthostatic hypotension Tachypnoea Oliguria Skeletal muscle weakness Drowsiness
10–15%	7–10.5 litres	Severe hypotension Tachycardia Anuria Confusion/coma

3

Signs and symptoms of uncorrected acute blood loss

Volume lost	For example in a 70 kg male	Signs and symptoms
10%	490 ml	Thirst Venoconstriction
20%	980 ml	Mild increase in heart rate Systolic blood pressure normal Slight rise in diastolic pressure Decreased urine output
30%	1470 ml	Tachycardia > 120/minute Moderate hypotension Tachypnoea Cool, clammy, pale Anxious/aggressive Oliguria
40%	1960 ml	Severe hypotension and tachycardia Tachypnoea Anuria Mental confusion
50%	2450 ml	Coma

4

Fluid losses

Blood loss: the signs and symptoms of unreplaced blood loss (Figure 4) can help to estimate acute losses if accurate measurements cannot be made. Estimates of intraoperative blood losses are derived from measuring or estimating observed losses. Prediction of postoperative losses requires knowledge of the type of surgery and expected postoperative bleeding, combined with measurement of losses in the drains, vital signs, and haemoglobin and haematocrit levels.

Third-space losses are caused by sequestration of extracellular fluid into the tissues. The composition of this fluid is the same as that of interstitial fluid and losses after major bowel resection may be as great as 8 ml/kg/hour. The extent of third-space losses depends on the severity of injury to the tissues.

Transcellular fluid losses: nasogastric aspirate can be measured but pleural effusions and ascites must be estimated. Losses from evaporation occur from the surgical site and during a laparotomy these can be as much as 10 ml/kg/hour.

Effects of anaesthetic agents and techniques

Ventilation with dry anaesthetic gases increases the pulmonary losses from evaporation. General and regional anaesthesia tend to decrease the patient's blood pressure by a reduction in sympathetic tone, vasodilatation or myocardial depression. Vasopressors and intravenous fluids are used to minimize these effects, complicating the assessment of perioperative fluid status. Central venous pressure monitoring can be invaluable in helping to manage more complex cases.

Choosing perioperative fluids

Crystalloids

Dextrose solutions disperse through all the body fluid com-partments and are required to replace combined intracellular plus extracellular water depletion. Once any deficit has been replaced, dextrose is used only perioperatively as part of the basal water requirements or in a diabetic regimen.

Physiological saline disperses throughout the extracellular fluid compartments and is commonly used perioperatively to replace blood loss, transcellular losses, evaporation and third-space losses. Only one-third remains in the intravascular compartment and therefore three times the volume of the blood loss must be given if saline is used as a replacement. When large volumes of saline are administered there is a risk of developing hyperchloraemic acidosis.

Ringer's lactate (Hartmann's solution) behaves as normal saline in distribution. It is often used as the first-choice replacement fluid because the electrolyte content more accurately mimics the extracellular fluid. Its constitution varies between laboratories but in general it contains 137 mmol/litre sodium, 4 mmol/litre potassium, 3 mmol/litre calcium and 142 mmol/litre chloride. There are fewer risks of electrolyte disturbances if large volumes are administered but it is hypotonic and large volumes reduce plasma osmolality.

Colloids

The contents of the commonly used colloids are listed in Figure 5.

Properties of commonly used colloids

	Average molecular weight	Sodium (mmol/litre)	Potassium (mmol/litre)	Chloride (mmol/litre)	Calcium (mmol/litre)
Haemaccel	35,000	145	5.1	145	6.2
Gelofusine	35,000	154	0.4	154	0.4
Hetastarch	450,000	154	0	154	0
Dextran 70 in saline	70,000	150	0	150	0
Albumin 4.5%	70,000	150	2	120	0

5

Colloids used for intravenous therapy have an increased osmolality with respect to plasma and can increase plasma volume by more than the volume infused by attracting water from the interstitial fluid compartment. Consequently they are used predominantly to replace intravascular losses and are unsuitable for the treatment of dehydration. The length of time a colloid stays in the intravascular compartment depends on the shape, size and charge of the molecules suspended and the porosity of the capillary endothelium.

Gelatins are colloid solutions derived from animal gelatin. They have an average molecular weight of 35,000 but there is a wide variation in molecule size. The two commonly used gelatins are *Haemaccel*, which is urea linked, and *Gelofusine*, which is a succinylated gelatin. Their intravascular persistence is low, about 2–3 hours with *Gelofusine* and less for *Haemaccel*. Gelatins are the colloids most likely to induce an anaphylactoid reaction. Cross-matching is unaffected by the use of gelatins. *In vitro* studies suggest they interfere with clotting and platelet aggregation but in clinical practice little effect is seen.

Hydroxyethyl starches (HES) are modified natural polymers of amylopectin, which are metabolized by amylase. They are divided into high, medium and low molecular weight starches according to the range of molecular weights in the solution. *Hetastarch* is a 6% solution with an average molecular weight of 450,000 and a mean molecular weight of 70,000. The intravascular persistence of *Hetastarch* is over 24 hours. Some enters the interstitial space and is taken up by the reticulo-endothelial system where it can persist for years. Hexastarch and pentastarch are lower metabolic weight starch solutions. High molecular weight HES solutions can cause a coagulopathy by reducing factor VIII and von Willibrand factor. The lower the average molecular weight of the solution the less effect it has on coagulation. The maximum recommended dose is 33 ml/kg/day, though this has often been exceeded without any adverse effects. Anaphylactic reactions have been reported, but the incidence is low.

Dextrans are branched polysaccharides produced by the action of bacteria on a sucrose medium. Dextran solutions are divided by their average molecular weight into 10% Dextran 40 (molecular weight 40,000) and 6% Dextran 70 (molecular weight 70,000). Dextran reduces blood viscosity, reduces platelet adhesiveness and increases fibrinolysis. Doses higher than 1.5 g/kg can increase bleeding. Only Dextran 70 is used for short-term plasma expansion. Severe anaphylaxis is uncommon but has been reported.

Albumin has a molecular weight of 69,000 and is a naturally occurring plasma protein that contributes significantly to the maintenance of plasma oncotic pressure. It has been used as a colloid to treat critically ill patients with hypoalbuminaemia but there is no evidence that this improves outcome. Recent research has suggested it may worsen outcome but this is not proven. The increasing cost of production of albumin has significantly reduced its use in clinical practice.

Crystalloid–colloid controversy
It has been argued that colloids are more appropriate than crystalloids for the replacement of intravascular losses because they stay in the intravascular compartment longer, necessitating a smaller volume of replacement and a more rapid result. As stated above, the intravascular persistence varies significantly between the different colloids, while this argument holds for hydroxyethyl starches it is not so strong for the gelatins.

Opponents of colloids emphasize the incidence of ana-phylaxis with colloids, which does not exist with crystalloids. The pragmatists suggest that the normal physiological response to an acute intravascular deficit is to draw water in from the interstitial fluid compartment and therefore it makes sense to initiate resuscitation with a crystalloid and then to continue with a colloid if the loss becomes significant.

Blood and blood products
Red cell transfusions: the indication for a red cell transfusion is to increase the oxygen-carrying capacity of the blood by raising the haemoglobin concentration of patients with acute or chronic anaemia. The extent to which it should be raised depends on the balance between oxygen consumption and supply, with the aim of avoiding tissue hypoxia. Factors that affect perioperative oxygen consumption are body temperature, sympathetic activity, metabolic activity, heart rate and drug therapy.

New safety requirements are making blood products more complex and expensive to produce. Recent research suggests the traditional trigger of a haemoglobin concentration of 10 g/dl for perioperative transfusion is too high. The rate of blood loss also needs to be taken into consideration when deciding to transfuse. Suggested British Society for Haematology guidelines are summarized in Figures 6 and 7.

Need to transfuse based on an estimate of lost circulating volume

Volume lost	Indication for transfusion
15%	Only if superimposed on existing anaemia or Patient unable to compensate because of severe cardiac or respiratory disease
15–30%	As above or In the presence of continuing blood loss
30–40%	Transfusion should be considered
> 40%	Transfuse

6

Need to transfuse based on consideration of haemoglobin concentration

Haemoglobin concentration	Indication for transfusion
< 7 g/dl	Transfuse
7–10 g/dl	Transfuse patients who would tolerate anaemia poorly (e.g. those with cardiac or respiratory disease, those over 65 years of age)
> 10 g/dl	No indication

7

Concerns about the safety of transfusion have encouraged the development of alternative strategies to minimize the need for homologous transfusions. These include the use of autologous pre-donation of blood, acute normovolaemic haemodilution, intraoperative cell salvage, preoperative administration of erythropoietin and the development of blood substitutes.

Fresh frozen plasma is valuable because it contains all the clotting factors. It is used to correct a coagulopathy due to a concurrent illness, the use of anticoagulants or a dilutional coagulopathy. A coagulation screen should be requested to establish the need for fresh frozen plasma, although in the presence of a massive haemorrhage, fresh frozen plasma may be given before laboratory results are available if there are clinical signs of impaired coagulation.

Platelets should be given only if there is clinical and laboratory evidence of abnormal coagulation.

Blood substitutes
There are three different areas of research in progress: free haemoglobin solutions, encapsulated haemoglobin cells, and perfluorocarbon emulsions.

Haemoglobin-based oxygen carriers: free haemoglobin has been used as a red blood cell substitute for decades but initially there were many adverse effects including hypertension, bradycardia, renal dysfunction and a short intravascular retention time. A problem was the lack of 2,3-diphosphoglycerate (2,3-DPG) and the higher pH of plasma compared with that inside the red blood cell. There is also an increase in oncotic activity which limits the concentration of free haemoglobin that can be used to about 5–7 g/dl.

Some of the adverse effects of free haemoglobin have been reduced by a variety of modifications including polymerization and conjugation to increase the intravascular retention time and the introduction of haemoglobin into cell-like structures, using stable, porous membranes that allow molecules such as glucose to enter. Some products have reached the stage of clinical trials.

Perfluorocarbon emulsions: perfluorocarbons are synthetic carbon–fluorine compounds. They dissolve gases including oxygen and carbon dioxide. They are not metabolized *in vivo* and most are excreted unchanged via the lungs. A small amount is taken up by the reticulo-endothelial system and excreted later. They are immiscible in water and have to be emulsified. Initial emulsifiers caused numerous adverse effects. Second-generation perfluorocarbons have reduced the complications, but high doses can still interfere with coagulation, elevate liver enzymes and produce a febrile response. They are in phase III trials as a blood substitute. ◆

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Positioning the Surgical Patient

Jonathan Warwick

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The correct positioning of a patient for surgery is a balance between optimizing surgical exposure and minimizing complications for the patient. The surgeon may request a particular position and it is often the role of the anaesthetist to ensure that this is accomplished safely. The anaesthetist must consider the limits of position that may be tolerated and ensure access to the airway, monitoring and vascular devices as far as possible. In general, complications may arise from physiological consequences of the position and the effects of direct pressure on soft tissue structures.

Supine position

Indications: the supine position is the standard for most surgical procedures. The orthopaedic fracture table is a modification that enables traction to be maintained on a lower limb and provides access for an image intensifier.

Physiological consequences: when an individual is upright, ventilation per unit lung volume is greater in the lower part of the lung, because here the weight of the lung makes the intrapleural pressure–volume curve steeper (see Figure 2). The apex of the lung is on a flatter part of this curve, representing a relatively larger change in pressure for a given change in lung volume, and hence a lower compliance. The lower part of the lung is better perfused as a result of gravity.

When an individual is supine, ventilation and perfusion become more uniform and the effects of gravity less marked. The differences between base and apex are then replaced by differences between dependent and non-dependent parts of the lung. Stroke volume and cardiac output may increase as a result of the increase in central venous pressure. Baroreceptors sense an increase in arterial pressure, leading to a fall in heart rate and systemic vascular resistance.

The physiological effects of a change of posture when anaesthetized depend on additional factors:

- pharmacological effects
- circulating blood volume
- method of ventilation.

The functional residual capacity (FRC) decreases by about 20% following induction, though closing capacity remains unchanged. Anaesthetized patients are vasodilated and have diminished compensatory cardiovascular reflexes. Therefore, all positioning movements must be made slowly. The basic supine position is generally well tolerated and has no additional physiological effects in healthy patients.

Pregnant patients may suffer from the supine hypotensive syndrome, where the weight of the gravid uterus reduces venous return by compression of the inferior vena cava (IVC). This can be avoided by a lateral tilt of the operating table, usually to the left side.

Direct pressure complications: the eyes should be taped closed to prevent corneal drying or injury from scratching. Limbs must be fully supported and moved with care to prevent joint dislocation or even fracture. The arms can be secured in the drawsheet, or by the use of padded arm supports.

Skin overlying all bony points is prone to pressure damage, especially the occiput, elbows, knees, greater trochanter of the femur and sacrum. As little as 2 hours of unrelieved pressure may result in a pressure sore; the duration of pressure is considered to be more important than its intensity. The ankles should be placed in soft foam-rubber boots to avoid pressure necrosis of the heel skin.

Injury to peripheral nerves (Figure 1) is often a consequence of the way in which the patient is positioned during surgery. Nerve injury is most likely to occur with the combination of muscle relaxation, an extreme position and prolonged surgery. Peripheral nerves are damaged by local ischaemia caused by compression or stretching. This produces segmental demyelination. Complete clinical recovery usually occurs within 6–8 weeks, but may take several months. Severe damage may be associated with permanent injury. Electromyography studies may aid the prognosis.

Supine position – nerve injuries

Nerve injury	Comments
• Supraorbital	Compression by catheter mount, trachael tube connectors
• Nerves to the eye	Compression from face mask
• Facial (VIIth)	Compression by anaesthetist's fingers against ramus of mandible, face mask harness
• Brachial plexus	Stretching injury, especially when arm is abducted > 90°, externally rotated, elbow extended and forearm supinated
• Ulnar	Most common nerve injury occurring during anaesthesia. Compression between the medial epicondyle of the humerus and the edge of the operating table. Pronation of the forearm may place the nerve more at risk than supination
• Radial	Compression between the edge of the operating table or armboard and the shaft of the humerus, compression from a head-screen support
• Pudendal	Compression from the post of an orthopaedic fracture table may cause pudendal nerve injury or genital trauma
• Sciatic	Direct compression in thin patients undergoing prolonged surgery on a hard table

1

Lateral ('lateral decubitus') position

Indications:

- thoracic surgery
- lateral approach to the kidney
- surgery to the hip.

Reference to the right or left lateral position indicates the side on which the patient is lying.

Physiological consequences: when lying awake in the lateral position, ventilation to the upper and lower lungs behaves in a similar fashion to the ventilation of lung apex and base when upright. The lower lung lies on the steeper, more compliant part of the intrapleural pressure–volume curve (see Figure 2, page 12). The weight of the abdominal contents pushes the lower lung diaphragm higher than the diaphragm of the upper lung, so that it is also able to generate a higher force of contraction. The lower lung is therefore better ventilated than the upper lung. Perfusion of the lower lung is also greater as a result of gravity.

Following anaesthesia, the distribution of blood flow remains unchanged but there are significant changes to the distribution of ventilation. Muscle tone is greatly reduced or absent and the FRC of each lung falls, especially in the lower lung as a result of the weight of the mediastinum pushing down from above and the weight of the abdominal contents below. This has the effect of moving the upper lung down to a more favourable (i.e. steeper and more compliant) part of the intrapleural pressure–volume curve. The lower lung moves down to a flatter, less compliant part of the curve. Therefore the upper lung becomes the better ventilated, but because it receives less of the pulmonary blood flow, ventilation–perfusion mismatch increases.

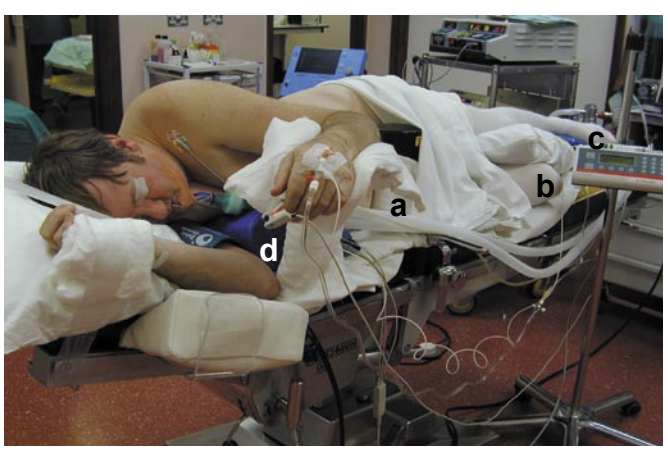
To expose the flank during the lateral approach to the kidney, the lateral flexed position over a support ('kidney position') may be necessary. Significant hypotension may result when the patient is positioned on the right side for a left kidney operation. Reduced venous return occurs as a result of partial obstruction of the IVC from the support. Hepatic encroachment on the IVC may also contribute. This problem is less common when the patient is in the left lateral position.

Direct pressure complications: the pelvis and shoulders must be well supported to prevent the patient from rolling backwards off the table, or forwards into the recovery position. The lower leg should be flexed and the upper leg extended, with a pillow between the two (Figure 2).

An axillary roll places the weight of the chest on to the ribcage and prevents direct compression injury to the shoulder and axilla, thus avoiding deltoid muscle ischaemia or neurovascular damage to the lower arm.

The lower leg is at risk from pressure damage, especially in obese patients. Compartment syndrome, myoglobinuria and acute renal failure have been reported.

Nerve injuries that may result from the lateral position are listed in Figure 3.



2 The lateral position.
a Padded supports to prevent patient rolling over – anteriorly next to iliac crests; posteriorly next to lumbar spine.
b Lower leg flexed and pillow between knees.
c Heel supported.
d An axillary roll places the weight of the chest on to the ribcage.

Lateral position – nerve injuries

Nerve injury	Comments
• Cervical spine	Lateral flexion may stretch cervical spinal nerves and make arthritic joint pain worse. May cause Horner's syndrome
• Brachial plexus	Stretching injury when the neck is extended and in lateral flexion. May occur when the arm is suspended from a bar or gutter and is inadequately supported
• Common peroneal	Compression between the operating table and the head of the fibula

3

Trendelenburg ('head-down') position

Indications:

- pelvic surgery
- insertion of central venous lines.

Friedrich Trendelenburg first described the 45° supine head-down position in 1890. This position facilitates access to the pelvis. Most head-down positions are now about 20° or less with acceptable results. The steep head-down position is now avoided because it is unnecessary and has too many disadvantages. A corrugated or non-slip mattress helps prevent patient movement.

Physiological consequences: there is a greater reduction in FRC than in the basic supine position as a result of pressure of the abdominal contents on the diaphragm. Usually ventilation is little impaired, especially in fit patients and for short periods. For longer operations and in obese patients, there is increased work of breathing against the weight of the abdominal contents, therefore controlled ventilation is preferable.

Central venous pressure rises, and cardiac output may increase. This may precipitate acute heart failure in patients with poor cardiac reserve. The position is not generally effective in improving the circulation during shock and can increase venous pooling in the upper half of the body. A prolonged head-down position will cause venous congestion and oedema in the head and neck.

Barrier pressure is the difference in intraluminal pressures either side of the gastro-oesophageal junction. The pressure within the oesophagus is normally 15–25 mm Hg higher than gastric pressure and gastro-oesophageal reflux is prevented. Barrier pressure is maintained by the action of the smooth muscle cells of the lower oesophageal sphincter and the skeletal muscle of the surrounding crural diaphragm. The head-down position may raise intragastric pressure, reduce barrier pressure and encourage reflux to occur.

There is an increase in intracranial and intraocular pressure. While inserting central venous lines in patients with head injury, care should be taken to limit the head-down tilt to the minimum necessary so as not to worsen cerebral perfusion pressure.

Direct pressure complications: injury to the brachial plexus was common when the steep 45° head-down position was used and patient movement was prevented by shoulder supports or wrist straps. Patient movement is prevented by the non-slip mattress when lesser degrees of head-down tilt are used (e.g. 20°). Brachial plexus injury is now uncommon.

Reverse Trendelenburg ('head-up') position

Indications:
- operations on the head and neck; this position reduces venous pressure and helps reduce bleeding
- surgical access to the gall bladder and proximal gastrointestinal tract, especially during laparoscopic surgery
- operations on the shoulder joint.

Usually, 15–20° head-up tilt is sufficient.

Physiological consequences: there is a small decrease in arterial pressure; but less of a decrease in FRC than in the basic supine position because less pressure is exerted on the diaphragm by the abdominal contents. There is a reduction in intraocular and intracranial pressure, mainly as a result of improved venous drainage.

Any open vein or sinus above the level of the right atrium can cause venous air embolism.

Direct pressure complications: injury to the brachial plexus may be caused by excessive rotation and lateral flexion of the neck away from the operative site.

Lithotomy position

Indications:
- urological procedures
- operations on the perineum, anus and rectum.

The patient is positioned in the supine position, with both hips and knees flexed and the thighs abducted. The ankles and feet may be supported by lithotomy poles using stirrups or calf supports, or by strapping into padded boots. The position is usually combined with some head-down tilt to aid surgical access.

Physiological consequences: the lithotomy position is generally well tolerated. There is a reduction in vital capacity and FRC as a result of diaphragmatic splinting from upward displacement of abdominal contents. This may cause difficulty with spontaneous ventilation in obese patients and controlled ventilation may be preferable. Care should be taken when the legs are lowered because this may reveal previously unrecognized hypovolaemia and cause sudden hypotension.

Direct pressure complications: backache is common and may be reduced by providing a support to maintain the normal lumbar lordosis. The sacrum must be supported and should not hang free over the end of the table. Marked flexion of the hips and knees may cause sacroiliac strain, and the legs must be moved together to avoid pelvic asymmetry. Slippage of the lithotomy poles once the legs are positioned can cause hip dislocation. Moving the thighs too far apart may strain the adductor muscles.

Compartment syndrome in the lower leg may be initiated by pressure of the calf muscles on the stirrup pole. 'Breaking' or raising the lower end of the table when the fingers have been inadvertently trapped in the gap has caused crush injury.

Anaesthesia should not be induced with the legs elevated because raised intra-abdominal pressure may predispose to regurgitation, and turning the patient will be difficult.

Nerve injuries that may occur with the lithotomy position are shown in Figure 4.

Lithotomy position – nerve injuries

Nerve injury	Comments
• Sciatic	Stretching as a result of maximum external rotation of the flexed thigh
• Common peroneal	Compression between lithotomy pole and the head of the fibula
• Tibial	Compression if the legs are supported by stirrups behind the knees
• Femoral	Compression beneath the inguinal ligament when the thighs are fully flexed on the abdomen
• Obturator	Compression at the obturator foramen when the thighs are fully flexed on the abdomen
• Saphenous	Compression between the medial condyle of the tibia and lithotomy post or stirrup

Prone position

Indications:
- operations on the spine and posterior cranial fossa
- operations on the buttocks and natal cleft
- percutaneous extraction of renal calculi.

Physiological consequences: there is often an improvement in gas exchange in the prone position. This may be as a result of the greater inspiratory pressures required to maintain the tidal volume, which decreases atelectasis, increases FRC and improves oxygenation. Pulmonary barotrauma caused by excessive inspiratory pressures should be avoided by correct positioning of the pelvis and upper chest.

The pelvis and the upper chest must be supported so that the abdomen is not compressed and the diaphragm can descend freely during respiration. This may be particularly difficult to achieve in obese patients. Patients may be positioned by using pillows, supporting the iliac crests with cushioned props, or by the use of a specialized hollowed mattress. Controlled ventilation is preferable in most patients.

There are no significant cardiovascular changes. Pulmonary blood flow is essentially unchanged from the supine position. Poor positioning and high inspiratory pressures may decrease venous return. Patients with previous coronary artery bypass grafting may be at risk from graft occlusion.

Direct pressure complications: turning the supine patient prone requires a team of four people. Great care must be taken with the head and neck to avoid twisting or hyperextension injury to the cervical spine. The face should rest on a cushioned horseshoe with the weight of the head evenly distributed. The eyes are naturally protected within their bony sockets, but exophthalmos or a flattened nasal bridge may allow transmission of pressure to the globe. Prolonged compression may result in central retinal vein thrombosis and blindness.

The tracheal tube must be securely fixed and its position checked after the turn. Some experienced anaesthetists may use the laryngeal mask for airway maintenance in prone patients, though the use of a reinforced tracheal tube is likely to be safer for the trainee. Excessive pressure on the breasts may cause ischaemic damage to the nipples, interstitial bleeding or rupture of breast implants. In men, the penis or scrotum may become trapped and compressed.

Possible nerve injuries are shown in Figure 5.

Prone position – nerve injuries

Nerve injury	Comments
• Cervical spinal cord	Stretching injury caused by overextensio plane
• Nerves to the eye	Compression from face support
• Facial (VIIth)	Compression from face support
• Brachial plexus	Stretching injury caused by extreme abduction of the arms. Limit abduction to 90°
• Ulnar	Compression between the medial epicondyle of the humerus and the mattress
• Lateral cutaneous nerve	Compression between iliac crest of the thigh and the positioning prop. If used, props should be angulated and positioned so that the patient is unable to slip sideways
• Anterior tibial	Stretching injury caused by forced plantar flexion of the foot

The sitting position

Indications:
- operations on the posterior cranial fossa and cervical spine
- dental chair anaesthesia.

The sitting position enables the surgeon to gain clear access, with optimal venous drainage, low arterial pressure and reduced bleeding. CSF drainage is good and brain swelling is minimized.

Dental chair anaesthesia in the sitting position is now uncommon.

Physiological consequences: the patient is anaesthetized in the standard supine position and the neurosurgical pins and head frame are applied. On the operating table, the patient is progressively sat upright with the neck flexed; the knees are slightly flexed and the legs are lowered. The arms rest in the lap on a pillow, with the elbows flexed.

A small fall in systolic blood pressure of 20 mm Hg usually occurs; this can be offset by prior volume loading with 500 ml of colloid solution. Occasionally, persistent instability of blood pressure can occur that may cause the position to be abandoned despite the use of vasopressors. Controlled ventilation is the method of choice, to enable control of Pa_{CO_2} and intracranial pressure. It maintains a higher mean intrathoracic pressure and reduces the likelihood of air embolus.

Air embolus is the major complication. All patients must be considered to be at risk throughout the procedure. For this reason, many neurosurgeons seldom use this position. It is still used when insufficient access is provided by the alternative prone or semi-prone positions.

Dysrhythmias, especially bradycardia, and blood pressure instability may occur following surgical manipulation in the region of the brain stem. This is a result of direct pressure effects on the autonomic control centres of the medulla.

Direct pressure complications: nerve injuries that may result from the sitting position are shown in Figure 6.

The sitting position – nerve injuries

Nerve injury	Comments
• Cervical spinal cord	Stretching injury and spinal cord ischaemia following excessive neck flexion. A two-finger breadth gap between chin and chest is recommended
• Brachial plexus	Stretching injury if the arms are unsupported
• Ulnar	Compression between the medial epicondyle of the humerus and the arm supports
• Sciatic	Stretching injury if thighs are flexed and knees extended. Maintain adequate knee flexion

Premedication

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Premedication involves the prescription of drugs before the induction of anaesthesia in order to alleviate the apprehension associated with surgery, to counteract the side-effects of anaesthetic agents or to reduce the risks of pre-existing pathology (Figure 1). When choosing a premedicant drug the anaesthetist must consider which of its properties are appropriate for the individual patient, the possible side-effects and its potential effect on the proposed anaesthetic technique. The ideal premedicant is:

- painless to administer
- highly reliable and specific
- of rapid onset and rapidly cleared
- free of side-effects and interactions with other drugs.

Premedicant drugs entered anaesthetic practice in the late 19th century. Early anaesthetic agents were delivered by open systems and induced unconsciousness slowly. Ether caused an increase in pharyngeal and bronchial secretions, which interfered with smooth gaseous induction. Chloroform caused marked vagal stimulation of the heart leading to bradycardia. Atropine was first used in premedication in 1890. Hyoscine, which combined anticholinergic effects with antiemesis and sedation, was often combined with an opioid (e.g. papaveretum) to produce ‘twilight sleep’. Opioids were prescribed to aid the induction of anaesthesia before the development of more potent anaesthetic induction agents.

The routine use of drugs for premedication is now in decline. There are several reasons for this.

- Modern anaesthetic agents are potent and have a rapid, smooth onset.
- The increased use of day-care surgery requires rapid patient recovery.
- In-patients are often admitted on the day of surgery and the time available between preoperative assessment and induction of anaesthesia is short.
- Pressures of high patient turnover and staffing constraints can make premedication difficult to deliver in practice.

Rationale of premedication

- Reduction of anxiety and fear
- Sedation
- Amnesia
- Antiemesis
- Reduction in volume and acidity of gastric secretions
- Attenuation of autonomic reflexes
- Maintenance of cardiovascular stability
- Reduction of airway secretions
- Provision of analgesia

1

Anxiolysis, sedation and amnesia

The preoperative visit: anxiety is common in preoperative patients. As well as being unpleasant, this anxiety is part of a stress response that may worsen coexisting pathology such as hypertension or angina. A preoperative visit by the anaesthetist is the most effective way to allay the fears and anxieties of forthcoming surgery. This visit can be used to establish rapport with the patient, to discuss the proposed anaesthetic technique in terms that they can understand and to address their worries in a sympathetic manner. Older children will benefit from inclusion in preoperative discussions and it is becoming usual for parents to stay with children during induction of anaesthesia.

For some patients, the preoperative visit alone is insufficient to allay anxiety and pharmacological methods are required. The nature of the surgical procedure, coexisting pathology or the need for a rapid recovery from anaesthesia may dictate extreme caution before the prescription of sedating premedication (Figure 2). Co-administration of an opioid and a benzodiazepine has a potent respiratory depressant effect.

Relative contraindications to sedative premedication

- Airway obstruction or airway surgery
- Poor ventilatory reserve
- Sleep apnoea
- Intracranial pathology
- Severe hepatic or renal disease
- Rapid-sequence induction
- Obstetric anaesthesia
- Day-case anaesthesia (delayed discharge)
- Extremes of age

2

Benzodiazepines
Benzodiazepines are the most commonly used premedication. They are safe and have a broad therapeutic index though they can cause unpredictable psychological effects at the extremes of age. Those that are suitable premedicants can usually be given by mouth about 1 hour before induction, have a short duration of action and produce inactive metabolites (Figure 3).

Benzodiazepines are agonists of γ-aminobutyric acid (GABA) receptors within the CNS. GABA is an important inhibitory neurotransmitter, which hyperpolarizes the neuron by causing an influx of chloride ion. Benzodiazepines also produce sedation and amnesia by their action on the limbic system. Both these effects are variable and depend on the drug used and the dose given.

Temazepam is an effective anxiolytic and is available in elixir or tablet form. It has a sufficiently short duration of action to allow its use in day-case surgery. Midazolam is presented in 2 mg/ml or 5 mg/ml glass vials. Unlike the other benzodiazepines it is water soluble at acid pH but becomes highly lipophilic at physiological pH. It can be given orally or nasally, which makes it an attractive premedicant for children in doses of 0.2–0.5 mg/kg. Lorazepam, 0.05 mg/kg (max. 4 mg), produces intense anterograde amnesia within 30 minutes, often lasting over 3 hours. Amnesia may be viewed as an advantageous property of a premedicant but some patients find the sensation unpleasant.

Benzodiazepines commonly used as premedication

Drug	Usual adult dose	Half-life of parent drug (hours)	Half-life of active metabolites (hours)
• Diazepam	5–10 mg p.o.	24–48	4–10
• Temazepam	10–30 mg p.o.	4–10	None
• Lorazepam	2–4 mg p.o.	10–20	None
• Midazolam	5–10 mg i.m. 0.5 mg/kg (maximum 20 mg) p.o. in children	1–3	None

3

Other anxiolytics and sedatives
Phenothiazines are major tranquillizers that have sedative and anticholinergic actions. They are histamine antagonists (via H_1-receptors) and have antidopaminergic and α-adrenoceptor blocking properties. They may cause pallor and restlessness in the presence of pain and hypotension. Trimeprazine elixir is sedating and is used for children in doses of 1.5–2 mg/kg, up to 2 hours before surgery. It is not licensed for use in children less than 2 years of age.

Droperidol is the only commonly used butyrophenone in current anaesthetic practice. It has antiemetic and sedating properties. Antidopaminergic side-effects such as dystonic reactions and agitation limit its routine use at sedating doses (e.g. 10 mg orally for adults).

Antiemesis

Postoperative nausea and vomiting (PONV) is a common problem, which is distressing for the patient. There are several risk factors:

- gender (incidence is three times higher in women than in men)
- patients undergoing operations on the ear, squint surgery, gynaecological procedures and laparoscopy
- previous history of PONV or motion sickness
- use of morphine
- anaesthetic technique (volatile anaesthetic maintenance is more emetic than intravenous propofol maintenance).

The vomiting reflex is coordinated by the vomiting centre within the dorsolateral reticular formation of the medulla. It receives multiple afferent pathways from peripheral and central chemoreceptors, nociceptors, the vestibular system and the cerebral cortex. The synapses in these pathways are predominantly muscarinic. The vomiting centre also receives stimuli from the chemoreceptor trigger zone in the area postrema on the floor of the fourth ventricle, but outside the blood–brain barrier. This structure is rich in dopamine (D_2) and serotonin (5-HT_3) receptors. The antiemetics commonly used in anaesthetic practice involve inhibition at one or more of these receptor sites.

Muscarinic antagonists: hyoscine (adults, 300 µg; children 4–10 years, 75–150 µg orally) is a more effective antiemetic and is more sedating than atropine. Antihistamines, including cyclizine, 50 mg orally, i.v. or i.m., and promethazine, children 2–5 years, 5–15 mg, 5–10 years, 10–25 mg orally; adults, 25–50 mg orally or intramuscularly, also have antiemetic properties, largely as a result of their antimuscarinic activity. Antimuscarinics cause dry mouth, blurred vision, and bowel and bladder dysfunction.

Dopamine antagonists are powerful antiemetics but extra-pyramidal side-effects, such as dystonia, dyskinesia, tremor and oculogyric crisis are not uncommon.

Prochlorperazine, 12.5 mg i.m., is the most widely used phenothiazine because it is less sedating and has fewer antidopaminergic and α-blockade side-effects than others of the same group.

Droperidol is an effective antiemetic at low dose, 0.625–1.25 mg, reducing the risk of unpleasant dopaminergic or psychological effects. It is usually given intravenously at induction.

Metoclopramide, 0.1 mg/kg i.v., i.m. or orally, is a dopamine antagonist with peripheral as well as central effects. Its prokinetic effects are more marked than its antiemetic properties and comparative studies have raised doubt about its effectiveness as a prophylactic antiemetic.

5-HT antagonists are powerful new antiemetics that are relatively free of side-effects. The most widely used agent is ondansetron, 4 mg i.v., given immediately before or at the end of surgery. Their relative expense has resulted in the cost-effectiveness of their prophylactic use being questioned.

Non-pharmacological measures including acupunture and acupressure have been explored. There is some evidence that these techniques are weakly effective.

Reduction in volume and acidity of gastric secretions

The potential for lung damage from the aspiration of gastric contents increases with the volume and the acidity of the aspirate. Risk of aspiration accompanies late pregnancy, emergency or trauma surgery, symptomatic oesophageal reflux, and obesity.

Acid secretion by gastric parietal cells can be reduced by the use of H_2-histamine antagonists such as ranitidine, 150 mg p.o. Proton pump inhibitors such as omeprazole, 20 mg p.o., are more powerful in reducing acid secretion but inhibit the metabolism of other drugs such as warfarin, phenytoin and diazepam.

A 0.3 molar solution of sodium citrate, 30 ml, will raise gastric pH and is less irritant to the airway should aspiration occur. The routine use of the prokinetic agent metoclopramide, 10 mg, is common practice but of no proven value in the prevention of gastric aspiration.

Attenuation of autonomic reflexes

Parasympathetic stimulation can lead to hypotension, bradycardia or even asystole mediated via the vagus nerve. Triggers include:

- traction on the extraocular muscles during squint surgery
- surgical dilatation of the cervix or of the anal sphincter
- repeated doses of suxamethonium
- laryngoscopy in children (especially on lifting the epiglottis with a straight-bladed laryngoscope)
- opioid analgesics, propofol and halothane.

Glycopyrronium, 0.2 mg i.v. at induction, provides prophylaxis without the discomfort of a dry mouth before surgery. It does not penetrate the blood–brain barrier and lacks the central side-effects of atropine.

An increase in circulating catecholamines may be caused by several factors:

- laryngoscopy and tracheal intubation
- surgical stimulation and pain
- drugs such as ketamine, cocaine and adrenaline (epinephrine) in local anaesthetics.

This increase may cause hypertension and increased myocardial oxygen demand. It may result in myocardial ischaemia in susceptible patients. A balanced anaesthetic technique reduces these risks, and β-blocker premedication (atenolol, 50 mg p.o.) may be of benefit.

There has been recent interest in the use of α_2-adrenoceptor agonists such as clonidine, 3 µg/kg p.o., as premedicants. They reduce sympathetic activity, cause sedation, a reduction in anaesthetic requirement (decreased minimum alveolar concentration) and reduce pressor responses including that of laryngoscopy. However, there appears to be a narrow therapeutic window with the potential for development of hypotension and bradycardia.

Reduction in airway secretions

Antisialogogues are occasionally prescribed as premedicants though their use in modern-day practice is uncommon. Glycopyrronium, 0.2 mg i.v. or i.m., may be used to improve conditions before fibre-optic intubation.

Analgesia

Opioids (e.g. morphine, 0.1–0.2 mg/kg i.v. or i.m.) should be used to relieve acute preoperative pain. However, in the absence of any preoperative distress and with the development of new potent opioid analgesics with a rapid onset given at induction, such as fentanyl, alfentanil and remifentanil, an opioid premedicant is seldom indicated.

Non-steroidal anti-inflammatory drugs decrease the requirement for opioid analgesia during and after a surgical procedure. Typically, ibuprofen, 400 mg p.o., or diclofenac, 50–100 mg p.o., p.r. or i.v., may be given. They should be avoided in patients with a history of peptic ulceration or renal impairment and used with caution in asthmatic patients. Other simple analgesics such as paracetamol, 1 g, can also be given p.o. or p.r.

The concept of pre-emptive analgesia is that nociception can be modulated at the level of the spinal cord by analgesia given before surgery, thereby reducing total postoperative analgesic requirements. While this concept is attractive and has been demonstrated in animal models, clinical studies have yet to prove its value.

Topical anaesthetics such as eutectic mixture of local anaesthetic (*Emla* cream) or amethocaine gel applied to the site of venepuncture, reduce the fear of intravenous anaesthetic induction in children and many adults.

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Principles of Anaesthetic Vaporizers

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Gases, liquids and vapours

Substances can exist in the solid, liquid or gaseous state. Below a certain temperature, known as the critical temperature, it is possible to liquefy gases by compressing them. When a gas is below this critical temperature it is referred to as a vapour.

Vapours consist of molecules that have left the surface of a liquid below the critical temperature. Vapour molecules have had sufficient energy to break away from the attraction of the molecules left behind in the liquid and are therefore the more energetic molecules. Molecules leave the surface of the liquid and return to it randomly. When the vapour is in equilibrium with the liquid, the number of molecules leaving the liquid is equal to the number returning to it, and the vapour is said to be saturated. If there is insufficient liquid for there to be a reservoir from which molecules can evaporate and to which they can return, then the vapour is unsaturated and behaves as a gas.

The pressure of a vapour in equilibrium with a liquid is known as the saturated vapour pressure (SVP).

Variation of SVP with temperature

As the temperature of the liquid increases, more molecules have sufficient energy to escape from the surface and therefore the SVP rises. When the boiling point is reached, all the molecules evaporate and the SVP is equal to atmospheric pressure. Figure 1 shows the variation of SVP with temperature for halothane, enflurane and isoflurane. Unsaturated vapours behave as gases so that the pressure is inversely proportional to the volume (Boyle's law).

Cooling due to vaporization

If molecules that have left the surface of a liquid are not allowed to return to it (e.g. if they are swept away by a stream of fresh gas) then the liquid cools. This is because the evaporating molecules are more energetic than those left behind, therefore there is a net loss of energy from the liquid, which causes a drop in temperature. The latent heat of vaporization is the heat required to convert a unit mass of liquid into its vapour phase at a constant temperature. Cooling may be prevented or reduced if the liquid is in contact with a surface that can supply heat by conduction. The amount of heat that a body can supply at a given temperature depends on its specific heat and its mass, or, in other words, on its thermal capacity. Heat is also supplied by conduction from the surroundings and the rate at which this occurs is determined by the thermal conductivity of the body.

The specific heat of a substance is defined as the amount of heat (or energy) required to raise the temperature of a unit mass of the substance through 1 deg C. The units of specific heat are joules per kilogram per Kelvin change in temperature (J/(kg.K)).

The thermal capacity of a body is the heat required to raise its temperature through 1 deg C (this is also equivalent to the amount of energy the body loses when cooled by 1 deg C). The units of thermal capacity are joules per kilogram (J/kg). The thermal capacity of a body is equal to the product of its mass and specific heat.

The thermal conductivity of a material is the rate of heat transfer per unit area when a temperature difference of 1 deg C is maintained across an insulated block of the material 1 m thick. The units of thermal conductivity are Watts per metre per Kelvin (W/(m.K)).

Values of specific heat, density and thermal conductivity for copper, aluminium, glass and stainless steel are shown in Figure 2. It can be seen from this table that copper has the highest thermal conductivity of these materials so that vaporizers made of copper are the most efficient at conducting heat from the atmosphere to replace the energy that the liquid agent loses due to evaporation. Copper has the lowest specific heat of these substances; however, since it is much denser than aluminium or glass, the thermal capacity of a given volume of copper is higher than that of either of these materials. A given volume of stainless steel has the highest heat capacity of these materials. In practice, most vaporizers are made of stainless steel because it is readily available. However, copper is thermally more suitable because its much higher thermal conductivity more than compensates for the lower heat capacity.

Anaesthetic vaporizers

The SVP of most anaesthetic agents at room temperature is too high for them to be delivered to a patient without dilution (Figure 1). For example, the SVP of isoflurane at 20°C is 236.5 mm Hg (i.e. 31% v/v if atmospheric pressure is 760 mm Hg). In general, concentrations below 2% v/v are required for maintenance of anaesthesia. An anaesthetic vaporizer is a device that dilutes the vapour to give a known concentration of the agent.

Fresh gas enters the vaporizer and is split into two portions (Figure 3). One portion flows through an area known as the vaporizing chamber, where it comes into contact with the anaesthetic vapour; the remainder of the gas bypasses this chamber. The two flows then recombine and the vapour is diluted. By varying the flow rate in the two paths the resultant vapour concentration can be varied. The concentration of agent depends on the flow through the vaporizing chamber, the total fresh gas flow and the saturated vapour pressure of the anaesthetic agent. The way in which the gas flow is split between the bypass and vaporizing chamber depends on the relative resistance of each pathway. If the total fresh gas flow (F) is split into a bypass flow (F_b) and a vaporizing chamber flow (F_v) then:

$F_v + F_b = F$

The flow rate emerging from the vaporizing chamber (F_e) will be greater than that entering it, due to the volume of vapour added:

$F_e = F_v + F_e \times SVP/100$

where SVP is expressed as a percentage.

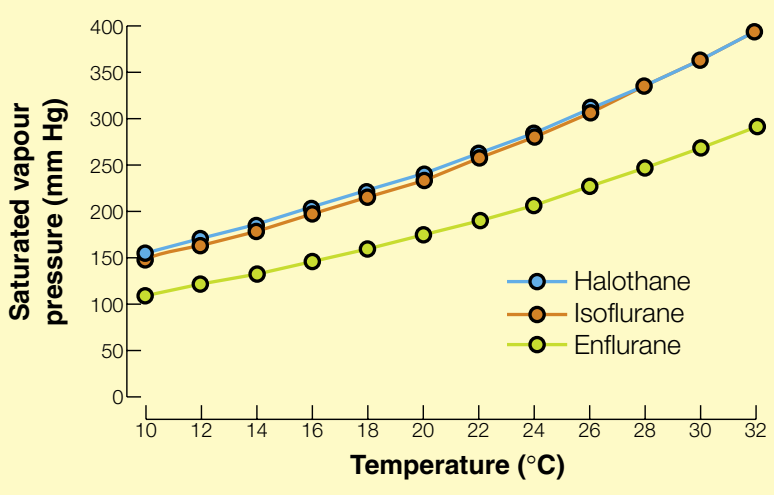
Therefore $F_e = F_v/[1-(SVP/100)]$

The concentration (C) of the vapour in the gas emerging from the vaporizer will be given by:

$C = F_e \times SVP/(F_b + F_e)$

This calculation assumes that the gas emerging from the vaporizing chamber is fully saturated with vapour. To ensure that this is the case, manufacturers increase the surface area of liquid that the gas passes over by introducing wicks made of cloth or metal into the vaporizing chamber. In many cases the gas is forced to take a long pathway through the chamber, which also helps to ensure saturation.

Variation of saturated vapour pressure with temperature



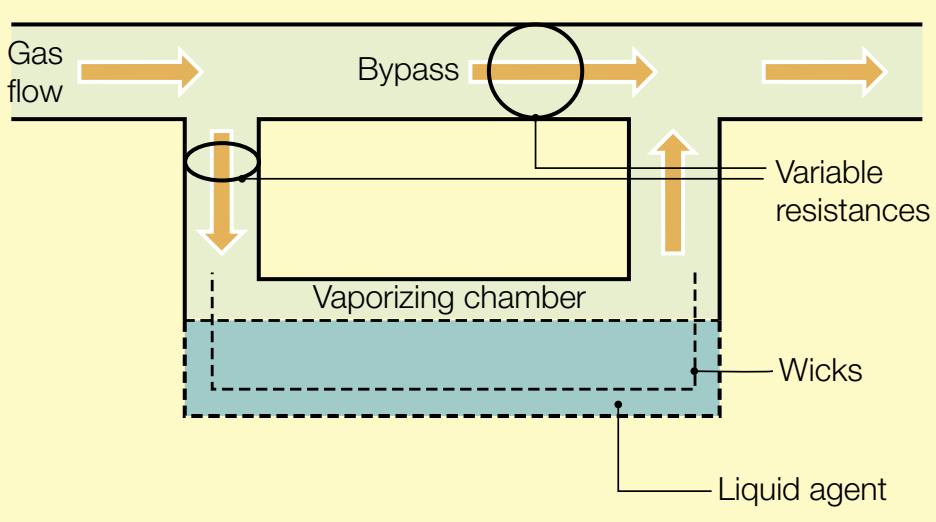
1

Physical properties of some common materials at 293K

	Specific heat (J/(kg.K))	Thermal conductivity (W/(m.K))	Density (kg/m³)
Copper	385	385	8930
Aluminium	913	201	2710
Glass	670	1	2600
Stainless steel	510	150	7930

2

An anaesthetic vaporizer



3

Temperature compensation

As liquid evaporates from the vaporizing chamber the temperature drops, and unless there is some means of compensating for this, the output of the vaporizer also drops. The temperature drop, and hence the fall in output, is lower if the vaporizer has a large heat capacity and can therefore supply energy to the liquid to compensate for that which it has lost. For this reason most vaporizers contain a large mass of metal that can also conduct heat from the surroundings into the liquid. In addition, most vaporizers incorporate some kind of temperature compensation, which reduces the resistance of the vaporizing chamber relative to that of the bypass as the temperature drops. As a result, more gas flows through the vaporizing chamber so that the vapour concentration is maintained.

Effect of intermittent positive-pressure ventilation (IPPV)

During IPPV, the pressure at the outlet of a vaporizer is not constant. When the pressure is high, flow emerging from the vaporizer reduces and the pressure in the vaporizing chamber builds up. As the pressure drops, the excess of vapour, which has accumulated in the vaporizing chamber at this time, emerges not only from the normal outlet of the vaporizing chamber but also from the inlet. This means that the bypass gas contains vapour and therefore the concentration rises. Manufacturers have compensated for this by introducing a long inlet tube into the vaporizing chamber. When the pressure inside the vaporizing chamber drops, the vapour enters this tube, but its volume is not enough to emerge into the bypass.

Effect of flow rate on vaporizer output

The vaporizer output is dependent on the resistance of the vaporizing chamber relative to that of the bypass. With varying flows the vaporizer output remains constant only if this does not change. In practice, this is difficult to achieve over the wide range of flows used in anaesthetic practice. Only if laminar flow is maintained in each pathway throughout the flow range will this be the case. Another factor influencing the output at high flows is the increased cooling, which occurs as a result of the large amount of evaporation taking place.

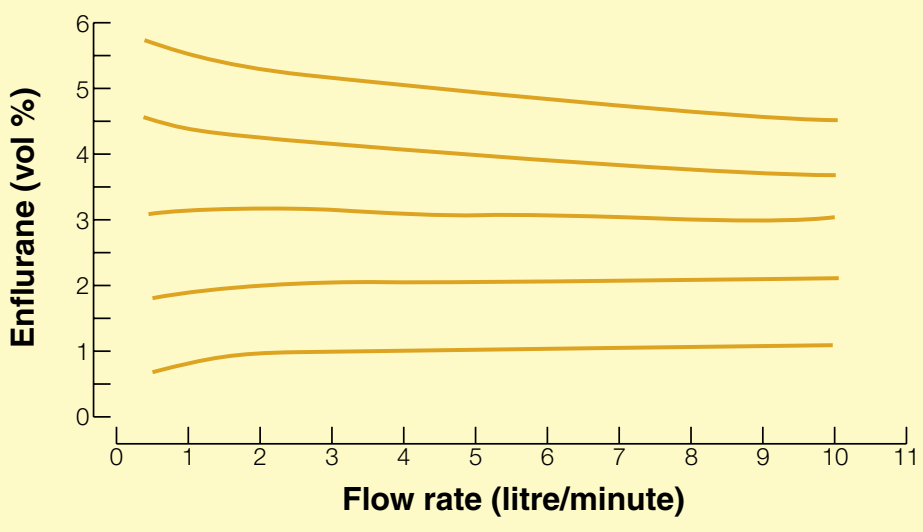
Figure 4 shows the variation of output with flow for a Penlon plenum enflurane vaporizer. It can be seen that the output of this vaporizer at high settings drops as the flow rate increases. However, at the lower settings more commonly in use, the output remains reasonably constant. This indicates that the temperature compensator in the Penlon plenum vaporizer (PPV) can adjust adequately for cooling due to evaporation except at the highest dial settings and flow rates.

Effect of gas composition

The relative flow rates through the bypass and vaporizing chamber at a given dial setting remain constant only if laminar flow is maintained in both pathways. As soon as the flow in one pathway becomes turbulent, its resistance rises causing less gas to flow through it, unless it is matched by a proportional rise in the resistance of the other pathway.

Nitrous oxide has different physical characteristics from oxygen (Figure 5); in particular, the ratio of viscosity to density, which determines the flow rate at which turbulence sets in, is much lower. The effect that this has on the output of the vaporizer depends on its design. In some vaporizers, output drops when the carrier gas contains nitrous oxide whereas in others it increases.

Variation of output with flow for the Penlon plenum vaporizer



Courtesy of Penlon Ltd.

4

Physical properties of oxygen and nitrous oxide

Gas	Density (kg/m^3)	Viscosity ($\mu N.second/m^2$)	Kinematic viscosity ($m^2/second$)
Oxygen	1.43	18.9	10.3×10^{-5}
Nitrous oxide	1.96	13.5	6.9×10^{-5}

5

Types of vaporizer

Vaporizers fall into two broad categories.

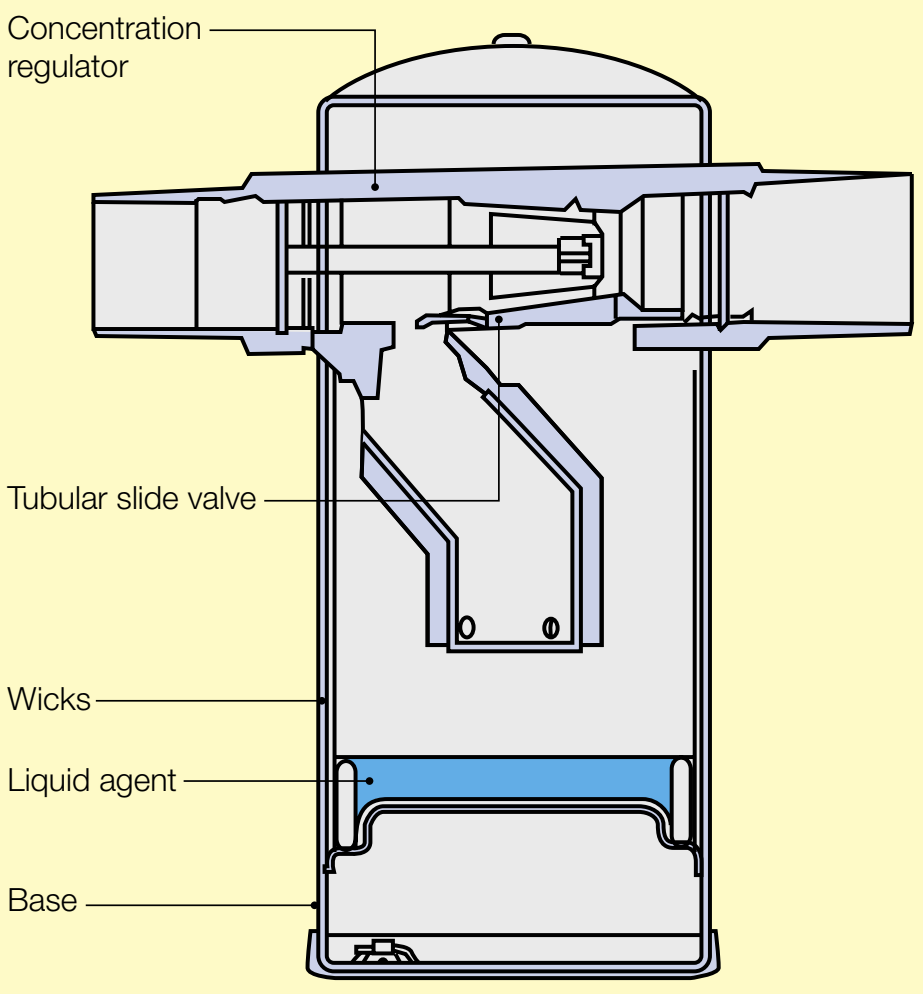
Drawover vaporizers – in a drawover vaporizer, gas is pulled through as the patient inspires (expiration is to atmosphere via a non-rebreathing valve). The flow rate of gas through the vaporizer is therefore not constant and it is necessary for the vaporizer to have a low resistance.

Plenum vaporizers – in a plenum vaporizer, gas is driven through under positive pressure. The term plenum is derived from the plenum system of ventilation where gas is forced into the system. Plenum vaporizers may have a higher resistance than drawover vaporizers though some vaporizers are designed to be used in either mode (e.g. the Oxford miniature vaporizer).

Oxford miniature vaporizer

The Oxford miniature vaporizer (Figure 6) is designed as a low resistance drawover vaporizer. It does not have any temperature compensation, but it has a water-filled jacket to increase its heat capacity.

Oxford miniature vaporizer



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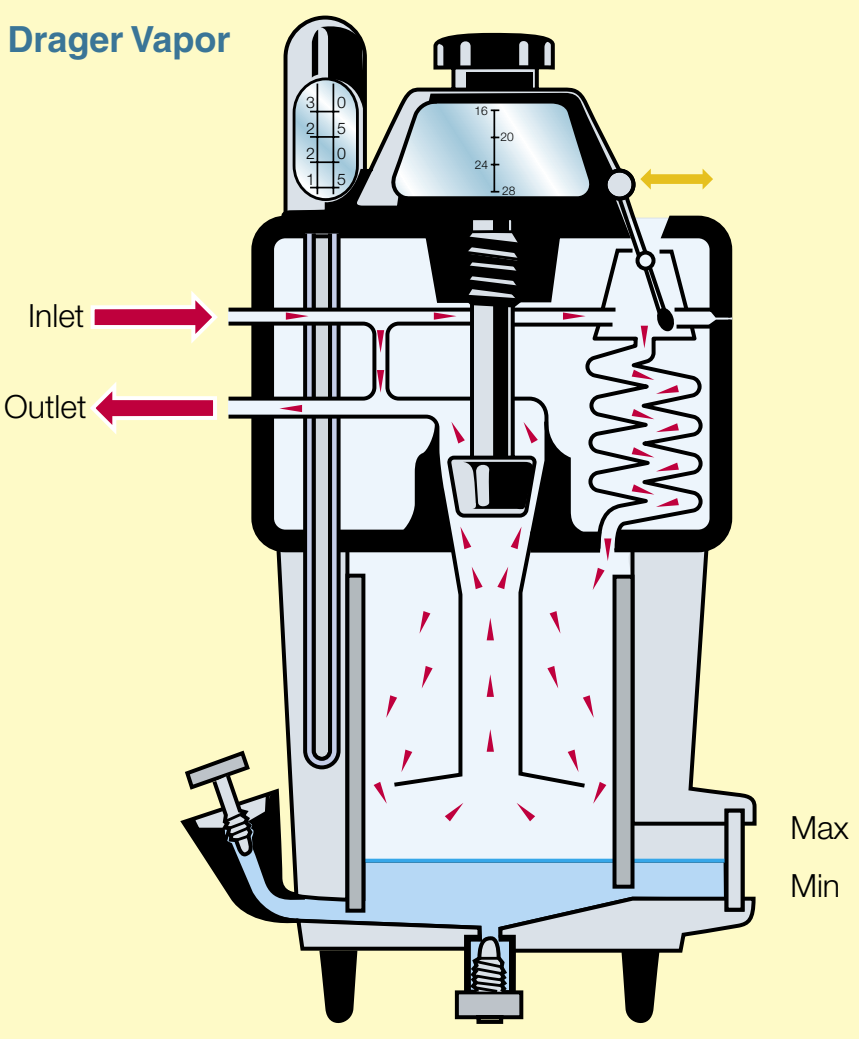
Drager Vapor

The Drager Vapor (Figure 7) is constructed from a large block of copper and is therefore thermally stable. It has a built-in thermometer so that the temperature of the liquid agent may be read and the position of the concentration dial is adjusted according to this temperature. In this vaporizer, the gas flow through the bypass and the vaporizing chamber is controlled by a pair of needle valves, which are carefully manufactured to ensure that gas flow is laminar in both pathways over a large range of flow rates. There is therefore little variation of output with flow rate for this vaporizer.

Drager Vapor



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PPV

In the PPV (Figure 8), when the control dial is in the zero position the vaporizing chamber is isolated by means of a spring-loaded valve attached to the push rod, which is aligned with the control knob. When the control knob zero lock button is pressed the push rod opens the valve and as the control knob is rotated the vapour control orifice opens to allow more gas to flow through the vaporizing chamber.

Temperature compensation is achieved by a moving needle valve within the bypass orifice, which increases the bypass resistance as the temperature drops, thus forcing more gas to flow through the vaporizing chamber. The movement of the valve is controlled by a push rod attached to an ether-filled metal bellows unit. As the liquid agent changes temperature, the ether in the bellows expands or contracts causing the bellows to expand or contract linearly. Compensation for fluctuating back pressure is achieved by the inclusion of a long narrow tube in the vaporizing chamber.

Penlon plenum vaporizer

8

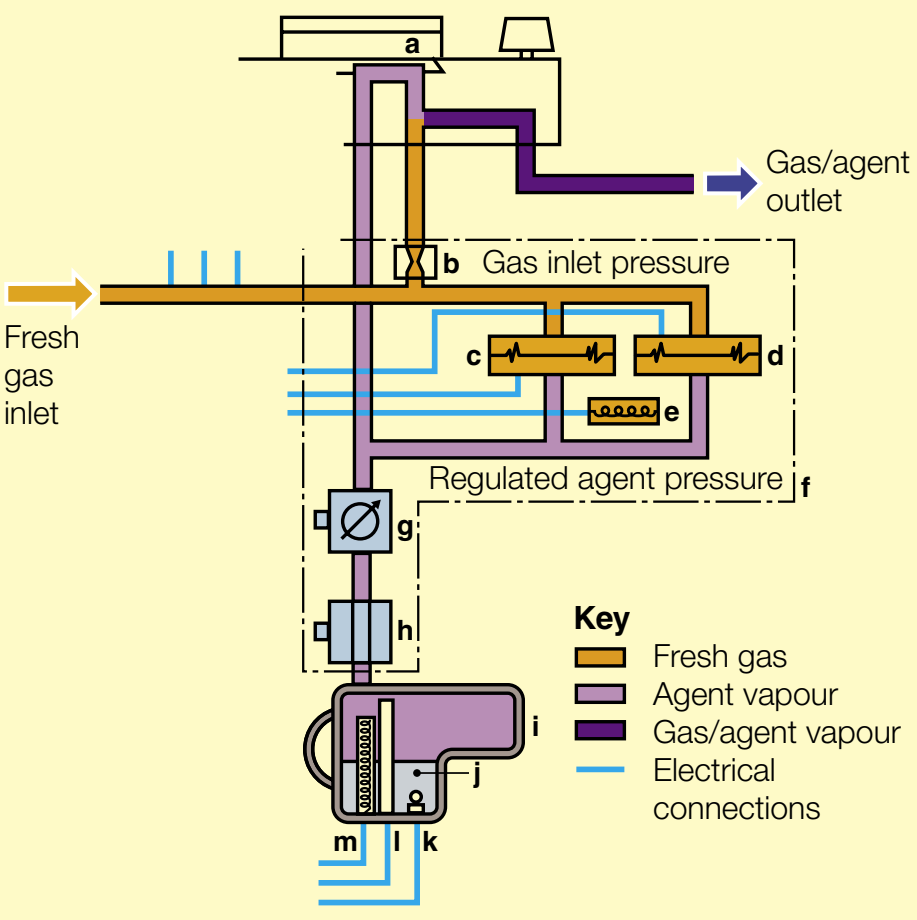
Tec 6 vaporizer

The Tec 6 vaporizer (Figure 9) varies from most other conventional vaporizers because it incorporates a heater element. This is necessary because desflurane concentrations up to 18% v/v may be required. The concentration knob has an interlock system, which means that it cannot be turned until the liquid agent has been heated to the correct temperature. When the control dial is turned, an electronic signal opens the shut-off valve. The pressure transducer measures the difference between the gas inlet pressure and the regulated agent pressure. The agent pressure is controlled electronically by opening or closing the pressure-regulating valve to balance the pressures. When the pressures are correctly balanced the vaporizer functions correctly.

Calibration of vaporizers

Anaesthetic vaporizers are calibrated in the factory using a refractometer (an accurate optical device) in a temperature-controlled room. In general, either oxygen or air at a medium flow rate is used for the carrier gas. The output of a vaporizer may vary under different conditions of temperature, flow or carrier gas – this is not surprising, considering the wide range of flow rates and concentrations over which a vaporizer is used. It has been said that one should expect vaporizers to produce concentrations only within 20% of their dial settings. While this is a wide margin, it is not at all unusual for concentrations to differ by 10% of the dial setting and as conditions become more extreme this difference may approach 20%. It is important that anaesthetists recognize the problems faced by manufacturers when designing vaporizers and that they do not always expect vapour concentration and dial setting to coincide.

Tec 6 vaporizer



a Dial and rotary valve, **b** fixed restrictor, **c** pressure control transducer, **d** pressure monitor transducer, **e** heater in vapour control manifold, **f** vapour control manifold assembly, **g** pressure-regulating valve, **h** shut-off valve, **i** sump assembly, **j** agent, **k** level switch, **l** level sensor, **m** sump heaters

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Recognition and Management of Anaphylactic and Anaphylactoid Reactions

Andrew McIndoe

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The term anaphylaxis was coined by Charles Richet in 1902 to describe the reaction of dogs to a second, and often fatal, injection of foreign protein (sea anemone toxin). The term was introduced to distinguish this later injection from the first 'prophylactic' injection that induced sensitization.

Anaphylaxis is now recognized to be an immediate hypersensitivity or type I immune reaction mediated by immunoglobulin E (IgE) and resulting in mast cell degranulation and basophil activation. It is not dose related and can occur in response to minute exposure to an allergen. Typically, the severity of the response worsens on re-exposure owing to progressive sensitization of the subject. The true incidence of anaphylaxis is unknown but is estimated to be 1/6000–20,000 anaesthetics or 1/10,000 of the general population/year. Women are more likely to suffer an anaphylactic reaction than men, with a quoted increase in risk of 3–10:1. Intravenous administration of the antigen is more likely to precipitate a severe generalized reaction. Cross-sensitivities with non-steroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants makes previous exposure unnecessary. Up to 80% of neuromuscular blocking agent reactions are not associated with known prior exposure.

Anaphylactoid reactions may present with a similar clinical picture, but do not result from hypersensitivity and are not mediated by IgE. Drugs such as opioids can directly stimulate mast cell degranulation with histamine release causing pruritus, rash and hypotension. They should be managed as potential anaphylactic reactions because confusion over the diagnosis merely delays effective treatment.

Pathophysiology

Primary exposure to an antigen results in the synthesis of specific IgE antibodies by lymphocytes and plasma cells. The Fc portions of these antibodies are able to fix themselves to the surface of tissue mast cells and circulating basophils. The antigen binding sites are thus presented externally. Subsequent contact with antigen causes IgE antibody:antigen cross-binding and triggers immediate degranulation of the host mast cell or basophil. Release of histamine and serotonin results in an acute inflammatory reaction, smooth muscle constriction, vasodilatation and increased capillary permeability. The clinical picture depends on the mode of exposure.

- Skin – urticaria, flare and weal reaction (hence the use of skin prick testing).
- Eyes – conjunctivitis.
- Mouth/airway – perioral and laryngeal oedema, broncho-spasm.
- Parenteral – generalized cardiovascular collapse.
- Eosinophils are mobilized by chemotaxis, attracted by histamine and other substances, they produce histaminase, helping to terminate the reaction.

History and examination

Anaphylaxis may present with a spectrum of clinical signs including hypotension, tachycardia, dysrhythmias, dyspnoea, laryngeal oedema, bronchospasm, angio-oedema, flushing, urticaria, conjunctivitis, rhinitis, abdominal pain and diarrhoea. It can therefore mimic a variety of other conditions. Diagnosis is further complicated by a variable time for exposure until symptoms develop, varying from a few seconds to several hours. 5% of patients show a biphasic response with symptoms recurring from 1–72 hours after the initial attack. Many patients do not develop all the classic signs (Figure 1).

Differential diagnoses are vasovagal faint with hypotension, bradycardia and pale, sweaty skin and panic attack with hyperventilation, tachycardia and an erythematous rash.

Percentage of patients presenting with classic signs of anaphylaxis

Signs	Patients (%)
• Cardiovascular collapse	88
• Erythema	45
• Bronchospasm	36
• Angio-oedema	24
• Rash	13
• Urticaria	8.5

1

Management

The management of anaphylaxis is summarized in Figure 2.

Management of anaphylaxis

Condition
IgE mediated immediate hypersensitivity reaction to an antigen resulting in histamine and serotonin release from mast cells and basophils

Presentation
- Cardiovascular collapse
- Erythema
- Bronchospasm
- Oedema
- Rash

Immediate action
- Remove trigger
- 100% oxygen
- Elevate legs
- Adrenaline (epinephrine) 500 μg i.m. or 50 μg increments i.v. titrated to effect
- 20 ml/kg i.v. fluid challenge

Follow-up action
- Chlorphenamine (chlorpheniramine), 10–20 mg i.v.
- Hydrocortisone, 100–300 mg i.v.
- Arterial blood gases

Investigations
- Plasma tryptase
- Urinary methylhistamine

Also consider
- Primary myocardial/cardiovascular problem
- Latex sensitivity
- Airway obstruction
- Asthma
- Tension pneumothorax
- Panic attack

2

Immediate management
- Check the airway, breathing and circulation. Stop the administration of or exposure to any potential triggers, particularly intravenous agents. Muscle relaxants, antibiotics and NSAIDs (and increasingly latex) are the most common triggers in an anaesthetic environment. Outside the operating theatre, foods (especially nuts, fish, shellfish, eggs and milk), insect venom, drugs (antibiotics, NSAIDs, contrast media, opioids) and latex are the most common precipitants.
- Call for help.
- Maintain the airway and give 100% oxygen. Reassess airway patency frequently and regularly, especially in known asthmatics and in those exposed to the allergen via the airway or mouth. If in doubt and the reaction is severe, intubate early because it may be impossible to do so later in the presence of increased oedema.
- Cardiovascular collapse is most likely following parenteral exposure to the allergen. Lay the patient flat with the legs elevated to increase central venous return.
- If the patient has a continuous ECG monitor attached, give adrenaline (epinephrine) in 50 μg i.v. increments (0.5 ml of a 1:10,000 solution) at a rate of 100 μg/minute until the blood pressure or bronchospasm improves. Alternatively, give adrenaline (epinephrine) 0.5–1 mg i.m. as 0.5–1.0 ml of a 1:1000 solution (repeated after 10 minutes if necessary). Adrenaline (epinephrine) stabilizes mast cell membranes, increases myocardial contractility, causes bronchodilatation and reverses vasodilatation; it therefore treats both cause and effect.
- Give intravenous fluid (colloid or suitable crystalloid), 20 ml/kg.
- Latex allergy may take up to 30 minutes to manifest itself. Removal of all latex triggers can then be a complex process. Allergen is more readily absorbed across mucous membranes (e.g. from surgical gloves or a urinary catheter, which should be removed immediately and hands should be re-washed to remove latex-impregnated starch granules). Inhalation of aerosolized particles within the breathing circuit is minimized by the use of an airway filter. Ensure that rubber 'corings' are not introduced intravenously (e.g. ampoule bungs and injection sets). Laryngeal mask airways are made of silicone and do not contain latex. *Diprivan* syringe bungs are also latex free.

Subsequent management
- Give an antihistamine (H_1-blocker) such as chlorphenamine (chlorpheniramine, *Piriton*), 10–20 mg by slow i.v. or i.m. injection. Consider H_2-antagonists, such as ranitidine, 50 mg slow i.v. injection.
- Give corticosteroids such as hydrocortisone, 100–300 mg by slow i.v. or i.m. injection, to inhibit later relapses.
- Give a catecholamine infusion because cardiovascular instability may last for several hours. Consider adrenaline (epinephrine) 0.05–0.1 μg/kg/minute (e.g. 4 ml/hour of 1:10,000 for a 70 kg adult) or noradrenaline (norepinephrine) 0.05–0.1 μg/kg/minute (e.g. 4 ml/hour of a solution of 4 mg made up to 40 ml in 5% dextrose for a 70 kg adult).
- Check arterial blood gases for acidosis and consider giving bicarbonate, 0.5–1.0 mmol/kg (8.4% solution = 1 mmol/ml).
- Check for the presence of airway oedema by letting down the tracheal cuff and confirming a leak before extubation.
- Consider bronchodilators for persistent bronchospasm (e.g. salbutamol, 5 mg by nebulizer or 250 μg slow i.v. injection, aminophylline 250–500 mg slow i.v. injection).

Complications

Hospital mortality to anaesthetic drug-induced anaphylaxis is 4%, despite the presence of good resuscitation facilities. Over half of those who die of anaphylaxis do so within the first hour. The deaths are related to asphyxia, from severe bronchospasm or upper airway obstruction, and from refractory hypotension.

The early use of adrenaline (epinephrine) is advisable but advice differs over the safest and most appropriate mode of administration. Adrenaline (epinephrine) is best administered by intramuscular injection (0.5 mg – usually 0.5 ml of 1:1000 solution) by first responders because it is a reliable means of achieving therapeutic plasma concentrations quickly and safely. The subcutaneous route is slow and unpredictable and is inappropriate during an acute life-threatening reaction. Anaesthetists often opt for intravenous administration of a 1:10,000 solution in incremental doses (of 50–100 μg). The intravenous route, while rapidly effective, can result in tachydysrhythmias. Cardiac complications are more common in the presence of hypoxia, hypercapnoea, and in patients taking tricyclic antidepressants or cocaine.

Patients taking β-blockers are likely to suffer more severe reactions and may be resistant to treatment with adrenaline (epinephrine). However, β-blockers are competitive antagonists and careful but continued titration of adrenaline (by sequential doubling of the initial dose in severe cases) should achieve a clinical effect.

Late diagnosis may be complicated by severe compromise of the airway and difficulty intubating the trachea.

Investigations

Investigations should be carried out when the patient has been stabilized.

Plasma tryptase: at least one 10 ml clotted blood sample should be taken 1–6 hours after the start of the reaction to perform a tryptase assay. The specimen must be spun down as soon as possible and the serum stored at –20°C, to stabilize the protein for later analysis. Tryptase is the main protein released during mast cell degranulation and is a specific marker of histamine release due to anaphylaxis or anaphylactoid reaction. Normal basal levels of serum tryptase are less than 1 ng/ml. However, unlike histamine, which is rapidly eliminated, tryptase levels remain elevated for up to 6 hours after an anaphylactic reaction. It is not a protein that is produced by RBCs or WBCs and is therefore not raised by haemolysis. Levels over 20 ng/ml may accompany an anaphylactic reaction.

Elevated metabolites in the form of urinary methylhistamine may also be measured. The value measured has to be corrected for urinary creatinine but levels in excess of 15–20 ng/ml/mmol creatinine/litre are considered higher than normal, and may indicate anaphylaxis.

Radio allergosorbent testing (RAST) is a means of searching for antigen-specific IgE in the serum. Tests are limited to specific allergens. At present only a few anaesthetic RASTs are available (e.g. suxamethonium). Fluoroimmunoassay is an alternative (*CAP System*, Pharmacia).

Follow-up and prognosis

The anaesthetist should follow up the investigation, report reactions to the Committee on Safety of Medicines via the 'yellow card' reporting scheme, and arrange skin prick testing in consultation with an immunologist. Having identified allergens, the patient should be advised to wear an alert bracelet at all times. Those who have suffered a severe reaction, especially anaphylaxis to allergens that are commonly encountered in everyday life, may be advised on how to carry and when to administer their own adrenaline (epinephrine). The *Epipen* syringe is preloaded with adrenaline (epinephrine) and will deliver a fixed intramuscular injection of 300 µg (0.3 ml of 1:1000) for adults or 150 µg for children.

Desensitization is a process that attempts to stimulate the production of IgG or IgA antibodies that competitively bind to the antigen and help block the IgE antibody–antigen hypersensitivity reaction that precipitates anaphylaxis. It is not without risk because it involves repeated inoculation with small doses of antigen.

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Recognition of Correct Placement of Tracheal Tubes

Simon Berg

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The technique of tracheal intubation is fundamental to anaesthetic practice. Critical incident reporting indicates that oesophageal intubation is a relatively common problem. Misplacement of a tracheal tube is not in itself harmful if the diagnosis is made promptly and corrective action taken. However, tracheal tube misplacement still accounts for a large proportion of anaesthetic deaths. It should be considered in any hypoxic intubated patient. Failure to detect incorrect tube placement is equally common for trainees and consultants. It is as likely with routine as with difficult intubation.

Methods of confirming correct tube placement

Clinical signs are often unhelpful in detecting tube misplacement and intubation should be confirmed by:

- direct visualization of the tube passing through the vocal cords
- auscultation over both axillae, lung bases and the epi-gastrium
- capnography
- oesophageal detector device or colorimetric detector if capnography is not readily available.

Visualization of larynx

The larynx is usually visualized and the tracheal tube is observed passing between the vocal cords into the trachea. However, a view of the larynx is not always possible. In routine laryngoscopy, an anaesthetist may become distracted at the moment of intubation, allowing the tube to slide past into the oesophagus. Occasionally the oesophagus may be mistakenly identified as the trachea or the tube may become displaced during fixation. Direct visualization is thus not totally reliable and may even delay a diagnosis of tube misplacement by promoting a false sense of security.

Repeat laryngoscopy is essential if a tube problem is suspected; oesophageal intubation, extubation or a kinked tube can all be identified and remedial action taken.

Chest movement

Bilateral symmetrical chest wall expansion should occur coincident with inspiration. It may be difficult to discern in the obese patient, in those with a rigid chest wall, or in chronic lung disease (e.g. emphysema). Oesophageal ventilation may imitate chest movement by expansion of the mediastinum, while gastric distension can simulate diaphragmatic and lower chest wall ventilation, especially in infants.

Auscultation

The combination of auscultation over each axilla, lung base and epigastrium achieves the most reliable results. Direct auscultation over the trachea may be of additional benefit; more obvious breath sounds can be heard, which are less likely to be confused with oesophageal ventilation.

Breath sounds over the chest wall do not always exclude oesophageal intubation. Air ventilating the oesophagus can be transmitted through the lungs to resemble convincing breath sounds. Conversely, breath sounds may be inaudible in the obese patient.

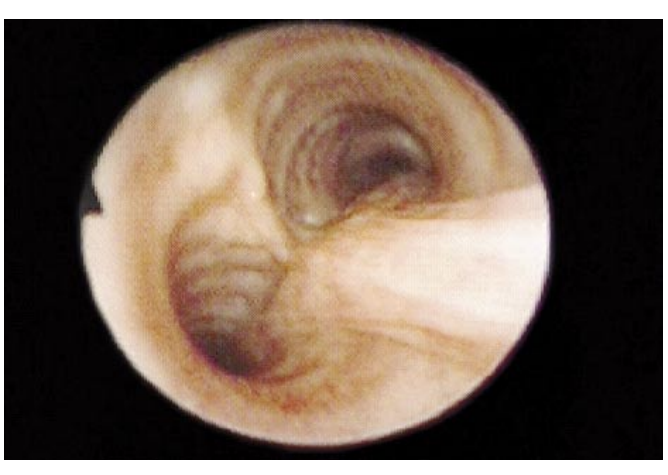
Breathing circuit

The ability to ventilate the lungs via the reservoir bag together with its typical compliance characteristics is a useful sign for the anaesthetist. In a spontaneously breathing patient the bag should empty and refill synchronously with the patient's breathing pattern. However, small movements (cardiac oscillations) can be demonstrated with oesophageal tube placement.

In contrast, it may be difficult to ventilate a morbidly obese patient via the reservoir bag or to differentiate between oesophageal intubation and partial or complete bronchospasm.

Fibre-optic laryngoscopy

The fibre-optic bronchoscope or laryngoscope can reliably confirm tracheal tube placement by identification of the tracheal rings and carina under direct vision (Figure 1). The technique requires operator experience and the equipment must be readily available.



1 View of the carina via a fibrescope, confirming the correct placement of the tracheal tube.

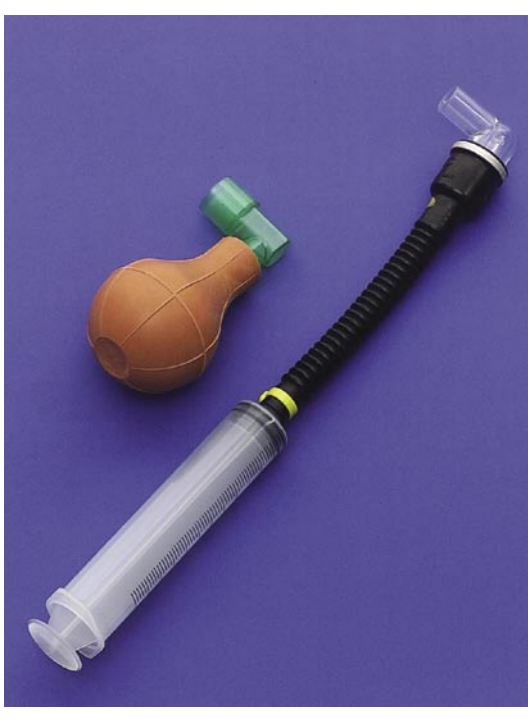
Oesophageal detector device

The Wee oesophageal detector device (ODD) consists of a 60 ml bladder syringe connected to a catheter mount. This is attached to the tracheal tube following intubation. The syringe freely aspirates gas from the patient's lungs if the tube is in the trachea (negative result). However, if this negative pressure is applied to a tube within the oesophagus, the oesophageal wall collapses and no air can be aspirated (positive result).

As a modification, the syringe has been replaced by a large rubber bulb (Ellick's evacuator) to enable the device to be used one-handed (Figure 2). In this case the bulb is first emptied and then failure to refill indicates oesophageal intubation.

The ODD is cheap, simple to construct, easy to use and reliable. It has been validated in several studies with only a small incidence of false-positive results, possibly related to endobronchial intubation or secretions blocking the lumen of the tracheal tube; there are no reported false-negative results.

It has been used successfully with uncuffed tubes in older children but is unreliable in those under 2 years of age.



2 Oesophageal detector device with Ellick's evacuator modification.

Capnography

Capnography is the real-time detection of carbon dioxide in the breathing gases and its display as a waveform that plots concentration versus time. Carbon dioxide is detected by infrared spectroscopy. It is the gold standard for verifying tracheal intubation. The guidelines of the Association of Anaesthetists state that during induction of anaesthesia, capnography is 'essential to the safe conduct of anaesthesia'.

For carbon dioxide to be detected, it must be produced in the tissues, then transported to the lungs, and finally exhaled in the expiratory gas. The capnograph is therefore an important monitor that gives information about:

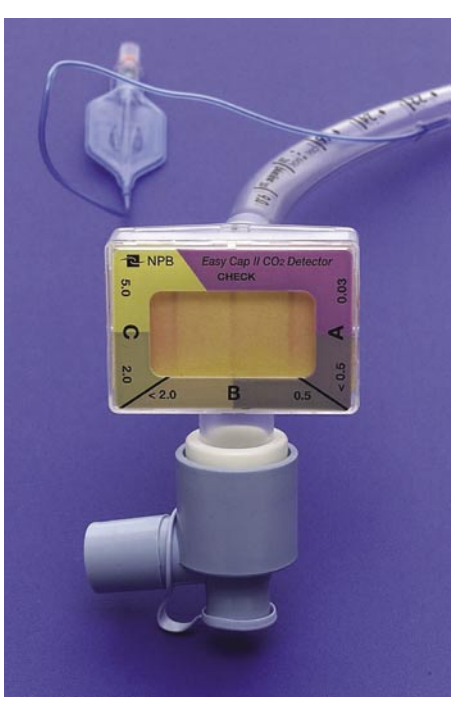
- metabolic rate
- pulmonary perfusion
- alveolar ventilation.

If metabolic rate and pulmonary perfusion (or cardiac output) are constant, then changes in the capnograph trace reflect the adequacy of alveolar ventilation.

Deceptively low values may result from a large leak around the tube. Gas arising from the stomach and oesophagus usually contains only a trace of carbon dioxide, but false-positive results occur if expired alveolar gas is introduced into the stomach from mask ventilation. Significant concentrations of carbon dioxide have been reported following ingestion of carbonated drinks ('cola complication'). In these circumstances, capnography following oesophageal intubation initially resembles the normal waveform for end-tidal carbon dioxide. This initial value rapidly diminishes towards zero as the carbon dioxide is washed out. It has been suggested that the waveform should be observed for a minimum of six breaths.

Colorimetric carbon dioxide detector

This small disposable device contains a pH-sensitive indicator that displays a colour change (e.g. from purple to yellow) when exposed to carbon dioxide (Figure 3). The colour change is rapid and the detector can be left in the breathing circuit for several hours allowing continuous ventilatory monitoring. The device is about the same size and weight as a heat/moisture exchange filter and requires no power source for operation. This portability makes it useful during cardiopulmonary resuscitation or in emergency situations when capnography may not be available. Reduced carbon dioxide concentrations often present in these clinical situations, which may reduce its sensitivity.



3 Colorimetric carbon dioxide detector.

Complications of oesophageal and endobronchial tube placement

Oesophageal intubation

Undetected oesophageal intubation is a major anaesthetic cause of permanent neurological damage and death. There should be a high index of suspicion in any situation in which hypoxia develops following intubation; the onset may be delayed if preoxygenation has occurred. Difficulty in ventilation, poor or absent chest movement, inaudible breath sounds and increasing abdominal distension should all alert the anaesthetist to the possibility of tube misplacement. In practice, clinical signs are not always obvious.

Progressive gastric distension may cause regurgitation and subsequent aspiration. Splinting of the diaphragm impairs ventilation even after the patient has been correctly intubated unless the stomach is actively decompressed using a nasogastric or orogastric tube.

If there is any doubt as to correct tube placement, it is essential to remove the tube and recommence mask ventilation.

Endobronchial intubation

Endobronchial intubation is more common in children owing to the smaller length of the trachea. Flexion or extension of the neck can move the tube a significant amount within the trachea (up to 5 cm in adults), leading to endobronchial intubation or inadvertent extubation. The right main bronchus is more commonly intubated than the left side because it arises at a straighter angle from the trachea.

One-lung ventilation causes hypoxaemia due to the shunt effect that failure to ventilate the opposite lung produces. Progressive lung collapse of this unventilated side occurs. There is a reduced uptake of volatile anaesthetic agent and bronchospasm is a common occurrence, probably as a result of vagal stimulation from irritation of the carina.

The diagnosis may be obvious with asymmetric chest movement and absent breath sounds on one side of the chest, but clinical signs are often unreliable. With an uncuffed tube, breath sounds can easily be transmitted to the non-ventilated lung. A chest radiograph confirms the diagnosis and provides an estimate of the distance that the tube needs to be withdrawn. Fibre-optic bronchoscopy can also be useful.

The chances of endobronchial intubation can be lessened by cutting tracheal tubes to an appropriate size (e.g. 22–24 cm in the adult) preceding intubation. The black marker line present at the distal end of some tracheal tubes can also serve as a guide to the length of the tube to be passed through the vocal cords.

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Regurgitation, Vomiting and Aspiration

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Regurgitation is the passive movement of gastric contents into the pharynx. The lower oesophageal sphincter normally prevents regurgitation. The sphincter is a physiological, rather than a distinct anatomical structure. Reflux is prevented because the lower oesophageal pressure is greater than the gastric pressure. This is referred to as the barrier pressure.

Vomiting is an active reflex usually occurring in the lighter planes of anaesthesia (i.e. induction and emergence). It is the forceful ejection of the contents of the upper gastrointestinal tract through the mouth. It is often secondary to stimulation from inappropriate airway manipulation.

The afferent limb of the reflex arc is composed of fibres from the gastrointestinal tract, the vestibular system, or from the chemoreceptor trigger zone in the brain stem. The vomiting centre' in the brain stem coordinates the reflex. The efferent limb involves autonomic outflow to the gastro-intestinal tract and also produces widespread effects such as pupillary dilation, sweating, salivation, vasoconstriction and tachycardia.

Pulmonary aspiration of gastric contents into the lungs is a serious, though infrequent, complication of modern anaesthesia. Mendleson first described it in detail in 1946 in 66 obstetric patients. Aspiration occurs following gastro-oesophageal regurgitation or vomiting when protective laryngeal reflexes are depressed or absent. Prevention of pulmonary aspiration is by measures aimed at reducing the incidence of regurgitation and vomiting.

Although silent regurgitation is thought to occur in up to 25% of patients under anaesthesia, the incidence of significant pulmonary aspiration in the general surgical population is much less at 1–6/10,000. For obstetric general anaesthesia the incidence is doubled. The mortality following aspiration is about 5%.

Pathophysiology

The adverse effects of pulmonary aspiration occur by three mechanisms.

Particle related – this could result in acute airway obstruction.

Acid related – the traditional view is that patients are 'at risk' if the gastric contents consist of a critical volume of more than 25 ml and have a pH of less than 2.5; there is little clinical evidence to support this. pH is the more critical factor for lung injury sustained following aspiration though there may not be an exact cut-off value. Significant morbidity can occur following inhalation of material with a very low pH even in small volumes due to chemical pneumonitis, and following large volumes of neutral fluid due to a 'near drowning' effect.

Bacterial related – aspirated fluid is not sterile and lung infection may result. Damaged lung is also more prone to secondary infection.

Risk factors

Predisposing factors for pulmonary aspiration are shown in Figure 1. Vomiting and regurgitation during induction of anaesthesia occur most often in emergency cases with acute abdominal pathology or following trauma. Pain, fear, anxiety and opioid administration all delay gastric emptying. These patients should be regarded as at high risk and appropriate precautions taken. The interval between last oral intake and time of injury in trauma patients is said to give a better guide to gastric emptying than the duration of fasting. In practice this is unreliable and it is often best to assume patients have a full stomach.

Risk factors for aspiration

Condition	Examples
Full stomach	Inadequate preoperative fasting Gastrointestinal obstruction, bleeding or ileus Trauma, burns, pain, anxiety Pregnancy Drugs (e.g. opioids)
Reduced lower oesophageal sphincter function	Hiatus hernia Drugs (e.g. opioids, atropine) Pregnancy Raised intra-abdominal pressure Obesity Lithotomy position
Material in oesophagus/ pharynx	Achalasia, scleroderma Strictures, carcinoma Pharyngeal pouch
Depressed laryngeal reflexes	Reduced consciousness (e.g. general anaesthesia, drug or alcohol intoxication, cerebrovascular accident, head injury, seizures or postictal state) Topical anaesthesia Neurological disease (e.g. myasthenia, multiple sclerosis, Parkinson's disease, Guillain–Barré syndrome) Muscular dystrophies
Others	Inexperienced anaesthetist Night-time surgery Emergency surgery Extremes of age

Obstetrics
In the third trimester, the enlarged uterus increases intra-abdominal pressure and therefore intra-gastric pressure. Before this, there is an increased risk of aspiration due to the production of:

- gastrin from the placenta, which increases gastric acid secretion
- progesterone, which relaxes smooth muscle and reduces gastrointestinal motility.

Anatomical changes in late pregnancy may increase the incidence of airway difficulties and thus of aspiration (e.g. increased body weight, large breasts, upper airway oedema). Surgery often occurs 'out of hours' as an emergency. Risks may be increased further during labour from the effects of pain, anxiety and opioid administration. Pregnant patients should be assumed to have a full stomach from the end of the first trimester until at least 18 hours post-partum. Regional anaesthesia should be used whenever possible to reduce the aspiration risks.

Prevention

Methods to prevent pulmonary aspiration are directed towards reducing the volume and increasing the pH of the stomach contents. The technique of cricoid pressure and induction of anaesthesia in the patient with a full stomach is elsewhere.

Fasting requirements
Traditionally, patients were fasted overnight before elective surgery. More recently it has been shown that the administration of clear fluids (e.g. water, non-particulate juice) up to 2–3 hours preoperatively does not increase residual gastric volume or alter pH. This increases patient comfort and reduces dehydration and hypoglycaemia in infants. An example of current fasting guidelines for elective, nonobstetric patients is shown in Figure 2.

Fasting requirements are less straightforward for emergency surgery. It is often necessary to provide anaesthesia to patients suspected of having a full stomach. Delaying urgent surgery to reduce the possibility of aspiration is usually of no benefit and may be detrimental. Patients requiring emergency surgery should be assumed to have a full stomach, irrespective of the duration of fasting, because gastric emptying is likely to be delayed. Following painful trauma, a significant gastric residue can be present after 24 hours. It is not currently recommended that emergency patients be allowed to drink clear fluids before surgery. Intravenous therapy should be used to prevent dehydration. At present there is no consensus regarding fasting during labour.

Preoperative fasting guidelines for patients undergoing elective surgery

	Length of fast (hours)
Adults	
• Solid food	6
• Clear fluid	2–3
Children	
• Solid food	6
• Formula milk	4
• Breast milk	3
• Clear fluid	2

Regional anaesthesia
Avoiding general anaesthesia reduces the risk of pulmonary aspiration. Both the proposed surgery and the patient must be amenable to the technique. The patient should be fasted because an inadequate or failed regional block, or adverse reaction, may make general anaesthesia necessary.

Gastric decompression
The insertion of a nasogastric tube to decompress the stomach may be useful. Liquid, but not solid, gastric contents can be aspirated via the tube. It is not usually possible to empty the stomach completely by this means, so the possibility of aspiration remains. If a nasogastric tube has been passed before surgery, it should be aspirated before induction. Effective cricoid pressure can be performed with the tube *in situ*.

Pharmacotherapy
Antacids: prophylactic administration of antacids to high-risk patients is recommended. These drugs neutralize gastric acid and raise gastric luminal pH. Neutral pH aspirate causes less lung damage than fluid of acidic pH. Antacids should be non-particulate to reduce the potential for lung damage if inhaled. 0.3 M sodium citrate, 30 ml, is effective in elevating the pH of gastric contents if given 15–20 minutes preoperatively; it remains effective for 1–3 hours. Antacids are used routinely in elective and emergency obstetric anaesthesia, but less often in the general surgical population.

H_2-receptor antagonists reduce the volume and acidity of gastric contents by the inhibition of hydrochloric acid secretion from gastric parietal cells. Cimetidine, 400 mg orally 90–120 minutes before induction, and ranitidine, 150 mg orally 120 minutes before induction, 50 mg intramuscularly or slow intravenous administration 45 minutes before induction, are commonly used H_2-antagonists. Ranitidine has a duration of action of at least 8 hours; about twice as long as cimetidine. It is also associated with fewer side-effects. Side-effects with cimetidine, though infrequent, include sedation and confusion, and the potentiation of other drugs through inhibition of hepatic enzymes. Hypotension, bradycardia and even cardiac arrest can follow rapid intravenous injection of cimetidine, and also of ranitidine, though ranitidine has a much lower incidence.

Prokinetics: metoclopramide, 10 mg orally 1–4 hours before surgery or intravenously shortly before induction, acts centrally and peripherally to stimulate gastric emptying, increases lower oesophageal sphincter pressure and is anti-emetic. Its central action is due to its antidopaminergic properties whereas peripherally it stimulates acetylcholine release, resulting in increased gastrointestinal motility.

Proton pump inhibitors: omeprazole, 40 mg orally at night and on the morning of surgery, inhibits the proton pump in the parietal cells of the gastric mucosa, resulting in prolonged suppression of acid secretion. It elevates gastric pH. Combining omeprazole with metoclopramide reduces gastric volume. It is seldom used in the UK despite proven effectiveness.

Anticholinergics (e.g. atropine, glycopyrollate) can decrease gastric acid secretion, but have an adverse effect on barrier pressure by decreasing lower oesophageal pressure. They are not used for aspiration prophylaxis.

Induction of anaesthesia
If general anaesthesia is chosen, a cuffed tube in the trachea should secure the patient's airway. The airway should be assessed to predict whether this is likely to be difficult. The laryngeal mask airway has become popular in modern anaesthetic practice, however, it does not protect the airway from aspiration of gastric contents as efficiently as a cuffed tube and should not be used routinely in patients at high risk.

Uncuffed tubes are used in children because the paediatric airway narrows at the cricoid ring. Uncuffed tubes prevent tracheal mucosal damage by excessive cuff pressure, and may allow passage of a slightly larger tube size permitting improved gas flow. There is no precise age or size at which cuffed tubes are chosen, but use of uncuffed tubes in children below 8–10 years is usual. The absence of a cuff may imply the theoretical risk that aspiration can still occur, although satisfactory airway protection still occurs in clinical practice.

Position:there is controversy regarding the optimum position for induction of anaesthesia in the patient at risk of pulmonary aspiration. Some anaesthetists argue in favour of a head-up (reverse Trendelenburg) or semi-sitting position, because this may reduce the incidence of reflux in patients prone to passive regurgitation. Others favour a head-down (Trendelenburg) position with the patient on their side, because this may decrease the likelihood of aspiration should regurgitation occur.

Patient safety is paramount and therefore clinicians should induce anaesthesia in the position in which they have the most experience and confidence. This will usually be a rapid sequence induction in the supine position.

Rapid sequence induction: if the anaesthetist is confident that tracheal intubation will be straightforward then an intravenous rapid sequence induction performed with cricoid pressure is indicated. Aspiration is most likely to occur in the time from loss of consciousness to intubation with a cuffed tracheal tube. Rapid sequence induction reduces this time to a minimum.

Awake intubation: if a difficult intubation is anticipated consideration should be given to securing the airway before induction. In modern practice this involves topical local anaesthesia to the airway, and intubation via a flexible fibre-optic laryngoscope. A 'blind nasal' technique used to be popular, but the arrival of modern fibre-optic instruments has allowed awake intubation to be performed under direct vision.

Inhalational (gaseous) induction may be indicated in a patient considered at risk from aspiration, in whom conventional laryngoscopy and intubation is predicted to be difficult and where awake intubation attempts may be hazardous (e.g. acute stridor, maxillofacial trauma). There is a trade-off between taking steps to prevent aspiration during induction, and maintaining and securing the airway. A senior anaesthetist should manage these cases and patient safety is paramount.

Extubation should be performed with the patient awake and following the return of upper airway protective reflexes. It is often safest to position the patient on their side with head-down tilt to facilitate clearance of the upper airway using suction, should regurgitation occur.

Diagnosis

Clinical signs and symptoms of aspiration are variable (Figure 3) and it is sometimes difficult to make a definitive diagnosis. 'Silent' aspiration may occur, and may not be diagnosed until after surgery when the patient has returned to the ward. The initial and most reliable sign of aspiration is hypoxia, which occurs following even mild cases. Wheezing is also common. In severe cases an acute respiratory distress syndrome can result. In such patients there is increased intrapulmonary shunting, ventilation–perfusion (V/Q) mismatch, increased lung water, increased airway resistance and reduced lung compliance. Although aspiration classically affects the posterior aspect of the right lower lobe, radiographic changes are variable, nonspecific and may be absent, particularly in the first few hours. The most usual findings are irregular fluffy den-sities, frequently bilaterally, collapse or pulmonary oedema (Figure 4).

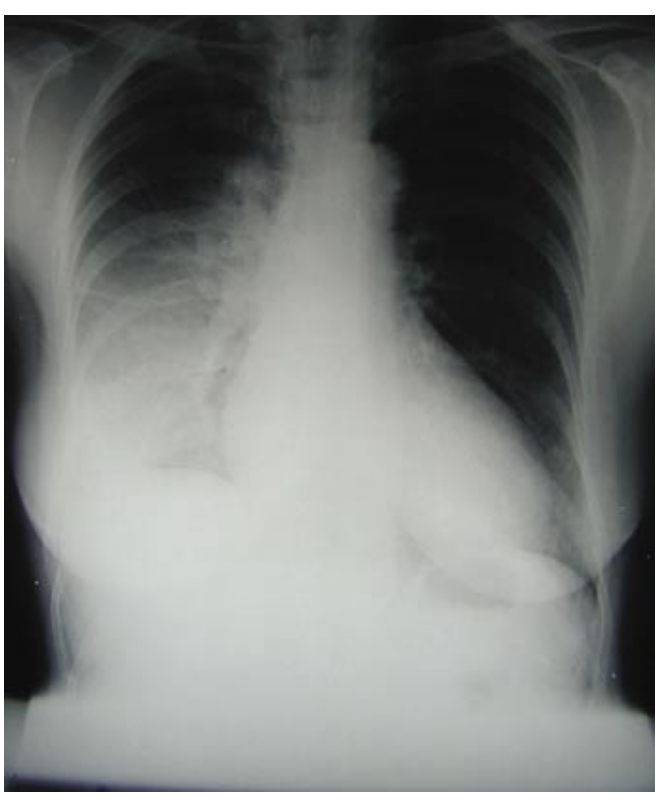
Differential diagnoses include anaphylaxis, cardiac failure, pulmonary embolism, fat embolism, sepsis and, in obstetric patients, amniotic fluid embolism.

Signs and symptoms of pulmonary aspiration

Symptoms
- Cough
- Breathlessness

Signs
- Stomach contents in oropharynx
- Tachypnoea
- Wheeze, crackles (mainly coarse)
- Cyanosis
- Tachycardia
- Pulmonary oedema
- Increased airway pressure
- Radiographic changes

3



4 Typical radiographic appearance of the chest in a patient with aspiration.

Management

If acute aspiration occurs the following procedure should be carried out.
- Place the patient in a head-down position, with head turned to one side.
- Suction material from the oropharynx.
- Administer 100% oxygen.
- Intubate the trachea if:

– adequate oxygenation cannot be maintained with spontaneous ventilation
– further tracheobronchial suction is required
– the patient is unable to protect their own airway.

The decision to continue with surgery depends on the severity of the aspiration and the urgency of surgery.

The management of established aspiration is largely supportive. Treatment is described in Figure 5.

Management of established aspiration

Oxygen therapy
- Guided by blood gas estimations or pulse oximetry

Ventilatory support
- Spontaneous ventilation may be adequate in mild cases
- Continuous positive airway pressure can be used for more severe cases, but requires alert, cooperative patient at no further risk of aspiration
- For severe cases, or those who cannot maintain a patent airway, mechanical ventilation via a tracheal tube is indicated
- Positive end-expiratory pressure is applied to increase functional residual capacity of the lung and minimize intrapulmonary shunting

Removal of aspirate
- Regular suctioning and physiotherapy are needed
- Bronchoscopy is required in more severe cases

Bronchodilators
- Given regularly by nebulizer

Antibiotics
- No proven benefit from prophylactic use
- Antibiotics often prescribed before identification of any pathogens

Fluid balance
- Shifts of fluid from the circulation to the lungs can result in pulmonary oedema
- Central venous pressure and urine output monitoring help guide fluid management
- A positive fluid balance worsens gas exchange and should be avoided

Corticosteroid therapy
- Routine use of corticosteroids is not indicated – no current evidence has shown benefit from their use

5

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Surgical Diathermy: Mechanisms, Use and Abuse

Andrew D Farmery

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The application of heat to wounds is evident in unearthed Neolithic skulls. Thermal cautery to ulcers and tumours of the breast was described in a papyrus from about 3000 BC, and later described by Hippocrates in 300 BC. Electrical diathermy is at least 250 years old, predating the practice of anaesthesia by a century.

Diathermy (*dia*, through; *thermy*, heat) strictly applies to the uniform heating of tissues by radiofrequency current or radiation. As a surgical tool, uniform heating is not required, but rather discrete and destructive heating in a specific area. This application is called 'electrosurgery' in the USA, and 'surgical diathermy' in the UK, but the term diathermy has remained.

Basic electrical principles

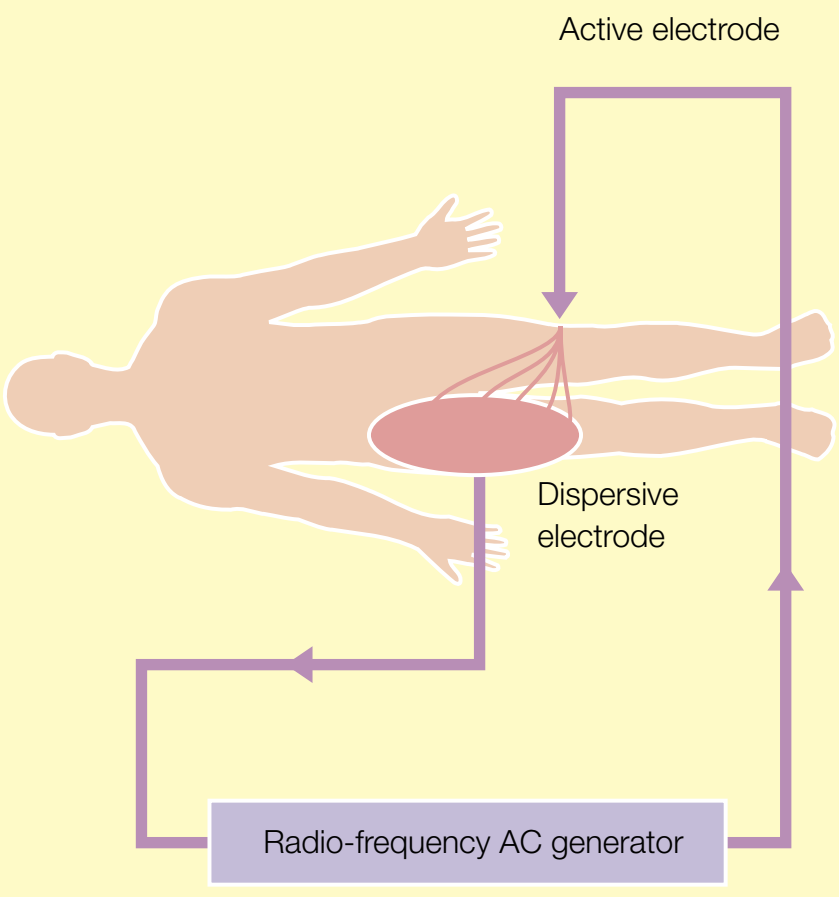
Forcing current through a resistance liberates heat

The power to heat, cut or vaporize tissues is derived from passing an electrical current through it. At any point in an electric circuit, the power dissipated is given by the formula:

$$\text{Power} = \text{Current}^2 \times \text{Resistance} \qquad (P = I^2 \times R) \quad 1$$

Current forced through regions of high resistance produces more heat than the same current passed through regions of low resistance. Figure 1 shows how the current density (and resistance) at the tip of a diathermy probe is many orders of magnitude higher than the current density elsewhere in the circuit, namely the patient's body and the large 'dispersive' electrode. This is analogous to a large crowd of people moving along a wide walkway to gain access to a football stadium. The flow is ordered and comfortable at the rear of the walkway, but when the same 'flow' is forced through a narrow turnstile, the 'power' of the crowd will be liberated (destructively) at this high resistance, high flow-density point.

Current density



The tiny active electrode/tissue contact has a high resistance, therefore a high power is liberated ($P = I^2 \times R$). Because this power is delivered to a small area, the power density, and ability to heat the tissue, is great. By contrast, the dispersive electrode, with its larger area of contact, has a low resistance and thus little power is liberated and it is distributed over a wide area, therefore the heating effect is negligible.

1

Using high-frequency alternating current prevents 'electrocution'

In Equation 1, both direct current (DC; e.g from a large battery) or alternating current (AC; e.g. from the mains supply) produce the same amount of heat for the same mean current. However, DC polarizes a tissue such that tissue connected to the anode becomes 'positive', and that connected to the cathode, 'negative'. This triggers ion channel opening and depolarizes important excitable tissues such as nerves, striated muscle and myocardium. The same is true of moderately low-frequency AC (e.g. 50 Hz), in which the tissue is alternately polarized and depolarized because the polarity of the applied voltage changes sinusoidally. This can result in convulsions, tetanic muscle twitch and ventricular fibrillation (i.e. electrocution).

High-frequency current is less prone to causing these phenomena because voltage-sensitive ion channels in excitable tissues do not respond instantly to an applied depolarizing voltage, but have a finite response time. An analogy is when the rudder of a tanker is turned suddenly, there is a delay before it slowly starts to change direction. If the rudder is turned from left to right with a low frequency, the tanker steers a course veering from left to right sinusoidally. However, if the rudder is oscillated from left to right with a high frequency, the ship steers a straight course because it does not have enough time to respond to a rudder movement in one direction before being directed to move in the opposite direction.

In the same way, a high-frequency AC voltage applied to the myocardium will neither polarize nor depolarize the membrane, because the ion channels will not have time to open or close before the polarity of the applied voltage is reversed and so the tissue will continue to function normally. Electrosurgical generators typically operate at frequencies of 0.5–4 MHz.

Surgical effects of diathermy

There are three main diathermy modes: desiccation, cutting and coagulation.

Desiccation

To cause desiccation (drying out), a low power current is passed through the tissues, as in Figure 1. The aim is to increase tissue temperature at the site of contact with the active electrode. Intracellular water is slowly driven off as steam and the tissue is dried out. This produces a blanching of tissue. Because the current is of low power, it is effective only in delicate tissues and small vessels (e.g. it is often used to blanch the fallopian tube before surgical division in laparoscopic sterilization). When tissue has been desiccated, its resistance to current flow becomes very high and current flow effectively ceases, thus terminating the heating process. It is impossible to 'cut' tissue in this mode. The current waveform is not important in this application.

Cutting

In the cutting mode, the aim is to make a discrete cut through the tissue. Initial contact with the electrode heats the tissue rapidly so that cells explode and their contents are instantly vaporized. Heat is not conducted very far from the site of contact because most of the liberated power is used to vaporize water (i.e. is consumed as latent heat of vaporization). The heating effect is therefore concentrated and neighbouring tissue is undamaged. Unlike desiccation, 'sparking' is a key feature.

The vaporized desiccated tissue is a poor electrical conductor and therefore breaks the circuit so that current flow ceases through this pathway. However, if the voltage (the driving force for current) is high enough, air around the electrode is ionized. Ionized air is a better conductor than desiccated tissue, and so current will now flow as a spark jumps to the nearest region of moist tissue. Tissue heating is produced by:

- current delivered by the spark ($I^2 \times R$)
- radiant heat from the spark
- collision of electrons bombarding the tissue.

This causes intense local heating, vaporization and thermal destruction. Cells are torn apart. The current waveform used is a continuous radiofrequency sinewave (Figure 2a).

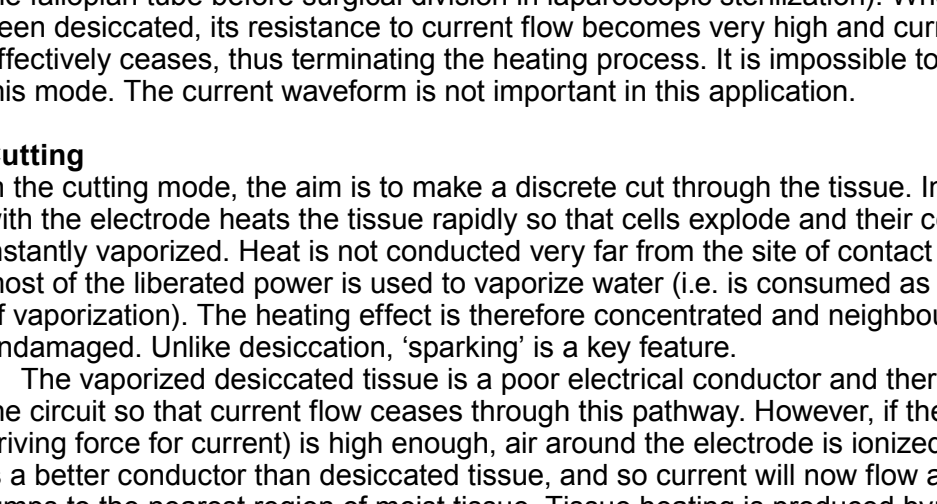
Coagulation

In coagulation mode (Figure 2b), the current waveform comprises short bursts of radiofrequency sinewaves (about 1 MHz), with bursts occurring about 20,000 times per second (burst frequency 20 kHz). The coagulation waveform can cause sparking to tissues. However, the radiofrequency current is delivered in intermittent bursts and therefore the ion cloud generated at each spark has a chance to disappear between bursts. Therefore, with each current burst, ionization occurs afresh, and because this is a random process sparking occurs more randomly and over a wider area than it does in cutting mode. This reduces the concentration of the sparking power and allows effective coagulation of vessels without tissue cutting. Peak voltages are much higher in the coagulation mode than in the cut mode because the current is zero for most of the time and so in order to deliver the same average power, the coagulation waveform generator has to deliver more power in the short periods when current is switched on.

Waveforms

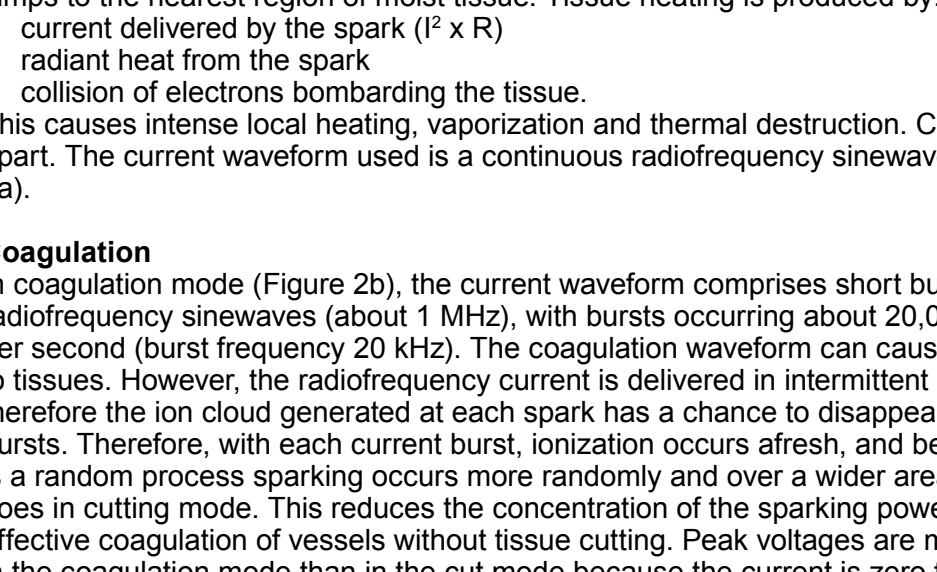
a Cutting waveform

A continuous radiofrequency sinewave of about 1 MHz



b Coagulation waveform

A 1 MHz sinewave delivered in bursts (20,000/second)



2

Monopolar and bipolar systems

Monopolar

The system described in Figure 1 is monopolar. Current is delivered via a pinpoint active electrode, which then passes through the patient (in a low-density path) to return via the dispersive electrode. This is the most widely used system because it is most effective in producing cutting as well as coagulation.

Bipolar
In a bipolar system, current is delivered via one arm of a pair of insulated forceps. It passes through any tissue grasped between the arms of the forceps and returns via the opposite arm. With a bipolar system, only desiccation can be achieved. The system is of limited power, and sparking does not occur. If the arms of the forceps are allowed to make contact with each other directly, despite there being some tissue in the path, current will be 'shorted-out', and diathermy will be less effective. Bipolar diathermy is indicated where it is undesirable to pass current through the patient's body to a distant dispersive electrode; some examples are given below.

Narrow current conduits to extremities (e.g. testicle surgery) – if a monopolar system were used, with the dispersive electrode placed on the abdominal wall, current would be forced to pass from the testicle along the vas deferens (the path of least resistance) to the trunk. Because the vas deferens is a narrow tube, current density would be high within it, and thermal injury might result.

Metal prostheses – if a metal prosthesis lies between the dispersive and active electrode, current preferentially passes through this low resistance route, producing a high current density and heating in narrow points such as a cortical screw. This may necrose bone or conduct heat to neighbouring soft tissue or vessels, sufficient to perforate an artery.

Cardiac pacemakers – the cable connecting a pacemaker generator box (implanted in the anterior chest) to the electrode in the right ventricle and/or atrium constitutes a low impedance pathway for radiofrequency current if it lies between the active and dispersive diathermy electrodes. This may result in a high current density at the point of pacemaker electrode insertion into the myocardium. Tissue desiccation may occur at this point, increasing the resistance of the contact. The 'threshold' potential may increase, such that the pacing pulse fails to trigger the heart.

More sophisticated pacemakers are capable of detecting intrinsic cardiac activity and withholding activation of the pacemaker. It is possible that stray radiofrequency current may be detected by the pacemaker, and interpreted as intrinsic cardiac activity, resulting in inappropriate inactivation of the pacemaker. For this reason, it is advisable, if possible, to have the pacemaker programmed so that this function is disabled. The safest precaution, however, is to avoid monopolar diathermy.

Patient safety

The principal issues are:
- avoidance of inadvertent thermal burns from stray diathermy current
- avoidance of inadvertent electrocution from stray 50 Hz mains current.

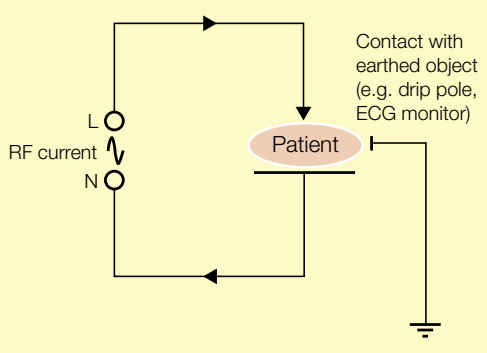
Isolated (unearthed) dispersive electrode system
Figure 3a shows a simple circuit in which neither live nor neutral terminals of the radiofrequency current generator are connected to earth.

A fundamental law of electricity is that all the current leaving the live terminal is returned to the neutral terminal. Therefore, if the patient makes contact with an earthed object (e.g. lithotomy pole, drip stand or faulty low impedance ECG electrode) none of the radiofrequency diathermy current should pass via this contact to earth because such a stray current would not be able to return to the neutral terminal. All the current should pass to the neutral terminal via the large dispersive electrode, thereby eliminating the potential for burns. This might seem a safe system but it is possible to burn patients inadvertently with isolated systems because of the phenomenon of 'capacitive coupling'. It is difficult to confine very high-frequency currents to wires, and currents tend to pass out of the cables like a radio transmitter because a wire and another conductor (e.g. earth) can behave like the two plates of a capacitor. Capacitors can conduct high-frequency current, even though insulation and a few feet of air separate the wire and earth. Radiofrequency leakage current flows only if there is a route for it to return to the neutral terminal; Figure 3b shows how this might happen. A certain amount of current from the active lead is leaked to earth via this capacitive coupling. This can return to the patient via any small, grounded contact point and potentially cause a burn at this site. From this point, the leakage current joins the main current and returns to the neutral terminal via the dispersive electrode.

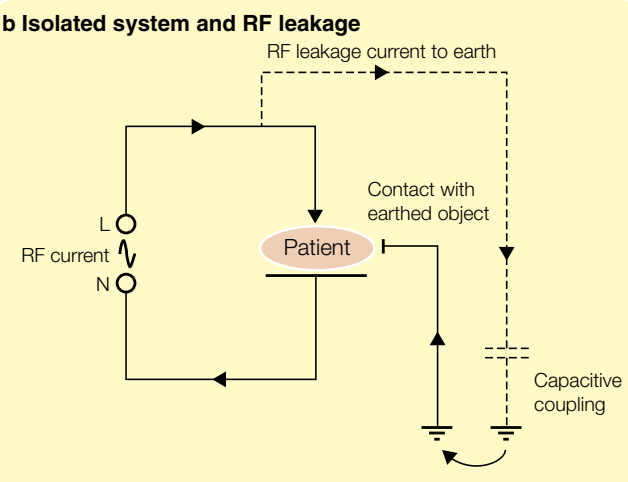
Early electrosurgical generators were not truly isolated. There was usually some connection of the neutral terminal and dispersive electrode cable to earth because of capacitive coupling between them, in a similar way to that described above. Figure 3c shows how this allows current to flow to earth through grounded contact points and complete the circuit to the neutral terminal via the 'virtual' earth connection. The amount of stray current passing through the grounded contact points depends on the relative impedance of the pathways. Given that one cannot avoid some current passing to ground, the best way to prevent this passing through unwanted pathways is to provide a route to ground via the dispersive electrode which is more 'attractive' than the alternative routes. This is done by physically earthing the dispersive plate and making the impedance of this connection as low as possible.

Isolated and earthed systems

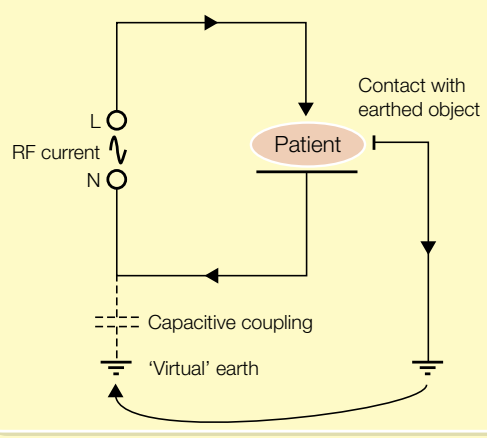
a Isolated system



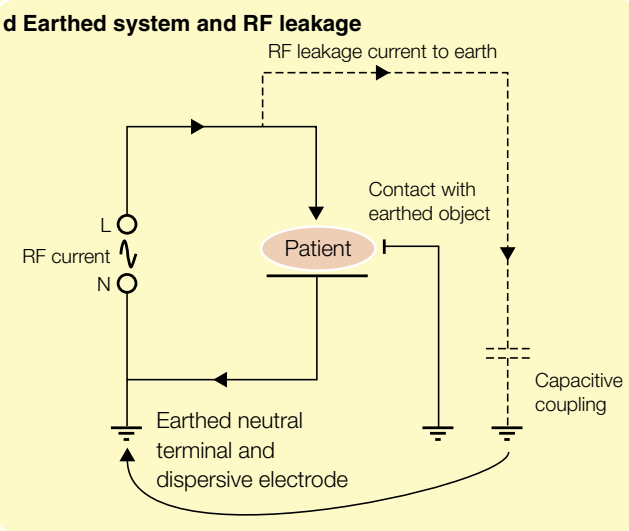
b Isolated system and RF leakage



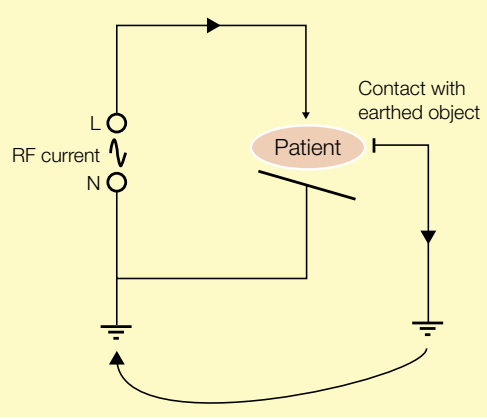
c Isolated system and 'virtual' earthing of dispersive electrode



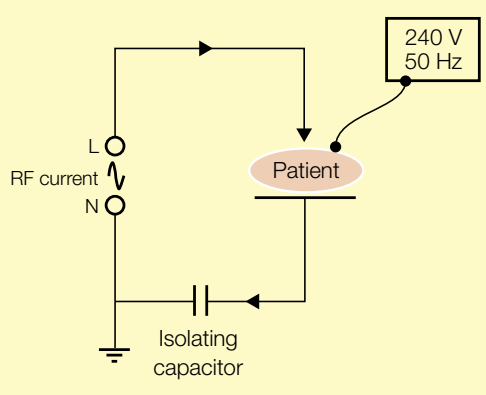
d Earthed system and RF leakage



e Earthed system and poor dispersive electrode contact



f Earthed system and isolating capacitor



L, live; N, neutral; RF, radiofrequency

Earthed dispersive electrode system
Earthing the dispersive electrode overcomes both the 'virtual' earth problem (Figure 3c) and the radiofrequency leakage problem (Figure 3b). Figure 3d shows how if the dispersive electrode and neutral terminal are earthed, any radiofrequency leakage current can return to the neutral terminal via a direct low impedance earth route that bypasses the patient. However, earthing poses other problems.

Dispersive electrode detachment: the dispersive electrode is an attractive route for ground-seeking radiofrequency current only if its impedance is many orders of magnitude lower than unwanted stray routes. If the dispersive electrode becomes detached or makes poor contact, all of the radiofrequency current can pass to earth (and hence return to the neutral terminal) via unwanted grounded contact point, as shown in Figure 3e, thus causing burns.

Mains electrocution: if the patient is exposed to a live mains voltage (e.g. via a faulty monitor lead) the earthed dispersive electrode provides a low impedance pathway for this dangerous 50 Hz current to pass through the patient to earth, thus causing electrocution. This is because mains voltage is ground seeking. This problem can be overcome by placing a capacitor in the circuit as in Figure 3f. This is capable of passing radio-frequency current, but does not conduct low frequency (50 Hz) current. Even though the patient is exposed to a live mains cable, no 50 Hz current will flow through the patient to the ground.

Techniques of Cricoid Pressure

Richard Vanner

Richard Vanner is Consultant Anaesthetist and Clinical Director in a large District General Hospital in the UK. He is a generalist with a specific interest in obstetric anaesthesia.

In 1956, the Association of Anaesthetists had collected 1000 reports of anaesthetic deaths; 110 from pulmonary aspiration of stomach contents. This often occurred during induction of general anaesthesia especially when muscle-relaxant drugs were used. Anaesthetic techniques were developed to prevent aspiration in patients at risk and included:

- emptying the stomach before induction
- intravenous induction with head-up tilt position
- inhalational induction in the lateral and head-down position.

In 1961, Sellick described cricoid pressure as a technique used to prevent regurgitation of stomach contents during the induction of general anaesthesia. It was brought into widespread practice in the UK by 1970 and largely replaced the other techniques, despite no randomized controlled trials demonstrating its benefit. It has become a routine part of anaesthetic practice for patients at risk of aspiration in combination with pre-oxygenation, an intravenous induction and tracheal intubation. All UK maternity units routinely apply cricoid pressure during induction of general anaesthesia.

Before the introduction of cricoid pressure, the incidence of aspiration pneumonitis in obstetric general anaesthetics was about 0.15%. If cricoid pressure prevents aspiration, the number needed to treat to prevent one case of aspiration would be 666. A controlled trial would be difficult because of the large numbers of patients needed and the difficulty of obtaining ethical approval.

Indications

In a patient who has been prepared for elective surgery and has not eaten for 6 hours or drunk for 2 hours, regurgitation of stomach contents during the induction of anaesthesia is unusual even when muscle-relaxant drugs are used, which relax the upper oesophageal sphincter. In these patients, cricoid pressure is unnecessary, because its benefits have to outweigh the risk of complications. However, cricoid pressure is indicated if:

- surgery is necessary before the patient is fasted
- gastric emptying is delayed
- the lower oesophageal sphincter is incompetent (e.g. in the last half of pregnancy or in reflux oesophagitis). With a full stomach from any cause, distention of the fundus causes reflex relaxation of the lower oesophageal sphincter.

Mechanism of action

Regurgitation is the flow of fluid from the oesophagus into the pharynx and is a passive process. When patients are awake the upper oesophageal sphincter prevents regurgitation. The pressure that this sphincter exerts is about 40 mm Hg and it relaxes during swallowing and during sudden distension of the oesophagus (e.g. belching, vomiting). The sphincter is mainly the cricopharyngeus muscle, a skeletal muscle, which is attached to the lateral aspects of the cricoid cartilage and is positioned behind it like a sling. The lumen of the hypopharynx within the cricopharyngeus is therefore crescent shaped. The oesophagus begins below the level of the cricoid cartilage.

The upper oesophageal sphincter relaxes during intravenous induction with thiopental (thiopentone), with heavy sedation, during deep sleep or following muscle-relaxant drugs. In all of these situations the sphincter pressure is reduced to less than 10 mm Hg, which is low enough to allow regurgitation. Following thiopental (thiopentone) the sphincter starts to relax just before loss of consciousness but is not fully relaxed until 30 seconds later. Ketamine does not relax the upper oesophageal sphincter, nor does an inhalational induction. Coughing during an inhalational induction increases upper oesophageal sphincter pressure to over 100 mm Hg.

Cricoid pressure prevents regurgitation by replacing the function of the upper oesophageal sphincter by compressing the hypopharynx against the prevertebral fascia muscles and vertebrae behind. The convex cricoid is pressed against the convex body of either the 5th or 6th cervical vertebrae. Inevitably the cricoid cartilage is deviated slightly laterally (Figures 1 and 2). Part of the crescent-shaped lumen is compressed against the vertebral body and the rest of it is less well compressed against the longus colli muscle to one side. A nasogastric tube is squeezed laterally towards the less well compressed part of the lumen and makes the occlusion of the hypopharynx more complete and therefore cricoid pressure more efficient.

A study of women undergoing emergency caesarean section under general anaesthesia with muscle relaxation showed that gastric pressure is likely to be less than 25 mm Hg in 99%. Oesophageal pressure can rise to equal gastric pressure during gastro-oesophageal reflux as the lower oesophageal sphincter relaxes to create a common cavity. A study of ten cadavers showed that 20 Newtons (N) of force applied to the cricoid cartilage prevented the regurgitation of oesophageal fluid at a pressure of 25 mm Hg in all cases and 30 N prevented regurgitation at a pressure of 40 mm Hg in all cases. Therefore, 20 N of cricoid pressure is probably sufficient and 30 N is more than enough to prevent regurgitation into the pharynx. Anaesthetic assistants can be trained to apply the correct force by practising on weighing scales and by doing this they can apply a range of forces between 5 N above or below the target force. A reasonable recommendation is to apply 30 N (3 kg).

Correct technique

Although cricoid pressure is apparently a simple technique there is growing evidence that incorrect application can cause serious problems during induction of anaesthesia. The anaesthetic assistant should practise the correct forces on weighing scales. The anaesthetist should be confident that the anaesthetic assistant knows the anatomical landmarks of the cricoid cartilage. Although Sellick suggested that the patient's head should be extended, the author recommends that it should rest on a pillow because intubation is easier and cricoid pressure is just as effective in this position. After pre-oxygenation, but before intravenous induction, lightly applied cricoid pressure should be started with a force of 10 N (1 kg), after loss of consciousness the force is increased to 30 N (3 kg). Forces of 20 N or more are not tolerated by awake patients and may cause them to retch and vomit. Normally the assistant applies cricoid pressure with their dominant hand because this can be maintained more accurately and for longer (3–5 minutes). There is no evidence that a bimanual technique, with the assistant's other hand supporting the patient's neck, improves the view at laryngoscopy when the correct forces are applied. The assistant's other hand is best kept free to assist with a difficult intubation if necessary.

Patients with small bowel obstruction should have a nasogastric tube inserted preoperatively. This should be aspirated before induction and left in place during induction. This does not make cricoid pressure less efficient and may improve it. As the tube is not compressed, it is possible, by leaving it open to atmospheric pressure, to vent liquid and gas remaining in the stomach, minimizing any increase in gastric pressure.

Sellick described the application of cricoid pressure with three fingers, thumb and middle finger on each side of the cartilage with the pressure applied with the forefinger. However, with the head on a pillow it is more comfortable to apply it with two fingers, forefinger and thumb on each side of the cartilage. This gives flexibility to apply upward and backward cricoid pressure, which improves the view at laryngoscopy if this becomes necessary. As the cricoid inevitably moves slightly laterally during cricoid pressure, it is better to ensure that it moves to the patient's right rather than to the left because this also makes intubation easier with a Macintosh laryngoscope.

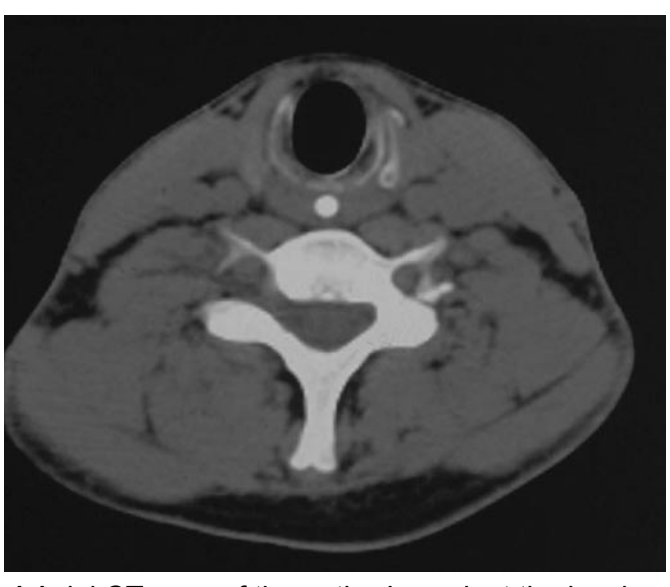
Complications

Excess force applied to the awake patient has caused retching and death from aspiration and ruptured oesophagus.

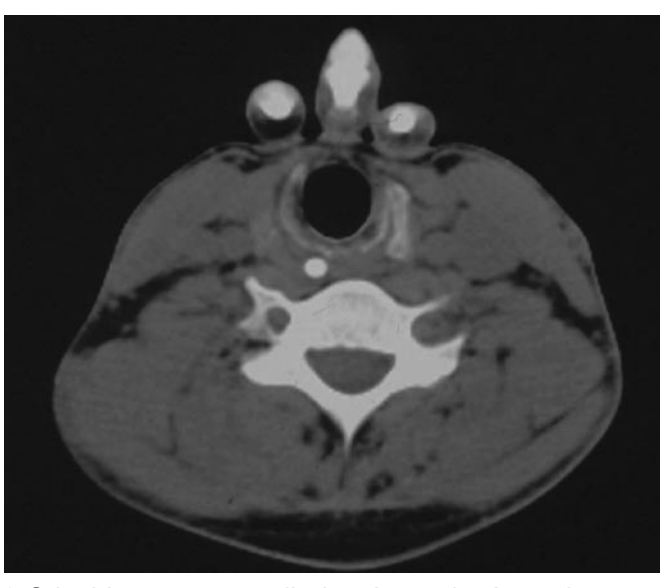
Difficult intubation can be caused by cricoid pressure if the force is applied to the thyroid cartilage or if the larynx is pushed laterally to the left or if too much force is used, which compresses the airway. When cricoid pressure is applied properly with a force of 30 N (3 kg) the view at laryngoscopy is improved compared with the situation when no cricoid pressure is used. However, if only the epiglottis can be seen, then the slight lateral displacement of the larynx, which is inevitable, will make the passage of a gum elastic bougie more difficult because this is normally passed in the midline.

The so-called 'cricoid yoke', a force transducer applied to the neck, is not ideal, because it may not be applied accurately to the cricoid cartilage and may cause tracheal compression or extreme lateral displacement of the larynx, resulting in difficulty with tracheal intubation.

Difficult ventilation – cricoid pressure can obstruct the airway and prevent ventilation of the lungs with a face mask and Guedel airway. This is proportional to the force applied; 30 N causes complete obstruction in 2% of patients and 40 N does in 35%. Upward and backward cricoid pressure at a force of 30 N causes airway obstruction in 56% possibly because it tilts the cricoid cartilage and opposes the vocal cords. Following a failed intubation in a patient with a full stomach when the lungs cannot be ventilated, the force of cricoid pressure should be reduced by half. If this does not allow ventilation, cricoid pressure should be released completely to allow ventilation, with laryngoscope and suction immediately available. Further airways that may then be necessary (e.g. laryngeal mask, *Combitube*, cricothyrotomy cannula) are all better placed without cricoid pressure applied.



1 Axial CT scan of the author's neck at the level of the cricoid cartilage showing a nasogastric tube filled with radio-opaque contrast media.



2 Cricoid pressure applied to the author's neck showing the slight lateral displacement of the cricoid and the lateral position of the nasogastric tube.

FURTHER READING

Brimaccombe J R, Berry A M. Cricoid Pressure. *Can J Anaesthesia* 1997; **44:** 414–25.
Sellick B A. Cricoid Pressure to Control Regurgitation of Stomach Contents during Induction of Anaesthesia. *Lancet* 1961; **2:** 404–6.
Vanner R G, Pryle B J, O'Dwyer J P, Reynolds F. Upper Oesophageal Sphincter Pressure and the Intravenous Induction of Anaesthesia. *Anaesthesia* 1992; **47:** 371–5.

Tracheal Intubation: Management of Difficult and Failed Intubation

Stuart W Benham

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Securing the airway with a tracheal tube is a core skill for anaesthetists. The technique may be required during anaesthesia, resuscitation or intensive care. The ability to manage patients when laryngoscopy is predicted to be difficult, or when intubation has previously failed, requires a methodical approach and a workable back-up plan. Indications for tracheal intubation are given in Figure 1.

Patients with depressed conscious levels (e.g. following head injury, self-poisoning, vascular accident, infections) need careful assessment. If there is any concern that airway reflexes are diminished, the airway must be secured with a tracheal tube. A low Glasgow Coma Score (e.g. GCS < 9) should not be relied on as the sole indication of airway compromise.

Intermittent positive-pressure ventilation can be achieved by non-invasive means without tracheal intubation. In the operating theatre this is often performed with the laryngeal mask airway (LMA), and in the ICU with a secure fitting face mask with head strapping.

Indications for tracheal intubation

Surgical indications
- Shared airway surgery
- Requirement for one lung ventilation
- Prone or sitting position for surgery
- Open abdominal or thoracic surgical procedures
- Major head and neck surgery
- Prolonged surgery

Emergency indications
- Prevention of aspiration in unfasted patients requiring general anaesthesia
- Impending airway obstruction (e.g. epiglottitis, airway burns)
- Maxillofacial trauma (blood in the airway)
- Depressed conscious level with poor airway reflexes

Ventilatory failure indications
- For intermittent positive-pressure ventilation
- Prevent aspiration of gastric contents
- Advanced ventilation strategies (e.g. partial liquid ventilation, high frequency jet ventilation)
- Prone ventilation strategies
- Ventilatory failure unresponsive to non-invasive positive- pressure ventilation

1

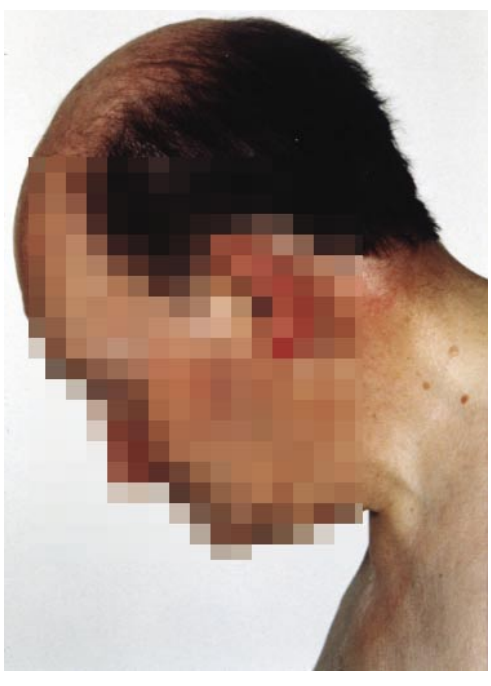
Management of difficult airway and failed intubation

The maintenance of alveolar ventilation is the most important aspect of difficult airway management. Patients in whom intubation is difficult or has failed, and in whom mask ventilation is also difficult are uncommon (about 1:10,000 routine anaesthetics). The anaesthetic plan must not render an awake patient who can maintain a patent airway into an unconscious patient with an unsafe and obstructed one. Preoperative assessment aims to identify patients in whom laryngoscopy and/or airway maintenance are likely to be difficult when consciousness is lost. Patients generally fall into one of three categories:
- anticipated difficult laryngoscopy
- elective unanticipated difficult laryngoscopy
- emergency unanticipated difficult laryngoscopy or failed intubation.

Anticipated difficult laryngoscopy
A comprehensive plan is required involving a primary plan and a secondary plan to be used if the primary plan fails. Two common pitfalls are:
- the operator is inexperienced in the technique chosen (e.g. flexible fibre-optic laryngoscopy – FFL)
- the back-up plan involves staff, skills and equipment that are not readily available at the time of induction (e.g. tracheostomy).

Anaesthetists have to develop plans with their own skill levels in mind, incorporating available equipment and supporting staff. Patient safety is of paramount importance. Generally, less invasive, atraumatic techniques should be preferred to surgical airway control, especially in elective patients. However, the emergency anticipated difficult airway (e.g. patients with severe maxillofacial trauma, or enlarging wound haematoma and stridor following head and neck surgery) may require a surgical airway as the primary plan.

Patients with bony abnormalities may have restricted mouth opening due to temporo-mandibular joint disease, or a cervical spine with limited neck flexion or extension (Figure 2). There is an expectation that the oropharynx and periglottic regions will be normal. In these patients, direct laryngoscopy may be impossible, but the normal oropharyngeal anatomy allows the passage of an FFL under general anaesthesia and assisted ventilation should be possible. If the primary plan fails during this elective surgery, the patient may be woken before implementing the secondary plan.



2 Restricted neck extension in ankylosing spondylitis.

Patients with obstruction in the supraglottic region include those with previous major oral surgery or radiotherapy. If there is evidence of stridor, the patient should be treated with extreme caution and one of the plans outlined below for periglottic or infraglottic obstruction should be considered. Stridor implies 50% airway narrowing. These patients may develop complete airway obstruction when anaesthetized and a surgical airway should be included in the management plan. Depending on the anaesthetist's skill, two options for the non-stridulous patient are:
- an awake fibre-optic endoscopy and intubation, before any relaxant or induction agent is given
- an inhalational induction and direct laryngoscopy to define the anatomical situation, and the feasibility of passing a tracheal tube.

Patients with obstruction in the periglottic region (including obstructing laryngeal tumours) require a thorough preoperative evaluation (e.g. CT, MRI) to assess the degree of obstruction and clinical assessment of the degree of stridor. Indirect laryngoscopy and flexible fibre-optic nasendoscopy are necessary to determine the extent of the obstruction and the feasibility of passing a tracheal tube, which should be performed by an experienced ENT surgeon. Non-stridulous lesions can be managed similarly to lesions causing supraglottic obstruction. Stridulous lesions are the most difficult to manage because neither awake fibre-optic endoscopy nor inhalational induction guarantees success. The choice of technique depends on the degree of stridor, the general condition of the patient and the experience of the anaesthetist. Severe cases may best be managed by awake tracheostomy under local anaesthesia. Depending on the level of the lesion, particularly with infraglottic obstruction, even emergency tracheostomy may not be realistic. For the most severe lesions it may be necessary to consider extracorporeal oxygenation as part of the secondary plan.

Elective unanticipated difficult laryngoscopy
Elective unanticipated difficult laryngoscopy is best managed using a stepwise approach.
- Reconfirm that assisted bag and mask ventilation is possible.
- Consider repositioning the head and neck and the use of a bougie.
- Avoid prolonged attempts at direct laryngoscopy. Change the length of laryngoscope blade once and the type of blade once to achieve the optimum view.
- Call for help and for the FFL if competent in its use.
- Consider the use of the LMA or the intubating LMA (ILMA) for ventilation.
- Consider using the LMA/ILMA as a conduit for intubation (see below).
- Consider abandoning anaesthesia, and performing an awake intubation.

Emergency unanticipated difficult laryngoscopy and failed intubation
This is a failure to secure the airway with a tracheal tube following a rapid sequence induction. Remember that it is failure of oxygenation, rather than a failure of intubation, that accounts for morbidity and mortality. The same stepwise approach as that for the elective unanticipated difficult laryngoscopy should be followed. All departments of anaesthesia should have a failed intubation drill for these circumstances, and clinicians should be familiar with their local protocols (see *Anaesthesia and Intensive Care Medicine* **2:6:** 221). It should be noted that in these situations the removal of cricoid pressure may help ventilation attempts, especially through the LMA. The risks of aspiration are small in comparison to the potential for morbidity and mortality caused by hypoxia from failed ventilation.

Techniques to overcome difficult intubation

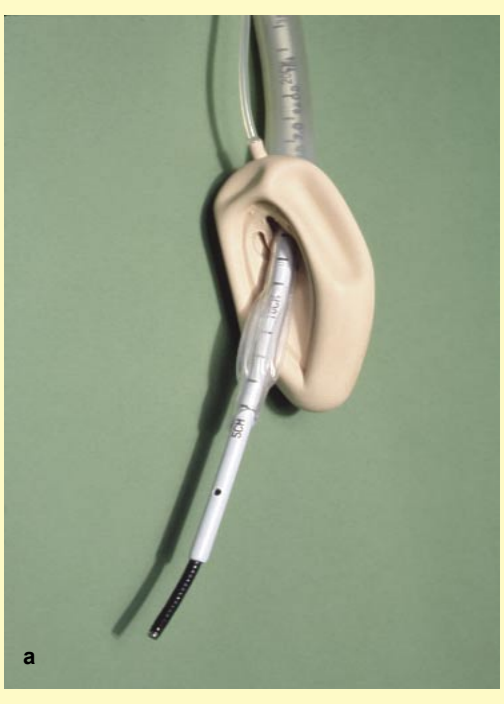
Many devices have been developed to improve the chances of securing the airway with a tracheal tube. Some of those used by practising clinicians are described below.

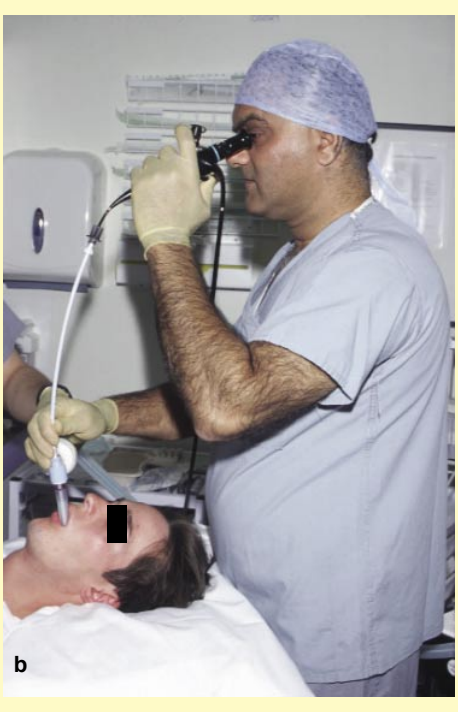
Position and simple manoeuvres
Optimizing the patient's position (flexion of the cervical spine and head extension at the atlanto-occipital joint – the 'sniffing the morning air' position) is the first step to improve the view at direct laryngoscopy. Simple manoeuvres such as external laryngeal manipulation, especially backwards, upwards and rightwards pressure on the larynx can improve the view by more closely aligning the visual axis with the laryngeal inlet.

Laryngoscopes
There is a range of curved and straight blades, as well as blades with movable hinged tips (McCoy), that may improve the view at direct laryngoscopy (see *Anaesthesia and Intensive Care Medicine* **1:1** 34). Many experienced anaesthetists, however, tend to use the same type of laryngoscope blade for all their patients. Skills in the use of different blades are best acquired during routine intubations. The McCoy, or the angled Belscope laryngoscope, may be able to convert a Cormack/Lehane grade 3 view to a grade 2 view, though familiarization with the technique is required.

Simple props and aids
Gum elastic bougies should be used when:
- direct laryngoscopy allows visualization of the epiglottis but not the larynx (a grade 3 view)
- visualization of the larynx is possible but direct passage of the tracheal tube is prevented by awkward oral anatomy or teeth
- a reinforced or flexible tracheal tube cannot be directed into the visualized larynx.

Aintree intubation catheter (Cook©) (Figure 3) can be used like a gum elastic bougie, or in combination with other airway and intubating devices such as the LMA or FFL. It is sufficiently long and thin to allow a tracheal tube to be railroaded over it. It is hollow and has a detachable tube connector/adaptor that allows ventilation during the intubation process. An FFL can also be passed through it if required.





a Flexible fibre-optic laryngoscope and Aintree intubation catheter passed through the laryngeal mask airway (LMA).
b Fibre-optic endoscopy through the LMA with the Aintree exchange catheter.

3

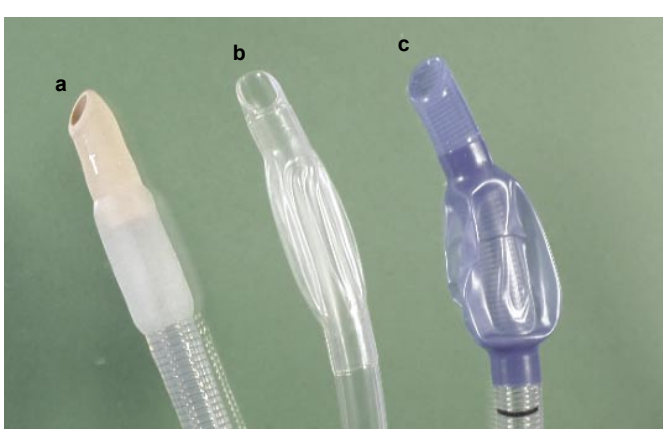
LMA and ILMA
Most anaesthetists use the LMA regularly for patients not requiring intubation. The ability to insert an LMA to allow spontaneous or assisted ventilation is a core skill for anaesthetists. It also provides a route guide for intubation, either blind or guided by an FFL. The LMA may help to achieve ventilation in patients who are otherwise difficult to intubate and ventilate.

The ILMA is modified to improve the chances of passing a tube blindly through the mask into the trachea. There is an initial short learning curve for the operator, and the clinician should practise using the ILMA in patients with normal airways before it is used in those with difficult or abnormal ones.

The main limitation on both devices is that there has to be enough mouth opening to permit inserting the device. Intubation can be blind, but both devices can be used with an FFL to visualize laryngeal anatomy and aid intubation.

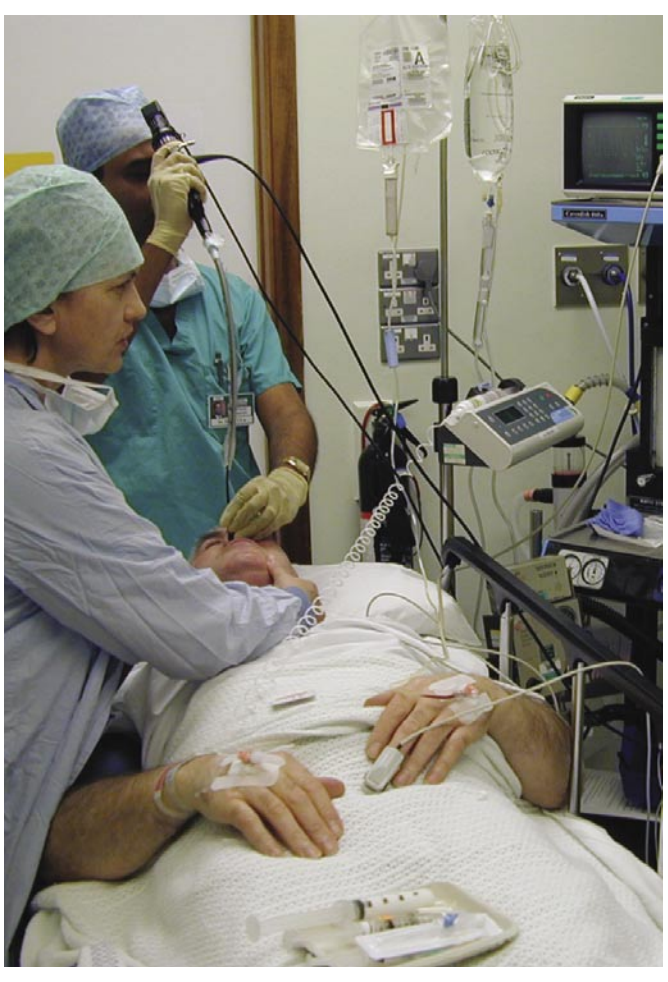
Railroading the tracheal tube
The need to railroad the tracheal tube over the guide is the final step in intubation. Two manoeuvres to increase its success rate and minimize laryngeal trauma are choice of tracheal tube and bevel direction.

- The ILMA tube (softer tip) or reinforced tracheal tube (less acute bevel and softer tip) has a higher chance of passing through the vocal cords (Figure 4).
- The bevel of the standard tracheal tube is directed to lie in the right or left lateral position as it reaches the vocal cords. It is then rotated 90° as it is pushed gently through the cords. If this is unsuccessful, the tube is rotated through 360° continuously with gentle pressure to slip through the cords. If still unsuccessful, direct laryngoscopy can be performed to check the position of the route guide, and to lift the epiglottis to facilitate tube railroading.



4 Tracheal tube tips. **a** The intubating laryngeal mask airway tube, **b** standard tube, and **c** the flexometallic tube

FFL and intubation
FFL and intubation can be performed with the patient awake or anaesthetized. Awake fibre-optic intubation performed by a competent endoscopist is safe (Figure 5). The patient remains awake and self-ventilating with maintained pharyngeal muscle tone.



5 Awake fibre-optic intubation. Note the use of propofol sedation and jaw thrust.

Suggested procedure for awake fibre-optic intubation
1 Premedication of morphine, 0.1–0.15 mg/kg i.m., and hyoscine (scopolamine), 200 µg i.m., 1 hour before procedure.
2 The patient should lie semi-reclined on a trolley in the anaesthetic room, facing the anaesthetist.
3 Intravenous sedation should be administered cautiously. Target-controlled infusion with propofol (plasma concentration 0.5–1.5 µg/ml) is well tolerated.
4 Topical anaesthesia of the upper airway should be provided:

- Nasal mucosa; mixture of 5% cocaine, 2 ml, and 8.4% bicarbonate, 2 ml, as topical spray, with the patient taking deep breaths in with each spray. If the patient requires orotracheal intubation the oropharynx can be anaesthetized with lidocaine (lignocaine) spray or gel. Oropharyngeal route guides (e.g. *Ovassapian* or *Berman* airway) can be used to aid orotracheal intubation. These allow the operator to pass the FFL and tracheal tube through them. They prevent soft tissue collapse and are sized to guide the FFL through the mouth, and emerge at the epiglottis, where it can be directed into the larynx.
- Spray as you go (SAYGO) with 4% lidocaine (lignocaine) through the working channel of the FFL. Insertion of an epidural catheter through the working channel to the tip of the scope, with the catheter end trimmed to produce one end-hole, can facilitate accurate delivery of the local anaesthetic injection. Inject 1 ml solution with 4–5 ml air to help disperse the anaesthetic. Before the first attempt to pass the FFL, and before each subsequent attempt, oropharyngeal suctioning with a Yankaur sucker may be required.
- Administer supplemental oxygen. This can be delivered conveniently via a flexible suction catheter passed into the opposite nostril.

5 Allow adequate time (at least 30 seconds) after topicalization before the FFL is advanced. Avoid passing the FFL blindly. If the view ahead becomes obscured, gently withdraw the insertion cord until airway anatomy is again identified. Ask the patient to take deep breaths when advancing towards the laryngeal inlet. This opens the airway and abducts the vocal cords. If visualization of the larynx is difficult, performing a gentle jaw thrust manoeuvre on the patient can help.
6 Once the scope has been advanced through the cords it should be advanced to just proximal to the carina. A common error is to allow the FFL to withdraw, or even become displaced from the trachea while the tube is railroaded into place. This happens more often if the patient coughs at this time. The operator should attempt to keep the FFL in the centre of the airspace at all times. This minimizes trauma to the delicate tracheal mucosa and reduces the amount of blood in the airway.
7 Railroading the tracheal tube is described above. It is helpful for the assistant to hold the FFL stationary allowing the operator to railroad the tube into place using both hands.
8 A final useful check to estimate the distance from the end of the tracheal tube to carina can be performed as follows. Once intubation has been performed, the FFL is passed down just proximal to the carina. The assistant lightly pinches the FFL as it enters the proximal end of the tracheal tube. The FFL is then withdrawn slowly until the distal end of the tracheal tube comes into view. As soon as this is seen, the distance from the assistant's fingers to the tube connector of the tracheal tube is noted. This is the distance from tip of tube to carina.
9 The breathing system with capnograph is connected. The patient may then be anaesthetized and laid flat. Satisfactory ventilation is confirmed, and muscle relaxant can be given if required.

Problems with flexible fibre-optic intubation: the FFL is an intubating tool, not a ventilation device. Oxygenation and ventilation must be maintained throughout the intubation procedure.

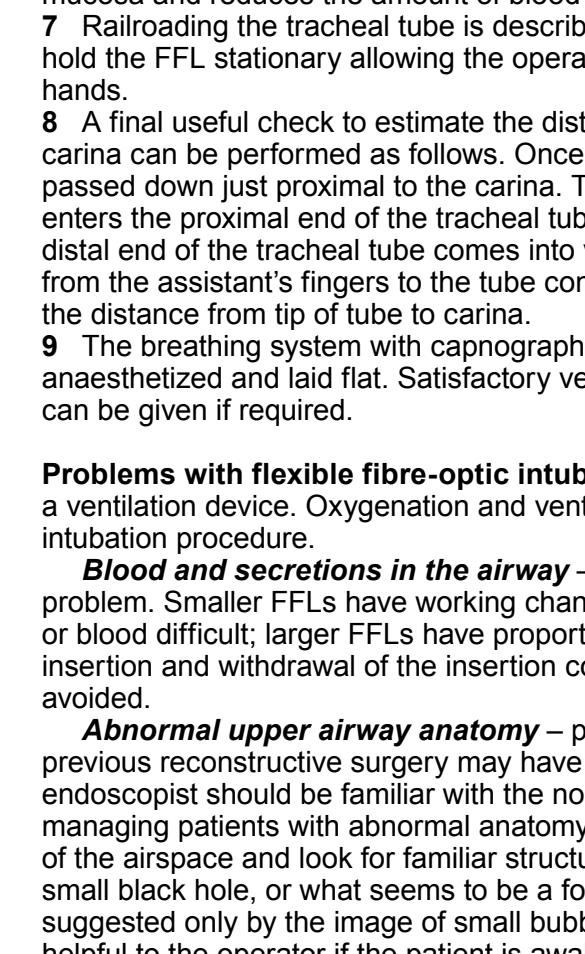
Blood and secretions in the airway – a poor view is the endoscopist's main problem. Smaller FFLs have working channels that make suctioning of sticky secretions or blood difficult; larger FFLs have proportionally larger suction channels. Repeated insertion and withdrawal of the insertion cord may precipitate bleeding and should be avoided.

Abnormal upper airway anatomy – patients with oro-pharyngeal lesions or previous reconstructive surgery may have abnormal upper airway anatomy. The endoscopist should be familiar with the normal appearances through the FFL before managing patients with abnormal anatomy. In all patients, keep the FFL in the centre of the airspace and look for familiar structures. Often the larynx is identified only as a small black hole, or what seems to be a fold in the mucosa. Identification is sometimes suggested only by the image of small bubbles appearing from a dark crevice. It is helpful to the operator if the patient is awake, semi-recumbent, and cooperating by taking deep breaths.

Equipment problems – the FFL should be checked and cleaned before use.

- The tracheal tube should be loaded on the FFL before endoscopy; forgetting to do this is a common mistake.
- Ensure that the light is on and working with white balance and focus optimal before commencing endoscopy.
- Lubricating jelly should be applied to the outside of the scope, and the tracheal tube, to facilitate easy nasal passage and tracheal intubation.
- Difficulties in railroading the tracheal tube can sometimes result from a large difference in the external diameter of the scope and internal diameter of the tracheal tube. This may be overcome by use of the Aintree intubation catheter. The intubation catheter can be railroaded over the scope, and then the tracheal tube railroaded over this.

Lack of hand–eye coordination can be remedied by practice on simulators, manikins and learning models such as an artificial bronchial tree or the Oxford 'hit-the-hole' box (Figure 6). It is indefensible to acquire these basic skills at the expense of the patient's mucosa.



6 The Oxford 'hit-the-hole' training box.

An inability to recognize anatomy is easily addressed by experience gained from instructional videos, clinical teaching and supervision. The case for using an FFL to aid routine nasal intubation is robust. In addition to the excellent learning opportunity afforded by routine use of the FFL, it assists in the selection of the best nostril and largest airspace, and identifies vulnerable nasal pathology such as polyps.

Transtracheal access

The final route for rescuing an obstructed airway is direct transtracheal access. This can be through the cricothyroid membrane, or through the upper trachea. Most anaesthetists never need to resort to this. Elective procedures, such as cricothyroid puncture used to inject local anaesthetic, or performing percutaneous tracheostomies in the ICU, provide valuable experience in tracheal access. The ability to identify the cricothyroid membrane and to insert a cricothyroid airway catheter rapidly may be a life-saving procedure. See Anaesthesia and Intensive Care Medicine issue 2:7: 268 for discussion of emergency tracheal access.

FURTHER READING

Latto I P, Vaughan R S, eds. *Difficulties in Tracheal Intubation.* 2nd ed. Philadelphia: WB Saunders, 1997.

Popat M. *Practical Fibreoptic Intubation. Oxford:* Butterworth-Heinemann, 2001.

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Airway Control

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Securing control of the airway is one of the most important skills required of the anaesthetist. Whether for elective or emergency surgery, and whether the need for airway control has been predicted or not, the safety of the patient depends on the anaesthetist's ability to intervene to ensure adequate oxygenation and ventilation should the need arise. The anaesthetist must:

- develop the skills of airway assessment and management
- be familiar with the equipment and techniques available for control of the airway
- be able to choose the appropriate measures for the individual patient.

This contribution focuses on these basic principles.

Assessment of the airway

The anaesthetist must assess the airway before undertaking any anaesthesia. When general anaesthesia is contemplated, assessment facilitates a planned approach to anticipated difficulties with laryngoscopy and intubation. When a regional or local technique is contemplated, the need for airway intervention may also arise, for example, following respiratory embarrassment as a result of a high spinal or epidural blockade level, over-zealous sedation, or more rarely, following an allergic reaction to a drug.

The patient's previous anaesthetic notes should be consulted if available. It is important to realize, however, that the patient's circumstances may have changed, and a previously easy intubation may have become difficult (e.g. as a result of pregnancy). A number of anatomical factors are associated with difficulty in laryngoscopy and intubation:

- obesity, pregnancy
- large protruding incisor teeth
- short neck, especially in a heavy patient
- reduced mobility of the neck (e.g. rheumatoid arthritis)
- instability of the neck
- reduced mouth opening
- intraoral masses
- large goitre.

Anatomical assessment

Whether laryngoscopy and intubation would be possible with reasonable ease should be assessed using a reliable and reproducible bedside method of airway assessment that has minimal false-positive and false-negative rates. No single test provides this information, but the modified Mallampati test in conjunction with an assessment of thyromental distance combines ease with reasonable accuracy.

The modified Mallampati test assesses the size of the base of the tongue in relation to the size of the oropharynx. The patient sits upright with the head in the neutral position. The assessor sits in front of the patient at the patient's eye level. The patient opens their mouth as wide as possible. Without phonating, the tongue is protruded as far as possible. The assessor inspects the pharyngeal structures visible and a score is allocated according to which structures are visible (Figure 1).

Modified Mallampati test

Class	Pharyngeal structures visible
1	Fauces, faucial pillars (the palatoglossal and palatopharyngeal arches), uvula, soft palate
2	Faucial pillars are obscured leaving the fauces, uvula and soft palate visible (i.e. posterior pharyngeal wall visible below soft palate)
3	Only the soft palate and the base of the uvula seen (i.e posterior pharyngeal wall not visible below soft palate)
4	Even the soft palate obscured

1

The measurement of thyromental distance as recommended by Frerk is obtained by maximally extending the head on the neck and measuring from the prominence of the thyroid cartilage to the bony point of the chin.

A modified Mallampati grade of 3 or 4 combined with a thyromental distance of 7 cm or less gives a bedside assessment system with a sensitivity of 81% and a specificity of 98% for difficulty with intubation.

The view of the laryngeal structures obtained at direct laryngoscopy is often classified according to the system described by Cormack and Lehane (Figure 2). In this system, grades 3 and 4 constitute difficult laryngoscopies. Fairly severe difficulty with intubation may occur with grade 3, and the use of a bougie/introducer, posterior to, but held up against the epiglottis may permit blind intubation. With a grade 4 view, intubation by standard methods is virtually impossible despite optimal positioning.

Cormack and Lehane classification system

Grade	Laryngeal structures visible
1	Most of the glottis visible
2	Only the posterior part of the glottis (posterior commissure, arytenoid cartilages) visible
3	Only the epiglottis visible, no part of the glottis seen
4	Not even the epiglottis seen

2

Airway patency

Partial obstruction of the airway in the awake patient may be caused by masses in the upper airway (e.g. tonsils, adenoids, tumour), foreign bodies, or epiglottitis. In the sedated or unconscious patient, laxity of the muscles that normally keep the tongue anterior to the posterior pharyngeal wall allows the tongue to fall back and obstruct the airway. Partial obstruction is recognized by noisy inspiration (stridor), tracheal tug, and dyssynchronous movements of the thorax and abdomen on inspiration.

In normal, unobstructed breathing, the abdomen expands as the diaphragm descends in inspiration and the thorax expands as indrawn gas fills the lungs. With obstruction, the abdomen still expands, but if inspired gas cannot be inhaled at a sufficiently fast rate, the sternum is drawn inwards by the increasing, unrelieved negative intrathoracic pressure. Partial obstruction and its cause (and therefore ease of reversal) must be recognized before embarking on anaesthesia. The technique of airway management is highly modified in the presence of partial obstruction.

Aspiration risk

For elective anaesthesia, the patient is fasted. Solid food, non-clear liquids (especially those containing milk) and chewing gum should not be consumed in the 6 hours before anaesthesia. Clear liquids are permissible up to 2 hours before induction.

For emergency anaesthesia, the interval between last food or drink and the injury or onset of illness is assessed. Gastrointestinal obstruction or other abnormal motility state (e.g. ileus, diabetes mellitus, renal failure, acute pain) all increase the risk of aspiration on induction of anaesthesia.

Equipment and techniques for routine airway management

Before embarking on general anaesthesia, the equipment required should be to hand and its correct function checked. A preoperative checklist such as that proposed by the Association of Anaesthetists of Great Britain and Ireland is particularly useful (see *Anaesthesia and Intensive Care Medicine* **1:2:** 65). The minimum equipment required includes:

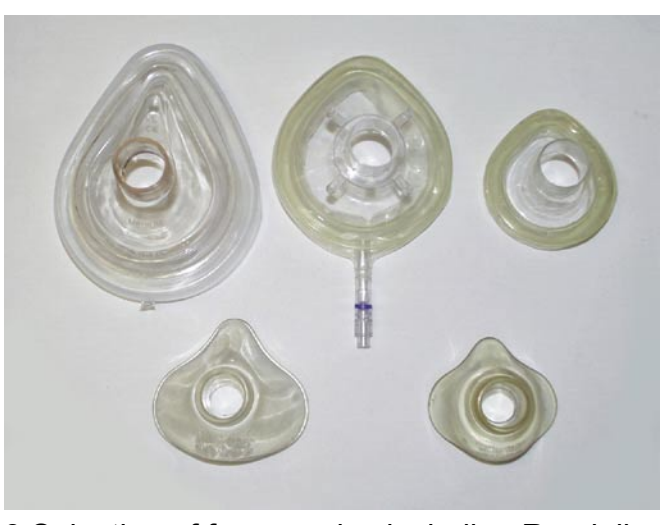
- source of pressurized oxygen (plus bag-valve-mask or anaesthesia circuit)
- selection of face masks
- selection of oropharyngeal and nasopharyngeal airways
- high-flow suction
- Yankauer suction catheter, and selection of narrow-bore suction catheters
- two laryngoscopes
- selection of tracheal tubes
- selection of laryngeal mask airways
- Magill's forceps
- sterile lubricating gel
- ties and padding to secure tracheal tube
- gum-elastic or other suitable bougie.

For non-emergency anaesthesia, several interventions to control the airway are available. These range from oxygen administration through a face mask, delivery of inhalational anaesthesia via an anaesthetic face mask or laryngeal mask airway, through to tracheal intubation.

Non-relaxant anaesthesia

If relaxant anaesthesia is not required (e.g. for body-surface surgery in the patient not at risk for aspiration) then inhalational anaesthesia via a face mask is appropriate. In the absence of flammable anaesthetic agents, the mask is usually clear plastic with an inflatable rim that provides a good seal in contact with the face. The size of the mask is determined by the patient's size and physical features, but a range of sizes (Figure 3) should be available. For paediatric anaesthesia, the mask should have as little dead space as possible (e.g. the Rendell-Baker–Souchet mask). Nasal masks are indicated for anaesthesia in the dental chair.

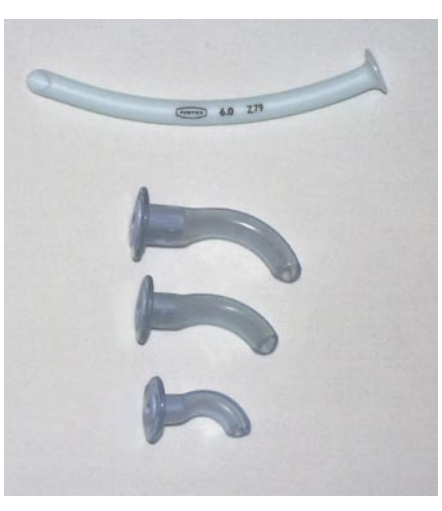
Induction in the absence of airway obstruction may be inhalational or by intravenous injection of a suitable induction agent. If there is any suggestion of airway obstruction then inhalational induction or another approach (e.g. awake fibre-optic intubation) is required.



3 Selection of face masks, including Rendell-Baker–Souchet paediatric masks (lower row).

Supporting the airway

Whatever the means of induction, once the patient is unconscious it is necessary to support the airway. There is a tendency for the airway to become partially obstructed at this stage because the tongue falls back against the posterior wall of the pharynx. Induction will normally have occurred with the patient supine, head resting on a pillow. This allows the anaesthetist to extend the head on the neck at the same time as applying a jaw thrust and opening the mouth. To achieve this triple manoeuvre, the mask is secured on to the face using one or both hands, with the thumbs on the upper part of the mask, index fingers on the lower part and the rest of the fingers effectively pulling the patient's mandible forward into the mask. It is crucial that unopposed downward pressure on the mask is not used to obtain a seal between mask and face because this will close the airway. Likewise, the third, fourth and fifth fingers must stay on the mandible and must not press on the floor of the mouth, which also tends to cause obstruction. If it is impossible to open the airway using these techniques, an artificial airway is required. Two methods are available: the oropharyngeal and the nasopharyngeal airway (Figure 4).



4a Nasopharyngeal airway.
b Selection of smaller oropharyngeal airways.

The oropharyngeal (Guedel) airway is a curved tube that has a flanged and reinforced oral end. The flange enables correct positioning at the incisor teeth, and the reinforcement prevents the patient from obstructing or severing the device by biting down. This airway is available in a range of sizes (size 3–4 is usually required for an adult, Figure 4b), and it is vital that the appropriate size is used for the patient. An easy way to determine size is to choose the airway in which the length is equal to the distance between the corner of the patient's mouth and the angle of the jaw. If the airway is too short it tends to push the tongue backwards and cause increased obstruction. If too long, the device tends to stimulate the larynx, provoking spasm, and it fails to sit securely with the flange at the front incisors. The Guedel airway is usually inserted upside-down (the pharyngeal opening facing the roof of the mouth, then rotated 180° as it passes the back of the tongue). A lightly anaesthetized patient may gag or cough with this intervention. It may also provoke laryngeal spasm.

The nasopharyngeal airway is a less stimulating intervention. It is a soft curved tube with a flanged nasal end and a bevelled pharyngeal end (Figure 4a). It is also available in a range of sizes. Sizes 6–8 mm (measured as internal diameter) are suitable for adults, the usual measure is the diameter of the patient's little finger. Before inserting the airway, a safety pin is inserted eccentrically at the flanged end, to prevent inhalation of the device. The airway should be coated with lubricating gel, and inserted into either nostril. It is advanced along the floor of the nose in a posterior direction, and should come to lie with the bevelled end in the oropharynx, behind the tongue and above the glottis. The eccentric positioning of the pin permits access of a catheter for suctioning secretions from the pharynx and airway.

Face mask: for brief procedures, anaesthesia can be maintained using a face mask, with or without airway adjuncts. For longer procedures, when it is desirable for the anaesthetist to have both hands free, the standard mask can be supported by a harness. It is now more common to insert a laryngeal mask airway for such procedures. This has the advantage of maintaining the airway without additional instrumentation, in addition to providing a more secure airway and providing hands-free operation.

The laryngeal mask airway (LMA) was designed to provide a connection between the artificial and anatomical airways in a less invasive way than with a tracheal tube, and yet with greater convenience and reliability than a conventional face mask. The standard LMA is made from silicone and is designed for multiple patient (up to 40) uses. It consists of a silicone bowl surrounded by a thin-walled elliptical ring that can be deflated to form a thin wedge shape, and which when inflated in the space posterior to the pharynx creates a seal around the laryngeal aperture. This seal permits ventilation of the airway under positive pressure. It also prevents insufflation of gas into the oesophagus and stomach, unless high inflation pressures (20–30 cm H_2O) are used. The device has a central aperture, with vertical bars, designed to prevent prolapse of the epiglottis into the tube that connects the mask to the anaesthetic circuit.

The LMA is available in a variety of sizes (Figure 5).

Correct placement is important to ensure a high-performance seal without overinflation of the cuff, and the appropriate size is chosen for the size of the patient (Figure 6).

The LMA is also available with a flexible, reinforced, non-kinking tube instead of the standard tube. This type is particularly useful for situations in which the head may be moved during surgery and for oral and ENT surgery. The intubating LMA is a development of the standard airway designed to act as a conduit permitting blind intubation of the trachea using a specially designed silicone tube.

A full description of the recommended technique for inserting the LMA is beyond the scope of this contribution. Briefly, the device is completely deflated (preferably using a cuff deflation tool, which will ensure deflation to the correct shape). The patient's head is supported on a pillow, in the classic intubating position. Extension of the head and flexion of the neck on the thorax is achieved by the non-dominant hand. The posterior surface of the LMA is lubricated with water-soluble gel. The LMA is held between index finger and thumb, with the index finger of the operator's gloved dominant hand at the junction of the mask and the tube. The aperture of the device faces caudally. An assistant holds the patient's mouth open, and the device is inserted under direct vision, with its posterior, lubricated surface firmly against the hard palate. The LMA is pushed, keeping it firmly against the palate at all times following the palate posteriorly and down into the hypopharynx. Resistance to insertion is met when the tip of the device is in the hypopharynx, with the tip resting at the upper oesophageal sphincter. It may be necessary to push the device using the non-dominant hand, if the inserting finger is not long enough. The device is released. The cuff is inflated with the recommended volume of air, at which point the tube may rise from the mouth as the device seats itself around the larynx. The tube of the LMA is connected to the anaesthetic circuit, if necessary using a swivel connector.

The LMA may be used to ventilate the anaesthetized muscle-relaxed patient, provided that the inflation pressures do not exceed about 20 cm H_2O. Above this pressure, the risk of gradual insufflation of the stomach with anaesthetic gas increases. This increases the risk of regurgitation and aspiration of gastric contents.

5a Standard laryngeal mask airways, sizes 2½, 3, 4. **b** Reinforced laryngeal mask airway, size 4.

Relaxant anaesthesia

Anaesthesia requiring a muscle-relaxant technique most commonly requires tracheal intubation. Indications for relaxant techniques and/or intubation are:

- provision of clear airway
- airway protection from blood, oral or gastric secretions
- facilitation of suctioning of airway
- prone or sitting patient, airway inaccessible
- abdominal, thoracic anaesthesia
- likelihood of postoperative respiratory support
- administration of positive end-expiratory pressure.

Tracheal intubation

Equipment: in addition to the equipment for inhalational anaesthesia using a face mask, a suitable laryngoscope, with a spare available, and a range of suitable tracheal tubes are necessary.

The laryngoscope consists of a handle (which houses the batteries) and a detachable blade, which has a screw-in bulb. Alternatively, the bulb may be in the handle, and a fibre-optic bundle transmits the light to the blade. Two basic types of laryngoscope are available (Figure 7):

- curved-blade (usually Macintosh)
- straight-blade (e.g. Wisconsin, Seward, Magill).

The curved-blade instruments are most commonly used for adults and larger children: the tip is placed in the vallecula, anterior to the epiglottis. Forward traction elevates the epiglottis without touching the posterior surface of the epiglottis. By contrast, straight-blade laryngoscopes are inserted posterior to the epiglottis and lift it from behind. These instruments are most often used for smaller children, because the epiglottis is longer and more floppy in this age group. The blades are available in a number of sizes, with the Macintosh 3 being suitable for most adults.

Tracheal tubes – an extensive range of tracheal tubes is available (Figure 8). They are most commonly made from polyvinylchloride or polyurethane and are bevel-ended. They may be plain or have a high-volume low-pressure cuff, which provides a seal enabling positive-pressure ventilation and preventing aspiration of secretions into the airway. Uncuffed (plain) tubes are used in children. This avoids the potential for ischaemic damage on the tracheal lining from high cuff pressure and maximizes tube size available. The presence of an air leak around the plain tube ensures that the fit is not too tight.

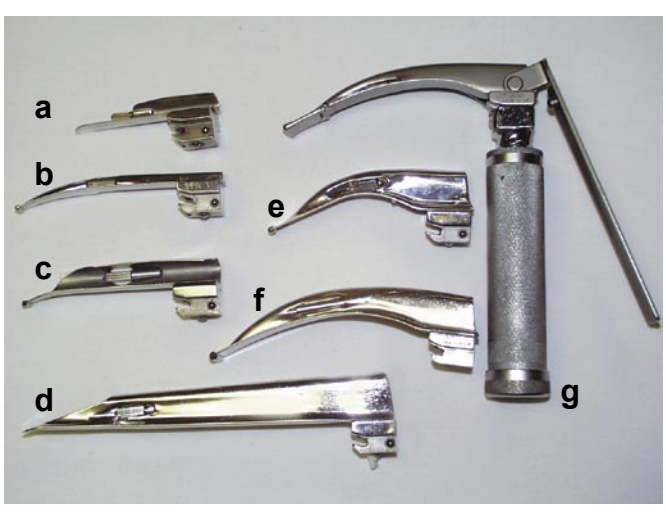
Tracheal tubes are usually inserted via the mouth, or if necessary via the nose (e.g. for intraoral surgery). Tube size is measured by the internal diameter, ranging from 2.5 mm to about 10 mm in 0.5 mm increments. The tube is usually cut to the appropriate length for the patient. Adult males usually require size 8–9 mm and adult females 7–8 mm, cut to 21–23 cm for oral intubation. For children, the tube size can be estimated from the formula (age/4 + 4 mm), and length (age/2 + 12 cm), with age being in years. This is an approximate size, and tubes 0.5 mm greater than and less than the estimated size should be available.

The tube is connected to the anaesthetic circuit at the proximal end with a tapered connector of suitable size (see *Anaesthesia and Intensive Care Medicine* **1:2:** 68). The distal end may have, in addition to the end hole, a side opening (Murphy eye) to allow passage of gas should the bevelled end be occluded by abutting on the tracheal wall.

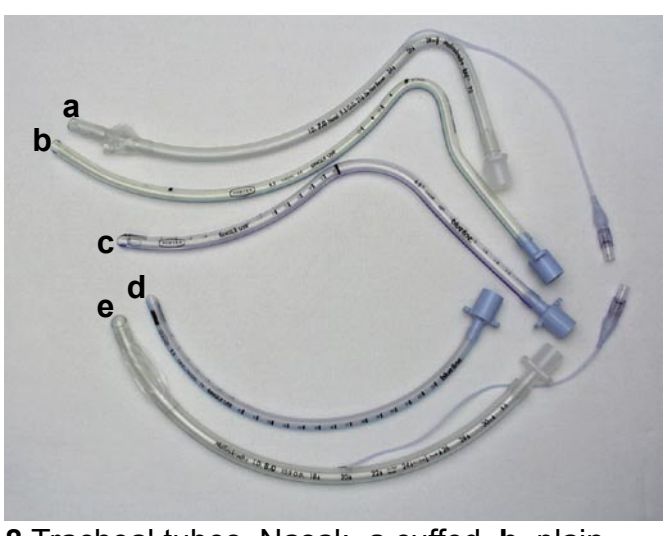
Sizes of laryngeal mask airway

Size	Patient	Cuff volume (ml)
1	Neonates up to 6.5 kg	4
2	Patients 6.5–20 kg	10
2½	Patients 20–30 kg	14
3	Children and small adults	20
4	Normal adults	30
5	Large adults	40

6



7 Selection of straight- and curved-blade laryngoscopes. **a** Wisconsin, **b** Seward, **c** Oxford, **d** Soper, **e** Macintosh size 2, **f** Macintosh size 3 **g** McCoy laryngoscope.



8 Tracheal tubes. Nasal: **a** cuffed, **b** plain. Oral: **c** North-facing plain polar. Magill pattern oral tubes: **d** plain, **e** cuffed.

Anaesthetic management

Positioning the patient correctly before intubation is crucial. Tracheal intubation requires approximate collinearity between the axes of the mouth, oropharynx and larynx. True collinearity of these structures is impossible, but appropriate positioning can make the difference between a relatively easy laryngoscopy and intubation, and failure to visualize the larynx at laryngoscopy. The classic intubating position is the sniffing position: the head is extended on the neck (atlantoaxial extension) and the neck is flexed on the thorax. For most adults this is easily achieved by having the patient lie supine on the trolley or bed and placing a pillow under the occiput. If the pillow is too caudad (elevating the shoulders) then extension of the neck on the thorax occurs. This almost always makes laryngoscopy more difficult. In small children, the relatively large head provides the correct position without the use of a pillow.

Induction – if the patient is not at risk of aspiration of gastric content, difficulty with laryngoscopy is not anticipated, and the airway is unobstructed, induction of anaesthesia is as for the mask techniques outlined above. Following induction, it is possible, providing the patient is deeply anaesthetized, to perform laryngoscopy and intubation. This practice is relatively uncommon. More usually, the anaesthetist confirms that it is possible to ventilate the patient using the mask (with an artificial airway if needed). Then an intubating dose of a muscle relaxant is given (e.g. suxamethonium, 1–1.5mg/kg). While the advantages of the speed of onset and quality of relaxation

obtained with suxamethonium are significant, its side-effects include myalgia (which can be quite severe), occasional profound bradycardia (especially in children, and particularly likely with second doses of the drug given shortly after a first dose), hyperkalaemia, and precipitation of malignant hyperthermia in susceptible individuals. To overcome these disadvantages, an intermediate-duration non-depolarizing drug such as vecuronium, 0.1 mg/kg, atracurium, 0.5 mg/kg, or rocuronium, 0.6 mg/kg, can be used. However, they commit the anaesthetist to providing ventilation by mask for a prolonged period if intubation proves more difficult than anticipated, or is impossible. With the exception of rocuronium they also take a longer time to achieve good intubating conditions, which makes them much less suitable for the patient at risk of aspiration of gastric content. The lungs are usually manually ventilated while awaiting the onset of muscle relaxation. A mixture of oxygen and the volatile agent chosen to maintain anaesthesia is used, together with nitrous oxide, if desired. The use of nitrous oxide reduces the interval allowable for laryngoscopy and intubation. The patient will become hypoxaemic more rapidly following cessation of ventilation if this gas is used, because available oxygen stores will be reduced. A peripheral nerve stimulator may be used to confirm the presence of adequate paralysis, as demonstrated by the absence of twitch response to a supramaximal stimulus.

Laryngoscopy is then performed. The right hand opens the patient's mouth and the assistant separates the patient's lips to expose the teeth. Using a curved-blade laryngoscope, held in the left hand, the blade is inserted into the right-hand side of the mouth, and advanced as far as the tonsillar bed. Sweeping the blade into the midline at this point should displace the tongue to the left, and give a view of the tip of the epiglottis. The blade is advanced, with force applied along the shaft of the laryngoscope directed upwards and outwards (at about 30–45° to the horizontal). The patient's upper incisors or gum must not be used as a fulcrum. The tip of the blade should enter the vallecula in front of the epiglottis, and the applied force elevates the epiglottis, exposing the larynx. The tracheal tube is picked up in the right hand and advanced from the right-hand side of the mouth, using the natural curvature of the tube to place the tip in the larynx under direct vision. Once the cuff of the tube is safely past the cords, the laryngoscope is carefully removed. The anaesthetic circuit is connected to the tube using a swivel connector and a catheter mount (if desired). The lungs are ventilated and the cuff of the tube inflated with just sufficient air (or gas mixture) to abolish the audible leak of gas on inflation of the lungs. Bilateral breath sounds and absence of sounds of gastric insufflation help confirm placement, however monitoring for appropriate and continuous concentration of carbon dioxide in the exhaled gas is mandatory.

Extubation – anaesthesia is maintained with inhalational agents, and the patient is ventilated using intermittent positive-pressure ventilation throughout the operation. At the end of the operation, residual neuromuscular blockade is reversed using a combination of a cholinesterase inhibitor and a muscarinic blocking drug (to prevent bradycardia). The drugs most commonly used are neostigmine, 0.05 mg/kg, with either atropine, 0.02 mg/kg, or glycopyrrolate, 0.01 mg/kg. Secretions and occasionally gastric content will have accumulated in the pharynx during the procedure. To prevent aspiration of these secretions and severe laryngeal spasm on removal of the tracheal tube, these are removed using a Yankauer sucker or equivalent, under direct vision (with a laryngoscope). The patient is ventilated with 100% oxygen. As the patient starts to breathe, the circuit is changed to permit spontaneous ventilation, with the reservoir bag providing visible confirmation of ventilatory effort and volume.

The tracheal tube is removed when the patient is breathing adequately and has regained protective airway reflexes (the patient is actively resisting the presence of the tube). The patient may be extubated in the supine position if the anaesthetist is satisfied that a clear airway can be maintained and the patient is not at risk for aspiration. If the patient is at risk, then extubation should take place in the lateral position, with the patient as fully awake as possible. Extubation should be performed during inspiration. Having deflated the cuff of the tracheal tube, the bag on the anaesthetic circuit is squeezed to expel secretions above the cuff into the oropharynx, away from the vocal cords. The tube is removed in a smooth movement, the breathing circuit rapidly reconnected to an anaesthetic mask, and the mask closely applied to the face.

Partial obstruction of the airway may occur at this stage if the tongue falls back into the pharynx, or more often because of mild laryngeal spasm. It may respond to the application of positive end-expiratory pressure. This may be achieved by partially closing the exhaust valve on the anaesthetic circuit, but the airway pressure must be monitored. If the airway is obstructed by the tongue, then an oral or nasopharyngeal airway may be required to relieve the obstruction. When the patient is breathing adequately, he is transferred to the recovery room, ensuring that he breathes supplementary oxygen during the transfer.

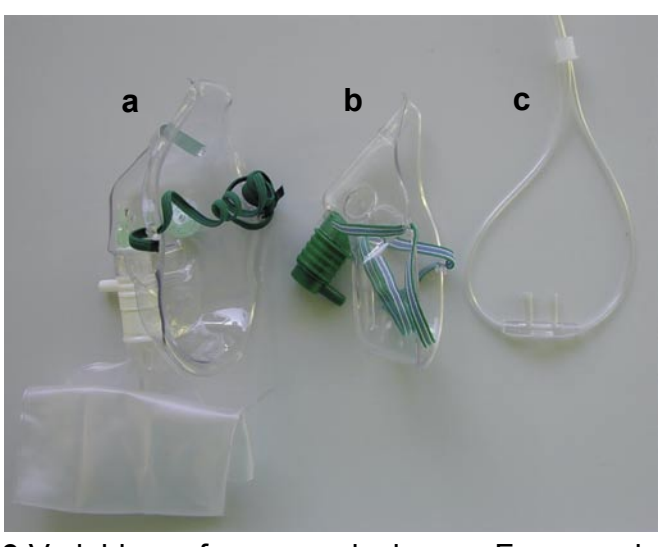
Recovery

Supplementary oxygen should be administered to all patients in the immediate recovery period. This is to prevent hypoxaemia that may otherwise occur from the ventilation–perfusion mismatch induced by surgery and anaesthesia, and the hypoventilation that may ensue from respiratory depressant drugs. Hypoxaemia may also be caused by dilutional hypoxia following cessation of nitrous oxide.

The duration of oxygen therapy may be limited to 15 minutes for young healthy patients undergoing minor day- case procedures, but extended for many hours or days for those with more serious pathology or complicated surgery. Therapy is guided by pulse oximetry or blood gas estimation, and oxygen therapy is usually titrated to achieve oxygen saturation greater than 95%.

Oxygen therapy devices may deliver either a variable or fixed concentration of supplementary oxygen to the inspired gas.

Variable performance devices include nasal prongs and simple 'Hudson'-type face masks with or without an oxygen reservoir (Figure 9). The oxygen flow delivered to the device is typically 2–4 litres/minute, which will be diluted by the air entrained during inspiration. The concentration of inspired oxygen depends on the oxygen flow rate, the patient's respiratory rate and peak inspiratory flow. Typically, 30–40% inspired oxygen is achieved when 4 litres/minute is delivered to a patient via a Hudson mask, and this concentration reduces as respiratory rate and inspiratory flows increase, due to increased air entrainment. The oxygen concentration delivered cannot be predicted accurately. This is usually of no consequence to a patient on the recovery ward, who simply needs supplemental oxygen, though the precise concentration is not critical. The inspired oxygen percentage can be increased further if an oxygen reservoir is used with the mask, and 80% inspired oxygen may then be achieved using a 12–15 litres/minute oxygen flow rate.

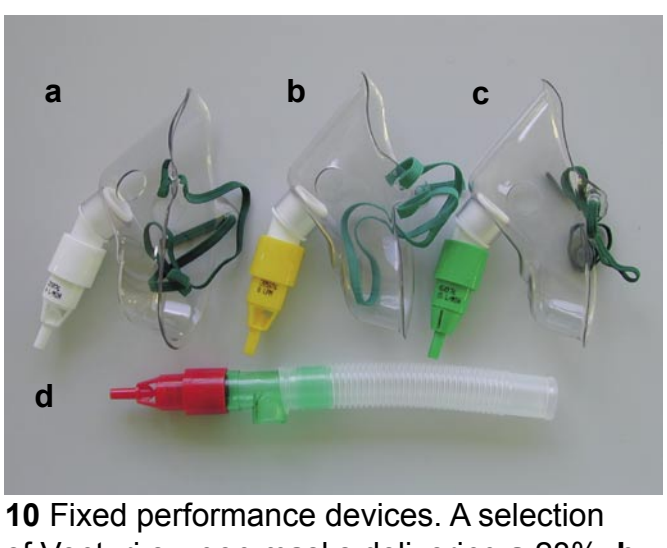


9 Variable performance devices. **a** Face mask with oxygen reservoir bag (folded); **b** simple Hudson-type oxygen face mask; **c** nasal prongs.

Fixed performance devices include face masks with Venturi-type injectors (Figure 10). They achieve a fixed inspired oxygen concentration by ensuring that a high flow rate of oxygen and entrained air is delivered, in excess of the patient's maximum peak inspiratory flow rate.

The use of a Venturi injector face mask delivers about 60 litres/minute of gas and so the inspired oxygen concentration is independent of the characteristics of inspiratory flow. Venturi devices are available to deliver fixed oxygen concentrations between 24% and 60%. The correct oxygen flow rate must be selected for the correct Venturi injector, and used with the correct mask. Details are printed on each Venturi, but typically 2 litres/minute delivers 24% oxygen, and 8 litres/minute delivers 35% oxygen. Venturi injector devices are not interchangeable with masks from different manufacturers, because the mask volume allows for adequate mixing of driving and entrained gases.

Fixed performance devices are often used in the high-dependency setting to enable accurate assessment of oxygenation, in patients with chronic lung disease who depend on a hypoxic respiratory drive, and on the general wards.



10 Fixed performance devices. A selection of Venturi oxygen masks delivering **a** 28%, **b** 35%, **c** 60% oxgen. **d** Venturi T-piece delivering 40% oxygen for use with laryngeal mask airway, tracheal tube or tracheostomy tube.

Anaesthesia for Laparoscopic Surgery

Michael W Platt

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Laparoscopic surgery is a revolution in modern surgical techniques and has reduced postoperative pain, respiratory complications and hospital stay considerably. However, it produces extra stresses on the heart and lungs, therefore patients should be screened carefully and the risks explained fully as part of obtaining consent for the procedure. Anaesthetists should consult their surgical colleagues about the relative risks in those with cardiac and respiratory disease and should be prepared to cope with complications as they arise.

History

The earliest recorded references to endoscopy are from Hippocrates in Greece (460–375 BC), who made reference to a rectal speculum. It was only in the 1970s that the problems of transmitting light, insufflation technology and optical technology were surmounted sufficiently for gynaecologists to embrace laparoscopic surgery. Laparoscopic techniques were not supported whole-heartedly by general surgeons until after 1987, when Mouret performed the first laparoscopic cholecystectomy in France. Following this, the rapid development of solid state video camera technology has further broadened the field of laparoscopic surgery.

The advantages of minimally invasive surgery are less ileus, the greatly reduced stress response to surgery and trauma, reduced acute phase reaction, reduced pain, reduced post-operative pulmonary dysfunction and reduced hospital stay. These also have economic advantages.

More procedures are being developed for laparoscopic surgery, including extraperitoneal inguinal hernia repair and retro-peritoneal nephrectomy and adrenalectomy. Routine general surgical laparoscopic procedures now include: oesophagectomy, Nissen's fundoplication, gastric banding, oversewing of peptic ulcer, intestinal resections, including hemicolectomy and col-ectomy, rectopexy and hernia repair.

Pathophysiology and complications of laparoscopy

The complications of laparoscopy include: haemorrhage, hypotension, decreased cardiac output, acidosis, pneumothorax, pneumomediastinum, subcutaneous emphysema, retroperitoneal carbon dioxide (CO_2), venous stasis, bradycardia, increased vagal tone, cardiac arrest, fatal venous CO_2 embolism, regurgitation and aspiration. Many of these complications are the result of peritoneal insufflation (pneumoperitoneum).

Pneumoperitoneum, the insufflation of the peritoneal cavity, is required to enable a gas milieu for visualization through the laparoscope (the operating telescope). CO_2 is used for laparoscopy because it is highly soluble in blood. Blood can carry large quantities of CO_2 as bicarbonate, carboxyhaemoglobin, and in plasma proteins. Carbon dioxide is eliminated rapidly and the lethal dose as an embolus is five times that of air. Usually a CO_2 gas embolism resolves rapidly, but if it is large, it can be fatal.

Pneumoperitoneum is achieved by insufflating the peritoneal cavity with CO_2 to a pressure of 10–18 mm Hg. The intra-peritoneal insufflation of CO_2 to these pressures causes respir-atory and haemodynamic changes.

Respiratory changes that occur as a result of pneumoperitoneum consist of a reduction of chest compliance by 30–50%. Airway pressures to maintain tidal volume rise to counter the reduction of chest compliance and the elevation of the diaphragm. Functional residual capacity of the lungs decreases and there is an increase in physiological dead space and shunt because of basal compression by the diaphragm and increased ventilation/perfusion mis-matching, which may result in a reduced arterial partial pressure of oxygen. Basal atelectasis may persist into the postoperative period. If minute volume is kept constant, end-tidal CO_2 increases due to absorption of CO_2 from the peritoneal cavity. The latter changes are usually countered by increasing the tidal volume and applying positive end-expiratory pressure (PEEP).

Haemodynamic changes also occur as a result of the pneumo-peritoneum. Compression of the inferior vena cava leads to a reduction in venous return, potentially followed by a fall in cardiac output. However, a reflex tachycardia and a massive increase in peripheral vascular resistance tends to maintain cardiac output at near-normal levels, by pulling blood centrally from the periphery, but with a concomitant increase in mean arterial blood pressure. This increase in myocardial work can result in myocardial ischaemia in those at risk and can lead to infarction, which may not occur until the postoperative period. Active vasodilatation and β blockade are often required to counter these effects.

Compression of the inferior vena cava causes reduced venous flow from the legs, resulting in venous stasis and an increased risk of venous thrombosis. Prophylactic anticoagulation and elastic stockings or pneumatic calf compressors should be used, especially in the elderly.

Respiratory and haemodynamic changes are affected by the patient's position. For example, head-up tilt, used for upper abdominal operations (e.g. cholecystectomy, Nissen's fundoplication) further inhibits venous return. Head-down tilt, used for colonic and pelvic surgery, promotes venous return, but aggravates respiratory changes, further reducing chest compliance and functional residual capacity and increasing basal compression.

Other complications of pneumoperitoneum include surgical emphysema, which can affect most tissues, including the conjunctivae and the scrotal sack. Cardiac arrhythmias can be secondary to vagal stimulation (bradycardia) or to hypercarbia (tachyarrythmias). Pneumothorax (including tension pneumo-thorax) may occur, particularly with upper abdominal procedures such as Nissen's fundoplication. Gastric reflux can occur because of increased intraperitoneal pressure, although retained gas in the stomach may obstruct the surgeon's view for upper abdominal operations. Pressure on the renal veins and arteries may cause a temporary reduction in renal function, due to reduced renal blood flow. Major CO_2 gas embolus seldom occurs and is usually the result of accidental direct injection of gas into a major vessel (e.g. the inferior vena cava). This may cause an obstruction to cardiac output when it reaches the heart. The treatment is to turn the patient onto the right side immediately and position them head down, causing the gas embolus to occupy the apex of the right ventricle, relieving the obstruction to ventricular outflow.

Anaesthetic technique

Preoperative assessment

Patients should be assessed carefully preoperatively, focussing on their cardiac function and reserve, because of the amount of extra cardiac work required during pneumoperitoneum. Patients with significant cardiac disease and limited cardiac reserve should be assessed by a cardiologist. It may be that an open procedure or even cancelling the procedure would be best for the patient. Patients with added risks of venous thrombosis should be treated prophylactically with fractionated heparin, elastic stockings and calf compressors during surgery. Surgery for patients with previously untreated hypertension should be postponed until treatment has stabilized. Respiratory function should also be assessed. Pulmonary function tests should be performed in those with significant pulmonary disease. Liver and renal function need to be ascertained because these organs may also be affected by pneumoperitoneum. Intercurrent medications (especially antihypertensives) should be given as normal on the morning of operation. A light sedative, such as a short-acting benzodiazepine, may be given before surgery.

Perioperative management

A routine intravenous induction is appropriate. It is preferable to intubate and ventilate patients undergoing laparoscopic surgery. This ensures a secure airway while ventilating with higher airway pressures and reducing the inherently small risk of aspiration from gastric regurgitation. A large-bore intravenous cannula should be placed to allow ready access for the management of major complications. In upper abdominal procedures a 12–16 FG oro- or nasogastric tube is passed to allow egress of gas from the stomach to facilitate the surgeon's view.

Maintenance may be by total intravenous or inhalational anaesthesia. Intermittent positive-pressure ventilation is preferable, to ensure adequate ventilation in the presence of the reduced compliance and elevated diaphragm caused by the pneumo-peritoneum.

Opioid supplementation aids analgesia and improves post-operative analgesia. This may be as intermittent morphine and diamorphine or as an infusion of a short-acting agent such as alfentanil or remifentanil.

Monitoring should be the minimum standard of non-invasive blood pressure, electrocardiograph, end-tidal CO_2, anaesthetic gases and pulse oximetry. For patients who require laparoscopic surgery, but who have very borderline cardiac function, invasive blood pressure and central venous pressure may be necessary, to allow closer control of cardiac function, in particular myocardial work. A pulmonary artery flotation catheter may be considered if there is concern regarding left heart function.

When peritoneal insufflation begins, there is often a reflex tachycardia and significant increase in blood pressure, even at deep levels of anaesthesia. To avoid hypertensive crises, with diastolic blood pressures above 120 mm Hg, it is advisable to have a vasodilator and β blocker available. Carefully titrated doses of labetalol can be effective, with its combined α and β effects. Occasionally, vagally-mediated bradycardia, even to the point of sinus arrest, may be seen. In this case, insufflation should cease immediately, while an appropriate vagolytic (e.g. atropine) is given. Ventilation should be adjusted to increase tidal volume and PEEP applied to counter the reduced compliance, elevated diaphragm and increased CO_2 load.

At the end of the procedure, it is preferable for the surgeon to infiltrate the small port wounds with long-acting local anaesthetic to reduce postoperative pain. The raw areas of tissue that occur after cholecystectomy can contribute to pain, due to carbonic acid formation by CO_2. Spraying the peritoneal cavity with bupivacaine may be effective in these cases.

Recovery

Pain in the immediate postoperative period can be severe, presumably due mainly to stretching of the tissues. Shoulder-tip pain is common, secondary to diaphragmatic irritation. Sitting the patient up and giving systemic analgesia should help this to settle. Occasionally, large doses of intravenous opioid are required for adequate relief. However, once the pain is controlled, recovery is rapid and the patient usually goes home in 2–3 days.

Postoperative complications

Surgical emphysema is occasionally alarming because it involves much of the trunk. It is advisable to deflate the scrotal sack before recovery. More generalized emphysema settles rapidly with time, but a pneumothorax should be excluded. The main problem with surgical emphysema is pain, which should be controlled systemically. Basal atelectasis with secondary pulmonary infection may also occur. It is more common in those with pre-existing pulmonary disease, and should be treated with antibiotics and physiotherapy. Aspiration may manifest as pleural effusions or rarely as Mendelson's syndrome. These may require the input of a respiratory physician, but are not usually a major problem in fasted patients.

The most serious complications are usually haemodynamic. Postoperative myocardial infarction can occur as a result of the increase in myocardial work during the procedure.

Deep venous thrombosis may occur due to venous stasis in the legs during surgery. This occasionally presents postoperatively with pulmonary embolus. ◆

FURTHER READING

Chui P T, Gin T, Oh T E. Anaesth Intens Care 1993; 21(2): 163–71.

Anaesthesia for Reconstructive Free Flap Surgery

Jane Quinlan

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Reconstructive free flap surgery is a complex method of wound closure for large wounds not amenable to linear (primary) closure. It involves the transfer of free tissue (skin, muscle, bone, bowel or a combination) to a site of tissue loss where its circulation is restored via microvascular anastomoses. A muscle flap produces a more even contour and better aesthetic appearance than that achieved by a simple skin graft and provides a better defence against infection. The defect may be caused by trauma, infection or extensive surgery (e.g. mastectomy, head and neck cancer). The site and size of the defect determines which flap is used. The most commonly used flaps are the gracilis muscle for lower leg trauma; latissimus dorsi and rectus abdominis for breast reconstruction; and pectoralis major and radial forearm flap for head and neck reconstruction.

In patients with lower third tibulofibular defects, free tissue transfer is typically required. The bony injury should be repaired and adequate debridement achieved before skin and muscle coverage begins. This should occur within the first 6 days after injury before colonization of the wound and the risk of complications increases. In patients with multiple trauma, any life-threatening injuries must be addressed first and the patient's haemodynamic status stabilized before reconstructive surgery is contemplated.

Flap transfer

The free flap is transferred with its accompanying artery and vein, which are then reattached to vessels at the donor site using microvascular techniques. The stages of flap transfer are:

- flap elevation and clamping of vessels
- primary ischaemia as blood flow ceases and intracellular metabolism becomes anaerobic (this is dependent on surgical time and lasts 60–90 minutes)
- reperfusion as the arterial and venous anastomoses are completed and the clamps released
- secondary ischaemia is subsequent to hypoperfusion of the flap (minimized by appropriate anaesthetic management).

Primary ischaemia

With cessation of blood flow, the flap becomes anoxic. In the presence of anaerobic metabolism, lactate accumulates, intra-cellular pH drops, ATP decreases, calcium levels rise and pro-inflammatory mediators accumulate. The severity of the damage caused by primary ischaemia is proportional to the duration of ischaemia. Tissues with a high metabolic rate are more susceptible to ischaemia, therefore skeletal muscle in a flap is more sensitive to ischaemic injury than skin. At the conclusion of primary ischaemia, the changes in the flap tissue include:

- narrowed capillaries due to endothelial swelling, vasoconstriction and oedema
- sequestration of leucocytes ready to release proteolytic enzymes and reactive oxygen intermediates
- diminished ability of endothelial cells to release vasodilators and degrade ambient vasoconstrictors
- end-organ cell membrane dysfunction and accumulation of intracellular and extracellular toxins
- up-regulation of enzyme systems to produce inflammatory mediators.

Reperfusion begins with the release of the vascular clamps. Normally, the re-establishment of blood flow reverses the transient physiological derangement produced by primary ischaemia. The flap recovers with minimal injury and normal cellular metabolism is restored. However, an ischaemia/reperfusion injury may result if factors in the flap are unfavourable. Prolonged ischaemia time or poor perfusion pressure make this more likely. Reperfusion injury occurs when the restored blood flow allows the influx of inflammatory substrates that may ultimately destroy the flap.

Secondary ischaemia occurs after a free flap has been transplanted and reperfused. This period of ischaemia is more damaging to the flap than primary ischaemia. Flaps affected by secondary ischaemia have massive intravascular thrombosis and significant interstitial oedema. Fibrinogen and platelet concentrations are increased in the venous effluent. Although skin flaps can tolerate 10–12 hours of ischaemia, irreversible histopathological changes in muscle can be seen after 4 hours.

Causes of flap failure: the general causes of poor flap perfusion may be classified as arterial, venous or resulting from oedema. The arterial anastomosis may be inadequate, in spasm or thrombosed. The venous anastomosis may similarly be defective, in spasm or compressed (e.g. by tight dressings or poor positioning). Oedema reduces flow to the flap and may be a result of excessive crystalloids, extreme haemodilution, trauma from handling or a prolonged ischaemia time. Flap tissue has no lymphatic drainage and is therefore susceptible to oedema.

Microcirculation: the blood flow through the microcirculation is crucial to the viability of a free flap. The microcirculation is a series of successive branchings of arterioles and venules from the central vessels. Regulation of blood flow and oxygen delivery is accomplished by three functionally distinct portions of the microcirculation: the resistance vessels, the exchange vessels and the capacitance vessels.

The resistance vessels are the muscular arterioles that control regional blood flow. Arterioles range in diameter from 20 μm to 50 μm and contain a relatively large amount of vascular smooth muscle in their walls. Alterations in vascular smooth muscle tone are responsible for active constriction and dilation in arterioles and thus control resistance to blood flow.

The capillaries constitute the network of vessels primarily responsible for the exchange function in the circulation. Small bands of vascular smooth muscle, the precapillary sphincters, are located at the arterial end of many capillaries and are responsible for the control of blood flow within the capillaries.

The venules act as the capacitance vessels, which collect blood from the capillary network and function as a reservoir for blood in the circulation.

The vascular bed of skeletal muscle has rich adrenergic in-nervation and therefore has a marked vasoconstrictor response to neural stimulation, primarily through the resistance vessels. Precapillary sphincters also constrict in response to sympathetic stimulation, but are sensitive to local factors such as hypoxia, hypercapnia, and increases in potassium, osmolality and mag-nesium, which may cause relaxation. Other vasoactive hormones (e.g. renin, vasopressin, prostaglandins, kinins) also have a role in microvascular control.

Transplanted vessels in a free flap have no sympathetic innervation but are still able to respond to local and humoral factors, including circulating catecholamines.

The flow behaviour (rheology) of blood in the microcirculation is determined by the red cell concentration, plasma viscosity, red cell aggregation and red cell deformability. Following all surgery under general anaesthesia, the changes in blood rheology include:

- increased platelet aggregation and adhesion
- an impairment of red cell deformability
- an increase in whole blood viscosity
- increased clotting factors
- increased plasma fibrinogen and red cell aggregation
- disturbance of fibrinolysis.

Normal levels of 2,3-diphosphoglycerate (2,3-DPG) are required for optimal red cell deformability. After blood transfusion, this deformability is impaired owing to the negligible amount of 2,3-DPG in stored blood.

Physiology

The physiological status of the patient has a major influence on the viability of the transferred tissues, so the conduct of anaesthesia and postoperative management have a direct effect on outcome. Surgery is long (often 6–8 hours) with multiple sites for tissue trauma, resulting in extensive blood and fluid losses as well as heat loss. The resulting hypovolaemic vasoconstriction and hypothermia, if not corrected, compromise blood flow to the flap and result in flap failure.

Even with good fluid management, blood flow to a flap may decrease by 50% for 6–12 hours postoperatively. The guiding principle of anaesthesia for free flap surgery is the maintenance of optimum blood flow. The determinants of flow are summarized by the Hagen–Poiseuille equation:

$$\text{Laminar flow} = \frac{\Delta P \times r^4 \times \pi}{8 \times \eta \times l}$$

where: ΔP is the pressure difference across the tube, r is the radius of the vessel, η is viscosity and l is the length of the tube.

From this we may deduce that the goals of anaesthesia for free flap surgery are vasodilatation, good perfusion pressure and low viscosity.

Vasodilatation

Vessel radius is the most important determinant of flow, for the vessels supplying the flap as well as those in the flap.

Temperature – the patient should be kept warm in theatre, the recovery room and the ward for the first 24–48 hours. This is best achieved by raising the ambient temperature in theatre and by using a warm air blanket. Active warming should begin before the start of anaesthesia because patient cooling occurs rapidly after induction of anaesthesia. In an awake patient, the central core temperature is higher than that of the peripheral tissue and skin temperature. After the induction of anaesthesia, vasodilatation modifies the thermal balance between compartments. The volume of the central compartment enlarges leading to a decrease in its mean temperature, while the temperature of the peripheral and skin compartments increases. At thermoregulation, the size of the central compartment becomes smaller owing to vasoconstriction, which leads to an increase in the mean temperature, although the peripheral and skin temperatures fall.

In addition to vasoconstriction, hypothermia also produces a rise in haematocrit and plasma viscosity, the aggregation of red blood cells into rouleaux, and platelet aggregation. These effects may reduce the microcirculatory blood flow in the flap.

Fluid – peripheral vasoconstriction due to an underestimation of fluid losses is common. There are two operating sites in free flap transfer: the donor site and the recipient site. Both have insensible fluid losses and both may have blood losses. A warm theatre environment also increases fluid loss. Modest hypervolaemia reduces sympathetic vascular tone and dilates the supply vessels to the flap. An increase in central venous pressure of 2 cm H_2O above the control measurement can double the cardiac output and produce skin and muscle vasodilatation. Figure 1 gives a guide to fluid management.

Guide to fluid management

Crystalloids
- 10–20 ml/kg to replace preoperative deficit
- 4–8 ml/kg/hour to replace insensible losses

Colloids
- 10–15 ml/kg for haemodilution
- To replace blood loss

Blood
- To maintain haematocrit at 30%

Dextran
- Often given postoperatively

1

Anaesthesia – isoflurane has the advantage over other volatile anaesthetics and propofol that it causes vasodilatation with minimal myocardial depression. Propofol inhibits platelet aggregation which could reduce the risk of thrombosis. This may be due to an effect of intralipid on the platelet–erythrocyte interaction, and by the increased synthesis of nitric oxide by leucocytes.

Vasospasm of the transplanted vessels may occur after surgical handling or after damage to the intima of the vessels, and can occur during surgery or postoperatively. The surgeons may use topical vasodilators such as papaverine, lidocaine (lignocaine) or verapamil during the operation to relieve the vasospasm.

Sympathetic blockade – epidural, brachial plexus or interpleural local anaesthetic infusions, used intraoperatively and postoperatively, provide sympathetic blockade to further dilate vessels. Concerns have been raised that the sympathetically-denervated transplanted vessels would be unable to dilate after lumbar epidural blockade, resulting in a 'steal' effect reducing flap blood flow. In fact, provided any hypotension due to the sympathetic block is treated appropriately, blood flow to the flap improves as a result of the increased flow through the feeding recipient artery. Other advantages of epidural analgesia include a reduction in intraoperative and postoperative blood loss and vessel spasm; a lower incidence of deep venous thrombosis; improved diaphragmatic function and more rapid post-operative recovery. Good analgesia reduces the level of circulating catecholamines and avoids the vasoconstrictor response to pain.

Perfusion pressure

The preservation of a good perfusion pressure with wide pulse pressure is essential to flap survival. Appropriate anaesthetic depth and aggressive fluid management are usually all that is needed. Most inotropes are contraindicated owing to their vasoconstrictive effects, but if required, dobutamine and low-dose dopamine could be used.

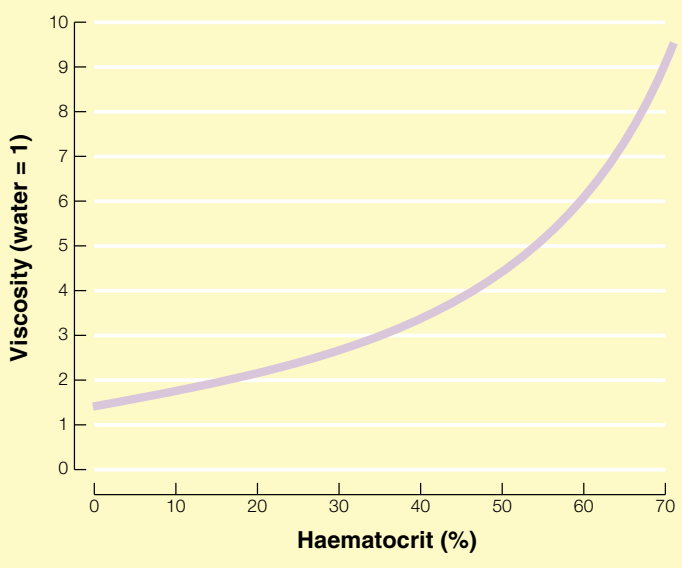
Viscosity

Isovolaemic haemodilution to a haematocrit of 30% improves flow by reducing viscosity, reducing reperfusion injury in muscle and increasing the number of patent capillaries, which decrease tissue necrosis. Further reductions in haematocrit do not provide much more advantage because the curve of viscosity versus haematocrit flattens off markedly (Figure 2). If the haematocrit falls further, the marginally improved flow characteristics from a lower viscosity may then be offset by a reduction in oxygen delivery:

$$DO_2 = CO \times [(Hb \times sat \times 1.34) + (PaO_2 \times 0.003)]$$

A low haematocrit also increases myocardial work, therefore care should be taken in patients with poor cardiac reserve.

Viscosity versus haematocrit



Source: MacDonald D J F. *Br J Anaesth* 1985; **57:** 904–21.

Practical conduct of anaesthesia

Monitoring

In addition to basic monitoring, these patients require invasive blood pressure monitoring to enable safe manipulation of the perfusion pressure. Direct measurement of arterial pressure gives a continuous record of the pressure and is more accurate than non-invasive indirect techniques. An arterial cannula also provides access to blood gas analysis and haematocrit estimations.

Central venous pressure reflects cardiac filling pressures and can be manipulated to increase cardiac output.

Core temperature measurement is essential when active warming is instituted. A nasopharyngeal or rectal probe is used intraoperatively for a continuous reading, while intermittent tympanic or axillary measurements are used in the recovery and ward areas.

Peripheral temperature is also measured because a fall in skin temperature can reflect hypovolaemia and vasoconstriction. A difference of less than 2°C between core and peripheral temp-eratures indicates a warm, well-filled patient. The temperature of the skin flap is sometimes monitored postoperatively because a drop in temperature may herald flap failure. However, this is not a sensitive test, because by the time the temperature has fallen the flap will have suffered sufficient vascular damage to render it virtually unsalvageable.

Urine output is another indicator of volume status. A urine output of 1–2 ml/kg/hour should be maintained intraoperatively and postoperatively with appropriate fluid management. Diuretics are contraindicated in these operations because volume depletion compromises flap survival.

Induction

Active warming starts before the patient is asleep. The ambient temperature in theatre is raised to about 22–24°C, a level high enough to reduce patient heat loss, but not too hot to be uncomfortable for the theatre staff. The patient is covered in a hot air blanket before induction of anaesthesia and this remains in place while the patient is prepared for theatre. Once in theatre, the blanket is moved to enable surgical access, but with as much surface area coverage as possible.

If appropriate, a regional block is inserted, preferably to cover the free flap recipient site (rather than the donor site) for the full benefit of the sympathetic block. The patient is intubated and ventilated; and a large gauge peripheral line, central line, arterial line, urinary catheter and core temperature and skin temperature probes are positioned.

Nitrous oxide diffusion into air in the stomach combined with gastric stasis results in gastric distension, with associated post-
operative nausea and vomiting. A nasogastric tube is therefore sited at intubation, left on free drainage, then aspirated and removed at the end of the operation.

Fluid, administered through a fluid warmer, is started in the anaesthetic room to compensate for preoperative dehydration.

Maintenance

Careful positioning of the patient is imperative for such a long operation. Limbs are positioned and supported to avoid neuro-logical damage or vascular compression. Eyes are taped and lightly padded to reduce the incidence of corneal abrasion and prevent drying of the cornea.

Prophylaxis against deep venous thrombosis is necessary for all patients. Subcutaneous heparin or low-molecular-weight heparin is given preoperatively, while anti-embolism (TED) stockings and compression boots are used intraoperatively.

The patient is ventilated to normocapnia. Hypocapnia increases peripheral vascular resistance and reduces cardiac output, while hypercapnia causes sympathetic stimulation. If the surgeon uses the microscope for vessel preparation or anastomosis on the chest or abdomen, the tidal volume is reduced to minimize movement in and out of the surgeon's field of vision. The respiratory rate is then increased to maintain minute ventilation.

Controlled hypotension is useful during the initial dissection and is most easily achieved using epidural local anaesthetic and/or isoflurane. An infusion of glyceryl trinitrate may be added if needed.

Crystalloids are used to replace the preoperative fluid deficit from starvation and to cover intraoperative insensible losses. The latter are high because the warm theatre increases evaporative losses from the two operating sites. Excessive use of crystalloid may precipitate oedema in the flap.

Hypervolaemic haemodilution is achieved using colloids.

Blood gas analysis and haematocrit measurement should be carried out at the start of the operation and repeated every 2 hours.

By the time the flap is reperfused, the patient should be warm, well-filled and sympathetically blocked with a high cardiac output.

Emergence and recovery

The patient should wake up pain-free. Analgesia is maintained postoperatively with local anaesthetic infusions for regional blocks, intravenous patient-controlled analgesia, or both. Coughing and vomiting increase venous pressure and reduce flap flow, so smooth emergence and extubation are needed. The principles of perioperative and postoperative care are listed in Figure 3. ◆

Principles of perioperative and postoperative care

- Maintain high cardiac output
- Normal arterial blood pressure (systolic >100 mm Hg)
- Low systemic vascular resistance
- Normothermia
- High urine output (> 1 ml/kg/hour)
- Effective analgesia
- Haematocrit 30–35%
- Monitoring of blood flow in flap (Doppler postoperatively)

FURTHER READING

MacDonald D J F. Anaesthesia for Microvascular Surgery. *Br J Anaesth* 1985; **57:** 904–21.

Sigurdsson G H, Thomson D. Anaesthesia and Microvascular Surgery: Clinical Practice and Research. *Eur J Anaesthesiol* 1995; **12:** 101–22.

The Anaesthetic Machine

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Many anaesthetic machines incorporate patient monitoring; conventionally this is considered separately and will not be discussed here.

Types of anaesthetic machine

Demand and intermittent flow machines
The patient's inspiration controls the flow of fresh gases. Such machines have been used for dental anaesthesia (e.g. the McKesson anaesthetic machine) and for military field anaesthesia (the Triservice apparatus).

Continuous flow machines (Boyle's machine)
Continuous flow machines are encountered in day-to-day hospital practice in the UK. The driving force for gas flow is compressed gases. This contribution discusses continuous flow machines.

Pressures in the anaesthetic machine

Units of pressure
To understand the anaesthetic machine, it is important to be able to relate the various different units that are used to describe pressure; 1 atmosphere pressure is approximately:

- 101 kPa
- 760 mm Hg
- 1035 cm H_2O
- 1 bar
- 15 psi.

Absolute and gauge pressure

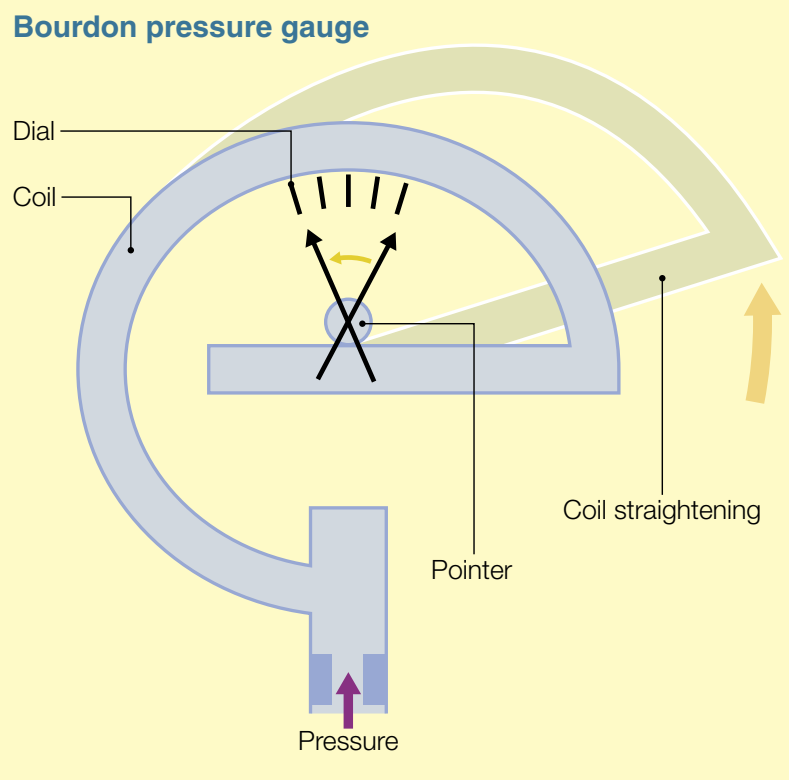
- Absolute pressure is pressure above that in a vacuum.
- Gauge pressure is pressure above atmospheric. Pressures in the anaesthetic machine are always quoted as gauge pressures.

All pipeline pressures are 400 kPa except for pressure in the air pipeline used to drive equipment such as orthopaedic drills, which is 700 kPa. Cylinder pressures are reduced to a machine working pressure of 400 kPa by pressure regulators (see below, page 66).

Pressure downstream of the flowmeters can range between zero (i.e. 1 atmosphere pressure), when the common gas outlet is open to the atmosphere, and about 33 kPa if the common gas outlet is completely obstructed and the safety valve in the back bar vents to the atmosphere.

Measurement of pressure
Cylinder and pipeline pressures are measured by a Bourdon pressure gauge (Figure 1). This is an aneroid (i.e. without liquid) gauge consisting of a coiled tube attached at one end to the gas supply and at the other to a pointer. The pressure of the gas causes straightening of the coil and thus movement of the pointer over the colour-coded, labelled and calibrated dial (Figure 2). The gauge is faced with heavy glass and designed such that leaks vent from the back of the valve casing and do not blow out the glass.

Bourdon pressure gauge



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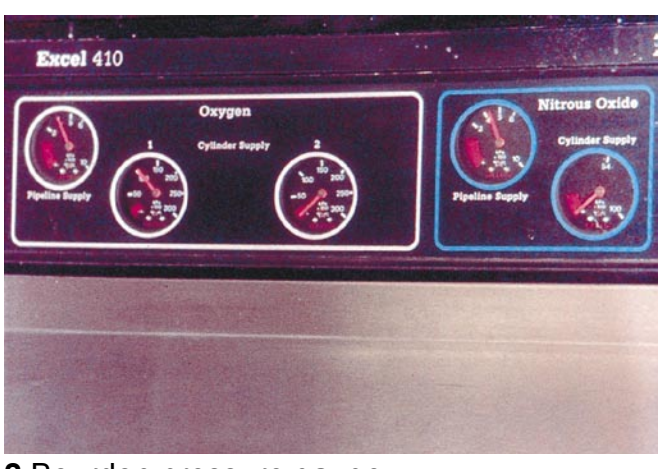
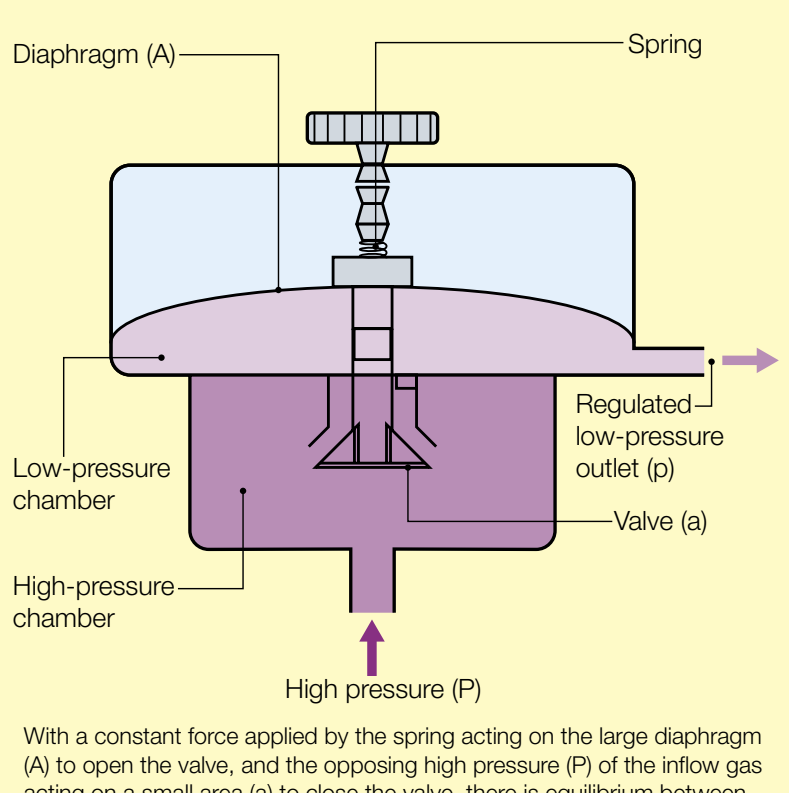


2 Bourdon pressure gauge.

Pressure regulators
Although sometimes referred to as pressure-reducing valves, the term pressure regulators is preferred because their function is not simply to reduce pressure, but in doing so to allow more accurate control of flow and to make up for the fall in cylinder pressures as they empty.

Figure 3 demonstrates the function of a pressure regulator. The principle is similar to that of the pressure-relief valve (see *Anaesthesia and Intensive Care Medicine* **1:3:** 107) except that there are two chambers, one of high pressure and the other of low, and two discs of different areas.

Pressure regulator



With a constant force applied by the spring acting on the large diaphragm (A) to open the valve, and the opposing high pressure (P) of the inflow gas acting on a small area (a) to close the valve, there is equilibrium between the high- and low-pressure chambers. To balance the equilibrium and keep the valve open, the pressure in the second chamber is thus reduced. Thus: P x a = p x A, where P = pressure in the high-pressure chamber; p = pressure in the low-pressure chamber; A = area of large diaphragm; a = area of small diaphragm.

Adjustment of the tension in the spring and thus the force it applies to the discs, regulates the pressure at the outlet to produce a constant operating pressure. As the inlet pressure falls during use of the cylinder, the force from the spring opens the valve wider, allowing more gas to flow into the second chamber and maintaining pressure at the outlet. The opposite happens if the inlet pressure rises, resulting in valve closure and thus less flow into the second chamber.

3

Flowmeters

Rotameters
Flow in most anaesthetic machines is measured by a variable orifice flowmeter known as a rotameter. A rotameter consists of a bobbin that floats in a glass tube with a diameter that increases with height up the tube. The pressure drop across the bobbin remains constant, and as flow increases it rises up the tube.

The two important properties of the gas flowing through a rotameter that influence its calibration are:

- viscosity
- density.

Gas flows in the annulus between the bobbin and the tube. At the lower end of the tube the annulus is long with respect to its cross-sectional area, and flow is laminar and dependent on the viscosity of the gas. Higher up the tube, the cross-sectional area of the annulus is greater, the gas is effectively flowing through an orifice, and flow is turbulent and dependent on the density of the gas (Figure 4).

Flowmeter

Laminar flow around the bobbin at the bottom of the tube, turbulent flow at the top. NB Pitch of the rotameter tube has been greatly exaggerated

4

Features of rotameters

- For any given gas, the flow through a rotameter depends on both its viscosity and its density. Rotameters therefore have to be calibrated individually for the gas they will be measuring.
- The bore may be varied to measure low flows accurately.
- The back plate may be luminous.
- Calibration is from the lowest accurate point, not zero.
- Accuracy is ± 2%.
- In many machines there is a constant low flow of oxygen.

Potential sources of inaccuracy in rotameters

- If the tube is not truly vertical, the annulus between the tube and the bobbin is altered.
- Static electricity can cause inaccuracies. To minimize this, glass is conductive and sprayed with antistatic material.
- Dust can collect on the bobbin or within the tube.
- Tubes may be damaged. In the UK, the oxygen rotameter tube is on the left (said to be because Boyle was left-handed). This can mean that any damage to the tubes would preferentially leak oxygen and result in the delivery of a hypoxic mixture. Many manufacturers now arrange the order in which the gases finally mix so that oxygen is the last gas added to the mixture.
- The top-sealing washer may be defective.
- The carbon dioxide bobbin may become stuck at the top of the tube.
- Back pressure from a minute volume divider such as a Manley ventilator increases the density of the gas and may cause the rotameter to under-read by about 7%.
- Atmospheric pressure affects density. Low pressure gives over-reading.
- Temperature affects density and viscosity. Increased temperature causes decreased density and increased viscosity.

Vaporizers

Vaporizers are discussed elsewhere.

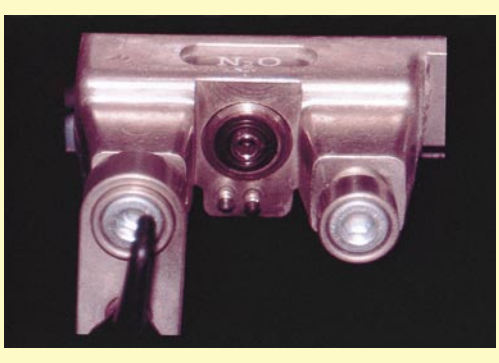
Safety

The anaesthetic machine has several in-built safety features that vary from machine to machine. The commonly found features that are of importance to anaesthetists are listed in Figure 5.

Perhaps the most important safety feature is that the machine should always be checked in a systematic fashion before use. The Association of Anaesthetists of Great Britain and Ireland has published a useful checklist, part of which is reproduced in Figure 6. These checks must be performed at the beginning of each theatre session.

Anaesthetic machine – safety features

- Non-interchangeable pipeline outlets (often referred to as Schrader connectors, though this is really a trade name)
- Pipelines are coloured and marked with the name of the gas
- Non-interchangeable screw thread connectors connect the pipeline to the anaesthetic machine
- The pin index system prevents accidental connection of the wrong cylinder to the wrong yoke
- Cylinders are coloured and marked with the name of the contents
- Grease can be flammable or explosive in contact with gases at high pressure. A Bodok seal (see below) makes a gas-tight connection between cylinder and yoke
- There are pressure gauges for pipelines and cylinders
- Rotameter knobs are identified by the oxygen knob being a distinctive colour and shape and more prominent
- The oxygen rotameter outlet may be diverted to enter the gas flow last
- Oxygen and nitrous oxide rotameters may be linked to prevent delivery of a hypoxic mixture
- The oxygen bypass can provide oxygen at high flow (> 30 litres/minute) directly to the common gas outlet
- There is an oxygen failure warning device triggered by a dropin the oxygen pressure, which also vents the flow of anaesthetic gases to the atmosphere to prevent delivery of a hypoxic mixture
- Vaporizer fillers are keyed to prevent a vaporizer being accidentally filled with the wrong agent
- Vaporizers may be arranged so that only one can be turned on at a time
- There is a machine pressure-relief valve in the back bar that prevents the pressure rising above about 33 kPa
- The machine is serviced regularly by a qualified engineer



Bodok seal.

Anaesthesic machine – safety checks

Anaesthetic machine

- Check that the anaesthetic machine and relevant ancillary equipment are connected to the mains electrical supply (where appropriate) and switched on
- Careful note should be taken of any information or labelling on the anaesthetic machine that might refer to its current status

Oxygen analyser

- The oxygen analyser should be placed where it can monitor the composition of the gases leaving the common gas outlet
- The analyser should be switched on, checked and calibrated according to the manufacturer's instructions

Medical gas supplies

- Identify and take note of the gases that are being supplied by the pipeline, confirming with a 'tug test' that each pipeline is correctly inserted into the appropriate gas supply terminal
- Check that the anaesthetic apparatus is connected to a supply of oxygen and that an adequate reserve supply of oxygen is available from a spare cylinder
- Check that adequate supplies of any other gases intended for use are available and connected as appropriate. All cylinders should be securely seated and turned ***Off*** after checking their contents. Carbon dioxide cylinders should not normally be present on the anaesthetic machine. A blanking plug should be fitted to any empty cylinder yoke
- All pressure gauges for pipelines connected to the anaesthetic machine should indicate 400 kPa
- Check the operation of flowmeters, ensuring that each control valve operates smoothly and that the bobbin moves freely through its range without sticking. With only the oxygen flow control valve open and a flow of about 5 litres/minute, check that the oxygen analyser display approaches 100%.

Turn off all flow control valves

- Operate the emergency oxygen bypass control and ensure that flow occurs without significant decrease in the pipeline supply pressure. Confirm that the oxygen analyser display approaches 100% during this test. Ensure that the emergency oxygen bypass control ceases to operate when released

Vaporizers

- Check that the vaporizer(s) for the required volatile agent(s) are fitted correctly to the anaesthetic machine, that any back bar locking mechanism is fully engaged and that the control knobs rotate fully through the full range(s). Ensure that the vaporizer is not tilted.

Turn off the vaporizers

- Check that the vaporizer(s) are adequately filled and that the filling port is tightly closed
- Set a flow of oxygen of 5 litres/minute and, with the vaporizer turned off, temporarily occlude the common gas outlet. There should be no leak from any of the vaporizer fitments and the flowmeter bobbin should dip.

Turn each vaporizer on in turn and repeat this test. There should be no leak of liquid from the filling port.

After this test, ensure that the vaporizers and flowmeters are turned off

Should it be necessary to change a vaporizer at any stage, it is essential to repeat the leak test.

Failure to do so is one of the most common causes of critical incidents

Removal of a vaporizer from a machine in order to refill it is not considered necessary

Source: Association of Anaesthetists of Great Britain and Ireland. *Checklist for Anaesthetic Apparatus, 1997.*

FURTHER READING

Association of Anaesthetists of Great Britain and Ireland. *Checklist for Anaesthetic Apparatus, 1997.*

Moyle J T B, Davey A. *Ward's Anaesthetic Equipment.* 4th ed. Philadelphia: Saunders, 1998.

Artificial Ventilation in the Operating Theatre

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Ventilators are used in two main settings: the operating theatre and the ICU.

- In the operating theatre, ventilators are used to maintain ventilation in anaesthetized, intubated, pharmacologically paralysed patients who have predominantly normal lungs. These ventilators are designed to interface with anaesthetic gas circuits to allow varying concentrations of oxygen, anaesthetic gases and volatile agents to be delivered to the patient. Most theatre ventilators are relatively simple, mechanical or electromechanical devices that do not have patient-sensing capabilities.
- Ventilators are often used in the ICU to ventilate patients with abnormal lungs, who require only air and oxygen as respiratory gases; these patients are seldom paralysed and often require only partial respiratory support. The ventilators used are almost all complex, computer-controlled devices with sensitive mechanisms to detect the patient's respiratory efforts.

This contribution discusses ventilators for theatre use, though many of the basic principles apply to ICU devices.

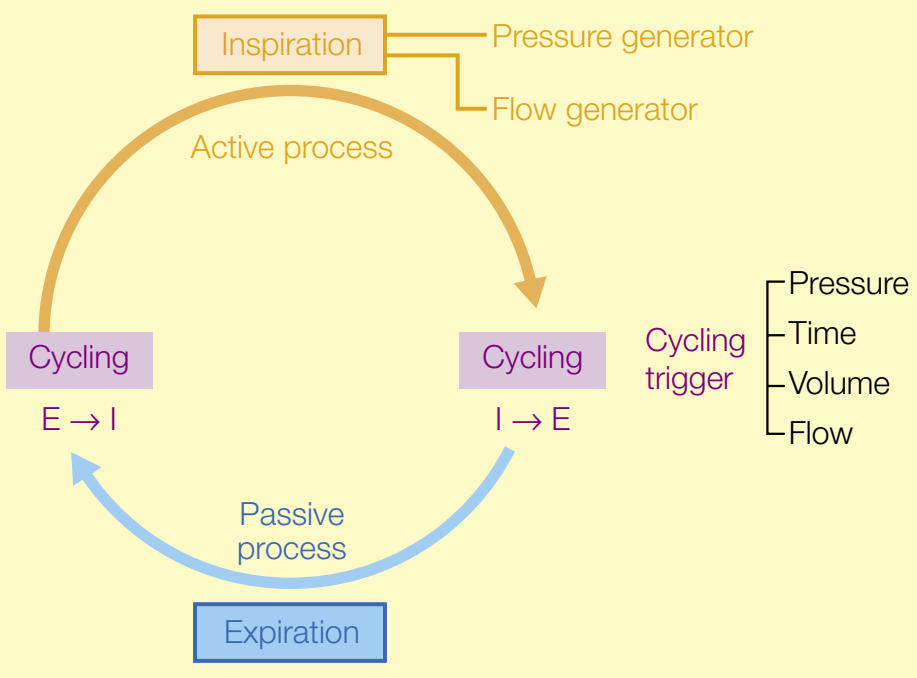
Classification of anaesthetic ventilators

Ventilators can be classified according to their function and operation.

- Functional classification is the most common and clinically useful system. It is based on the pattern of gas that the ventilator generates during inspiration, and the mechanism that cycles between inspiration and expiration (Figure 1).
- Operational classification is based on parameters such as power source or driving mechanism. Operational classification is not covered in this contribution.

Ventilator classifications were devised when most ventilators had only one mode of ventilation. Examples of such ventilators are the Manley ventilator (a time-cycled pressure generator), the Nuffield 200 ventilator (a time-cycled flow generator) and paediatric theatre ventilators (time-cycled pressure generators). Modern theatre ventilators and all ICU ventilators can operate in two or more ventilatory modes and so do not fit neatly into one single category of the traditional functional classification.

Functional classification of the respiratory cycle during intermittent positive-pressure ventilation



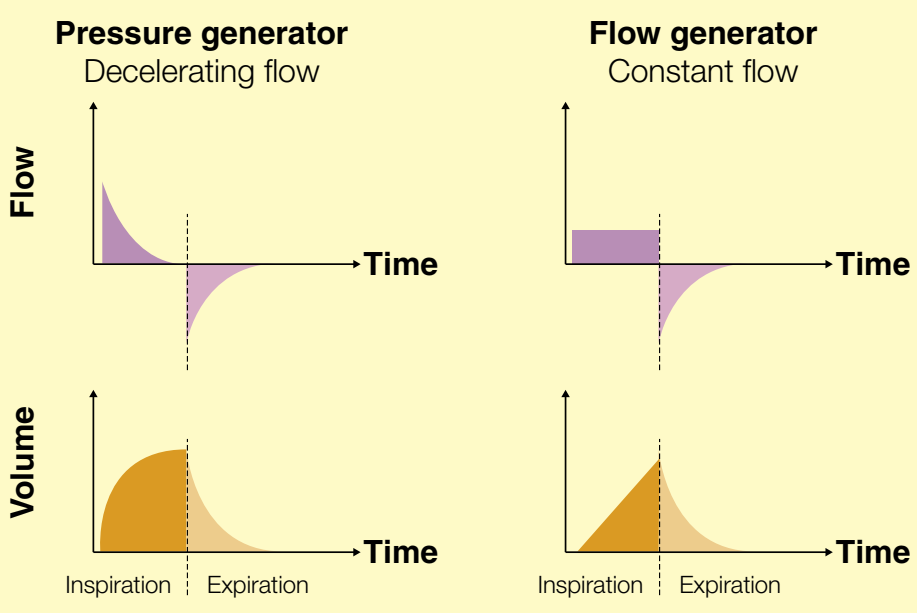
Based on Mapleson classification. I, inspiration; E, expiration

1

Functional classification of ventilators

The important difference between pressure and flow generators is the pattern of gas flow produced during inspiration. This influences the effects of changes in airway resistance, or lung and chest wall compliance, or if there is leak of delivered gases from the system. A summary of the important differences between pressure and flow generators is shown in Figure 2. Knowledge of the basic respiratory mechanics is vital to understanding ventilator–patient interactions.

Pressure generators and flow generators



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Resistance, compliance and time constants: the pressure required to cause gas to flow into the lungs has two components:

- that required to maintain gas flow along the airways, overcoming airways resistance
- that required to overcome the elastic recoil of the respiratory system, determined by compliance.

The interaction of these components determines the time constant (TC).

TC defines the rate of a simple (first-order) exponential process. It is equivalent to the time taken for the exponential process to complete if it were to continue at the same rate as that at which it began. TC describes how fast the lungs fill with a constant applied airway pressure or how fast they empty during expiration. (TC = compliance x resistance.) It increases with increasing resistance (e.g. in asthmatics) and decreases with decreasing compliance (e.g. in pulmonary fibrosis).

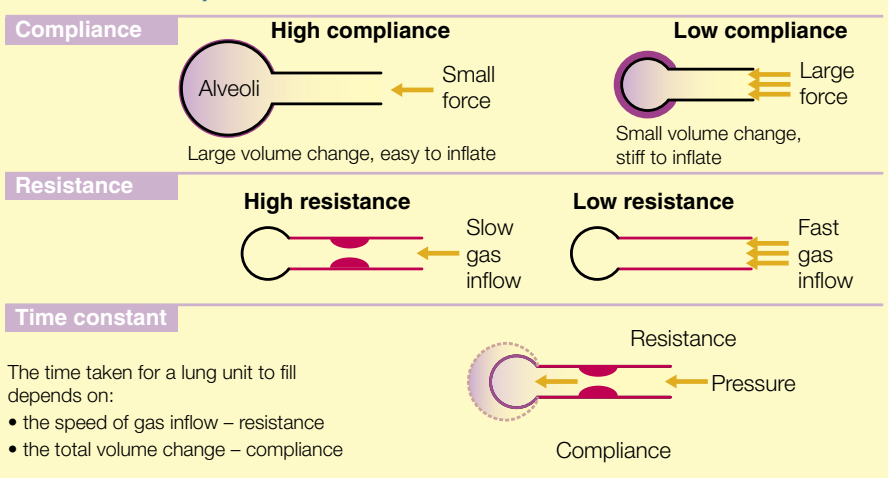
Resistance is a measure of the resistance to gas flow. The major site of respiratory resistance is in the medium-sized bronchi, but total respiratory resistance during positive-pressure ventilation also includes the contribution of the endotracheal tube and to a lesser extent the circuit. In a patient with normal lungs, this increases the total respiratory resistance from 2 to 4–6 cm H_2O/litre/second.

Compliance describes the elasticity of the respiratory system, or the ease with which it inflates, and is measured as the volume change per unit pressure. Total respiratory compliance consists of combined lung and chest wall compliance and is normally 50–70 ml/cm H_2O.

Within the normal working range of the lung compliance is constant though it decreases at extremes of volume. The contribution to compliance from the ventilator circuit is usually small. The exception is during anaesthesia in neonates and infants when the tidal volume is small compared with the circuit volume, and compression of gas within the circuit can make it difficult to ensure that accurate and adequate tidal volumes are delivered (Figure 3).

Effect on artificial ventilation − increased airways resistance and reduced lung and chest wall compliance are the most clinically significant changes in respiratory mechanics affecting artificial ventilation. Some causes are shown in Figure 4.

Resistance, compliance and time constant



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Causes of increased airways resistance and reduced respiratory compliance

Increased airways resistance	Reduced respiratory compliance
• Bronchospasm – asthma, chronic obstructive airway disease (COAD)	• Within lung – pulmonary oedema, adult respiratory distress syndrome, fibrosis, atelectasis
• Mucosal swelling – asthma, COAD	• Around lung – pleural effusion, upward compression from abdominal contents when supine, especially if obese
• Luminal obstruction – excessive secretions	• Chest wall – surgeon compressing chest, expiration retractors, scoliosis, contractures
• Foreign body – tumour	
• Emphysema – dynamic airway compression during	
• Low lung volume	

4

Pressure and flow generators: an understanding of the different types of ventilator and how they function helps predict the behaviour and limitations of each type of machine when resistance and compliance of the lungs change (Figure 5).

Pressure generators - a pressure generator applies a preset positive-pressure waveform to the airway for the duration of inspiration. In its simplest form this pressure is constant (Figure 6).

If the inspiratory time is sufficiently long, the respiratory compliance determines the tidal volume delivered when a given airway pressure is applied. The respiratory compliance decreases linearly with lung size, therefore a pressure generator set at 15−20 cm H_2O delivers an appropriate tidal volume to a small child or an adult with normal lungs.

Pressure generators can maintain the required airway pressure, even in the presence of a leak, within reasonable limits. As a result, the main use for pressure generators in anaesthetic practice is to ventilate children. The cricoid ring is the narrowest point of the airway in children. The insertion of endotracheal tubes can lead to compression of the tracheal mucosa against the cricoid cartilage, resulting in pressure necrosis. This can be avoided by using uncuffed endotracheal tubes; the presence of an air leak during inspiration confirms that the endotracheal tube is not lodged tightly in the cricoid ring.

The pressure generator ensures that adequate tidal volumes are delivered because a consistent pressure is maintained despite the leak. Paediatric patients, particularly neonates, are prone to ventilator-induced lung damage, and constant pressure generators ensure that even when lung dynamics change, the applied pressure remains constant.

Pressure generators are designed for use with normal lungs that remain normal during surgery (delivered tidal volume = pressure x compliance.) The main disadvantage of a pressure generator is that tidal volume is determined by compliance and reductions in compliance may cause significant reductions in delivered tidal volume and minute ventilation. Therefore, pressure generators may not be appropriate when precise control of arterial carbon dioxide tension ($PaCO_2$) is important, for example, during neurosurgery.

Flow generators (Figure 7) are devices that produce a constant gas flow independent of respiratory compliance or resistance. The volume delivered per unit time remains constant even in the presence of high airway pressures. All flow generators need a high-pressure gas source. This can be delivered by compressing bellows or by using proportional control valves, which control gas flow from the pipeline supply.

The delivered tidal volume is determined by control of the inspiratory flow rate and inspiratory time. The peak and mean airway pressure generated depends on the tidal volume, inspiratory flow rate, respiratory compliance and resistance.

The main advantage of a constant flow generator is that a constant tidal volume and minute ventilation are maintained even when the mechanics of the lung are changing. The tidal volume can be set precisely and minute ventilation is predictable and consistent, giving precise control of $PaCO_2$.

The main disadvantage is the potential for high airway pressures and barotrauma if changes in lung mechanics occur. There is also no ability to compensate for leaks. Flow generators are used mainly for adults, particularly where lung mechanics are abnormal, and when precise control of $PaCO_2$ is required.

Cycling parameters - cycling is the process of stopping one phase of ventilation and changing to the next. This occurs twice within each delivered breath. For the purposes of classification, cycling marks the end of inspiration and the beginning of expiration. Ventilators may be:

- time-cycled – cycling occurs after preset time
- volume-cycled – cycling occurs after preset volume delivered
- pressure-cycled – cycling occurs after preset pressure attained
- flow-cycled – cycling occurs when flow falls below a preset value.

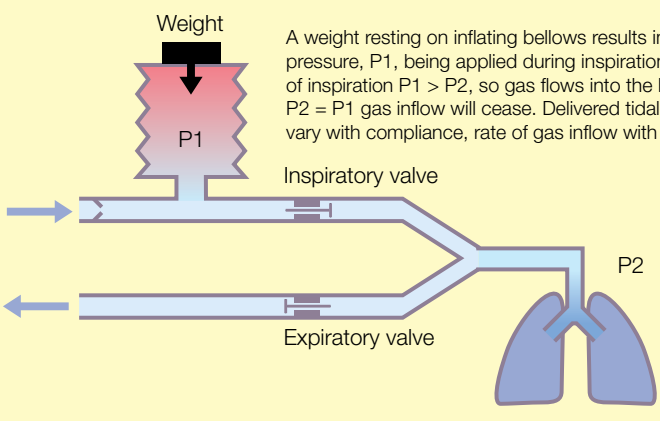
Time cycling is the most common technique. Flow cycling is used in inspiratory pressure support in the ICU but seldom in theatre. Volume and pressure cycling are used infrequently. In most ventilators, cycling from expiration to inspiration is by time.

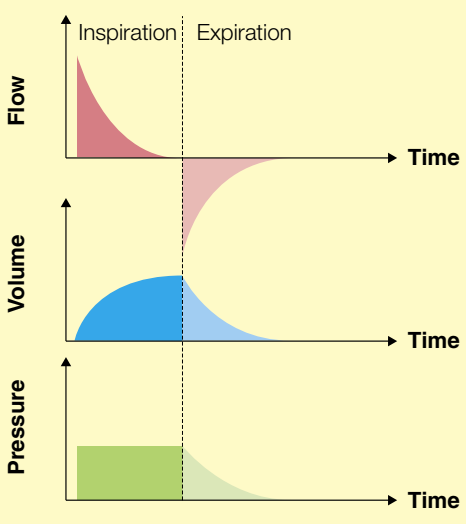
Advantages and disadvantages of pressure and flow generators

	Pressure generators	Flow generators
Advantages	• Protection from high airway pressures and barotrauma • Compensate for leaks	• Ability to maintain a constant tidal volume and minute ventilation even with significant changes in lung mechanics • Precise control of $PaCO_2$
Disadvantages	• Hypoventilation as a result of changes in lung mechanics	• Potential for high airway pressures and barotrauma • Inability to compensate for leaks

5

Constant pressure generator





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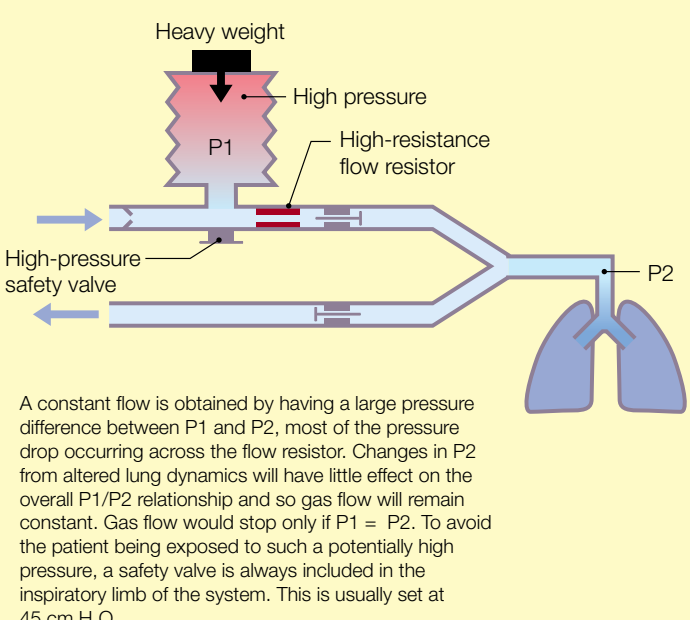
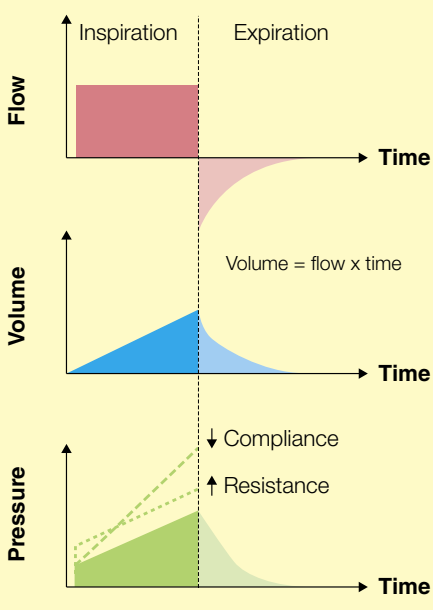
High-pressure, high-resistance flow generator



A constant flow is obtained by having a large pressure difference between P1 and P2, most of the pressure drop occurring across the flow resistor. Changes in P2 from altered lung dynamics will have little effect on the overall P1/P2 relationship and so gas flow will remain constant. Gas flow would stop only if P1 = P2. To avoid the patient being exposed to such a potentially high pressure, a safety valve is always included in the inspiratory limb of the system. This is usually set at 45 cm H_2O.



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Single- and double-circuit ventilators

In a single-circuit ventilation system the anaesthetic gas is also the driving gas. A well-known example is the Manley ventilator, where the fresh gas flow set on the rotameters is divided into tidal volume (hence the term minute volume divider). The fresh gas flow powers the ventilator and is also delivered to the patient.

In a double-circuit ventilation system the anaesthetic gas and the driving gas are in separate circuits. The clearest example of this is a 'bag in bottle' or bellows ventilator. The anaesthetic gas is contained within the circuit and a set of bellows, which act as a reservoir. After delivering the tidal volume, the bellows refill during expiration. The bellows are contained within an air-tight cylinder and a separate high-pressure driving gas is used to pressurize the cylinder periodically, compressing the bellows and thereby generating inspiratory gas flow. Most modern circle/ventilator systems are double circuits.

Bellows can be of the standing or hanging variety. Standing bellows rise as they refill; hanging bellows are mounted inverted and fall as they refill. The advantage of standing bellows is that a leak of anaesthetic gases will be noticed by a failure of the bellows to rise to the full height. This is especially useful during low-flow circle anaesthesia. Hanging bellows are usually weighted at the base and entrain room air if there is a circuit leak.

The Nuffield 200 series of ventilators are functionally double circuit. Although there is no physical separation of the driving and fresh gas flow, the configuration of these ventilators ensures that fresh (anaesthetic) gases and driving gas do not mix. This is achieved by using a connector hose with an internal volume that is greater than the tidal volume.

Pulmonary physiology and the effects of intermittent positive-pressure ventilation (IPPV)

When a patient breathes spontaneously the expansion of the chest wall creates a negative pressure relative to atmospheric pressure between the visceral and parietal pleura. The transpulmonary pressure gradient created causes the lung to expand and fill. Thus, during inspiration the intrathoracic pressure is negative.

During IPPV the patient makes no respiratory effort and the transpulmonary pressure gradient required to expand the lung is generated by raising the airway pressure. With inspiration, intrathoracic pressure is positive. During artificial ventilation the mean intrathoracic pressure is increased compared with spontaneous ventilation and this has effects on the respiratory, cardiovascular, renal and endocrine systems. The effects of IPPV are wide ranging and must be viewed in the context of the position of the patient on the operating table and the effects of general anaesthesia.

Normal respiratory physiology and the effects of general anaesthesia

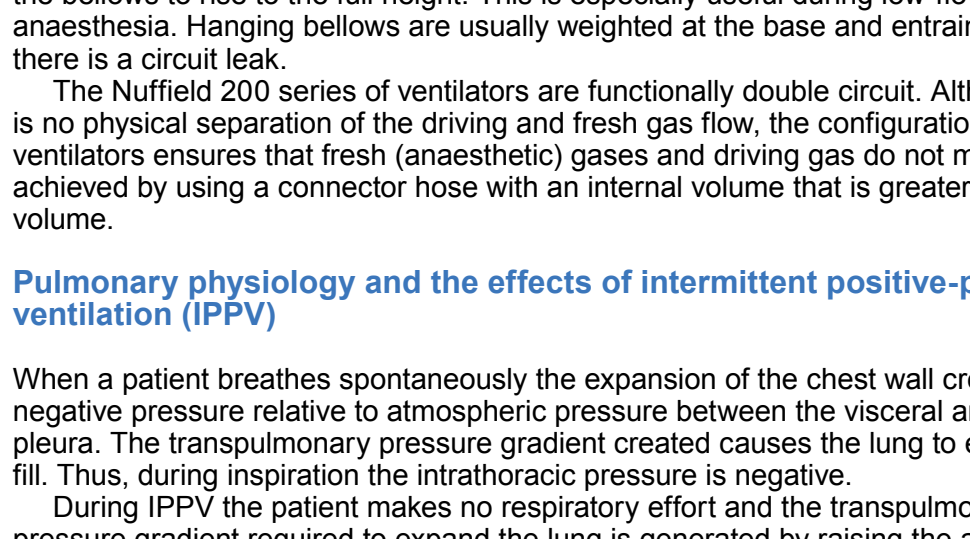
The primary function of ventilation is to move air in and out of the lungs so that carbon dioxide can be eliminated and arterial oxygenation maintained. In healthy individuals it is the requirement to eliminate carbon dioxide that is the prime determinant of minute ventilation. A normal tidal volume is about 500 ml in an adult (8 ml/kg); of this, about 150 ml (2 ml/kg) remains in the conducting airways (anatomical dead space), and the remaining 350 ml enters the alveoli and is available for gas exchange. The respiratory rate depends on the requirement for carbon dioxide elimination, but is usually 10−15 breaths per minute in adults. Effective ventilation maintains a normal arterial $PaCO_2$ of 4.5−5.5 kPa and an arterial oxygen tension (PaO_2) of 13.5 kPa in healthy young adults breathing room air.

Functional residual capacity (FRC): the various subdivisions of lung volume that can be determined by spirometry, whole-body plethysmography or helium dilution are shown in Figure 8. Of these, the most important for anaesthesia and the care of patients in the ICU is FRC. FRC is the end-expiratory volume of the lungs and is determined by the balance between:

- the elastic recoil of the lungs
- the outward recoil of the chest wall
- the respiratory muscle tone
- the position of the diaphragm.

FRC gradually reduces with age and is reduced on lying supine (by 500−800 ml) as a result of upward displacement of the diaphragm by the abdominal contents. This effect is enhanced in patients with abdominal distension or obesity. During general anaesthesia, reduction in diaphragmatic and chest wall tone and function lead to a reduction in FRC of about 20%. The effects of general anaesthesia and the supine position are additive, and can cause a significant reduction in FRC.

Lung volumes (70 kg adult)



Normal values

- Functional residual capacity 2.5 litres
- Inspiratory reserve volume 2.5–3.0 litres
- Tidal volume 0.5–0.6 litres
- Expiratory reserve volume 1.5 litres
- Residual volume 1.5–2 litres
- Vital capacity 3.5–5.5 litres
- Total lung capacity 6 litres

Minute ventilation 7.5 litres/minute
Alveolar ventilation 5 litres/minute
Vd/Vt 0.3

8

Closing capacity (CC) is the lung volume at which small airway closure begins. Closing volume is an alternative term that is equivalent to CC minus residual volume (RV). Normally CC is less than FRC, but they converge with increasing age. When FRC decreases to below CC, airway closure occurs during normal expiration and the resulting decrease in ventilation to areas of the lung distal to the closure worsens the ventilation-perfusion (V/Q) relationship. FRC usually remains greater than CC when supine until about 45 years of age but the additional reduction in FRC that occurs during general anaesthesia makes it more likely that FRC will fall below CC during anaesthesia. The resulting increase in V/Q mismatch leads to a decrease in arterial oxygenation, which is normally countered by increasing the inspired oxygen fraction.

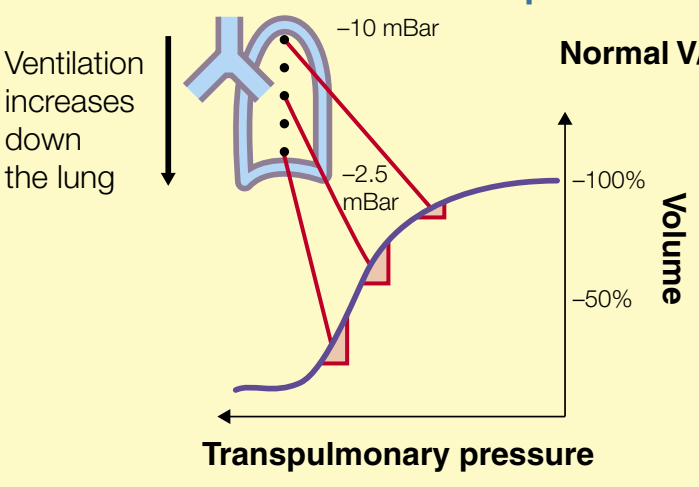
Distribution of ventilation and perfusion: during spontaneous ventilation in an upright position, distribution of ventilation and perfusion are not uniform throughout the lungs. Blood flow increases linearly from the top to the bottom of the lungs as a result of the effects of gravity on the low-pressure pulmonary circulation. The lower zones ventilate better than the upper zones because the dependent parts are on a more compliant (i.e. steeper) part of the pressure-volume curve. During normal inspiration, diaphragmatic contraction is enhanced in the parts of the diaphragm most displaced, aiding increased ventilation of the dependent parts of the lung (Figure 9).

Ideally, ventilation and perfusion at the alveolar level should be matched. Alveolar ventilation should equal perfusion and the V/Q ratio equal 1. In this situation no ventilation or perfusion is 'wasted'. However, the normal V/Q ratio is 0.8. The further the V/Q ratio deviates from 1, the more inefficient the ventilatory process becomes (Figure 10).

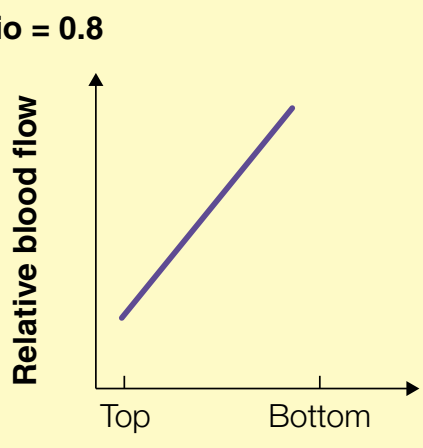
In the supine position, the gravitational effects on the lung are more limited, and perfusion is more homogeneous. However, the reduction of FRC, which is compounded by anaesthesia and the patient's position, leads to uneven ventilation because of airway closure and the tendency of the dependent portions of the lung to reduce in volume more than the superior parts (compression atelectasis).

Therefore, in the supine position (especially under anaesthesia) V/Q relationships worsen. This tends to cause hypoxaemia, which, because it is caused by a V/Q mismatch rather than a true shunt, can be reversed with added inspired oxygen.

Distribution of ventilation and perfusion in the lungs



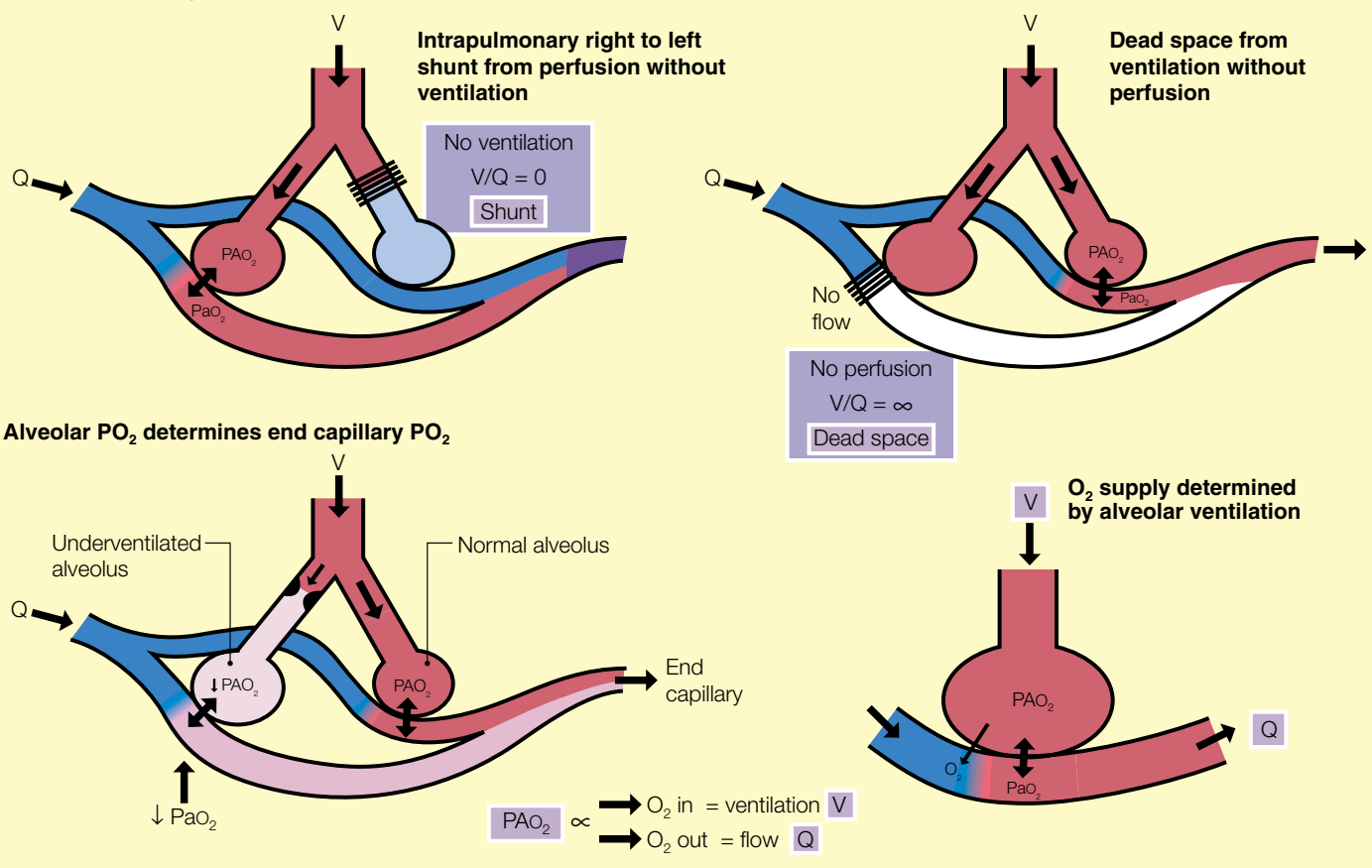
Ventilation increases from the apex to the base. Dependent parts of the lung are on a more compliant part of the pressure–volume curve



Perfusion increases on moving down the lung. The low-pressure pulmonary circulation is affected by gravity

9

Ventilation and perfusion



In an ideal alveolus capillary P_{O_2} (Pa_{O_2}) comes close to alveolar P_{O_2} (PA_{O_2}). PA_{O_2} is determined by the balance between the rate of O_2 uptake by the pulmonary capillaries (Q) and continued supply of O_2 by alveolar ventilation (V). The rate of O_2 removal is determined by the rate of O_2 consumption (metabolic rate). In an under-ventilated alveolus, the supply of O_2 is reduced. If O_2 uptake continues, the result is for PA_{O_2} to fall and so Pa_{O_2} will fall

10

Hypoxic pulmonary vasoconstriction (HPV): when the alveolar PO_2 or, to a lesser extent, the mixed venous PO_2 decreases, smooth muscle contraction occurs in small pulmonary arterioles. This diverts blood from unventilated areas to better-ventilated areas and helps minimize the effects of V/Q imbalance. Volatile anaesthetic agents as well as many vasodilators (e.g. sodium nitroprusside) inhibit HPV, worsening the effects of V/Q mismatching.

Respiratory effects of IPPV

Changes in distribution of ventilation: the preferential ventilation of the non-dependent parts of the lung in the anaesthetized, supine position is increased by IPPV. The non-dependent areas are more compliant than the dependent zones after induction of anaesthesia and muscle relaxation, and so preferentially expand in response to positive pressure. This effect is further exaggerated if the lungs have an increased density, as in the adult respiratory distress syndrome or in patients with cardiogenic pulmonary oedema. It is also compounded by compression of basal areas of the lung as a result of the upward displacement of the paralysed diaphragm.

Changes in distribution of perfusion: normal distribution of perfusion is usually maintained during IPPV. However, in the presence of high intra-alveolar pressures, compression of the alveolar capillaries occurs and flow stops. Capillary pressures are lower in the upper zones because of the effect of gravity on the low-pressure pulmonary circulation, and these zones are particularly vulnerable to increases in airway pressure. These preferentially ventilated upper zones now have much reduced flow and V/Q mismatch is further increased. This is more likely to occur when mean airway pressures are high and with the use of positive end-expiratory pressure (PEEP).

PEEP is the application of a residual positive pressure to the airway at the end of expiration instead of atmospheric pressure. This improves oxygenation by increasing FRC and thus reduces the effects of airway closure and lung volume reduction on V/Q relationships. PEEP may also reopen previously collapsed lung units and maintain their patency (alveolar recruitment).

Barotrauma is the result of excessive pressure gradients between alveoli and the interstitium, with rupture occurring. Air can spread along perivascular spaces into the mediastinum, pericardium, up into the neck, down into the abdomen or into the pleural cavity (pneumothorax). Risk factors include:

- large tidal volumes
- excessive inflation pressures, especially > 40 cm H_2O
- use of PEEP
- non-uniform lung disease
- increased airway resistance.

Recently, the term ‘volutrauma’ has been used in the ICU setting. This refers to overdistension of ‘normal’ areas of the lung by the high pressures required to inflate the diseased areas.

Other respiratory effects of IPPV: during general anaesthesia with intubation and ventilation, there is loss of the ability to cough and so secretions are retained. Inhaled anaesthetics and cold, dry gases inhibit ciliary activity in the bronchial tree, again leading to a tendency to retain secretions. In addition, if the anaesthetic gases are not warmed and humidified, the respiratory tract can be a major source of heat loss.

Cardiovascular effects of IPPV

The major effect of IPPV is to reduce cardiac output via a reduction in venous return. In most patients, this can be counteracted by fluid loading (e.g. 500−1000 ml crystalloid). There are additive effects on the pulmonary circulation and heart, but their relative contribution is thought to be minor, and significant changes occur only with high mean airway pressures.

Cardiac output: a decrease in cardiac output occurs when beginning IPPV, which can cause significant hypotension. The increase in mean intrathoracic pressure during inspiration with positive-pressure ventilation causes the low-pressure veins in the chest to be compressed. Cardiac output falls because of the reduction in venous return to the heart. The decrease in cardiac output and mean arterial blood pressure can be particularly marked in patients who are hypovolaemic or have limited cardiovascular reserve and is further worsened by PEEP. The expected fall in cardiac output can be reduced by prompt infusion of fluids to increase central venous pressure and maintain venous return.

Effects of IPPV on pulmonary vascular resistance and the heart: increased pulmonary vascular resistance occurs when airway pressures are high, from direct compression of alveolar capillaries. As pulmonary vascular resistance increases, there is an increase in right ventricular afterload and right ventricular end-diastolic volume. If end-diastolic volume becomes significantly raised, bulging of the intraventricular septum into the left ventricular cavity can occur, reducing left ventricular compliance and reducing left ventricular stroke volume. In addition, the increased wall tension in the right ventricle, coupled with a reduced arterial pressure, can compromise right ventricular perfusion in compromised patients. The final effect is right heart strain further augmenting a reduction in cardiac output. Paradoxically, in patients with existing heart failure, the increase in transpulmonary pressure transmitted to the thorax can occasionally help to off-load the left heart by reducing venous return from the pulmonary veins, thus reducing left atrial pressures. Left ventricular performance may then improve.

Other effects of IPPV

Renal: mechanical ventilation causes a reduction in urine volume, and thus sodium and water retention. A fall in renal perfusion pressure associated with the reduced cardiac output and a rise in renal venous pressure as a result of impedance of venous return, along with increased levels of antidiuretic hormone associated with IPPV, are thought to be important. An increase in sympathetic stimulation triggered by baroreceptors sensing the changes in pressure and flow may also contribute. The renal effects are persistent and are not fully reversed with fluid infusion or improvement in cardiac output.

Liver: the reduction in cardiac output and increased venous pressure leads to a fall in hepatic blood flow proportional to the drop in cardiac output. Hepatic blood flow may be reduced by up to 50% and hepatic metabolism is reduced. This can be reversed by infusion of fluid. The increased venous pressure caused by the positive intrathoracic pressure can cause hepatic venous congestion, and hypocapnia will lead to vasoconstriction.

Endocrine: antidiuretic hormone levels are increased during IPPV, with corresponding increases in renin and angiotensin levels. This contributes to salt and water retention.

Practical aspects of positive pressure ventilation

Adequate ventilation requires an adequate tidal volume and minute ventilation to be delivered, time for gas distribution and gas exchange to occur, and sufficient time for expiration to be completed. Adequate ventilation results in a normal $PaCO_2$ tension (4.5−5.0 kPa), and in anaesthetic practice this is usually estimated by the end-tidal carbon dioxide tension ($P_{E'}CO_2$). In patients with normal lungs the arterial $PaCO_2$ is about 0.5 kPa greater than the $P_{E'}CO_2$. $P_{E'}CO_2$ is measured from alveolar gases from all ventilating lung units with a spread of V/Q ratios. Units with high V/Q ratios have a reduced alveolar PCO_2 and so ‘dilute’ the gas from units with a V/Q ratio close to unity. This relationship is lost in patients with lung disease; arterial blood gas monitoring may be required in these patients. The minute volume and tidal volumes used should aim for peak airway pressures of 15−20 cm H_2O in most patients.

Arterial oxygenation is determined primarily by the inspired oxygen, which should never be below 30% (FiO_2 0.3) initially. The required inspired oxygen is determined by the saturation recorded by the pulse oximeter; 95% or greater is appropriate. After monitoring the effect of the initial settings in each patient, appropriate alterations can be made to suit the individual.

Initial IPPV settings for routine general surgical cases

Adults:

- flow generator mode of ventilation
- tidal volume 8−10 ml/kg
- respiratory rate 10−12 breaths/minute
- inspiratory/expiratory (I:E) ratio 1:2
- Fi_{O_2} 0.4 (40% oxygen)
- maximum airway pressure 30 cm H_2O.

If a circle absorber system is in use, an initial fresh gas flow of 6 litres/minute should be used.

A tidal volume of 8−10 ml/kg is appropriate for adults. An I:E ratio of 1:2 allows sufficient time for equilibration in inspiration and time for full expiration, in relation to the TC of normal lung. A starting inspired oxygen concentration of 40% helps to prevent a fall in PaO_2 and overcomes the expected increase in V/Q mismatch that occurs during IPPV. Barotrauma is avoided if peak pressures are kept below 30 cm H_2O.

Flow generators are the preferred method of ventilation in adults. A reliable and predictable tidal volume and minute ventilation can be achieved even when there are alterations in lung mechanics from pre-existing lung disease or when temporary peroperative changes occur related to the effects of patient positioning and surgery.

Children:
- pressure generator mode of ventilation
- inspiratory pressure 20 cm H_2O irrespective of weight
- respiratory rate 30−40 breaths/minute for neonates; 20−25 breaths/minute for infants; 15−20 breaths/minute for older children
- I:E ratio 1:2
- Fi_{O_2} 0.5 (50% oxygen).

Owing to their increased basal metabolic rate relative to their weight, neonates and infants have an oxygen requirement (6 ml/kg/minute) twice that of adults. As a result, they have a high carbon dioxide production, hence the need for a high respiratory rate. Young children also have a reduced FRC, high CC and relatively high airways resistance with low respiratory compliance. Their increased metabolic rate and relatively low FRC means they have limited oxygen stores and so their arterial oxygen saturation falls rapidly if ventilation is inadequate. Loss of respiratory gases as an air leak from around their uncuffed endotracheal tube is expected and indeed desirable. It provides evidence that the endotracheal tube is not so tightly fitting as to cause tracheal mucosal compression at the level of the cricoid ring. Pressure generators, which compensate for gas losses and limit peak pressures, are commonly used in paediatric anaesthesia. At puberty, differential growth of the cricoid ring and laryngeal aperture means that the larynx becomes the narrowest part of the airway as in adults, so cuffed tubes may then be used.

Safety issues

Detection of ventilator disconnection

Anaesthetized, paralysed patients are wholly dependent on the ventilator and the anaesthetist to keep them alive. In this respect, a paralysed patient is much more vulnerable than one who is breathing spontaneously. The anaesthetist should be alerted to a disconnection promptly by a disconnect alarm, which may also indicate when inadequate ventilation is occurring.

Disconnections can be sensed by:
- loss of the rhythmic increase in airway pressure
- reduction in expired gas volume
- loss of expired carbon dioxide.

Monitoring of airway pressures and exhaled CO_2 are part of minimum monitoring requirements during mechanical ventilation.

Airway pressure sensors are either aneroid gauges or, more commonly, electronic pressure transducers. The gauge the anaesthetist uses for monitoring and the alarm system are often separate devices. Airway pressure alarms detect an increase above a threshold pressure. If an increasing pressure that exceeds the threshold is not detected in the preset time, an alarm is sounded. This system does not normally detect a blocked endotracheal tube, but an alarm for the excessive inspiratory pressures generated in this scenario is usually incorporated in the same system.

Expired tidal volume or expiratory flow over time can also be measured. A minimum preset volume must be exhaled at a frequency above the preset minimum rate or the alarm will be triggered. Expired tidal volume is usually measured by integrating the expired flow signal.

Capnographs are fitted with limit alarms and often with apnoea detectors, which detect apnoea from the carbon dioxide waveform. In addition, respiratory movements are sometimes sensed via ECG leads and as a very late indicator, pulse oximeters will alarm if significant arterial desaturation occurs.

Ventilator checks

The anaesthetist is responsible for the state of the equipment he or she uses. It is expected that equipment is systematically checked before use. Although on occasion this may be delegated to trained assistants, the final responsibility lies with the anaesthetist. To this end, guidelines for machine checks have been issued by the Associaton of Anaesthetists of Great Britain and Ireland (Figure 11). With the increasing use of sophisticated, electronically controlled anaesthesic machines and ventilators, a ‘generic’ checklist must be used only with reference to the manufacturer’s suggested protocol for each machine.

Ventilator checks

- Ensure that ventilator tubing is correctly configured and securely attached
- Set the controls for use and ensure that an adequate pressure is generated during the inspiratory phase
- Check that the pressure relief valve functions
- Check that the disconnect alarm functions correctly
- Ensure that an alternative means to ventilate the patient’s lungs is available

Source: Association of Anaesthetists of Great Britain and Ireland. *Checklist for Anaesthetist Apparatus*, 1997.

11

FURTHER READING

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Breathing Systems

Gordon W G French

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A 'breathing system' is the name given to apparatus that delivers and removes gas and vapour to or from a patient. The three main functions of the breathing system are:

- to supply adequate oxygen
- to remove carbon dioxide
- to supply adequate inhalational anaesthetic agent.

The perfect system has yet to be developed but the ideal breathing system should:

- be simple and safe
- deliver the intended mixture
- allow manual and intermittent positive-pressure ventilation (IPPV) in all age groups
- be efficient (able to use low gas flows)
- protect the patient from barotrauma
- be sturdy, lightweight yet compact
- be easy to scavenge
- be cheap.

Essential components of a breathing system

Tubing (hose): originally this was carbon-impregnated rubber (an antistatic design), corrugated to prevent kinking, but it was heavy and prone to perishing. Modern tubing is usually plastic, disposable or designed for single use, and often has a smooth inner bore that reduces resistance to airflow. Early systems had various means of inter-linking tubes, including tapered metal connectors that pushed into each other and screw mountings. These were manufactured in various sizes, with many systems being non-interchangeable, clearly a dangerous situation. The International Standards Organization (ISO.5356, 1987) and British Standard (BS 3849) recommend the following sizes for all breathing systems:

- 30 mm tapered connections for scavenging hose to breathing systems
- 22 mm taper for connections within breathing systems
- 15 mm connections between the breathing system and the endotracheal tube.

An upstream 'male' connector traditionally fits into a downstream 'female' part. The ISO 15 mm standard connector is cumbersome for small paediatric endotracheal tubes (2–6 mm internal diameter). Smaller, lighter 8.5 mm connectors may be used, which have adapters to connect to the 15 mm standard system. Tapered connections between plastic, metal and rubber can be 'locked' by giving them a slight twist after connecting. Systems designed for repeated use can usually be autoclaved, which does not affect their connectors. Single-use systems often distort if heated, making the connectors unsafe.

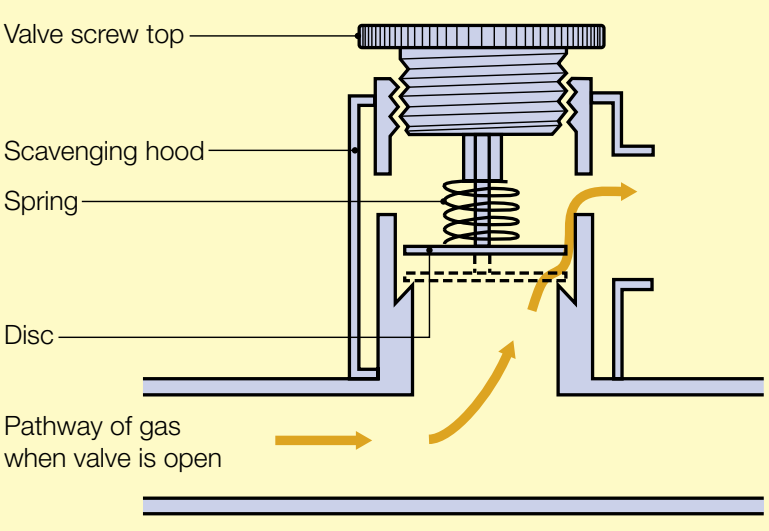
There is controversy among practising anaesthetists as to exactly what 'for single use only' means. Clearly it would be expensive to use a new breathing system for each patient, and almost certainly unnecessary. Many departments employ a cost-effective compromise by using a new disposable antibacterial filter for each patient, but only changing the actual breathing system weekly. It may be changed more often depending on clinical need (e.g. after use in a patient with known lung infection such as tuberculosis).

Reservoir bag: this stores fresh gas when the patient is exhaling and accommodates the high peak inspiratory flow rates during inspiration. Made of rubber or plastic, the common adult size is 2 litres and 0.5 litres for children, but some ventilators use other sizes up to 6 litres. The bag's motion allows observation of ventilatory patterns but does not reflect the tidal volume accurately. As the bag stretches, the pressure in its walls reaches a limit of about 40 cm H_2O (Laplace's law); further distension does not result in greatly increasing pressures. This partly protects the lungs from barotrauma should the breathing system outlet become obstructed, such as when the adjustable pressure-limiting (APL) valve is left fully screwed down. An open-ended reservoir bag is commonly used in paediatric circuits, allowing manual ventilation and assessment of the compliance of a child's lungs (e.g. Mapleson type F).

APL valve: this is a one-way, spring-loaded valve consisting of a thin, lightweight disc (made of hydrophobic material) held by an adjustable spring against knife-edged seating. This arrangement (Figure 1) reduces the area of contact between the disc and the seating, lessening any surface tension that condensed water vapour might create, causing the disc to stick. The disc prevents movement of air into the system when the patient inhales, but opens at low pressure (about 1 cm H_2O) to allow exhaled and surplus gas to be vented during expiration. When fully screwed down, modern valves open at about 60 cm H_2O positive pressure, acting as a safety feature.

Expired gases can be conveniently scavenged by surrounding the valve with a hood. If the valve is sucked open continuously by a faulty scavenging system, a huge increase in the dead space of the apparatus will result. The APL valve should be fully open during spontaneous respiration, partially closed during manual IPPV and fully closed during ventilator IPPV.

Cross-section of an adjustable pressure-limiting valve



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Classification of breathing systems

The historical development of breathing systems was largely based on the intuition and practical experience of individual anaesthetists. As a result, there are many different systems. One classification based on function is described below.

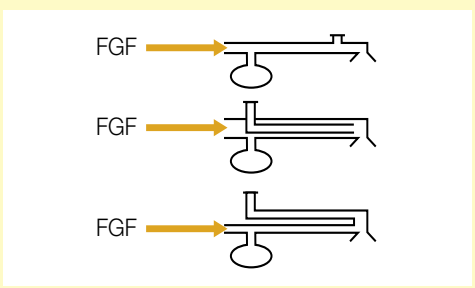
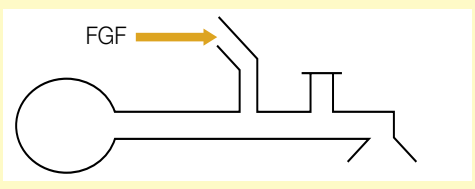
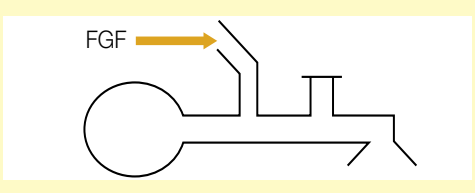
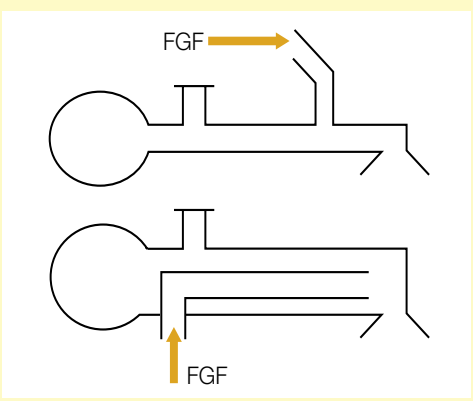
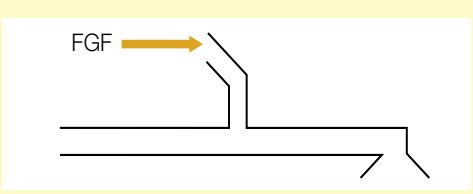
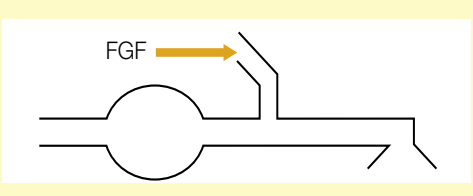
Non-rebreathing systems

Non-rebreathing systems use one-way valves to separate inspired and expired gases. When the patient inspires, the expiratory valve closes and the inspiratory valve opens, allowing inhalation of fresh gas. There is usually a reservoir bag on the inspiratory limb, which provides enough gas for the maximum peak inspiratory flow rate (often > 30 litres/minute), and collects fresh gas when the inspiratory valve is closed in expiration. It may also allow for manual-assisted ventilation. Resuscitation devices commonly include a bag constructed of foam-lined rubber or silicone, which remains inflated in the resting state, in addition to a thin-walled reservoir bag. Manual ventilation is provided by squeezing this bag, which automatically refills from the oxygen inlet and reservoir bag when hand pressure is released. The fresh gas flow (FGF) should at least equal the patient's required minute volume. Examples are resuscitation devices such as the Ambu bag, Laerdal silicone resuscitator, drawover units and the 'Triservice' apparatus.

Rebreathing systems

In rebreathing systems, the inspiratory and expiratory gases can mix in the tubing and re-inhalation of expired gas can occur. Rebreathing refers to inhaling part or all of the previously exhaled tidal volume. In particular, it is the inhaling of previously exhaled carbon dioxide (i.e. alveolar gas) which is of most concern to the anaesthetist. A system is efficient if it can preferentially vent alveolar gas, retaining dead space (non-carbon-dioxide-containing) gas and thus use an FGF that approximates to the patient's alveolar minute ventilation. The extent of carbon dioxide rebreathing thus depends on the FGF flushing the expired gas away before the next inspiration. The normal respiratory cycle consists of an inspiration followed immediately by expiration, but there is then an expiratory pause. It is during this period that the FGF flushes the system. In 1954, Mapleson classified five commonly used systems according to their efficiency at eliminating expired carbon dioxide in spontaneously breathing patients (Mapleson systems A–E). An F system was added in 1975 (Figure 2).

The Mapleson classification of anaesthetic breathing systems and adaptations

Mapleson type		Recommended fresh gas flow	General points
System A **a** Magill **b** Lack **c** Parallel Lack		**Spontaneous** AMV (70 ml/kg/minute) **IPPV** 2–3 x AMV	**a, b, c** Efficient for spontaneous, not for IPPV Heavy, especially at patient end Unsuitable for children < 25 kg because large dead space **b** Lack: coaxial, APL and reservoir bag at machine end Inspiratory gases through outer (30 mm) tube Expiratory via inner (14 mm) **c** Parallel Lack: separate inspiratory and expiratory tubes
System B		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	FGF near patient end. Performs similarly in both modes. Seldom used
System C		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	Similar arrangement to system B. The large-bore tubing to bag is shorter **a** Waters' 'to and fro' circuit: inefficient but small size and simplicity means useful for resuscitation and patient transfers **b** Waters' canister: heavy because incorporates a 1 lb soda lime container between bag and mask or ET tube Channelling occurs if incompletely packed. Nylon pot scourer compresses at bag end. Filter at patient end prevents soda lime dust movement. NB Filter to patient = dead space. Easily sterilized. Now little used. Superseded by circle absorber systems
System D **a** Bain		**Spontaneous** 2–3 x AMV **IPPV** AMV (70 ml/kg/minute)	Inefficient for spontaneous but good for IPPV Manley ventilator on spontaneous ventilation mode is a Mapleson D Safety problems include kinking of inner tube Disconnection of inner tube increases dead space. Both lead to hypoxia and hypercarbia **a** Bain: coaxial D. Length of tube does not affect properties (180–540 cm). FGF through inner tube (opposite to Lack) Ventilate with Penlon 200 replacing bag. Connecting tube long > 500 ml (usually 1 m) to prevent driving gas entering circuit. Lightweight, easy to scavenge. Ga in expiratory limb warm inspiratory gases
System E		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	Used for children up to 30 kg. Low resistance, small dead space, lightweight, no valves. Inefficient but used for spontaneous and IPPV. Expiratory limb is reservoir and should be > V_T to prevent air entraining Ayre's T-piece: developed for neuro/cleft palate surgery
System F		**Spontaneous** 2–3 x AMV **IPPV** 2–3 x AMV	Jackson Rees modification. Reservoir bag allows rate and chest compliance to be monitored, ventilation by hand and continuous positive airway pressure application. Barotrauma and humidification a problem

AMV, alveolar minute volume; FGF, fresh gas flow; IPPV, intermittent positive-pressure ventilation; V_T, tidal volume

2

Mapleson A: classically describes the Magill system. The APL valve and any scavenging device make this system cumbersome at the patient's end. Lack solved this problem by creating a co-axial arrangement where the expiratory gases were carried up an inner hose to the APL and scavenging system, both of which were thus distant to the patient. However, this system is bulky, even though it is less weighty at the patient's end. In addition, if the inner tube breaks and this goes unrecognized, the system may become dangerous because carbon dioxide elimination is drastically reduced. It is also difficult to use with a ventilator. A parallel hose breathing arrangement (parallel Lack) eliminates this problem.

The Mapleson A system is an efficient system for spontaneous ventilation because it selectively vents alveolar gas through the APL valve. The first part of the exhaled tidal volume (non-carbon-dioxide-containing dead space gas) is retained in the system and is available for inhalation during the next breath. This efficiency is lost when the system is used for IPPV.

Mapleson B and C: in both systems the FGF, reservoir bag and APL are near the patient, creating a compact and portable system. However, they are both inefficient and only the Waters' 'to and fro' system is commonly used, mainly for patient transport and in postoperative recovery units.

Mapleson D: exhaled gas passes into a reservoir bag along with the fresh gas, so rebreathing occurs unless the FGF is high. The system is efficient for IPPV.

The Bain system is a coaxial version, which is particularly useful for limited-access surgery because of its light weight and the fact that the tubing can be lengthened without affecting the flow characteristics. The system can be connected to a ventilator by replacing the reservoir bag with tubing connected to a ventilator such as the Penlon Nuffield 200. The tubing should be of sufficient length to prevent the ventilator driving gas entering the breathing system (in practice > 500 ml or 1 metre of standard hose). In this system, the FGF is along a narrow internal tube (the opposite of the Lack system), and the expired gas moves along the outer tube, usefully heating up the dry FGF. It is vital that the inner tube is intact because disconnection leads to a huge increase in dead space and possible hypercarbia or hypoxia.

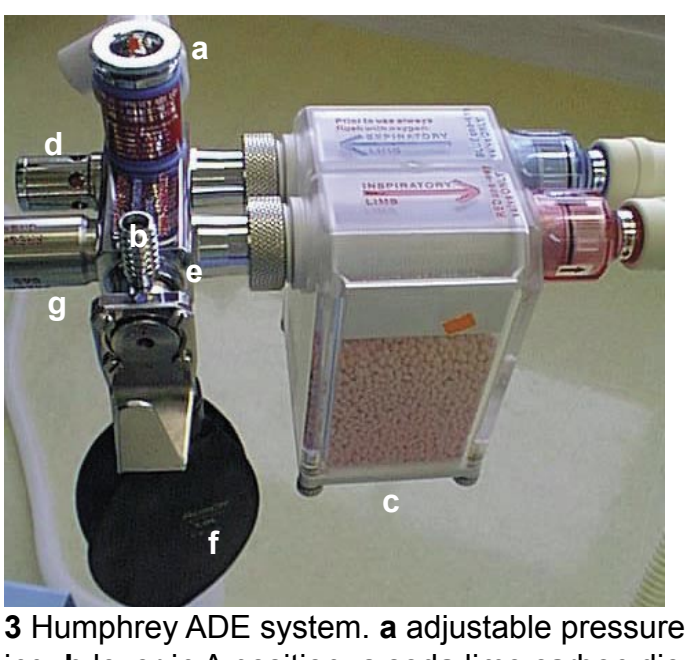
Mapleson E: the Ayre's T-piece is a valveless, lightweight system, with low internal resistance and dead space. In inspiration, gas is inhaled from both the inspiratory and expiratory limb. The volume of the expiratory limb needs to be at least equal to the tidal volume or air may be entrained. If it is too large, then rebreathing can occur because expired gas may not have vented to air before the next inhalation. Occluding the outlet intermittently allows IPPV.

Mapleson F: adding an open-ended reservoir bag to the expiratory limb of the Ayre's T-piece allows manual control of ventilation, observation of breathing and assessment of lung compliance. Some continuous positive airway pressure (CPAP) is also achieved with the system during spontaneous respiration, which, in an infant, may help to increase the functional residual capacity. Scavenging is a problem for both the Mapleson E and F systems. The routine use of capnography allows the FGF to be tailored precisely to achieve normocapnia in individual patients for all these systems.

Humphrey ADE system (Figure 3) is one of a number of hybrid systems that has become popular. It is a low-flow multipurpose system that appears to combine the best of the Magill, Lack and T-piece systems but not their disadvantages. It is cost effective in all modes, being more efficient than the Magill for spontaneous ventilation. The 15 mm, smooth-bore tubing has one-quarter of the resistance to flow of 15 mm corrugated tubing, which allows use in adults and children; 8.5 mm tubing is available for neonates. The reservoir bag, APL, scavenging shroud and a pressure-limiting valve are all located on the 'Humphrey block'. The system tubing connects to the patient via a symmetrical Y-piece, which probably accounts for much of its efficiency as it produces less turbulence than the conventional Magill–patient interface. One lever allows conversion from A mode to E mode, with only a slight increase in FGF being required to eliminate rebreathing. In E mode, the reservoir bag and APL are isolated from the system, and the expiratory tubing acts as the reservoir limb of a T-piece. This is open to the atmosphere via a port on the block to which a bag squeezer ventilator such as the Manley Servovent or Penlon Nuffield 200 or 400 can be attached. The D mode could be engaged by simply attaching a reservoir bag and APL to this port for spontaneous ventilation, but this is much less efficient than the A mode.

The APL valve provides positive end-expiratory pressure of 1 cm H_2O without increasing the airway resistance of the apparatus. The APL valve does not have to be screwed down for IPPV, except if used in the A mode. However, there is a long orange valve seat stem that can be temporarily held down instead. This also moves slightly during spontaneous respiration and gives a visual indication of respiratory movement. A separate 60 cm H_2O pressure-limiting valve lies behind the APL valve on the block. This is always in-line, whatever mode is being used. The system can be fixed on to the anaesthetic machine via a locking nut. A 500 g soda lime canister (lifespan 12 hours), which has a low resistance to flow and is autoclavable, can be fitted in front of the block. This circle system arrangement requires no other alterations in FGF for adults or children.

The entire system is MRI compatible, being made of plastic and brass. In addition, tubing lengths of over 3 m can be used without compromising its function. The main disadvantages are that it protrudes out of the anaesthetic machine, is heavy and can be knocked, which theoretically could fracture old anaesthetic machine outflow pipes.



3 Humphrey ADE system. **a** adjustable pressure limiting valve with scavenging; **b** lever in A position; **c** soda lime carbon dioxide absorber; **d** pressure relief (60 cm H_2O) valve; **e** port for ventilator; **f** reservoir bag; **g** fresh gas flow. Fresh gas flow: A mode (lever up) = 50 ml/kg/minute; E mode (lever down) = 70 ml/kg/minute. Children start at 3 litres/minute.

Systems using carbon dioxide absorbers

The circle system (Figure 4) was first described in the 1920s. It uses soda lime to absorb exhaled carbon dioxide. Partial rebreathing of other exhaled gases can thus be undertaken, depending on the arrangement of the components and the FGF.

Circle systems can be classified as follows:

- semi-open – no rebreathing, very high FGF, APL valve wide open
- semi-closed – rebreathing occurs, low flow, APL valve partly closed
- closed – FGF inflow exactly matches uptake by patient; complete rebreathing of exhaled gases after carbon dioxide uptake and APL valve fully closed.

A circle system consists of:

- FGF source
- inspiratory and expiratory unidirectional valves
- inspiratory and expiratory corrugated tubes
- a Y-piece connector
- an APL valve or pop-off valve
- a reservoir bag
- a canister containing a carbon dioxide absorbent.

Fresh gas enters the circle by a connection from the common gas outlet of the anaesthetic machine. Various arrangements of components are possible, but there are three golden rules to prevent carbon dioxide rebreathing.

- A unidirectional valve must be located between the patient and the reservoir bag on both the inspiratory and expiratory limbs of the circuit. These valves commonly have a clear plastic cover so that their correct movement can be observed during use.
- The FGF cannot enter the circuit between the patient and the expiratory valve.
- The APL valve cannot be located between the patient and the inspiratory valve.

The most efficient circle system has the unidirectional valves near the patient and the APL valve just downstream from the expiratory valve. This arrangement conserves dead space gas and preferentially eliminates alveolar gas. The advantages and disadvantages of a circle system are listed in Figure 5.

Nitrogen washout – at the start of anaesthesia, non-nitrogen-containing gas (unless medical air is being used) is inspired and body nitrogen passes into the lungs. This effectively reduces the oxygen concentration in the alveoli and circle system, producing a potentially hypoxic mixture. The use of high flows of gas at the start of anaesthesia can 'washout' this nitrogen. Pre-oxygenation with 100% oxygen for 7–10 minutes is also effective and can theoretically then allow low circle FGF to be used from the start. Basal metabolic oxygen requirements are about 250 ml/minute, but to allow for leaks in the circle and patient variability, 500 ml/minute oxygen is the minimum recommended flow rate. 'Low flow' anaesthesia is usually regarded as less than 1 litre/minute FGF.

The uptake of volatile agents is highest initially. Fast FGF inflows and large minute volumes produce fast induction of anaesthesia as well as facilitating denitrogenation. As equilibrium is reached, the expired concentration of volatile agent begins to reflect the inspired value, and flows can be reduced. The exhaled gases are added to the fresh gas and have a dilutional effect on the concentration of oxygen and vapour, which will be proportionally greater at low flows. A potentially hypoxic alveolar concentration of oxygen can develop as the FGF reduces. Using an inspired oxygen concentration of 50% to prevent these low oxygen levels in the circle was customary before the advent of in-line gas/vapour analysers. However, this was associated with an increased chance of awareness if the inspired volatile concentration was not increased to compensate for the lower inspired nitrous oxide and volatile concentrations.

Vaporizers can be placed outside (VOC) or inside (VIC) the circle (Figure 6). Most modern vaporizers tend to be outside the circle (e.g. Back bar units such as a TEC vaporizer) and are accurate at low flows. With this set-up, the concentration of volatile gas in the circle is reduced with increased patient uptake and low FGF (due to the dilutional effect of exhaled gas), until uptake reduces and equilibration begins to occur. With a vaporizer in the circle (e.g. Goldman vaporizer), both the fresh and exhaled gas (which already contains vapour) pass through the vaporizer. When the FGF is low and alveolar ventilation high, the concentration of volatile will rise. Thus the concentration of the alveolar and circle vapour is a function of ventilation. In spontaneous ventilation, with deepening anaesthesia and depression of ventilation, the concentration of volatile gas will fall and result in the patient becoming lighter, a useful safety feature. However, low flow controlled ventilation may result in high levels of volatile gas.

Future developments in circle technology may incorporate the VIC arrangement but use a system of vapour injectors instead of the vaporizer. This would be linked to a feedback mechanism incorporating circuit vapour analysis.

Carbon dioxide absorption – closed or semi-closed circle systems require carbon dioxide absorption to make rebreathing possible. Desirable features of a carbon dioxide absorption mechanism are lack of toxicity (intrinsic or with common anaesthetics), low resistance to air flow, low cost, ease of handling and efficiency. Soda lime and baralyme are the two formulations commonly used for carbon dioxide absorption (Figure 7). Both need water but because baralyme contains water as a barium hydroxide octohydrate salt it performs better in dry climates. Soda lime (but not baralyme) is capable of some regeneration after exhaustion. Maximum absorbency of both systems is 26 litres of carbon dioxide per 100 g absorbent.

Dyes (acids or bases) are also added, which change colour as the hydrogen ion concentration changes:

- ethyl violet (colourless to violet; fluorescent light deactivates it)
- phenolphthalein (white to pink)
- Clayton yellow (red to yellow)
- ethyl orange (orange to yellow)
- mimosa z (red to white).

The chemical reaction in soda lime is:

$CO_2 + H_2O \rightleftarrows H_2CO_3$

$H_2CO_3 + 2NaOH\ [KOH] \rightleftarrows Na_2CO_3\ [K_2CO_3] + 2H_2O + heat$

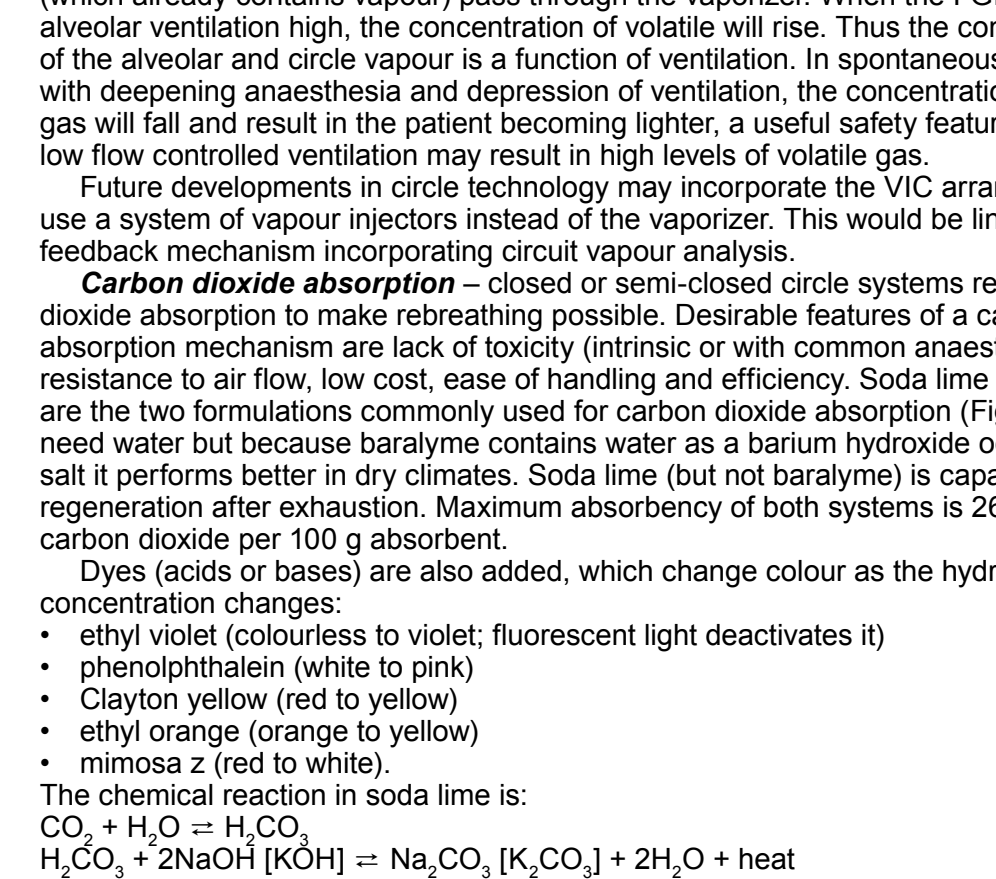
$Na_2CO_3\ [K_2CO_3] + Ca(OH)_2 \rightleftarrows CaCO_3 + 2NaOH\ [KOH]$

Some carbon dioxide reacts directly with calcium hydroxide but this is much slower. In baralyme the carbon dioxide acts directly with barium hydroxide and much more water is released. In the UK, the size of granules is 4–8 mesh (a compromise between surface area for absorption and air flow resistance). Mesh refers to the number of openings per linear inch in a sieve through which the granules pass. A 4-mesh screen indicates four quarter-inch openings per linear inch.

Soda lime and baralyme are not inherently toxic, but at low flows intrinsically produced acetone can accumulate and has been linked to nausea and vomiting. Carbon monoxide can also accumulate at low flows of dry gas (e.g. oxygen running overnight) leading to the formation of carboxyhaemoglobin.

The volatile agent trilene degrades into dichloroacetylene (a neurotoxin causing cranial nerve damage and encephalitis) and phosgene (a potent pulmonary irritant causing adult respiratory distress syndrome).

Sevoflurane and halothane are slightly unstable in soda lime, the rate of degradation increasing with temperature. Sevoflurane degrades into several compounds. Compound A (a vinylether) has been associated with lung haemorrhage and renal tubular necrosis in rats, but neither compound has been shown to cause problems in humans. Many of these problems are resolved by flushing the system regularly.



Properties of a circle system

Advantages	Disadvantages
• Heat/moisture conservation • Easy scavenging • Reduced cost • Small dead space • Good for long cases	• Multiple connections • Valves can stick • Open – leads to rebreathing • Closed – leads to asphyxia • Bulky • Inefficient for short cases • Soda lime changeover a hazard • Gas analyser necessary for accuracy • Potential for infection

5

Properties of vaporizers

Inside the circle	Outside the circle
• Low internal resistance • Low efficiency desirable • Higher concentrations at low fresh gas flow	• High internal resistance (plenum) • High efficiency desirable • Lower concentrations at low fresh gas flow (diluted)

6

Properties of soda lime and baralyme

Soda lime	Baralyme
• Calcium hydroxide (94%) • Sodium hydroxide (the catalyst) (5%) • Potassium hydroxide (1%) • Silica (calcium and sodium silicate harden it and reduce dust formation)	• Calcium hydroxide (80%) • Barium hydroxide (the catalyst) (20%) • More stable so does not contain silica • Denser and 15% less efficient than soda lime

7

System checks

All systems should be checked visually for broken parts and disconnections and a push-and-twist connector test performed. In addition, there are checks specific to individual systems.

- Occluding Mapleson types B and C causes their reservoir bags to fill, testing the air-tightness of the system. Releasing the valve causes the bag to deflate if the valve is functioning normally.
- The Bain system inner tube can be tested in two ways. Occluding the end of the inner tube causes the rotameter bobbin to dip and the pressure alarm/valve to blow if there are no leaks/disconnections up to that point. Occluding the patient end of the system will fill the reservoir bag, testing overall air- tightness. Releasing the occlusion causes the bag to deflate, then continue to empty as a result of the negative pressure caused by the Venturi-effect of the fast FGF leaving the inner tube. The connection of the inner tube can also be visually inspected because the outer corrugated tubing is often made from transparent plastic. This outer tubing may also be temporarily disconnected and a secure inner tube connection confirmed.
- To carry out the low-pressure circle leak test, the end of the system should be occluded and the APL valve closed off. The system is filled using the oxygen flush until the airway pressure gauge registers 30 cm H_2O. The pressure should remain at 30 cm H_2O if no leaks are present.

FURTHER READING

Humphrey D, Brock-Utne J G, Downing J W. Single Lever Humphrey ADE Low Flow Universal Anaesthetic Breathing System. *Can Anaesth Soc J* 1986; **33(6):** 698–718.

Cleaning, Disinfection and Sterilization of Equipment

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Hospital-acquired infections have significant implications for the morbidity and mortality of patients as well as for the economics of health care. The protection of patients and medical staff from medical equipment that has come into contact with patients or their body fluids, requires the adoption of various processes enforceable by law. Changes in these laws and guidelines, published by the Department of Health and the Medical Devices Agency, are expected in the near future. One of the reasons for the introduction of new guidelines is the development of new variant Creutzfeldt–Jakob disease, which is resistant to the standard methods of decontamination used in hospital sterile services departments.

Contamination is the soiling or pollution of an inanimate object with harmful, potentially infectious, material. In the clinical setting, this is most likely to be organic material or microorganisms. Contamination may place the patient at risk and may adversely affect equipment.

Decontamination is a method used to remove contamination and prevent microorganisms reaching a susceptible site in large enough numbers to initiate infection or other adverse effects. The three methods of decontamination routinely used are cleaning, disinfection and sterilization. The method of decontamination chosen takes into account the infection risk from the reprocessed piece of equipment. The risk is dependent on:

- the amount of contact the patient has with the piece of equipment (i.e. how invasive)
- the susceptibility of the patient (i.e. immunocompromised, potential hypersensitivity)
- the nature, extent and amount of microbial contamination on the piece of equipment (the bio burden).

The type of equipment and its intended use determine the method of decontamination used (Figure 1). The manufacturer should provide instructions for cleaning, disinfection and sterilization techniques that are effective without affecting the performance of the equipment.

It is essential that records are kept to demonstrate the number of times an item has been decontaminated and the effectiveness of each process. The documentation should allow patients to be traced in the event of any malfunction in the decontamination process.

Risk of contamination for equipment and suggested decontamination process

Risk	Application of equipment	Recommendation
High	• In close contact with a break in the skin or mucous membrane • For introduction into sterile body areas	Sterilization
Intermediate	• In contact with mucous membranes • Contaminated with particularly virulent or easily transmissible organisms • Before use on immunocompromised patients	Sterilization or disinfection (Cleaning may be acceptable in some agreed situations)
Low	• In contact with healthy skin • Not in contact with patient	Cleaning

1

'Single use' equipment

Manufacturers should state in the product literature any restrictions on the number of re-uses. Any device deemed by the manufacturer as unsuitable for reprocessing is labelled 'single use'. Devices labelled 'single patient use' may be used for an extended period of time or intermittently on the same patient. Users who disregard the manufacturer's guidelines, for example by reprocessing single use items or reprocessing more than the recommended number of times may be transferring legal liability for the safe performance of that product from the manufacturer to themselves or the organization for which they work.

Many anaesthetic departments routinely use disposable anaesthetic breathing systems marked as single use for extended periods with multiple patients. The wisdom of this practice is the subject of much controversy. The advantages of these breathing systems include safety (often pre-assembled with fewer opportunities for connection errors by the user), lightweight and low cost if used on several patients. The disadvantage is that this practice may contravene the manufacturer's recommendation for single use only and risk transmission of infection. The responsibility for use of equipment marked single use then lies with the hospital. Departments of anaesthesia should have an operational policy on the management of breathing systems marked for single use. This may include:

- the use of a new bacterial (heat and moisture exchanger type) filter for each patient
- change of all breathing systems weekly
- change of breathing system following use on a patient with known or suspected lung infection
- change of breathing system whenever there is visible contamination from blood or body fluids.

Cleaning

Cleaning physically removes contaminants without necessarily destroying microorganisms. It removes organic material and is required before disinfection or sterilization.

Manual cleaning

Manual cleaning does not disinfect. It should be used only when other mechanical methods are inappropriate or unavailable.

Immersion – wearing appropriate protective clothing, the cleaner should submerge the device in compatible water/detergent solution at the correct dilution and not exceeding 35°C. It is important to ensure that the cleaning solution reaches all surfaces of the device, including lumen surfaces. Endoscopic equipment that may be totally immersed for cleaning is marked with a blue line, usually around the eyepiece adjacent to the focussing ring. The device should be brushed or agitated to remove any visible contaminants. The device should be thoroughly drained and rinsed in clean water. This method is generally satisfactory for the routine cleaning of laryngoscopes between patients. Disinfection with an alcohol spray is then commonly used.

Non-immersion – wearing appropriate protective clothing, the cleaner should immerse a cleaning cloth into the detergent solution and wring it out. The equipment should be cleansed by wiping its surfaces. The surfaces should be hand dried using a cloth, hot air dryer or drying cabinet. This method of cleaning is often used for electrical or electronic equipment which cannot be immersed in water.

Mechanical cleaning

Mechanical cleaning uses automated washers to clean equipment and often combines cleaning with disinfection.

Thermal washer – cleaning occurs by continually spraying the equipment with water and detergent during a timed cycle. During the first process, cleaning occurs at 35°C. The second wash heats the surface of the equipment to a minimum temperature of 71°C for a minimum of 3 minutes, 80°C for 1 minute, or 90°C for 1 second to disinfect it.

Chemical washer – the first part of the cleaning process is the same as the thermal washer. Disinfection occurs by exposing the equipment to an approved disinfectant for a particular period of time at less than 60°C. The residue disinfectant is then removed by a rinse cycle.

Ultrasonic cleaners are often incorporated into washer disinfectors. These work by rapidly forming bubbles in the liquid, which immediately collapse (cavitation). This cavitation agitates the liquid, producing a highly effective cleaning system. The process does not disinfect.

Disinfection

Disinfection is used to reduce the number of viable micro-organisms, but it may not kill all microbial agents such as some viruses and bacterial spores.

Low temperature steam disinfection

Low temperature steam disinfection is also known as pasteur-ization. It kills most vegetative microorganisms and viruses by exposure to moist heat. The equipment is exposed to dry saturated steam at a temperature of 73°C for at least 10 minutes at below atmospheric pressure. The low temperature steam kills vegetative microorganisms and some heat-sensitive viruses. It cannot be used for sealed, oily or greasy pieces of equipment or those with sealed cavities due to the variation in pressure.

The advantages of this system are its broad spectrum of disinfection, it is non-toxic, non-corrosive and the equipment is relatively safe and simple to use. The disadvantages are that it requires a trained operator and that much equipment is unsuitable for disinfection in this way. The capital cost of the disinfector is high and the equipment is fixed and not portable.

Boiling water disinfection

Boiling water is an effective disinfectant against many microorganisms. Immersing a piece of equipment in soft water and boiling at 100°C for at least 5 minutes produces disinfection. Boiling inactivates most non-sporing microorganisms, fungi, viruses and some heat-sensitive spores. This method is not used if a better method is available. It is unsuitable for heat-labile pieces of equipment, hollow or porous items into which the water will not penetrate, or tubing over 1 metre in length.

The advantages are that boiling water has a broad disinfecting effect. The process is non-toxic and inexpensive. The disadvantages are that boiling water is a potential cause of injury. Following disinfection, items are wet and unfit for immediate use and must be allowed to dry and cool, which may allow recontamination. There is also no method of checking the efficacy of the process.

Washer disinfectors

Washer disinfectors are described above. They inactivate all microorganisms except bacterial spores and some heat-resistant viruses. They are unsuitable for equipment that may be heat labile or corroded by chemical disinfectant, and for hollow or porous equipment that does not allow all surfaces to come into contact with the chemical disinfectant or heat.

These methods are safe for the operator. There is minimal handling of the equipment by staff and therefore a low risk of recontamination. Another advantage is that they combine cleaning and disinfection. The disadvantages are the high cost of the equipment and the requirement for trained staff.

Liquid chemical immersion

Liquid chemical immersion relies on good contact between the chemical disinfectant and the equipment. The equipment therefore requires thorough cleaning beforehand. It is then immersed in the chemical disinfectant, ensuring that the disinfectant reaches all surfaces. The equipment is immersed for a predetermined time depending on the chemical disinfectant used. The spectrum of activity also depends on the type of chemical disinfectant used (Figure 2).

The method is unsuitable if the corrosive nature of the chemical disinfection may damage the equipment or if the equipment has areas inaccessible to liquid. It requires trained staff wearing protective clothing. It is potentially toxic, corrosive or volatile. Also, the equipment may have to be hand dried after disinfection allowing possible recontamination.

Equipment disinfectants commonly used and their spectrum of activity and physical properties

Disinfectant	Microbiological activity					Stability	Inactivation by organic matter	Corrosive/ damaging matter	Irritant
	Spores	Mycobacteria	Bacteria	Viruses[1] Enveloped	Viruses[1] Non-enveloped				
• Glutaraldehyde 2%	+++ (slow)	+++	+++	+++	+++	Moderate (fixative)	No	No	Yes
• Peracetic acid 0.2–0.35%	+++	+++	+++	+++	++	Poor (< 1 day)	No	Slight	Slight
• Alcohol (ethyl alcohol) 60–80%	None	++	+++	+++	++	High	Yes (fixative)	Slight	No Flammable
• Peroxygen compounds	None	+	+++	+++	++	Moderate (7 days)	Yes	Slight	No
• Chlorine-releasing agents >1000 ppm average Cl_2	+++	+++	+++	+++	++	Poor (< 1 day)	Yes	Yes	Yes
• Clear soluble phenolics 0.6–2%	None	+++	+++	+	None	Good	No	Slight	Yes
• Quarternary ammonium compounds	None	Variable	Moderate	+	+++	Good	Yes	No	No

[1] Activity varies with concentration of product.

Sterilization

Sterilization is used to produce an object free from viable microbial organisms including viruses and bacterial spores. There are several types of sterilizer (Figure 3).

Steam

When steam is pressurized it reaches a temperature greater than that of boiling water at atmospheric pressure and destroys or renders non-viable, bacteria, viruses and their spores. For this process to be effective, direct contact between the pure dry saturated steam and the object being sterilized is required at the specific temperature and in the absence of air. The temperature reached by the object determines the time required for sterilization. The lowest temperature recommended is 121°C for 15 minutes; the highest temperature of 134°C requires only 3 minutes.

This process is effective against all microorganisms with a significant safety factor. Problems occur with wrapped items because all air must be removed. To overcome this, porous load sterilizers are used, which incorporate a vacuum pump. Air is removed before steam is added. This is the most commonly used method for sterilization in hospitals today (Figure 4). However, it cannot be used for any material that cannot withstand the temperatures or pressures required for sterilization (e.g. thermo-labile plastics, fibre-optic endoscopes).

The advantages of this process are that steam is non-toxic, non-corrosive and a highly effective sterilizing agent. This system can be incorporated into a fully automated process on a large scale, coping with a high turnover of equipment. Disadvantages are that the operator must wear protective clothing to avoid direct contact with the steam.

Different types of hospital sterilizers

Types of sterilizer	Use	Minimum time / temperature
• Steam sterilizer		
Porous load	Wrapped instruments, dressings, utensils	134–138ºC for 3 minutes
Fluid cycle	Fluids in sealed containers	121–124ºC for 15 minutes,
	or 115ºC for 30 minutes	
Unwrapped instruments	Unwrapped instruments and utensils	134–138ºC for 3 minutes
• Hot air sterilizer	Oils, powders, heat-resistant instruments that must be kept dry	160ºC for 2 hours
• Low temperature steam formaldehyde sterilizer	Heat-sensitive equipment	73ºC for 3 hours
• Ethylene oxide	Heat-sensitive equipment	Various temperatures and times

Dry hot air

In this process, sterilization takes place by raising the ambient temperature. Typical processes consist of 160°C for 2 hours, 170°C for 1 hour, 180°C for 30 minutes. If all the items are completely clean and dry before this sterilization process starts, then all microorganisms will be killed. However, it cannot be used for materials that would be damaged by these temperatures (e.g. rubber, plastic).

Dry heat can be used to sterilize stable powders, waxes and non-aqueous liquids. It is also effective for non-stainless metals, hollow needles and glass syringes. However, the sterilization time is long compared with other methods, and items have to cool slowly afterwards. Many pieces of equipment cannot withstand these high temperatures for the allocated time.

Ethylene oxide

Ethylene oxide at ambient pressure and temperature vaporizes easily and thus has good penetrative properties. It is also non-corrosive and has a wide spectrum of activity against bacteria, spores, fungi, viruses and other living cells. Sterilization is usually carried out at 20–60°C for 2–24 hours.

Ethylene oxide is most often used under three different conditions:

- normal atmospheric pressure using undiluted ethylene oxide – the gas is very flammable, and so is often diluted to reduce explosion risk
- ethylene oxide with a diluent gas such as nitrogen at a pressure of 2 bar
- ethylene oxide diluted with carbon dioxide at a pressure of 6 bar.

This process should not be used if heat sterilization is possible. Organic material has a marked protective effect and therefore prior cleaning is essential. Ventilatory or respiratory equipment is contraindicated. Ethylene oxide does not penetrate plastic; therefore items must be wrapped in sterilization paper.

Ethylene oxide is a highly effective sterilizing agent. In particular it is used to sterilize single use medical items that would be damaged by the excessive heat used in other sterilization methods. Disadvantages of ethylene oxide are that it is toxic and long periods of aeration are required after sterilization therefore turn-around time is long. The process is expensive and there are significant health and safety issues concerning ethylene oxide and the equipment required to use it. Because of this, ethylene oxide is not often used in hospitals but is commonly used by industry.

Low temperature steam and formaldehyde

This process uses a combination of dry saturated steam and formaldehyde, which together kill vegetative bacteria, spores, fungi and most viruses. Objects are placed in the sterilizer to allow maximum contact with the steam. Air is actively removed from the container and replaced by dry saturated steam at 73°C at subatmospheric pressure. Formaldehyde is entrained as the steam enters the sterilizer.

The subatmospheric pressure may damage hollow objects. Formaldehyde may be corrosive with certain materials and some fabrics may absorb formaldehyde. This method cannot be used for items contaminated with body fluids, because the proteins in the fluids congeal and produce hard fixed deposits.

Advantages of the process are that it can provide dry, packaged items in a sterile form and the process is fully automated. Disadvantages are that the process is complex and formaldehyde is toxic, irritant and possibly mutagenic. The equipment required is also expensive, with the added problem of toxic waste products.

Irradiation

Irradiation uses γ rays or accelerated electrons. A dose greater than 25,000 Gray produces sterility. Irradiation is often used to sterilize single use items on an industrial scale. It has a broad spectrum of activity. Irradiation can cause significant degradation of materials and is unsuitable for the resterilization of hospital equipment.

The advantages are that it is reliable on an industrial scale for heat-labile pieces of equipment. However, irradiation can damage equipment particularly on re-exposure. Monitoring the process and the required safety equipment is expensive.

Special circumstances

Recent work has identified that the prion strain causing bovine spongiform encephalopathy (BSE) in cattle has infected humans, manifesting itself as a novel human prion disease, new variant Creutzfeldt–Jakob disease (vCJD). The abnormal prion protein is a new class of transmissible agent that demonstrates resistance to the standard methods of sterilization used in hospital sterile services departments.

Affected individuals accumulate prion protein in lympho-reticular tissues (e.g. appendix, tonsils), as well as in the CNS. The number of people incubating the disease is unknown, and there are concerns that prions might be transmitted iatrogenically via contamination of surgical instruments. Such risks remain unquantified, and there have been no identified cases involving vCJD transmission via surgical instruments. All neurosurgical instruments used on patients suspected of carrying vCJD are destroyed. However, there are significant implications for the safety of surgical instruments in ENT and other surgical practice.

The Spongiform Encephalopathy Advisory Committee (SEAC) has recommended that, where feasible, the move to single use instruments is appropriate. From January 2001, the Department of Health requires tonsillectomy and adenoidectomy to be performed using single use instruments in England and Wales. The recommendations are that instruments used to dissect or cut lymphoid tissue are to be disposed of. Anaesthetic equipment may also provide theoretical risk for prion disease transfer. This risk is as yet unquantified and accepted practice is continuing to evolve. It is likely that, in the near future, anaesthetic practice will change to incorporate disposable, single patient use equipment wherever possible (e.g. disposable laryngoscope blades and laryngeal mask airways).

Critical Incidents: The Cardiovascular System

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Hypertension

Hypertension is a common critical incident during anaesthesia. Whether it is harmful depends on its severity, cause and duration, and on the condition of the patient. These factors also determine how actively it needs to be treated. Hypertension is difficult to define because of observer and subject variation, and the arbitrary nature of cut-off values, but definitions include:

- elevation of blood pressure at least 15% above patient's baseline
- systolic blood pressure greater than 160 mm Hg and/or a diastolic blood pressure greater than 95 mm Hg. Figure 1 lists the causes of hypertension during or persisting after anaesthesia.

Causes of hypertension during or persisting after anaesthesia

- Inadequate anaesthesia/analgesia
- Tracheal intubation/extubation
- Inadequate muscle relaxation
- Pre-existing hypertensive disease
- Hypoxaemia
- Hypercapnia
- Aortic clamping
- Raised intracranial pressure, cerebral ischaemia or cerebrovascular accident
- Drugs (e.g. ketamine, adrenaline (epinephrine))
- Metabolic disorders (e.g. malignant hyperpyrexia, thyroid crisis, phaeochromocytoma, carcinoid syndrome)
- Postoperative urinary retention, pain, anxiety

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Complications

Cardiovascular – hypertension may precipitate myocardial ischaemia (especially subendocardial), infarction or failure.

Neurological – cerebral haemorrhage may result, especially in patients with vascular malformations. Cerebral oedema or encephalopathy are less common complications of uncontrolled hypertension.

Haemorrhage at the operation site or from pre-existing vascular malformations.

Renal – severe hypertension may precipitate acute renal failure.

Management

Management of hypertension should be directed towards the underlying cause. The usual cause is inadequate anaesthesia for the level of surgical stimulation being employed and treatment requires an increase in the inhalational or intravenous anaesthetic drug, or an increase in analgesia. Confirmation of the diagnosis may require a trial of therapy. If the cause of the hypertension cannot be diagnosed or removed, an appropriate antihypertensive drug may be used. The following are examples of drugs commonly used.

- Labetalol – combined α- and β-blockade; dose 5–20 mg i.v. over 2 minutes with increments up to 200 mg. Onset 5–30 minutes, duration 50 minutes.
- Metoprolol –β_1 (cardioselective) blockade; 2 mg increments slow i.v., maximum dose 15 mg.
- Esmolol – rapid onset; short half-life of 9 minutes; 500 µg/kg loading dose; 50–200 µg/kg/minute infusion.
- Nifedipine – calcium-channel blocker, sublingual or intranasal; onset 1–5 minutes following a 10 mg dose.
- Phentolamine – α-blockade; 0.5–2 mg i.v., repeated as necessary, rapid onset, short half-life 10–15 minutes.
- Hydralazine – direct-acting arteriolar dilator, peak action after about 20 minutes following 10–20 mg slow i.v. injection over 20 minutes. Onset occurs after 15–20 minutes; duration is 2–6 hours.
- Glyceryl trinitrate – arterial and venous dilator; use 1 mg/ml solution i.v. (preferably a central vein) via syringe driver, dose 10–200 µg/minute, maximum effect after 1–2 minutes.
- Sodium nitroprusside – arteriolar dilator; very rapid response, administered by continuous intravenous infusion via a dedicated vein, 0.5–1.5 µg/kg/minute. Direct arterial blood pressure recording is mandatory. Doses greater than 4 µg/kg/minute may cause cyanide poisoning.

Hypotension

Mild-to-moderate falls in blood pressure are common during anaesthesia, but seldom result in any harm to the patient. It is difficult to determine what is a dangerous level of hypotension; it depends on the duration of hypotension and the patient's preoperative medical condition. Two signs of inadequate myocardial perfusion are the development of ST segment depression and ectopic beats. Increased ventilation–perfusion mismatch secondary to pulmonary hypotension causes a fall in oxygen saturation (SpO_2). In awake patients receiving regional anaesthesia, nausea and dizziness are common symptoms of excessive hypotension. The lower limit of cerebral, renal and hepatic autoregulation occurs at a mean arterial pressure of about 60 mm Hg in otherwise healthy individuals.

Causes

Anaesthesia

- Volatile agents produce a dose-related fall in blood pressure (vasodilatation, myocardial depression, impaired baroreceptor response).
- Induction agents cause a dose-related fall in blood pressure owing to a complex combination of effects involving myocardial depression, vasodilatation, altered baroreceptor reflex and bradycardia (especially propofol).
- Opioids may precipitate histamine release and vasodilatation. Larger doses are associated with bradycardia.
- Non-depolarizing muscle relaxants may produce hypotension secondary to histamine release.
- Positive-pressure ventilation increases intrathoracic pressure and produces a decrease in venous return and cardiac output.
- Spinal and epidural anaesthesia produce sympathetic blockade. This results in vasodilatation, reducing venous return, cardiac output and systemic vascular resistance. Although reflex vasoconstriction occurs above the level of the block, blood pressure usually falls. Higher blocks (T4 or above) obtund the cardiac sympathetics, preventing a compensatory tachycardia.
- In obstetrics, aortocaval compression impairs venous return and in combination with spinal and epidural anaesthesia may produce profound hypotension.

Hypovolaemia, regardless of aetiology, becomes less concealed following induction of anaesthesia owing to impairment of compensatory mechanisms. Hypotension then ensues. Hypovolaemia may occur in patients with:

- trauma or burns
- gastrointestinal disease (e.g. haematemesis, melaena, small bowel obstruction, acute inflammatory bowel disease)
- dehydration from poor fluid intake, vomiting or diarrhoea
- metabolic disorders (e.g. diabetic ketoacidosis, diabetes insipidus, hypercalcaemia).

Surgical causes of hypotension include:

- haemorrhage
- head-up position
- excessive intra-abdominal pressure during laparoscopic surgery may impair venous return causing hypotension
- release of aortic cross-clamping or lower limb tourniquets causes an acute fall in systemic vascular resistance and blood pressure secondary to vasodilatation in the ischaemic tissues.

Cardiovascular disease may lead to hypotension:

- ischaemic heart disease with impaired cardiac contractility (including unstable angina and recent myocardial infarction)
- heart failure
- valvular heart disease (mitral or aortic stenosis and regurg-itation)
- dysrhythmias (fast atrial fibrillation, complete heart block)
- hypertension, especially if poorly controlled
- others (e.g. myocarditis, cardiomyopathy, constrictive pericarditis, myocardial contusion, tamponade, aortic coarctation, congenital cardiac anomalies).

Cardiovascular medication such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, nitrates, α_1-antagonists (prazosin) and centrally acting α_2-agonists (e.g. clonidine, methyldopa) may cause hypotension.

Autonomic neuropathy produces impaired baroreceptor response and may be present in a variety of disease states:

- diabetes mellitus (incidence and severity increase with the duration of the disease)
- Guillain–Barré syndrome
- spinal cord injury and following cerebrovascular accident
- Parkinson's disease
- AIDS.

Other causes

- Anaphylaxis may result in massive histamine-mediated vasodilatation, producing cardiovascular collapse.
- Pulmonary embolus from deep vein thrombosis, or emboli from air, carbon dioxide or fat may reduce cardiac output. Hypotension is accompanied by desaturation and a fall in end-tidal carbon dioxide.

Management

- Identify and remove the precipitating cause.
- Increase fraction of oxygen in inspired air (F_iO_2) to maintain SpO_2.
- Position patient supine, possibly with the legs raised to improve venous return. The head-down position is no longer recommended because it also raises cerebral venous pressure and therefore cerebral perfusion pressure may not be improved.
- Give a rapid intravenous infusion. The type and amount of fluid depends on aetiology and patient factors. A useful guide is to infuse 10 ml/kg of colloid or 20 ml/kg crystalloid initially and assess the response.
- Vasopressors may be considered, particularly if the cause of hypovolaemia is non-haemorrhagic (e.g. ephedrine, 3–6 mg i.v., metaraminol, 0.5–1.0 mg i.v., or phenylephrine, 0.5–1.0 mg i.v.).
- Consider an infusion of a positive inotrope (e.g. adrenaline (epinephrine), dobutamine) or vasoconstrictor (e.g. noradrenaline (norepinephrine)).

Massive haemorrhage

Bleeding is a significant cause of mortality and morbidity because of the loss of blood volume and its constituents and also the effects of infusions of products aimed at compensating for the loss. Massive blood transfusion can be defined as the transfusion of blood, blood products and fluids equivalent to the circulating blood volume in any 24-hour period. The most profound physiological, haematological and biochemical effects occur in those who have the most rapid loss and replacement therapy.

Causes of massive haemorrhage include:

- trauma
- major elective surgery such as orthopaedic or vascular surgery, especially rupture or dissection of the aorta
- during pregnancy and the puerperium (e.g. massive antepartum or post-partum haemorrhage)
- urgent operations and/or procedures in patients with abnormalities of haemostasis or coagulation.

Management

Measuring blood loss: the quantity of blood lost can be estimated by a number of methods.

- Weighing swabs and measurement of blood aspirated into suction apparatus. With major haemorrhage, these methods become less useful because a considerable amount of blood is spilled on to the drapes and floor. In traumatized patients, major blood loss may have occurred before arrival in hospital or may be concealed in the chest or abdomen, or in the limbs and pelvis at the site of fractures.
- Measuring packed cell volume. Blood lactate concentration gives an indication of the adequacy of organ perfusion.
- Clinical observation. The monitoring of cardiovascular variables such as heart rate, arterial pressure, capillary return, central venous pressure, and in some cases pulmonary capillary wedge pressure and cardiac output, allows a clinical impression of the adequacy of volume resuscitation to be made.

Compensatory mechanisms initially maintain the blood supply to vital organs. Unless adequate and appropriate corrective measures are taken, these mechanisms will decompensate. With increasing volumes of blood loss, there is an increase in heart rate, decrease in stroke volume, reduced pulse pressure, increased respiratory rate and a reduction in cerebral blood flow leading to a reduction in conscious level. These compensatory mechanisms are less efficacious in the elderly and very young and may be impaired by disease or medication. Figure 2 shows the relationship between the changes in vital signs and the volume loss from the circulation.

Relationship between the changes in vital signs and the volume loss from the circulation

	Blood loss (ml)			
	≤ 750	**750–1500**	**1500–2000**	**≥ 2000**
Loss as % of blood volume	≤ 15	15–30	30–40	≥ 40
Heart rate	< 100	> 100	> 120	≥ 140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal	Decreased	Decreased	Decreased
Capillary return	Normal	Slowed	Slowed	Slowed
Respiratory rate (breaths/minute)	14–20	20–30	> 30	≥ 35
Urine output (ml/hour)	> 30	20–30	5–15	Negligible
Mental status	Normal	Anxious	Confused	Drowsy
Suggested volume replacement	Crystalloid	Crystalloid/colloid	Blood	Blood

Active management: the rapid and effective restoration of an adequate circulating blood volume is the primary responsibility of the anaesthetist during periods of heavy blood loss.

Establish adequate venous access by siting at least two large-bore cannulae to allow rapid fluid infusion. The most important pre-determinants of the flow rate of fluid are the diameter of the cannula and the ability to apply a continuous pressure of 2–300 mm Hg via a pressurized infusion system. Crystalloids and synthetic colloids may be used initially and should be followed by the administration of blood if bleeding continues.

Commence intravenous fluids – internationally accepted practice is to use Hartmann's solution as the initial resuscitation fluid for trauma and burns. The success of initial resuscitation in an acutely hypovolaemic patient probably depends more on adequacy of repletion than on which fluids are used. For a given blood volume expansion about twice the volume of crystalloid compared with colloid is required. In practice, combined therapy using both crystalloids and colloids is often used.

Fluids should be warmed – a transfusion system should have the ability to transfuse blood at fast flow rates (up to 500 ml/minute) and at temperatures greater than 35°C. Some systems use a constant-pressure infusion device combined with an efficient blood warmer and a purpose-designed blood-warming coil (e.g. *Level One*™). Priming or flushing blood through the system after fluid containing calcium has been used (such as *Haemaccel*) should be avoided, because this may cause blood clot formation in the tubing by reversal of the anticoagulant effect of citrate.

Blood should be taken for grouping and cross-matching, for coagulation studies and for biochemical analysis. Accurate identification of transfusion specimens and of designated units of blood, platelets and fresh frozen plasma (FFP) is particularly important in patients undergoing massive transfusion. It should be noted that most incompatible blood transfusions occur in emergency situations. For operations where significant blood loss is anticipated, replacement therapy should be available in advance of surgery.

Red cell transfusions are given to increase the haemoglobin concentration and thus improve or normalize the delivery of oxygen to the tissues. The haemoglobin concentration at which blood transfusion is commenced depends to a certain extent on the individual patient (e.g. elderly patients are at greater risk of complications from anaemia). A haemoglobin value below 8.5 g/dl would be an indication to transfuse in all apart from the younger fitter patient. A postoperative haemoglobin level of about 10 g/dl is widely accepted as a general guideline in adult surgical patients. However, it is more appropriate to base transfusion decision on a clinical assessment of the patient. If a major surgical procedure is planned, it may be possible to decrease the amount of donor blood transfusions by using an automated cell saver system.

About 80% of patients who have massive haemorrhage develop diffuse ooze from raw or cut surfaces. The causes are multifactorial but include relative hypothermia, abnormal platelet function, dilution of clotting factors, consumption of factors and enhanced fibrinolysis. It is critically important to monitor platelet numbers and the coagulation process during major bleeding and its resuscitation. The platelet count falls steadily with the transfusion of each successive unit of blood. Platelet infusion is indicated if there is:

- a platelet count less than 50 x 10^9/litre and there is impending surgery or an invasive procedure
- diffuse microvascular bleeding and transfusion greater than one blood volume and a platelet count of 50 x 10^9/litre or less, or the result is unavailable
- diffuse microvascular bleeding following cardiopulmonary bypass and the platelet count is 100 x 10^9/litre or less, or the result is unavailable
- bleeding in a patient with a qualitative platelet defect, regardless of platelet count.

Moderate deficiency of coagulation factors is common in massively transfused patients, but does not contribute to microvascular haemorrhage until levels fall below 20% of normal. These levels are reliably reflected by prolongation of the prothrombin (PT) and activated partial thromboplastin times (aPTT) to values of more than 1.5 times the control value. If the PT and aPTT are more than 1.5 times normal, 4 units of FFP should be given. If PT and aPTT are prolonged and fibrinogen is less than 0.8 g/litre, cryoprecipitate is indicated.

Arterial and central venous lines may be sited to allow rapid blood sampling, for acid–base and potassium status, and the direct measurement of arterial and central venous pressures. The central venous catheter also provides access for intermittent bolus administration of drugs or drug infusions.

A urethral catheter should be passed unless contraindicated by pelvic or urethral injury, and urine output monitored.

Core temperature should be measured continuously and every effort made to prevent heat loss. Hypothermia causes platelet dysfunction, reduced metabolism of citrate and lactate and an increased tendency to cardiac arrhythmias. This may result in bleeding diathesis, hypocalcaemia, metabolic acidosis and cardiac arrest.

Arrhythmias

Arrhythmias are one of the most commonly reported critical incidents. About 12% of patients undergoing anaesthesia develop arrhythmias; this increases to 30% in patients with cardiovascular disease. Treatment may not be required; this depends on the nature of the arrhythmia and its effect on cardiac output. Single supraventricular or ventricular ectopic beats, and slow supraventricular rhythms, do not require treatment unless cardiac output is compromised.

Management

Fluid, electrolyte and acid–base disturbances should be corrected preoperatively. Particular attention should be paid to the level of potassium ions in the plasma because they have a vital role in the generation of the resting membrane potential and thus muscle and nerve function. Patients with hypokalaemia may be prone to the development of supraventricular or ventricular extrasystoles and tachycardias. ECG changes of hypokalaemia include a long PR interval, ST depression, T wave flattening and a prominent U wave. Rapid treatment is indicated if arrhythmias are present. Intravenous administration of potassium supplements should not exceed 0.5 mmol/kg/hour.

Continuous intraoperative ECG monitoring is essential. The ECG gives no indication of cardiac output or tissue perfusion, therefore the detection of an abnormal cardiac rhythm should be followed by clinical assessment of the circulation. An absent pulse, severe hypotension or ventricular tachycardia or fibrillation should be treated as a cardiac arrest.

Correcting the precipitating factor is often the only treatment required. Hypoxaemia and inadequate anaesthesia or analgesia must be excluded. Factors associated with the development of arrhythmias are listed in Figure 3.

Intervention with a specific antiarrhythmic agent or cardioversion is indicated if there is:

- a risk of developing ventricular tachycardia or fibrillation (e.g. frequent, multifocal ectopic beats, or 'R on T' complexes)
- a significant decrease in cardiac output (causing dizziness or hypotension)
- evidence of myocardial ischaemia (causing chest pain or ST segment changes).

Factors associated with the development of arrhythmias

Preoperative conditions

- Ischaemic heart disease
- Pre-existing arrhythmias
- Congestive heart failure
- Hypertension
- Valvular heart disease
- Electrolyte disorders
- Medications (theophylline, β_2-agonists, tricyclic antidepressants)
- Others (thyrotoxicosis, myocarditis, cardiomyopathies, trauma, drug and solvent abuse)

Anaesthetic factors

- Hypoxaemia
- Hypo/hypercapnia
- Hypo/hypertension
- Laryngoscopy
- Drugs (e.g. volatile anaesthetic agents, suxamethonium, central venous pressure lines)

Surgical factors

Catecholamines

- Exogenous (e.g. infiltrated adrenaline (epinephrine))
- Endogenous (inadequate analgesia, inadequate anaesthesia)

Autonomic stimulation

- Oculocardiac reflex
- Laryngoscopy, bronchoscopy, oesophagoscopy
- Carotid artery and thyroid surgery
- Peritoneal and visceral traction
- Peritoneal insufflation

Direct stimulation of the heart

- Cardiac and thoracic surgery

Embolism

- Thrombus, fat, air, carbon dioxide, amniotic fluid

Others

- Limb reperfusion
- Aortic cross-clamping

Bradycardia can be treated with an anticholinergic agent such as atropine, 0.6 mg i.v., or glycopyrrolate, 0.2–0.4 mg i.v. If the bradycardia is refractory to treatment, cardiac pacing or an intravenous infusion of isoprenaline, 0.5–10 µg/minute, may be indicated. An anticholinergic drug may be given prophylactically if there is risk of bradycardia (e.g. strabismus surgery or following a second dose of suxamethonium).

Sinus tachycardia associated with myocardial ischaemia may be controlled by administration of a β-blocker such as metoprolol, 2 mg increments slow i.v., maximum dose 15 mg, or esmolol, 500 µg/kg, loading dose followed by 50–200 µg/kg/minute infusion.

Junctional rhythms are usually associated with the use of halothane. A reduction in concentration and/or changing the volatile agent is indicated. An anticholinergic drug may restore sinus rhythm.

Accelerated nodal rhythms may be precipitated by an increase in sympathetic tone in the presence of sensitizing volatile agents. Treatment includes adjusting the depth of anaesthesia and/or changing the anaesthetic agent.

Supraventricular tachycardia (SVT) can occur in susceptible patients, such as Wolff–Parkinson–White or other 'pre-excitation syndromes'. Treatment of SVT consists of:

- carotid sinus massage
- adenosine, 3–12 µg i.v.
- DC cardioversion if haemodynamic decompensation is present
- if there is no decompensation give verapamil, 5–10 mg slow i.v. over 30 seconds; the injection should stop when the SVT is controlled
- in sepsis-related or refractory SVT, volume loading plus amiodarone, 300 mg i.v. by infusion over 20 minutes, then 900 mg over 24 hours
- if the patient is thyrotoxic a β-blocker is useful.

Atrial fibrillation or flutter is often seen as a paroxysmal increase in the ventricular rate in patients with pre-existing atrial fibrillation or flutter. Having corrected any precipitating factors, the therapeutic options include:

- digoxin, 10 µg/kg by slow i.v. injection over 20 minutes, repeat after 4 hours according to response, maintenance dose 125–500 µg/day. Peak effect after 2 hours. Slows the ventricular rate and is a positive inotrope
- amiodarone produces a more rapid ventricular response and may re-establish sinus rhythm, give 300 mg i.v. by infusion over 20 minutes, then 900 mg over 24 hours
- β-blockers, especially in thyrotoxicosis, in combination with digoxin (e.g. propranolol 1 mg slow i.v. repeated every 2 minutes, maximum 5 mg)
- cardioversion is an option if the ventricular rate is fast with a clinically reduced cardiac output.

Premature ventricular contractions are common in healthy patients. Perioperatively they seldom progress to more serious arrhythmias unless there is underlying hypoxaemia or myocardial ischaemia. An underlying cause should be sought before antiarrhythmic agents are considered. If associated with a slow atrial rate, increasing the sinus rate with an anticholinergic drug will abolish them. Halothane lowers the threshold for catecholamine-induced ventricular arrhythmias; this is exacerbated by hypercapnia. Halothane should be used with care in patients receiving sympathomimetic drugs (including local anaesthetics containing adrenaline), and in patients taking tricyclic antidepressants and aminophylline.

Ventricular tachycardia and fibrillation should be treated as a cardiac arrest.

Malignant hyperthermia

Malignant hyperthermia is a rare inherited complication of general anaesthesia triggered by inhalational agents or suxamethonium in susceptible patients. The inheritance is complex and it is a genetically heterogeneous condition. These patients have a defect in intracellular calcium binding within the sarcoplasmic reticulum of skeletal muscle cells. Calcium ions are released on exposure to trigger agents, which initiates widespread skeletal muscle contraction and generalized membrane permeability. There is severe metabolic disturbance and catabolism runs unchecked, because raised levels of myoplasmic calcium ions result in increased production of pyruvate and heat. A successful outcome relies on making an early diagnosis, discontinuation of trigger agents, prompt treatment with intravenous dantrolene and supportive care. The mortality today has decreased to about 25% owing to increased awareness, monitoring and prompt treatment. The mode of presentation is variable and a high index of suspicion is required for early diagnosis.

Signs of malignant hyperthermia include:
- unusual muscle rigidity following suxamethonium (especially masseter spasm)
- unexplained tachycardia and arrhythmias
- rise in end-tidal carbon dioxide
- metabolic acidosis
- fall in oxygen saturation
- hyperkalaemia
- rise in core temperature (about 1–2°C/hour)
- evidence of a coagulation disorder, oozing from wound sites.

Management

Immediate actions
- Discontinue inhalational agents and inform the surgeons. Stop surgery if feasible, make the operating site safe and close wounds.
- Continue sedation or anaesthesia with a total intravenous technique. Hyperventilate with 100% oxygen using a clean breathing system. Change the circle system using fresh soda-lime, or use a non-rebreathing system.
- Immediately instruct staff to prepare dantrolene and commence as soon as available in an intravenous infusion of 1 mg/kg repeated at 10 minute intervals up to 10 mg/kg.
- Remove drapes, fully expose the patient and promote surface cooling with avoidance of vasoconstriction.
- Insert an arterial line to aid monitoring, and allow regular estimation of arterial blood gases, potassium and creatine kinase.
- Monitor the patient's core temperature.

Intermediate actions
- Control life-threatening dysrhythmias (e.g. β-blockers).
- Control hyperkalaemia with intravenous glucose or insulin.
- Control metabolic acidosis by hyperventilation, consider sodium bicarbonate (2–4 mmol/kg) if acidosis is severe (e.g. pH < 7.0).

Later actions
- Send blood for clotting screen (PT, aPTT, fibrinogen).
- Catheterize the patient. Test their urine for myoglobin. Collect samples for vanillylmandelic acid estimation to exclude phaeochromocytoma. Promote diuresis with intravenous fluids and mannitol, 0.5 g/kg over 20 minutes.
- Request a chest radiograph. Send blood for full blood count, biochemistry and thyroid function tests.
- Notify the intensive care unit.
- Repeat the creatine kinase estimation in 24 hours.
- Consider other diagnoses such as recreational drug ingestion (e.g. Ecstasy), neuroleptic malignant syndrome or myopathy.

Future care

The patient and their family should be counselled as to the likely diagnosis and the implications for future anaesthetics. Wearing a Medic-Alert bracelet should be encouraged. The patient and immediate family should be referred for further investigation and muscle biopsy to:

UK MH Investigation Unit, Academic Unit of Anaesthesia
Clinical Sciences Building
St James's University Hospital Trust
Leeds LS9 7TS
Tel: 0113 206 5274
Emergency hotline: 07947 609601

Future anaesthetic care can be provided safely with the avoidance of trigger agents – the volatile anaesthetics and depolarizing muscle relaxants. Prophylactic dantrolene is not recommended. Phenothiazines, antidepressants and haloperidol have been suggested as possible trigger agents, because of the similarity between malignant hyperthermia and the neuroleptic malignant syndrome, but this is unlikely. All other anaesthetic drugs appear to be safe.

Critical Incidents: The Respiratory System

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A critical incident during anaesthesia is any event that may result in actual or potential harm to the patient if uncorrected. It may cause severe morbidity or even mortality. It is often preventable by a change in practice. Incident reporting is the key to preventing future disaster. There is observer bias concerning which incidents are recorded, and the problem for anaesthetists is to distinguish between a critical incident and the normal course of clinical practice.

This contribution deals with life-threatening problems in the management of the respiratory system including the clinical and physiological presentation of some commonly encountered critical incidents and their treatment. All may be a cause of alarming cyanosis under anaesthesia. Not all the problems discussed can be prevented and so some may not meet the precise definition of critical incidents. The recommendations aim to provide the anaesthetist with fast and effective solutions that may be used in clinical, examination or simulation situations. In all cases, the trainee anaesthetist must request senior help at the earliest opportunity.

Aetiology

The 2000 report of the National Confidential Enquiry into Perioperative Deaths (NCEPOD) cites hypotension, hypoxaemia, arrhythmia and cardiac arrest as the most common critical events that occur during or immediately following surgery. It also concludes that modern anaesthetic equipment, when properly checked, is very reliable. Human factors often play a major role in the aetiology of adverse events (Figure 1).

Factors involved in avoidable deaths

- Error of judgement
- Error of clinical expertise
- Lack of experience
- Lack of assistance
- Lack of equipment
- Equipment failure

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Preparation is an important factor in predicting and treating these events and should involve:

- thorough preoperative patient assessment
- check of all anaesthetic equipment
- appropriate selection of drugs
- appropriate level of clinical expertise.

The Association of Anaesthetists of Great Britain and Ireland (AAGBI) has recently published new recommendations for standards of monitoring during anaesthesia and recovery. The Royal College of Anaesthetists (RCA) has a web page (http://www.rcoa.ac.uk/critincident/ciweb.html) that deals with the processing of critical incidents. The RCA is committed to setting up a national database so that even rare incidents can be reported and acted on. Critical incidents should be discussed locally at regular departmental audit meetings to complement the process of clinical governance.

Respiratory obstruction and increased peak airway pressure

Obstruction to the airway is an immediate threat to life and is the most common critical incident registered. The 'airway' can be considered as the conducting pathway responsible for the delivery of oxygen from anaesthetic machine to the alveolar/blood interface. Thus, obstruction may occur from outside or within the patient. The anaesthetic machine, breathing system and connections must be checked to ensure their patency and correct function before anaesthesia.

Obstruction of the airway within the patient may arise from the upper, supraglottic region, to the lower bronchiolar region. It may be caused by the devices used during anaesthesia or result from airway anatomy, pathology or trauma. Figure 2 shows some of the likely causes of airway obstruction in the perioperative period.

Possible causes of airway obstruction

Supraglottic

- Tongue
- Periglottic abscess, tumour, haematoma
- Regurgitation of solid material
- Blood or secretions
- Laryngeal mask airway (LMA) or tracheal tube luminal occlusion or misplacement

Laryngeal

- Laryngospasm
- Tumour or oedema
- Post-thyroidectomy (laryngeal nerve injury)
- LMA or tracheal tube luminal occlusion or misplacement

Tracheal or bronchial

- Aspiration
- Asthma
- Anaphylaxis
- Pneumothorax
- Pulmonary oedema
- Tracheal obstruction by retrosternal goitre
- LMA or tracheal tube luminal occlusion or misplacement

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Respiratory obstruction during induction of anaesthesia

Preoperative evaluation of the airway is vital and should include mouth opening, dentition, Mallampati score, jaw movement, thyromental distance and neck movement. The aim is to predict which patients may present difficulty with direct laryngoscopy and intubation and those in whom difficulty may arise with airway maintenance following loss of consciousness, such as those with:

- obesity or a 'bull neck'
- limited mouth opening (e.g. trismus, following infection, trauma)
- restricted head and neck movement (e.g. severe ankylosing spondylitis, rheumatoid arthritis)
- stridor resulting from tumour, trauma, infection or haem-atoma
- upper airway soft tissue swelling (e.g. burns, pre-eclampsia). About 10% of reported critical incidents occur in the anaesthetic room. Patient monitoring during induction of anaesthesia should follow the guidelines established by the AAGBI. The patient must be monitored adequately during this stage of anaesthesia. If the required equipment is unavailable, induction should take place in the operating theatre.

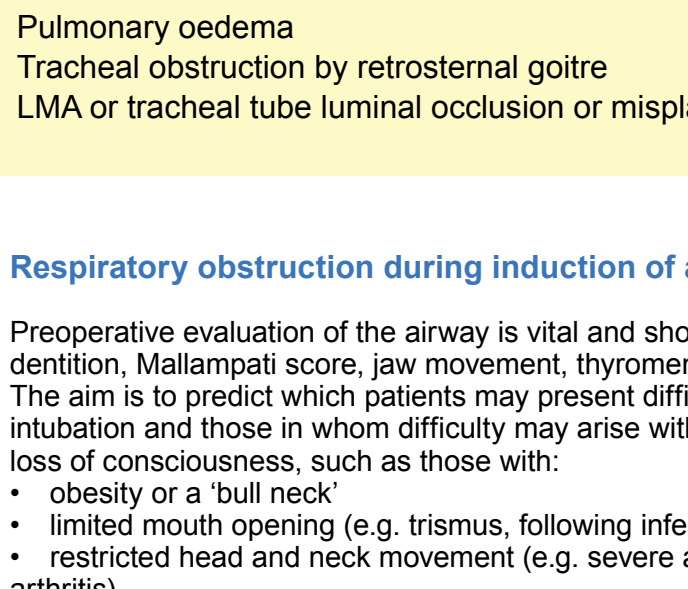
Induction of anaesthesia in patients with upper airway obstruction requires specialized expertise. Management must involve a clear plan of how to proceed in the event of total airway obstruction during induction. These patients are best managed in the operating theatre with surgeons gowned and ready to perform immediate tracheostomy under local anaesthesia if necessary.

In routine practice, airway obstruction that occurs following induction is apparent from:

- paradoxical (see-saw) chest movement (when breathing spontaneously)
- noisy airway
- absent or diminished movement of the reservoir bag
- absent or diminished capnograph trace
- increased airway pressure (when mechanically ventilated)
- progressive oxygen desaturation.

Simple airway manoeuvres such as chin lift and jaw thrust, often combined with the insertion of a correctly sized oropharyngeal or nasal airway are necessary to maintain airway patency following induction. In apnoeic patients or those requiring assisted ventilation, bag and mask ventilation by two operators is more effective than that provided by one operator (Figure 3), allowing more effective face mask application and upper airway management. Manual ventilation with bag and mask is then easier to perform. If management is difficult, it is important to switch to 100% oxygen and call for senior help early on.

Two operators providing bag and mask ventilation



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If airway obstruction persists, a laryngeal mask airway (LMA) often corrects the situation. While tracheal intubation provides a definitive airway, it may be difficult to insert in a patient who has not received muscle relaxants. Neuromuscular blockade should never be administered unless airway patency can be assured. However, if airway maintenance is lost following the administration of muscle relaxants then swift direct laryngoscopy and tracheal intubation should be attempted. Some patients (e.g. those with adenotonsillar hypertrophy, the obese or heavy snorers) are often easy to intubate despite having a difficult airway to maintain with bag and mask. The LMA is also the technique of choice following a failed intubation if subsequent airway management is difficult. Numerous reports testify to the ability of the LMA to provide a clear airway following a failed intubation. The *Combitube* may also be useful, though it is less commonly used in the UK. Both are 'supraglottic' airway devices, therefore it is unlikely that the *Combitube* will provide a clear airway if the LMA does not.

Can't intubate, can't ventilate (CICV)

The inability to intubate or ventilate a patient is rare, with an estimated incidence of 1/10,000 anaesthetics. It occurs when alveolar ventilation cannot be maintained despite best attempts at intubation and bag-mask ventilation (Figure 4).

Analysis of closed-claims in the USA revealed that the most common predisposing factor in the development of CICV was repeated and continued attempts at intubation. With each successive period of re-oxygenation between intubation attempts, bag-mask ventilation became increasingly difficult as laryngeal oedema evolved. The anaesthetist should limit intubation attempts to a maximum of three. The decision must be made early to abandon further attempts at intubation and the anaesthetist must use an alternative airway device, or wake the patient. The main causes of CICV are:

- repeated failed attempts at intubation
- airway or neck trauma
- burns to the head and neck
- pregnancy (especially pre-eclampsia)
- tumour (e.g. larynx)
- infection.

Requirements for optimum best attempts

Optimum best bag-mask ventilation

- Correctly sized oral or nasal airway
- Two-operator technique

Optimum best laryngoscopy

- Trained anaesthetist (3 years' training)
- Optimal intubating position
- Optimal external laryngeal manipulation
- Optimal laryngoscope

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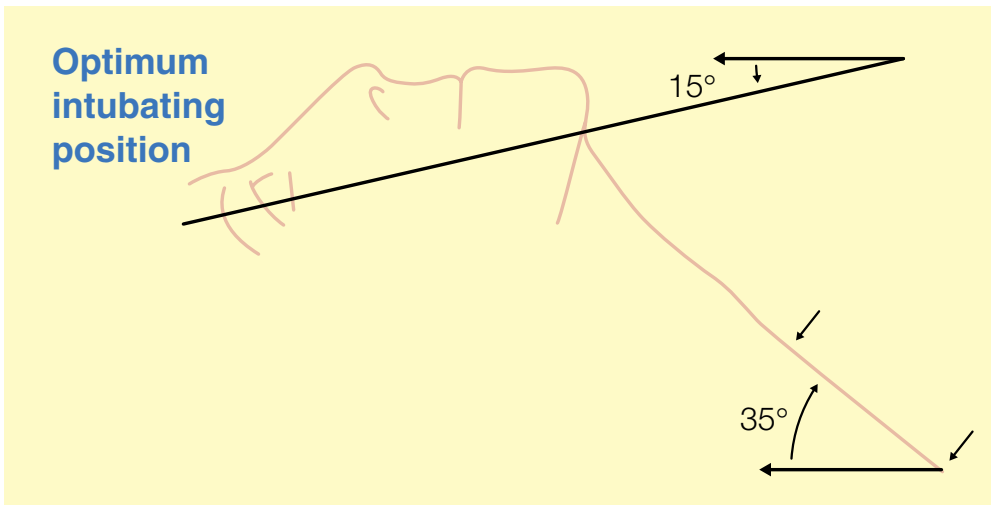
The optimal intubating position is shown in Figure 5. Flexion of the cervical spine, and extension of the head at the atlanto-occipital joint, aligns the glottis with the visual axis. In the obese or pregnant woman at term, this may require at least one pillow under the shoulders and two pillows beneath the head and neck. Anaesthetic induction and tracheal intubation should be avoided when patient positioning is not ideal.



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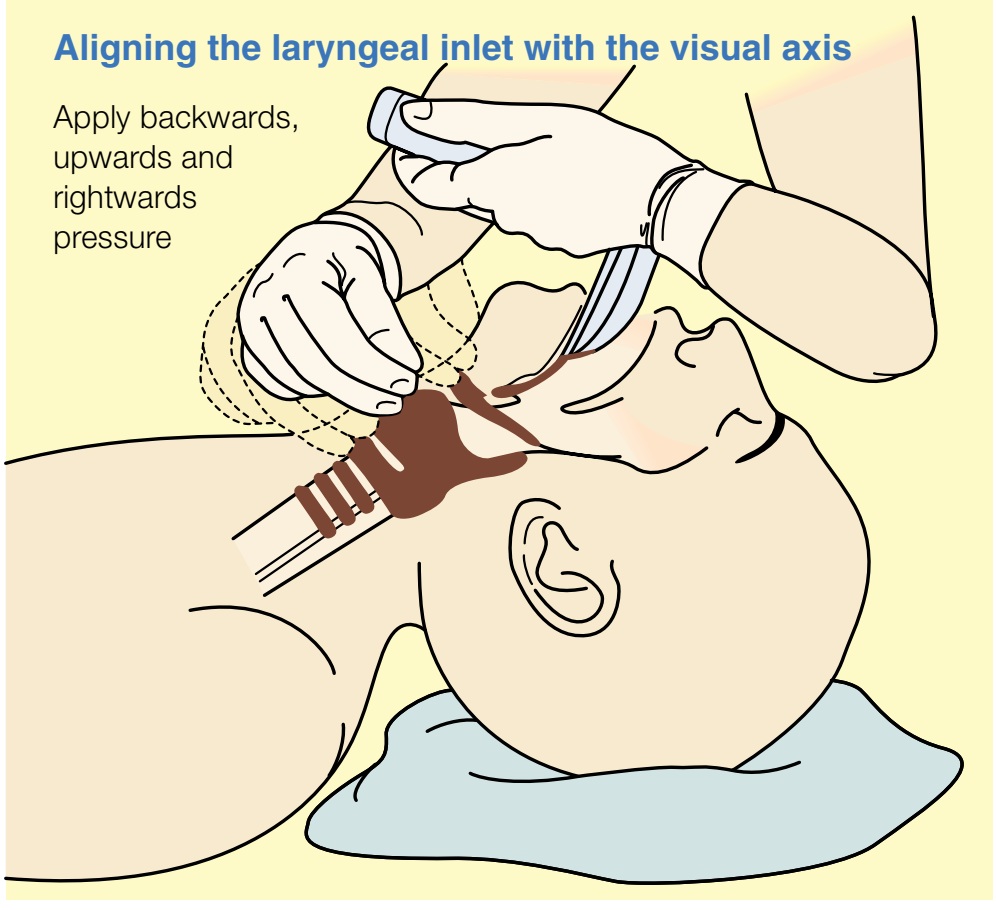
The larynx should be manipulated from the front of the neck by the operator's free hand to help provide the best view. This position is maintained by the anaesthetic assistant while intubation is performed. Optimum external laryngeal manipulation does not mean 'cricoid pressure', which may further distort the view and make direct laryngoscopy more difficult. Optimum manipulation involves direct manipulation of the thyroid cartilage of the larynx. The application of backwards, upwards and rightwards pressure aligns the laryngeal inlet more closely with the visual axis. Correct optimum external laryngeal manipulation is shown in Figure 6.



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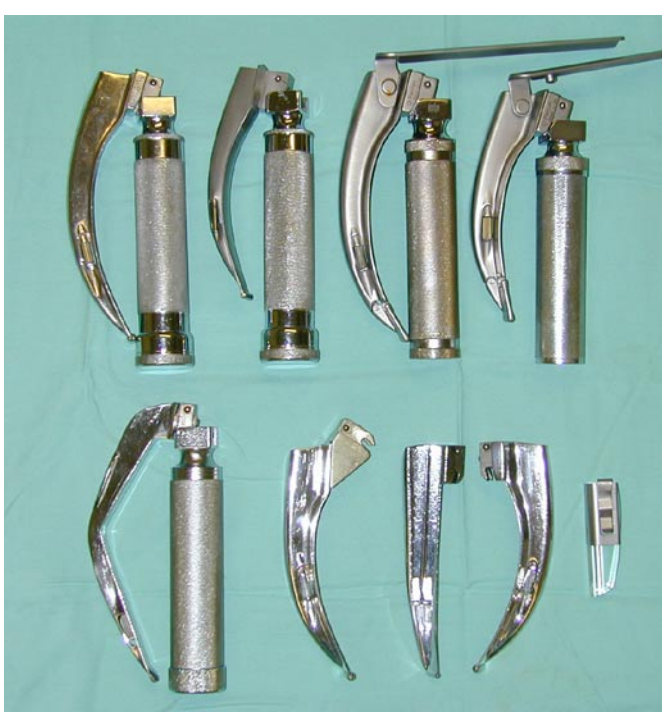
The choice of laryngoscope blade is important. A useful guideline is to change the length of blade once, and the type of blade once, to achieve the best view. A variety of blades is available in clinical practice. The standard Macintosh blade (size 3) may need to be changed to a longer blade (size 4) or to a levering blade such as the McCoy. The McCoy blade can be successful in improving the laryngoscopic view by one grade (Cormack and Lehane grade 3 to 2). The Belscope blade has a 45° angle and a detachable prism, and may similarly improve a grade 3 view. The Polio blade is inclined at an angle greater than 90° to the handle, which may aid insertion into the mouth (Figure 7).



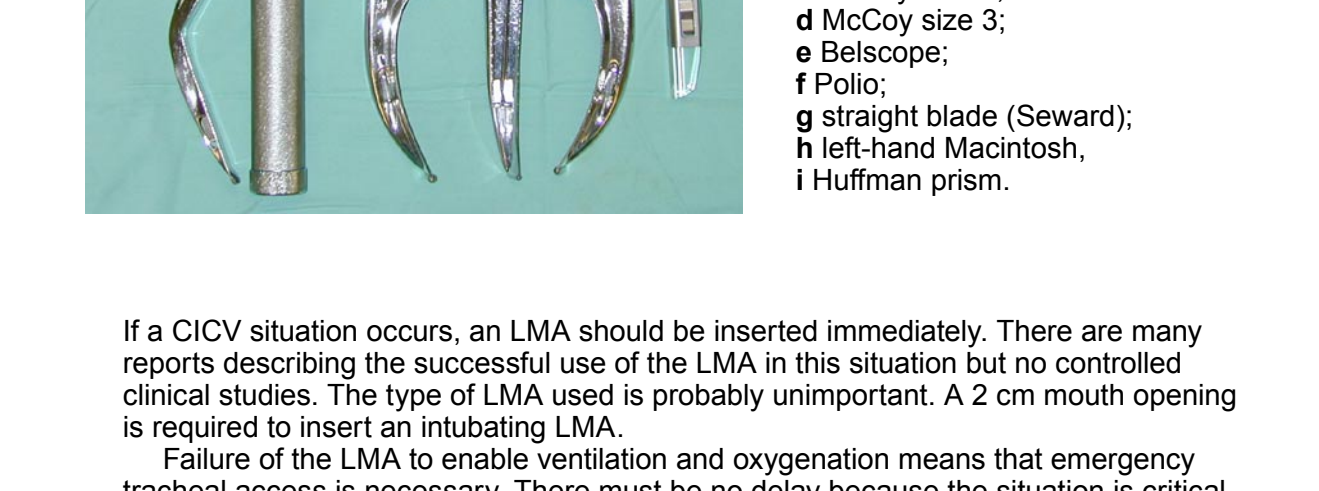
7 Laryngoscope blades:
a Macintosh size 4;
b Macintosh size 3;
c McCoy size 4;
d McCoy size 3;
e Belscope;
f Polio;
g straight blade (Seward);
h left-hand Macintosh,
i Huffman prism.

If a CICV situation occurs, an LMA should be inserted immediately. There are many reports describing the successful use of the LMA in this situation but no controlled clinical studies. The type of LMA used is probably unimportant. A 2 cm mouth opening is required to insert an intubating LMA.

Failure of the LMA to enable ventilation and oxygenation means that emergency tracheal access is necessary. There must be no delay because the situation is critical in a patient with marked hypoxia. Tracheal access is best achieved via the cricothyroid membrane by needle puncture, percutaneous cricothyrotomy or surgical cricothyrotomy. The precise technique depends on: the equipment available; the experience of the anaesthetist; and the nature of the emergency.

It is impossible to give firm recommendations but whatever the means used, the immediate aim is to achieve oxygen delivery to the trachea (and alveoli) via the cricothyroid membrane. This membrane lies subcutaneously between the cricoid and thyroid cartilages of the larynx and in the adult measures 1 x 3 cm. It will accept a tracheal tube of maximum size 7.0 internal diameter (ID). Paired cricothyroid arteries arise from the superior border and pass laterally. The patient's head and neck should be extended to bring the cricothyroid membrane closer to the skin surface to facilitate access. Placing a sandbag or 1 litre fluid bottle between the patient's scapulae may help to achieve this.

Needle cricothyrotomy is minimally invasive but requires a jet ventilator to achieve satisfactory alveolar ventilation. A cannula is inserted via the cricothyroid membrane (Figure 8), free aspiration of air confirms correct placement. Resistance through the cannula is too high to enable conventional bag ventilation. Simple emergency systems can be constructed using green oxygen tubing connected to a flowmeter (e.g. 10-15 litres/minute). A side hole or three-way tap allows for intermittent insufflation by finger occlusion of the hole. The green oxygen tubing is inserted into the barrel of a 2 ml syringe which then allows connection to the cannula. The free end is connected to an oxygen flowmeter or to the anaesthetic machine via a 15 mm connector. Oxygen insufflation techniques provide tracheal oxygen delivery but not satisfactory carbon dioxide elimination. It is recommended that all sites where anaesthesia is administered have access to a jet ventilator. The inspiratory time of about 1 second should be followed by a 3 second expiratory time. It is unlikely that airway obstruction is absolute and passive exhalation will occur via the glottis. If this is deemed inadequate a second cannula should be placed to allow exhalation and prevent overinflation and barotrauma. A needle cricothyrotomy is a temporary measure and preparations should be made for a formal tracheostomy.



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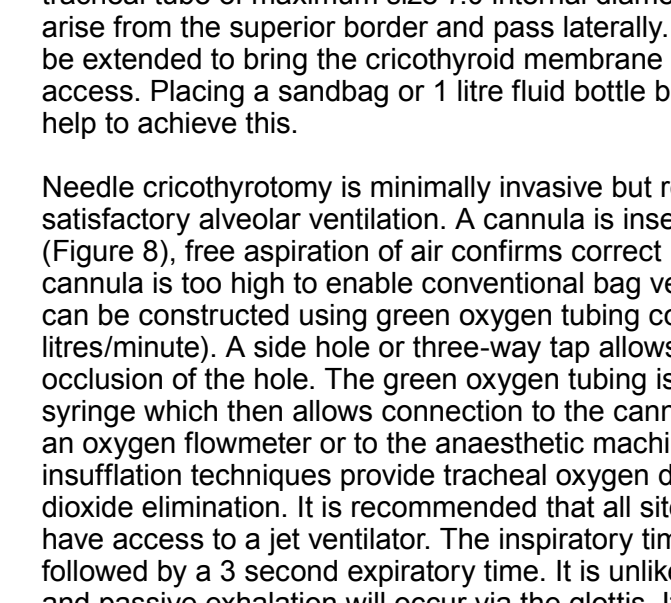
Specific cricothyroid cannulae are available for emergency tracheal access (Figure 9). The Ravussin 13 G jet ventilation catheter (VBM Medical) is flanged to simplify fixation, and has both Luer-lock and 15 mm connections. The Cook 6 F emergency transtracheal catheter is spiral reinforced and kink-resistant; a standard 14 G intravenous catheter is easily kinked and difficult to fix. The main complication of the technique is incorrect needle position and subcutaneous/mediastinal emphysema.



9 Cricothyrotomy needles.
a 13 G Ravussin jet ventilation catheter (VBM Medical);
b 6 F Cook emergency transtracheal catheter;
c 14 G Venflon cannula.

Percutaneous cricothyrotomy allows emergency placement of a tracheal tube to allow more conventional ventilation via bag and mask. Several commercial kits are available, which differ in insertion technique (Seldinger or non-Seldinger), size of tube (3.5-6.0 ID), and time taken for tube placement. There are insufficient data to make recommendations concerning the optimum technique and the anaesthetist should be familiar with the equipment available in their hospital. A non-Seldinger kit (e.g. VBM Quicktrack, 4.0 mm ID) generally allows the most rapid access by direct cricothyroid puncture using a large diameter sharpened stylet. A Seldinger technique (e.g. Cook Melker kit 3.5-6.0 mm ID) may be safer to perform but requires several stages including the use of a dilator. All techniques require familiarization. Complications include bleeding, malposition and subcutaneous emphysema.

Surgical cricothyrotomy rapidly provides a definitive airway, though it requires more surgical experience and bleeding is likely to be considerable. It is ideally suited to the emergency trauma setting in the presence of severe maxillofacial, neck or laryngeal injury. Thorough training is necessary for this seldom performed but life-saving procedure. Practising on the sheep's larynx provides a realistic training model.

With finger and thumb either side, the cricothyroid membrane should be stabilized. A 22 scalpel blade is used to make a 2 cm vertical skin incision to part the skin. The scalpel should then be horizontally inserted into the cricothyroid membrane, perpendicular to the skin. This incision should be enlarged laterally. The scalpel handle should be inserted through the cricothyroid incision and rotated through 90°, then removed. A well-lubricated size 7.0 ID cuffed tracheostomy tube should be inserted. The main complications are bleeding and malposition.

Respiratory obstruction during the intraoperative period

If respiratory obstruction occurs during surgery, the following procedure will help to diagnose the cause of obstruction (Figure 2) and guide appropriate action to correct the situation. Surgery can then recommence.

- 100% oxygen should be commenced.
- The surgeons should be alerted to the problem and advised to stop surgery. The surgical stimulation may have caused the obstruction. Procedures such as dilation of the cervix or anus may precipitate severe stridor especially if anaesthesia is 'light'.
- The anaesthetic delivery circuit should be checked rapidly.

If it is patent, the obstruction must be within the patient.

- Access to the airway may be difficult, especially in head and neck surgery. Extreme circumstances of continued patient deterioration require the complete uncovering of surgical drapes and exposure of the airway.
- The upper airway should be checked for secretions, signs of regurgitation or obvious tube or LMA obstruction. The mouth and trachea should be suctioned if indicated.
- The capnograph confirms alveolar ventilation by displaying a carbon dioxide trace. Absence of a trace is a sign of complete airways obstruction. The normal capnograph trace may change in airways obstruction with a characteristic marked upslope to the alveolar plateau.
- The urgency of the situation is indicated by the oxygen saturation. If there is any doubt about the tracheal tube position, immediate replacement is needed. An LMA will need repositioning or changing to a tracheal tube. Careful observation of the chest wall during manual ventilation may show unilateral or little chest movement. Auscultation of the chest may detect unilateral air entry, wheeze or absent breath sounds. Withdrawing the tracheal tube slightly may alleviate this if the distal end has migrated to the endobronchial position, or is in contact with the carina.
- Fibre-optic bronchoscopy will confirm the position of the tracheal tube and that there is no intraluminal obstruction such as a sputum plug, blood clot or in rare circumstances, an endoluminal tumour.

Bronchospasm during anaesthesia

Bronchospasm is reversible airways obstruction most commonly associated with patients who have asthma or chronic chest disease. The incidence of asthma is 5-10% with a higher prevalence in children. Smokers and patients with upper respiratory tract infection are also at increased risk of bronchospasm. Bronchospasm occurs as a result of smooth muscle constriction within the respiratory subepithelial layers in the bronchioles. It may be accompanied by other pathological effects (e.g. mucosal oedema, cellular infiltrates, mucus secretion, desquamation of surface epithelial cells, goblet cell hyperplasia) which exacerbate smooth muscle contraction. Contraction is stimulated by neural or paracrine effects. Chemical mediators such as histamine and products of arachidonic acid, the leukotrienes, may act locally to initiate bronchoconstriction.

Bronchospasm is not the only cause of intraoperative wheeze (Figure 10). Luminal occlusion from eccentrically inflated tube cuffs (cuff herniation) used to occur with red rubber tracheal tubes, but modern disposable materials have made this complication less common, however the tracheal tube cuff should not be over-distended. The old adage 'if in doubt – take it out' remains true. A monophonic wheeze developing immediately after intubation may indicate tube occlusion, or a distal position next to the carina or within a bronchus.

Bronchospasm is suggested by:

- increased respiratory effort, tachypnoea and intercostal recession (if spontaneously breathing)
- expiratory wheeze (wheeze throughout the respiratory cycle may indicate obstruction within the breathing equipment)
- rise in inspiratory airway pressure (if mechanically ventilated). Management of wheeze while under anaesthesia is as follows.
- The surgeons should be alerted and asked to stop surgery.
- 100% oxygen should be delivered and anaesthesia deepened. Bronchospasm may result from a depth of anaesthesia that is too light for the degree of surgical stimulation. This includes stimulation of the airway by the anaesthetist. All modern inhalational agents are bronchodilators.
- The breath sounds over both lung fields and over the stomach should be listened to. Capnography confirms tracheal intubation. Tracheal tube position should be adjusted if necessary. Signs of pulmonary oedema or tension pneumothorax should be sought.• The position of the tracheal tube should be adjusted if necessary.
- The airway should be checked and the trachea should be suctioned looking for signs of aspiration.
- Full monitoring should be in place. Extreme tachycardia and cardiovascular collapse suggest anaphylaxis.

The treatment of bronchospasm includes the following.

- The inspired concentration of volatile anaesthetic agent should be increased.
- The patient should be treated with continuous inhaled salbutamol nebulizers, 5 mg, and ipratropium, 500 µg, until the wheeze settles. This is best delivered using a separate oxygen cylinder with nebulizer attachment, connected to the tracheal tube on the patient side of any heat/moisture exchange filter.
- If wheeze persists, aminophylline, 250−500 mg (5 mg/kg) i.v.in 500 ml normal saline over 20 minutes can be given (if notalready treated with theophylline or aminophylline preparations); continue with an infusion of 0.5 mg/kg/hour if needed.
- If bronchospasm is severe, salbutamol, 250 µg bolus i.v. over 5−10 minutes may be given, and continued as an infusion of 5 µg/minute, adjusted according to the heart rate and bronchospasm response.
- It may be necessary to adjust ventilator settings. A longer expiratory time may be needed to allow more complete exhalation, though a short inspiratory time will produce higher peak inspiratory pressures. An I:E ratio of 1:2 or 1:1.5 is usual.
- Hydrocortisone, 200 mg i.v., is not immediately effective but provides bronchospasm relief within 6–12 hours.
- Management of anaphylaxis will be covered in **CLINICAL ANAESTHESIA.**

Causes of intraoperative wheeze

- Endobronchial intubation
- Mechanical obstruction of the tracheal tube
- Bronchospasm
- Anaphylaxis
- Pulmonary oedema
- Tension pneumothorax
- Aspiration of gastric contents

Failure to breathe

A delay in the return of spontaneous respiration following anaesthesia is most commonly the result of an imbalance between the:

- patient requirements of anaesthesia and analgesia (differences caused by normal variation and the effects of coadministered drugs or disease)
- doses of drugs used
- timing of their administration.

In all patients, maintain ventilation to ensure satisfactory oxygenation and carbon dioxide removal. The patient is likely to be unconscious and usually all that is required is more time. If there is continued apnoea, inconsistent with the clinical picture, then a careful evaluation of the cause is needed. The patient should be reassured if they are conscious.

Assess neuromuscular block − a train-of-four ratio of 75% is usually adequate for satisfactory ventilation following anaesthesia. The presence of four good twitches with absent fade implies adequate reversal. Modern nerve stimulators (e.g. the train-of-four watch) can provide more accurate assessment of neuromuscular function by measurement of thumb acceleration (and thus force, because the mass of the thumb is constant). The standard 1 ml ampoule of glycopyrrolate, 0.5 mg/neostigmine 2.5 mg, is the correct reversal dose for a 50 kg patient. The ability to sustain a 5-second head lift from the pillow is a useful clinical indicator of neuromuscular recovery. Figure 11 shows factors that prolong the action of a non-depolarizing neuromuscular block.

Factors that may increase duration of non-depolarizing neuromuscular block

- Hypokalaemia
- Hypothermia
- Hypocarbia
- Neuromuscular disease (e.g. myasthenia gravis, Eaton-Lambert syndrome)
- Inhalational anaesthetic agents
- Aminoglycosides
- Calcium antagonists
- Magnesium
- Local anaesthetics
- Lithium
- Frusemide

Partial reversal of neuromuscular block presents as respiratory inadequacy together with jerky, uncoordinated gross muscular movement. Laryngeal muscle weakness can produce airway obstruction and stridor. The best treatment is to:

- reassure the patient (they may be distressed and feel unable to breathe, with tachycardia and hypertension) and administer 100% oxygen
- help allay anxiety by giving midazolam, 2 mg i.v. or reintroduce general anaesthesia for a short period of time
- correct any underlying cause
- administer further neostigmine (with glycopyrrolate) to a total of 70 µg/kg i.v. (maximum dose 5 mg) if necessary.

Plasma cholinesterase activity − if suxamethonium (or mivacurium) has been used and return of adequate neuro-muscular function is delayed, it is likely that plasma cholin-esterase activity is decreased. This may be an inherited abnormality of cholinesterase activity or an acquired reduction in enzyme activity (Figure 12). The genetic variants have autosomal dominant inheritance, and the prevalence of homozygotes for the atypical gene is 1:2500 of the Caucasian population. Only homozygotes display significantly prolonged apnoea. This may produce many hours of continued paralysis. The patient will come to no harm providing ventilation is supported and adequate sedation is continued (e.g. propofol, 4−6 mg/kg/hour). Neuromuscular block should be monitored with a nerve stimulator and eventually wears off. Infusion of fresh frozen plasma containing cholinesterase enzyme speeds recovery of neuro-muscular function. The benefits must be balanced against the cost and infection risk. Acquired conditions (Figure 12) that reduce plasma cholinesterase activity may slightly increase suxamethonium duration.

Factors that may cause decreased plasma cholinesterase activity

Congenital

- Autosomal dominant inheritance of abnormal enzyme Four alleles have been identified: $E1^n$ normal, $E1^a$ atypical, $E1^f$ fluoride-resistant, $E1^s$ silent

Acquired

- Infections
- Malignancy
- Chronic disease
- Liver disease
- Renal failure
- Pregnancy, oral contraceptives
- Hypothyroidism
- Drugs (monoamine oxidase inhibitors, ecothiopate eye drops, organophosphorus compounds, chemotherapy)

Doxapram is a central respiratory stimulant that may reverse the respiratory depression caused by general anaesthetic agents and potent analgesics. It does not reverse the other effects of opioids. It acts by direct stimulation on the carotid body chemoreceptors. A maximum dose of 1.5 mg/kg slow i.v. can be given.

Benzodiazepines − flumazenil can be used to reverse the central sedative effects of benzodiazepines. It has a shorter half-life than midazolam and diazepam, and therefore re-sedation is possible. Flumazenil, 200 µg i.v., should be given followed by 100 µg i.v. every minute as necessary. The maximum total dose is 1 mg. While benzodiazepines may contribute to postoperative sedation, they seldom cause apnoea unless large doses are used or the patient is elderly and frail.

Opioid drugs − if excessive narcotic is suspected, then give naloxone by titrating dose to effect. Dilute 400 µg in 10 ml normal saline and give 1−2 ml every few minutes to achieve the desired effect. It is important not to use excessive naloxone to prevent reversal of the analgesic effect. Pain, hypertension and tachycardia may result. The patient must be observed closely for the next 4−6 hours because the duration of the naloxone effect may be shorter than that of the opioid.

Check end tidal carbon dioxide tension ($P_{E'}CO_2$) – hyperventilation during anaesthesia results in reduced respiratory drive. Spontaneous ventilation is unlikely to occur until the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and $P_{E'}CO_2$ have normalized. The addition of 5% carbon dioxide to the inspiratory gas mixture was common in older anaesthetic practice to stimulate respiratory drive. Hazards associated with carbon dioxide use, in particular the inadvertent use of carbon dioxide from incorrect flowmeter settings, have removed the use of this gas from modern practice.

The $P_{E'}CO_2$ should be allowed to rise by itself by either reducing minute volume, or adding dead space into the breathing system (e.g. disconnection of the absorber from a circle system).

Body temperature – hypothermia delays recovery from anaesthesia, prolongs the duration of neuromuscular blockade and is an important cause of postoperative hypoventilation. The fall in core temperature that occurs with anaesthesia should be anticipated and minimized using passive or active rewarming (see *Anaesthesia and Intensive Care Medicine* **1:3:** 122). Continued ventilation in the recovery area or ICU may be required until rewarming is completed and spontaneous ventilation is satisfactory.

Neurological vital signs − an intracranial bleed during surgery is a rare cause of continued unconsciousness and apnoea. It may occur as a result of an undetected head injury in patients undergoing surgery for trauma, or coincidentally in patients with cerebrovascular disease. A CT scan is required for diagnosis.

Investigations in the patient who fails to breathe following anaesthesia should include:

- blood gases, electrolytes and glucose
- body temperature
- neuromuscular function (nerve stimulator)
- ECG and chest radiograph
- CT head scan
- blood for serum cholinesterase activity if indicated.

Air embolism

If bubbles of gas enter the circulation, they may accumulate in the right ventricle. Unlike liquid, gases are compressible, and therefore adequate ejection of blood is not achieved, reducing stroke volume and cardiac output. This can present clinically as a minor fall in blood pressure, hypoxaemia or complete cardiovascular collapse with electromechanical dissociation. If a patent foramen ovale is present, or any other shunt-causing communication between the right and left sides of the heart, the air could enter the systemic circulation and cause neurological injury or coronary artery embolism and infarction (paradoxical air embolism). The effects of air embolism depend on the:

- volume of air entrained
- rate at which it enters the circulation
- general condition of the patient.

Experiments in dogs suggest that volumes greater than 20 mlare potentially fatal.

Some operations carry an increased risk of air embolus (Figure 13). Air may be entrained into an open vein when the venous pressure is subatmospheric. Air embolism occurs in 25−50% of all craniotomy operations in the sitting position and the incidence has reduced now this position is seldom used. The prone position with head tongs appears to be safer for posterior fossa surgery.

Procedures with increased risk of air embolus

- Posterior cranial fossa neurosurgery (especially in the sitting position)
- Lumbar laminectomy and head and neck surgery when the vertebral column is positioned above the level of the heart
- Hepatic surgery that carries a risk of opening the inferior vena cava
- Any patient with a central venous pressure catheter in situ that may result in accidental entrainment of air
- Varicose vein ligation
- Surgery combined with low venous pressures (e.g. in children)

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Signs that alert the anaesthetist to the development of air embolism are usually detected by monitoring. Early diagnosis allows prompt institution of preventive measures before the situation becomes critical. The signs of air embolus include:

- sudden fall in $P_{E'}CO_2$ despite unchanged ventilatory settings (if breathing spontaneously the patient may develop respiratory distress)
- turbulent blood flow (monitored by precordial Doppler probe; conventional auscultation may reveal continuous ‘millwheel’ murmur as a late sign)
- fall in oxygen saturation
- pulmonary artery pressure increases during air embolism (it is not often monitored)
- arterial hypotension
- tachycardia, dysrhythmias or cardiac arrest.

Management (Figure 14) comprises prevention of further air entrainment, attempts to remove the air and supportive measures.

Management of air embolus

- Ventilate the patient with 100% oxygen. Stop nitrous oxide administration
- Flood the surgical site with normal saline, wet packs, and apply bone wax to any area of exposed bone cortex. Manually compress the proximal veins to stop further air entrainment
- Attempt to increase venous pressure
  - Position patient head down (or surgical site down)
  - Give rapid fluid bolus (250−500 ml) and observe effects
  - Use vasopressors if the arterial blood pressure is severely affected
  - Compression of the abdomen
  - Activation of antigravity venous compression device (G suit) if fitted
- If a central venous catheter (CVC) is in situ, try to aspirate air from all lumens. Insert a CVC (right internal jugular or subclavian) if one is not present
- The left lateral position may transfer air from the pulmonary artery to the right ventricle, thereby improving pulmonary flow (there is little evidence that this is of benefit)
- Give cardiopulmonary resuscitation if required

14

Pneumothorax

The pleural cavity usually exists only as a potential space between the parietal pleura (attached to the innermost intercostal muscle, the transversus thoracus), and the visceral pleura (continuous with the lung parenchyma). A pneumothorax occurs when this potential cavity is opened, either by breaching the chest wall structures (an open pneumothorax), or by injury to the lung parenchyma (a closed pneumothorax).

- The clinical management is concerned with releasing the accumulation of air from the cavity and correcting the chest wall injury. Understanding the anatomy of the chest cavity allows cause and effect to be identified rapidly.
- The dome of the lung protrudes superiorly above the thoracic inlet to the level of the 6th cervical vertebra. The tip of a needle inserted towards the internal jugular vein could pass more posteriorly where it may cross the pleural space and enter the apices of the lung parenchyma. This is possible even with a relatively high approach.
- The inferior part of the chest cavity extends to the costo-diaphragmatic recess. This reaches to the crura of the diaphragm at the level of the 12th thoracic vertebrae. The cavity can be entered inadvertently in this low position by surgery to the renal bed or lower thoracic and upper lumbar vertebrae.
- The mediastinal pleura lies against the vertebral bodies, oesophagus, aorta, large veins, heart and trachea. Damage to many of these mid-chest structures could allow air or blood to enter the pleural cavity. Trauma from accidents or surgical instrumentation of the oesophagus or trachea may cause this.

The signs and causes of a developing pneumothorax while under general anaesthesia are shown in Figure 15; some or all may be present depending on the nature of the pneumothorax (simple or under tension), its speed of onset, the general health of the patient and whether they are breathing spontaneously or are mechanically ventilated.

Signs and causes of pneumothorax

Signs

- Hypoxaemia
- Wheeze
- Increasing airway pressure
- Unilateral chest wall motion
- Reduced air entry
- Hyperresonance
- Distended neck veins
- Shock
- Shifted trachea away from affected side

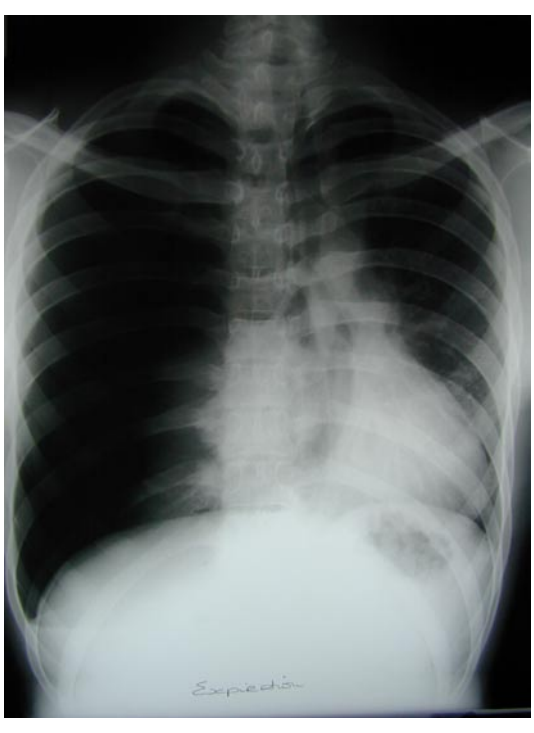
Causes

- Central venous catheter insertion
- Penetrating or blunt chest trauma
- Diaphragmatic, tracheal, oesophageal or cardiac surgery
- Chest drain clamping
- Spontaneous bullae rupture

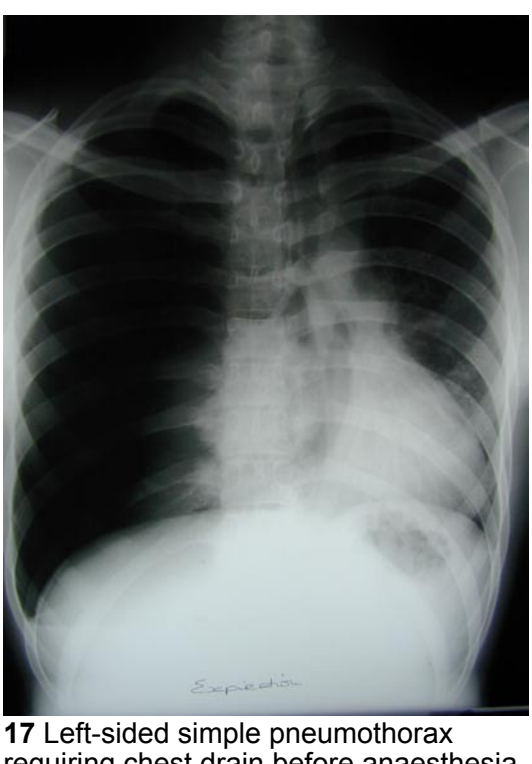
15

In trauma patients, pneumothorax should be identified and treated by chest drain insertion before anaesthesia to avoid the dangers of tension pneumothorax following the start of positive pressure ventilation (Figures 16 and 17). If there is obvious chest injury, but no clinical sign or chest radiograph appearance of pneumothorax, ‘prophylactic’ bilateral chest drains may be indicated. The risks of chest drain insertion must be balanced against the consequences of a tension pneumothorax developing during interhospital or intrahospital transfer or during the perioperative period.

Immediate management of a tension pneumothorax is chest decompression using a 14 G cannula inserted in the midclavicular line and second intercostal space. This should be followed immediately by formal chest drain insertion.



16 Right-sided tension pneumothorax requiring immediate needle decompresion followed by chest drainage. Gross mediastinal deviation is shown to the left.



17 Left-sided simple pneumothorax requiring chest drain before anaesthesia.

Electrical Hazards: Their Causes and Prevention

John Moyle

John Moyle is Consultant in Palliative Medicine in Milton Keynes and a Chartered Engineer. He trained with Philips Electrical Industries. He read medicine at St Bartholomew's Hospital, London and trained in anaesthesia and intensive care at King's College Hospital, London.

Before 1940 there was little electrical equipment in the operating theatre apart from crude radiofrequency diathermy. Since then there has been an invasion of electronic monitoring equipment and many surgical tools are electrically powered. The operating theatre and ICU are unique in electronic engineering because deliberate electrical contact is made with the human body.

The body should be protected from electric current. The body may be considered as an electrolyte solution, which is a good conductor of electricity, contained in a leather bag. Dry leather is a good electrical insulator but conducts electricity easily when damp especially with electrolyte-containing liquids such as sweat.

Electrical injury is caused primarily by the intensity of the current passing through. Current is dependent on the potential difference or 'voltage' across the body and the resistance of the tissues through which it passes (Ohm's law).

$$I = \frac{E}{R}$$

where: E, potential difference (volts); R, resistance (ohms); I, current (amperes)

Severity of injury also depends on the current pathway through the body, environmental factors and the pre-existing health of the patient.

Pathophysiological effects

The pathophysiological effects of electricity range from a mild 'tingling' feeling to ignition in extreme cases. Any electrical current passing through a resistance loses some energy by conversion to heat. The amount of heat generated depends on the current and the value of the resistance; this may be beneficial and forms the basis of coagulation by radiofrequency diathermy. Electricity may stimulate excitable tissues, both nerves and muscles. In a controlled way, this effect may be used medically (e.g. peripheral nerve stimulator, defibrillation). Direct currents, even of low intensity, may cause electrochemical effects. Very high currents, generated by high voltages, cause arcing or sparking and char the tissues. This effect may be harnessed when radiofrequency diathermy is used to cut tissues.

Complications of the inadvertent application of electric currents to the body are:

- cardiopulmonary arrest
- cardiac arrhythmia
- skin and tissue damage
- associated injuries caused by gross muscle contraction.

In the hours after an electric shock there may be further heart rhythm disturbances, hypoxia and electrolyte disturbances, and acute renal failure due to myoglobinuria. It is difficult to predict the effect of electricity on the body because of variables such as body size, proportion and general health. Pre-existing heart problems make the heart more susceptible to arrhythmias.

The current pathway through the body dictates the type of injury. Current passing through the head or across the thorax may cause loss of consciousness and respiratory arrest with or without ventricular fibrillation. Current passing from hand to hand (Figure 1) may cause ventricular fibrillation. Current passing vertically through the body is more likely to cause cardiac muscle damage and injury to other vital organs especially the spinal cord. These injuries depend on the intensity and duration of the current.

The resistance of the human body is not uniform, therefore electricity does not pass evenly through it. Skin resistance is low and allows electricity to pass easily, especially when wet with sweat. Blood has a relatively low resistance, therefore highly vascular areas or inflamed areas of skin have lower resistance. The highest skin resistance is found over heavily calloused areas such as the palm or sole.

The pathway of the current inside the body depends on the resistance of each tissue type. Tissues with the lowest resistance (the best conductance) are nervous tissue, blood, mucous membranes and muscle; the poorest conductors are tendon, bone and fat.

Direct and alternating currents have different effects on the body. Direct current of sufficient intensity causes short duration muscle spasm which may throw the victim from the source. There may be a disturbance of heart rhythm and blunt mechanical trauma. Alternating current, especially at 50 Hz (60 Hz in North America) is approximately three times more dangerous than direct current. Alternating current (40–110 Hz) causes continuous muscle spasm or tetany. As the flexor muscles are more powerful than the extensors, tetany may cause the victim to grip the offending conductor more tightly, thus prolonging the duration of current. Local diaphoresis also reduces skin resistance at the point of contact thus increasing the current.

50 Hz (or 60 Hz) is a bad choice of frequency for the public utility electricity supply because it is the frequency to which the body is most sensitive. At higher frequency the body is progressively less sensitive to the excitable effects of electricity. Radiofrequency surgical diathermy uses frequencies greater than 100 kHz at which comparatively large current may be passed, taking advantage of the heating effects of electricity without affecting excitable tissues.

Effects of hand-to-hand 50 Hz alternating current

1 mA	Tingling sensation
5 mA	Pain
15 mA	Severe pain with local muscle spasm
50 mA	Respiratory muscle spasm
80–100 mA	Dysrhythmias, pump failure, ventricular fibrillation

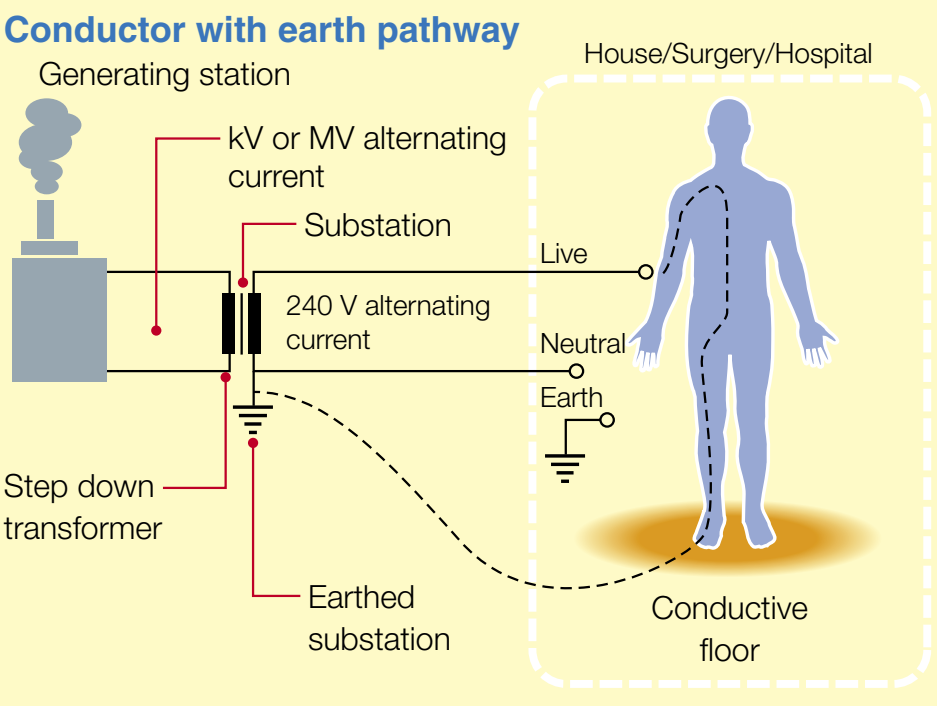
1

Electrical safety

The basic principle of electrical safety is to prevent the body becoming part of an electrical circuit. This requires good design of equipment, cables and connectors. Even with the highest quality of design, the user has the responsibility of using and handling equipment sensibly.

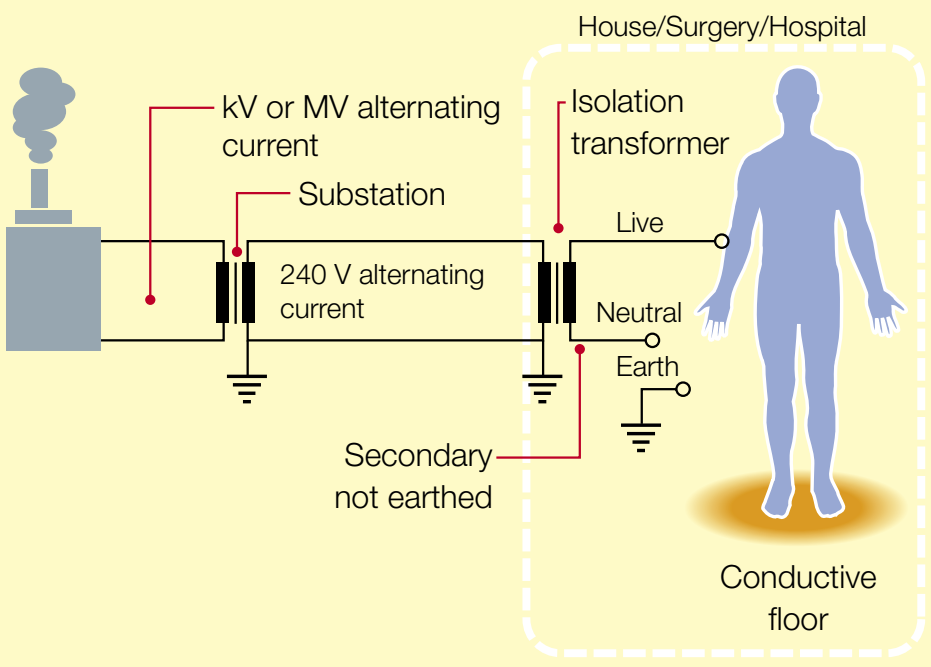
The conventional single-phase mains supply has two conductors: live and neutral. The live conductor is at a voltage dependent on the supply, normally 220–240 volts (110 volts in the USA) with respect to the neutral conductor which is 'tied' to earth at the substation. A safety or earth conductor may also be present which is connected to earth locally and therefore may be at a slightly different potential from the neutral conductor. It is unusual to get an electric shock from the neutral conductor alone but a circuit may be completed between a live conductor or component and either the neutral conductor or, more commonly, an earth pathway (Figure 2). This condition may be eased by the use of an isolation transformer (Figure 3) which will protect against electrocution via earth but not between earth and neutral. Isolation transformers are the most common form of basic protection with medical equipment and are often contained inside the equipment. (Further isolation is required when connection is made directly to the patient, this is described below.)

Conductor with earth pathway



2

Conductor with isolation transformer



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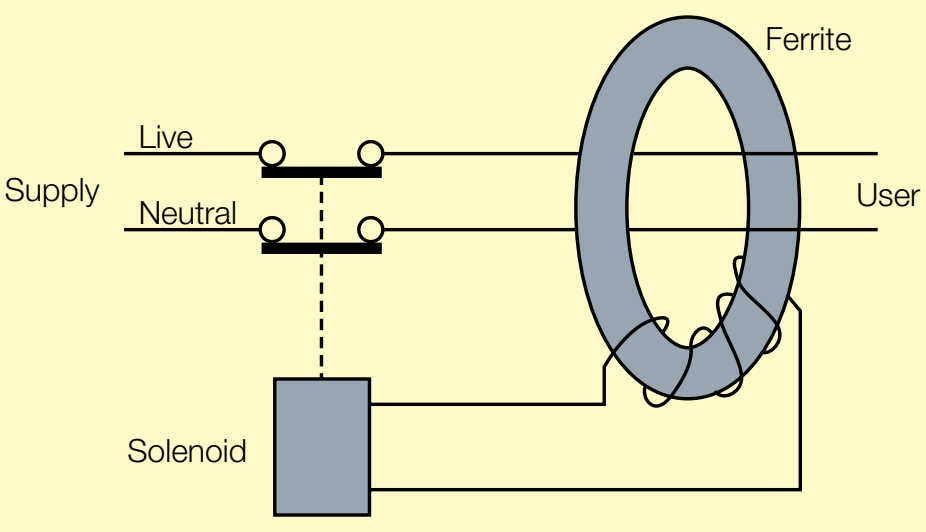
Electrocution depends on the duration of exposure and current. The shorter the duration, the higher the current required before damage is done. The earth leakage or residual circuit breaker stops the current passing through the body before any serious damage occurs. This phenomenon is used as the final level of protection from electrocution in the domestic situation and is commonly used commercially for power tools. The principle of the earth leakage circuit breaker (ELCB) is shown in Figure 4. The ferrite ring forms the core of an electrical transformer. The live and neutral conductors pass together through the ring, forming a single-turn primary of the transformer. The secondary of the transformer consists of many turns of much finer wire and is connected to a solenoid. When the solenoid is energized it breaks the supply. In the normal state, current passes down the live conductor, through the appliance and back through the neutral conductor. The current in the neutral is equal and opposite to that in the live and so their magnetic fields are cancelled out and no current is generated in the secondary winding. If some current leaks out of the appliance due to a fault or someone touching a live part, there is an imbalance between the live and neutral and a much amplified current is generated in the secondary, energizing the solenoid and disconnecting the supply.

Earth leakage circuit breaker



4

Microshock: electrocution of the intact human body is commonly referred to as macroshock to distinguish it from microshock in which smaller currents can lead to cardiac dysrhythmia or arrest because one of the points of contact is on or in the heart. 50 Hz mains electricity at a current as low as 50 μA by this route may have serious consequences. Contact may be made with the heart during thoracotomy but a more common and less obvious route is via electrolyte solutions in catheters in or near the heart. Therefore, any equipment that might make connection with the heart must be specially designed to protect against the unintentional passage of these very small currents. Such equipment includes ECG recorders, intravascular pressure monitoring systems, pacemakers and defibrillators.

Leakage current may be defined as electric current that has passed through insulators. It is difficult to design equipment with perfect insulation. The reduction of leakage in medical equipment requires special design features. The designer has to ensure that no electrically live parts are accessible. Any outer metal casing has to be connected to earth; an extra layer of insulation may also be used – the 'double insulation' often used on power tools. These techniques may make a piece of medical equipment safe to be in the patient environment. However, if there is any possibility of connection with the heart, special isolation techniques have to be employed by the equipment designer to ensure that any leakage current is less than 10 μA. This is a stringent limit to achieve.

Safety standards

All medical equipment manufacturers have to comply with published international standards. Each nation also has its own standards organization; in the UK it is the British Standards Institute (BSI). To make standards applicable on a worldwide basis, all national organizations cooperate to write international standards. The International Standards Organization (ISO) deals with everything excluding electricity; the International Electrotechnical Committee (IEC) deals with the standards of anything electrical. Both the ISO and the IEC are based in Geneva.

IEC-60601 is the basic standard for medical equipment. It classifies equipment in two ways; the method of electrical protection and the degree of protection.

- Class I equipment uses a 'protective' earth connection to the outer conductive casing.
- Class II protection is by double insulation. The degree of protection required is classified as B, BF or CF (C, intra cardiac or near cardiac; F, floating) as shown in Figure 5. Figure 6 shows the same symbols, with the indication that the equipment may withstand a defibrillator pulse without damage.

Three types of protection required

Type B applied part

- Maximum leakage current 0.1 mA
- Single fault condition 0.5 mA
- Allowed in patient care area but not in direct contact with patient
- Can be used in X-ray and suction equipment and operating theatre lights

Type BF applied part

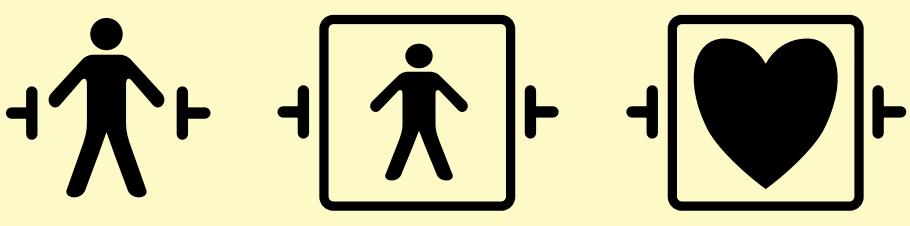
- Maximum leakage current 0.1 mA
- Single fault condition 0.5 mA
- Floating/Isolated
- May be deliberately in contact with patient but not in direct contact with heart
- Can be used in temperature measurement, non-invasive blood pressure measurement, ultrasonography, pulse oximetry, capnography

Type CF applied part

- Maximum leakage current 0.01 mA
- Single fault condition 0.05 mA
- Floating/Isolated
- Suitable for direct cardiac application
- Can be used in ECG, EEG, direct blood pressure measurement, electromagnetic blood flow

5

Symbols indicating equipment is able to withstand a defibrillator pulse



B BF CF

6

Two values of leakage current are given for each category; the lower refers to the equipment in its normal state; the higher value is the maximum allowable leakage current with a single fault condition (SFC). The Standard lists the allowable SFCs for each type of equipment. All medical equipment has to be marked with symbols to show the degree of protection. Figure 7 includes other relevant safety markings that are published in IEC 60601.

Electrical symbols

~	Alternating current
3~	3 Phase alternating current
3N~	3 Phase alternating current with neutral
⎓	Direct current
⏚	Protective earth (ground)
⏚	Earth (ground)
N	Neutral conductor (only on permanently installed equipment)
⏚	Equipotentiality

7

Fires and Explosions

John Moyle

John Moyle is Consultant in Palliative Medicine in Milton Keynes and a Chartered Engineer. He trained with Philips Electrical Industries. He read medicine at St Bartholomew's Hospital, London and trained in anaesthesia and intensive care at King's College Hospital, London. He teaches physics and clinical measurement to trainee anaesthetists.

Less emphasis is placed on the risk of fire and explosion in the operating theatre today than previously mainly because the use of flammable agents has decreased; for example, ether and cyclopropane are no longer used in anaesthesia. This has lead to a false sense of security and little attention to fire safety. It must not be forgotten that alcohol as an antiseptic and dry drapes are flammable and that the microenvironment around a patient may have an increased concentration of oxygen. Nitrous oxide supports combustion better than oxygen. There are also new sources of ignition, such as the intense energy at the end of fibre-optic 'light pipes' and surgical lasers as well as the dangers associated with the use of surgical diathermy.

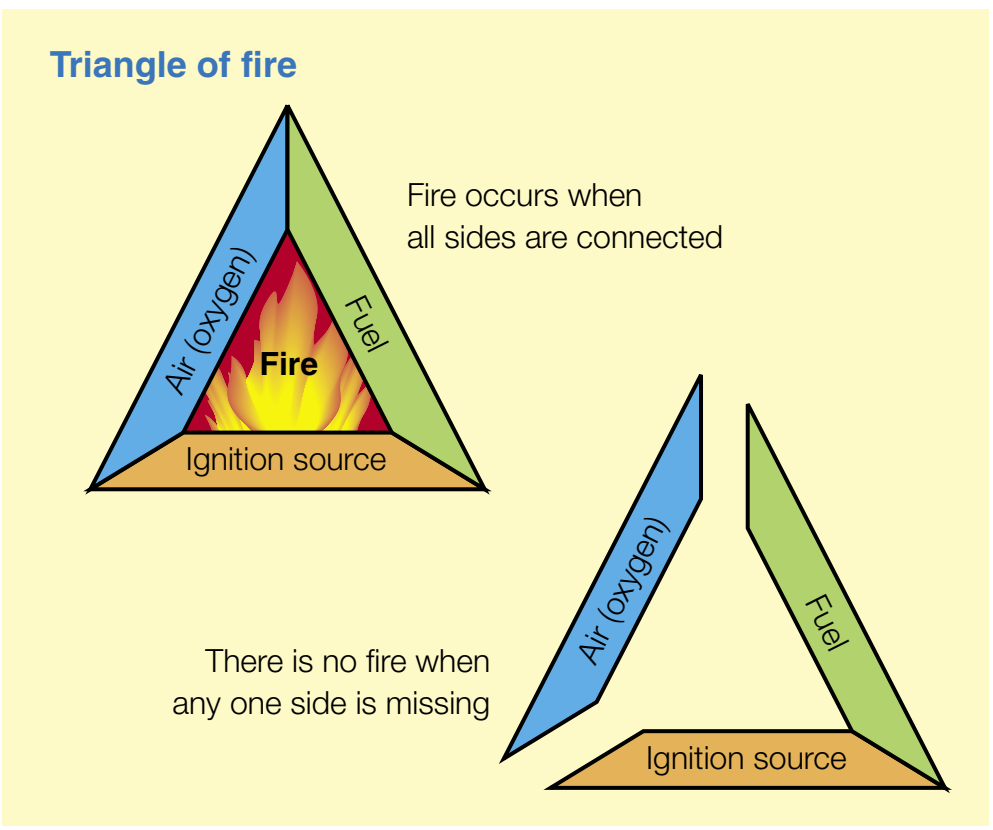
Fire and explosion

Fire or explosion occurs when a substance combines with an oxidizing agent with the release of energy. The reaction requires activation energy to trigger it (Figure 1). If the reaction occurs slowly, heat may be the only obvious evidence, though it usually leads to fire. If the reaction proceeds rapidly, large amounts of heat, light and a rapid increase in pressure occur, making sound; this is an explosion. Fire burns slowly at atmospheric pressure at a temperature of 200–500°C. An explosion is a fast, sudden increase in pressure to a high level at a much higher temperature than fire.

If the rate of liberation of heat is equal to the amount of heat required to maintain the process, the flame will stay still as long as the reactants are made available by convection. If the rate of generation of heat is larger than that required to continue activation, the flame will travel through the mixture. The greater the difference, the greater the likelihood of the reaction travelling so fast that a shock wave occurs; this is an explosion.

On a molecular basis, combustion is a chemical process. In oxidation, the intermolecular bond energy of the end products is less than the bond energy of the reactants and the excess energy is dissipated as heat. To induce the initial deformation of the molecules which allows the rearrangement of these bonds, activation energy has to be added to the system; in the case of fires and explosions this is usually in the form of heat. When the oxidation process begins, positive feedback has to occur to maintain the reaction; if not, the process would cease immediately, before the reaction was complete.

The speed of reaction is greatest for a stochiometric mixture: defined as a mixture in such proportions that none of the reactants is left at the end of the reaction.



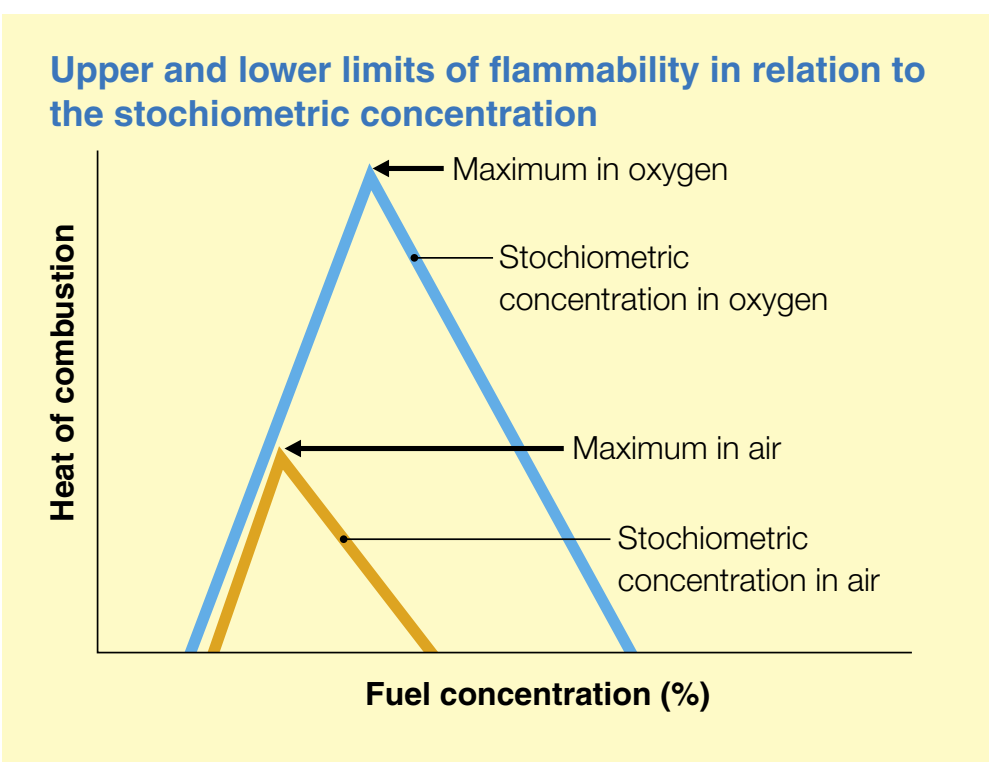
1

Fuel

A gas or vapour may be flammable over a range of concentrations with lower and upper limits of flammability. The stochiometric concentration occurs between these limits. Limits of flammability vary depending on the atmosphere in which the flammable gas or vapour is found (Figure 2).

Anaesthetic gases and vapours are not the only flammable substance that may put the patient at risk.

- Methane and hydrogen are found in bowel gas.
- Alcohol forms the basis of many skin preparation solutions and is in the exhaled gases of the inebriated. Isopropyl alcohol is commonly used to clean the skin before cannulation. Methyl alcohol is used in spirit burners and by down-and-out alcoholics.
- Drapes are often applied to the patient before the alcohol in skin preparation solution has evaporated completely. There may be a high concentration of the vapour, and even some of the liquid alcohol, beneath the drapes.
- Some surgeons use hydrogen peroxide to clean wounds. It rapidly decomposes by enzyme catalysis when poured on to open wounds, producing a froth of hydrogen and oxygen; the gas given off is highly flammable.
- Dry cotton or paper drapes are flammable.
- The plastic compounds used in the manufacture of conventional tracheal tubes may become flammable in high concen-tration of oxygen and high ignition energy levels.



2

Oxygen

Oxygen in the air is the usual source of oxygen involved in a fire. Figure 3 shows that the risk of ignition of any flammable gas or vapour is increased with increased concentration of oxygen above ambient level. Any fire burns more vigorously if the concentration of oxygen is increased.

Nitrous oxide is not combustible but it vigorously supports combustion.

Risks of fire and explosion arise from the strong oxidizing action of nitrous oxide and from its thermodynamic instability. At about 400°C, nitrous oxide breaks down to oxygen and nitrogen and if this comes into contact with combustible material, fire or explosion may result. The concentration of oxygen and nitrous oxide is increased around the mouth and upper airways if a tracheal tube or laryngeal mask does not seal perfectly. There is often an increased concentration of oxygen and nitrous oxide trapped between the patient and the surgical drapes.

Limits of flammability of gases and vapours encountered in the operating theatre[1]

Gas or vapour	Air		Oxygen		Nitrous oxide		30% oxygen 70% nitrous oxide		20% oxygen 80% nitrous oxide	
	L[2]	U	L	U	L	U	L	U	L	U
Diethyl ether	1.9	48	2.0	82	1.5	24				
Cyclopropane	2.4	10	2.5	60	1.6	30				
Ethyl chloride	4.0	15	4.0	67	2.0	33				
Enflurane			4.0				5.75		4.25	
Isoflurane			6.0				7.0		5.25	
Halothane							4.75		3.25	
Methoxyflurane	7.0		5.0	28	4.6					
Trichloroethylene			9.0	65						
Fluoroxene				4.0						
Hydrogen	4.0	74	4.6	94	5.8	86				
Methane	5.3	15	5.4	59	4.0	40				
Sevoflurane			12		11					
Isopropyl alcohol	2.5	12								
Methyl alcohol	6.0	36.5								
Ethyl alcohol	3.3	19								

[1]This is a compilation of information from a number of sources
[2]L, lower limit; U, upper limit.
All values are percentages.

3

Ignition source

Sources of ignition may be sparks generated by static electricity, flames or hot surfaces. Even shaking a bottle containing an organic compound in combination with a peroxide, may cause ignition.

The flash point of a liquid is the lowest temperature at which it gives off enough vapour to form an ignitable mixture with air. At flash point, the vapour will burn, but only briefly because inadequate vapour is produced to maintain combustion. The flash point of a liquid is always quoted but is of less significance to theatre staff than the autoignition temperature.

The autoignition temperature is the minimum temperature above which a flammable mixture is capable of extracting enough energy from the environment to self-ignite. Figure 4 shows the flash points and autoignition temperatures of some compounds in the operating theatre.

If anaesthetic agents that are flammable at clinical concen-trations are used, care must be taken to keep any possible source of ignition outside the zone of risk. There are two zones of risk around the anaesthetic machine, breathing circuit and head and neck of the patient:

- 5 cm if only air is used as the source of oxygen
- 25 cm if nitrous oxide and/or oxygen are used.

Equipment must be marked as AP where air is the only source of oxygen and APG when nitrous oxide or high oxygen concentrations are used.

Possible sources of ignition

Open flames are an obvious source of ignition; they comprise spirit and gas burners, matches and cigarette lighters.

Hot surfaces may cause ignition if the temperature is above the autoignition temperature of the liquid, vapour or solid. In some cases the high temperature of a surface is obvious because it glows or is incandescent.

Hot wire filaments used for cautery may be of high enough temperature to cause ignition. Miniature filament bulbs used in old-fashioned endoscopes may have a surface temperature of 250°C; sufficient to ignite diethyl ether in air.

Light sources – powerful light sources and fibre-optic light-guides have replaced miniature light bulbs but they should always be extinguished when not in use because the energy emitted from the light-guide when not connected to an instrument is intense enough to cause a burn on a surgical drape or the skin. The likelihood of igniting a drape is higher if the concentration of oxygen or nitrous oxide is high in the atmosphere trapped beneath it.

Surgical lasers – see below.

Sparks due to current electricity, as in radiofrequency surgical diathermy and static electricity, are the most obvious sources of ignition in surgical practice. Even sparks that are so small as to be almost invisible may be of sufficient energy to cause ignition.

Sudden increase in gas pressure causes gases to heat. Therefore it is important that no oil, grease or other flammable substance comes into contact with oxygen or nitrous oxide under high pressure.

Lasers

The energy emitted from the tip of a laser applicator is extremely high. The risk of causing ignition is higher than with any other source of emission. Extreme care must be taken to ensure that a laser beam does not come into contact with anything flammable. Any drapes or swabs in the vicinity must be kept wet with water. Care must also be taken to ensure that the beam is not inadvertently reflected on to a flammable surface. If the laser is being used in the mouth, the trachael tube should be of a non-flammable type or be suitably protected. In the case of laser in the bronchi or trachea the oxygen concentration should be 21% or only slightly higher.

Precautions

- Avoid the use of flammable liquids, gases and vapours.
- Keep unsuitable equipment out of zones of risk when flammable anaesthetic agents are in use.
- Observe antistatic precautions.
- Remember bowel gases are flammable.
- Relative humidity should not be less than 50% (a dry atmosphere promotes the generation of static electrical charge).
- At least 15–20 changes of air per hour in the operating theatre will reduce the risk of build-up of flammable vapours.
- High energy light sources must not remain on dry drapes (these sources are of high enough energy to damage tissues).
- Radiofrequency surgical diathermy is a potent source of ignition energy; evaporation of flammable skin preparation solutions must be complete and the atmosphere cleared of the vapour before diathermy is used.

Flash points and autoignition temperatures of flammable liquids encountered in the operating theatre

Compound	Flash point (°C)	Autoignition temperature (°C)
Methyl alcohol	–16	385
Ethyl alcohol	12	363
Diethyl ether	–45	160
Isopropyl alcohol	11.7	455.6

Induction of Anaesthesia

James Austin

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Induction is the process that produces a state of surgical anaesthesia in a patient. The term is used only in the context of general anaesthesia and not with local anaesthesia. It is the first step in the process of anaesthesia whereby the patient is rendered unconscious, preventing both awareness of, and response to, surgical stimuli. Anaesthesia and physiological sleep are different because sleep has structured, specific EEG patterns and endocrine changes, whereas anaesthesia is associated with a diffuse damping-down of EEG function and a stress-type endocrine response.

The process of induction should ensure patient safety, produce a state of unconsciousness, ensure optimal conditions for the surgeon and prepare the patient for waking and recovery.

Before anaesthesia is induced, the anaesthetist must:

- assess the patient as completely as circumstances allow, and institute preoperative preparations (e.g. intravenous fluids, sedative drugs, analgesics)
- discuss the surgery with the surgeon, particularly in complex or unusual cases
- plan the anaesthetic technique
- ensure all necessary equipment and drugs are available, and that the equipment is working.

On arrival in the anaesthetic suite, the anaesthetist must ensure:

- the correct patient has arrived
- the correct operation is planned on the correct side
- consent has been given
- jewellery or prostheses have been removed or declared
- blood for transfusion is available if required.

Anaesthetic room

In the UK, most inductions take place in a dedicated anaesthetic room; however, in many other countries induction takes place on the operating table in theatre. The main advantage of using a dedicated induction room is the quicker change-around as the theatre is cleaned and prepared between patients. If staffing permits, induction may take place while the previous case is being completed. A separate induction room also avoids the psychological stress (for some patients) of seeing the operating theatre. The anaesthetic room must be equipped with the necessary anaesthetic and monitoring equipment for the induction to be completed safely. The duplication of equipment between anaesthetic room and operating theatre may be a financial constraint in some locations. In urgent cases, with potentially unstable patients or with the morbidly obese, theatre is the best place for induction, because it saves the time, physical hazards and period of reduced or absent monitoring associated with transfer.

Equipment checks: successful induction requires planning and attention to detail. Before the procedure begins, checks of the anaesthetic machine must have been completed and the following must be available:

- the patient must be on a tilting bed or trolley
- two working laryngoscopes (in case of bulb failure), including standard and long blades (sizes 3 and 4)
- a selection of laryngoscope blade types (e.g. the Macintosh and the McCoy levering blade)
- a selection of tracheal tube sizes, with their cuffs checked
- suction equipment
- equipment to deal with difficult or failed intubation, including oral and nasal airways, gum-elastic bougie, laryngeal mask
- standard monitoring equipment (e.g. pulse oximeter, ECG, capnometer, blood pressure monitor).

Monitoring

In addition to the clinical observations made by the anaesthetist, the Association of Anaesthetists of Great Britain and Ireland has published recommendation for standards of monitoring equipment during anaesthesia and recovery. Monitoring should be instituted before induction whenever possible and should consist of a pulse oximeter (ideally with continuous display of pulse rate and plethysmography), an ECG and non-invasive arterial blood pressure monitoring. Following unconsciousness, other variables should also be monitored, including:

- carbon dioxide (using a capnometer)
- the anaesthetic vapour concentration
- body temperature
- neuromuscular function if muscle relaxants are used (assessed using a nerve stimulator)
- invasive arterial or central venous pressures and urine output monitoring may be required.

Induction methods

Most anaesthetic inductions are performed using intravenous or inhalational (‘gas’) induction; each has advantages and disadvantages (Figure 1). Less commonly, induction may be carried out by the intramuscular route in uncooperative patients, children or those with difficult venous access. Ketamine,10 mg/kg, provides up to 30 minutes of surgical anaesthesia, but induction times are unpredictable (15–45 minutes) and recovery is slow. Rectal induction with thiopentone, methohexitone, chloral hydrate or benzodiazepines was popular for children at one time, but is seldom used now. Oral induction is effectively a heavy sedative or ‘premedicant’, rather than induction, and recovery time is prolonged.

There are several tasks to be accomplished with any form of induction:

- last-minute preliminary checks (as specified above)
- establish monitoring
- establish intravenous access
- produce unconsciousness
- secure the airway
- establish ventilation
- commence analgesia (systemic or local)
- position the patient
- establish maintenance of anaesthesia.

Intravenous and inhalational induction

Intravenous	Inhalation
Advantages	*Advantages*
• Rapid onset • Patient comfort • Airway protection in rapid-sequence induction	• Does not require IV access • Useful for children • Useful for adults with needle-phobia
Disadvantages	*Disadvantages*
• Contraindicated in patients with a ‘difficult airway’	• Slow induction • ‘Excitement’ phase • Risk of vomiting • Risk of arrhythmias • Volatile agents contraindicated in patients susceptible to malignant hyperpyrexia

1

Intravenous induction

Pulse oximetry and ECG monitoring should be established before intravenous access because occasionally a cardiovascular event (e.g. vasovagal syncope) occurs during cannulation. Intravascular access commonly consists of a simple venous cannula; however, complex cases may require an arterial line, a central venous line and/or a pulmonary artery catheter. These may be sited with local anaesthesia before induction, to provide additional monitoring if haemodynamic instability is expected.

Following intravenous access, preliminary drugs (e.g. analgesics, antibiotics, anti-emetics) may be given. These vary according to the clinical circumstances and a detailed discussion is beyond the scope of this article. A regional analgesic block, if required, may also be given at this stage. Whether to insert the block before or after the patient is anaesthetized is the subject of some controversy (Figure 2).

Advantages of regional nerve blockade performed either before or after induction

Before induction	After induction
• Patient cooperation with correct positioning • Patient may provide feedback to minimize neural damage by needle or injection • Less requirement for anaesthetic monitoring	• Patient preference • Correct positioning may be easier (e.g. patients with painful fractures or skeletal deformity)

2

Pre-oxygenation: some anaesthetists routinely pre-oxygenate their patients before induction. The correct technique is for the patient to breathe 100% oxygen via an anaesthetic circuit and close-fitting mask for about 3 minutes of tidal volume breathing. Alternatively, pre-oxygenation by three vital capacity breaths has been demonstrated to be effective. The aim is to replace nitrogen-containing air in the resting volume of the lungs (the functional residual capacity, FRC) with a high oxygen concentration. The gas within the FRC acts as an important oxygen store, and therefore pre-oxygenation lengthens the time before hypoxaemia occurs following the onset of apnoea. This may provide valuable time in which the airway can be secured if an unexpectedly difficult airway is encountered. Mask phobia and the difficulties in achieving a mask seal in non-compliant patients and children are the only significant contraindications to pre-oxygenation. Pre-oxygenation is mandatory in rapid-sequence induction.

Intravenous drugs: slow, smooth injection of an intravenous anaesthetic agent usually results in loss of consciousness in less than 1 minute. Thiopentone, for example, starts to work in a period of one ‘arm–brain circulation time’. This is the period of time taken for the drug to travel from the site of injection (the arm) to the site of action (the brain) and is about 15 seconds in a healthy patient. The dose is carefully titrated according to patient response. Typical induction doses for healthy individuals are shown in Figure 3, but dose reduction may be required in:

- patients who are less fit
- the elderly or frail
- neonates
- patients with hypotension or poor cardiac reserve
- patients with chronic renal or liver disease
- patients with raised intracranial pressure
- patients who have been premedicated.

It can be difficult to judge when enough induction agent has been given. Care and experience are needed to titrate dose to effect but some indicators include:

- loss of response to verbal command
- loss of eyelash reflex (in which brushing the eyelash produces a blink response)
- relaxation of a motor posture (e.g. a raised arm or a grip on an object)
- cooperation with bag/mask ventilation.

The eyelash reflex has conventionally been regarded as a good end-point for thiopentone induction, but it is less reliable in propofol induction, for which loss of verbal response or motor relaxation is a more useful end-point.

Induction doses of intravenous drugs

Drug	Typical adult induction dose (mg/kg)	Notes
• Propofol	1.5–2.5	Popular and widely used drug associated with rapid and ‘clear-headed' recovery. Rapid metabolism and lack of cumulative effects has made it popular for total intravenous anaesthesia
• Thiopentone	3–5 (2.5% solution)	The ‘gold-standard’ against which all other drugs are judged. Smooth induction in one arm–brain circulation time
• Methohexitone	1–1.5 (1% solution)	Lowers the convulsive threshold, mainly used in anaesthesia for electroconvulsive therapy
• Etomidate	0.2–0.3	Marked cardiovascular stability makes this drug popular for use in unstable patients
• Ketamine	0.5–2	Useful for sedation with profound analgesia. Increases pulse rate and blood pressure and useful for the induction of patients suffering from acute trauma
• Midazolam	0.15–0.5	A benzodiazepine that may provide stable induction for the elderly and frail, in combination with an opioid

3

Further procedures: the induction agent may be followed by a muscle relaxant, particularly if tracheal intubation is planned. It is important to confirm that the patient's lungs can be ventilated via a bag and mask before paralysing. A muscle relaxant should not be given until it has been confirmed that ventilation is possible. Once anaesthesia is adequate, a clear airway is established using a simple face mask (with or without an oral or nasal airway), laryngeal mask airway or tracheal intubation. If the level of anaesthesia proves to be inadequate to allow an airway or tracheal tube to be tolerated, it may be deepened either with supplementary doses of intravenous agent, or by ventilating with volatile anaesthetic. With the airway secure, ventilation can continue by the patient's own effort, by manual 'hand' ventilation, or by mechanical ventilator.

At this stage, further invasive procedures may take place, such as additional vascular access, regional blocks, bladder catheterization, passing of a nasogastric tube or insertion of a temperature probe.

Transfer to theatre: if anaesthesia has been induced in the anaesthetic room, the patient is now transferred to theatre. This is potentially hazardous because for a short time the patient is separated from monitoring equipment and the mechanical ventilator. The patient is also potentially unstable because of the effects of induction drugs and is at risk of injury during the physical transfer. It is the anaesthetist's responsibility to guarantee the patient's safety. It should be ensured that ventilation and anaesthetic maintenance are re-established in good time, that tubes and lines are not dislodged, and that changes in clinical condition are detected promptly, in particular, cardiovascular instability, desaturation or signs of waking from anaesthesia.

Once in theatre, the priorities are:

- prompt transfer on to the operating table
- prompt re-establishment of ventilation
- prompt re-establishment of anaesthetic maintenance if using volatile anaesthetic drugs
- check correct drug delivery if using intravenous maintenance technique
- prompt re-establishment of monitoring equipment
- safe positioning of the patient
- commencement of maintenance fluids and temperature control.

Rapid-sequence induction

Rapid-sequence induction is used to decrease the risk of aspiration if the patient may have a full stomach, for example in an emergency. In patients presenting for elective surgery, a period of starvation of 2 hours for clear fluids, or 6 hours for food, is considered appropriate. Bowel obstruction, incompetent lower oesophageal sphincter, pregnancy and gastroparesis caused by disease, pain or drugs such as opiate analgesics are also causes of a potentially 'full stomach'.

The incidence and severity of aspiration of gastric contents are made worse by the nature, volume and pH of the gastric solution. Mendelson's studies on aspiration pneumonitis showed that aspiration of solid particles produced more damage than purely fluid aspirates. A potential gastric aspirate greater than 25 ml in volume and/or with a pH less than 2.5 is considered dangerous, though there is little direct clinical evidence for this. In these 'at-risk' patients it is sensible to attempt to raise gastric pH, and to try to promote gastric emptying. Pre-medication with ranitidine, 50 mg i.v., to decrease gastric acidity, and metoclopramide, 10 mg i.v., to enhance gastric emptying and increase the tone of the lower oesophageal sphincter is popular with some anaesthetists; both take at least 1 hour to take effect. A non-particulate antacid, such as sodium citrate, 30 ml of 0.3 M solution orally, given on leaving the ward or arriving in the anaesthetic room, further neutralizes residual stomach acid, but at the expense of raising gastric volume further.

Some anaesthetists advise that a nasogastric tube should be passed to drain the stomach, but it is uncomfortable and may induce vomiting. The counter argument is that any vomiting is better done while the patient is fully awake with protective airway reflexes. If a nasogastric tube is already in place it should be aspirated. If the gastric contents are still acidic on litmus test, consideration should be given to instilling sodium citrate. The old practice of inducing vomiting with ipecac or apomorphine is no longer advised.

The 'rapid sequence' of drug administration aims to produce unconsciousness and intubation conditions as rapidly as possible. The airway is swiftly protected by a cuffed tracheal tube without prior inflation of the lungs via bag and mask. This is to prevent possible gastric distension with an increased risk of gastric reflux. It is performed with the help of a trained assistant, competent in the technique of cricoid pressure.

Muscle relaxants are administered before the airway is controlled, and in this way rapid-sequence induction breaks an important rule of anaesthesia. Careful preoperative assessment of potential airway difficulty is therefore vital, and rapid-sequence induction must not be performed if this assessment predicts difficulty with intubation. The trainee anaesthetist must seek further advice, because an awake intubation technique may then be indicated.

Pre-oxygenation is mandatory, though it may be difficult to achieve in children. Pre-oxygenation reduces the need to ventilate the lungs before intubation. The correct technique is described above. Oxygen must be delivered via an anaesthetic breathing system capable of delivering 100% oxygen; standard 'Hudson' type face masks are inadequate.

Drug injection: the chosen drug is rapidly adminstered (Figure 3). Thiopentone is the drug of choice because of its rapid onset of action in one arm–brain circulation time, but propofol or etomidate are alternatives, albeit slightly slower-acting. The use of rapid-acting opioids such as alfentanil, 10 μg/kg, or fentanyl, 1 μg/kg, helps to reduce the pressor response to laryngoscopy.

Cricoid pressure: or Sellick's manoeuvre, is traditionally practised in rapid-sequence induction and is applied by the anaesthetic assistant as the patient starts to lose consciousness. Pressure is applied to the cricoid cartilage to compress it against the oesophagus, preventing passive regurgitation of stomach contents.

If active vomiting occurs, it is recommended that cricoid pressure be removed to prevent oesophageal rupture – suction, head-down tilt and turning the patient's head to one side is then used instead. Otherwise, cricoid pressure is removed only on the instruction of the anaesthetist, once the airway has been secured with a cuffed tube. Occasionally, it may be removed to facilitate an intubation that is being made more difficult by its continued application.

Muscle relaxation: suxamethonium, 1.5 mg/kg, is the drug of choice. Its rapid onset produces ideal intubating conditions, with a peak effect of muscle relaxation within 50 seconds of injection. It is important to allow the drug time to work, and not to begin the intubation sequence before muscle fasciculations have subsided.

The duration of apnoea is usually about 5 minutes in healthy individuals, and thus spontaneous respiration may be re-established early in the event of a failed intubation. Suxamethonium is contraindicated in patients with:

- previous allergy
- susceptibility to malignant hyperpyrexia
- myotonia
- severe burns, muscle damage or paraplegia (of over 1 week's duration)
- known raised serum potassium.

In these patients, rocuronium, 0.6–0.9 mg/kg, may provide relaxation as rapidly as suxamethonium, but with longer duration. Rocuronium is also the drug of choice in patients with reduced or absent plasma cholinesterase activity, in whom suxamethonium has a long and unpredictable duration of action.

Intubation: the trachea is intubated with a cuffed tube following unconsciousness and muscle relaxation. Uncuffed tubes are used in children to avoid local pressure on the tracheal wall and to maximize the internal diameter of tube available. If difficulty is encountered with direct laryngoscopy, then simple steps may be taken to facilitate intubation:

- manipulate the larynx (the assistant providing the cricoid pressure may be distorting the view of the larynx)
- change to a larger blade laryngoscope
- change to a different type of blade (e.g. a McCoy levering blade)
- use the gum-elastic bougie (this thin, flexible stylet may be used to pass through the cords providing a 'track' over which the tracheal tube can be railroaded).

Before the cricoid pressure is released, the correct position of the tube must be checked carefully by auscultation and capnometry. Once the cuff has been inflated and the airway has been secured, a nasogastric tube should be passed and aspirated, if not done previously. The rest of the anaesthetic proceeds as usual; but at the end of the procedure extubation should take place with the patient awake, with their protective airway reflexes re-established, positioned on their side in a head-down tilt, and with suction available.

Failed intubation drill – if the trachea is not successfully intubated, a failed intubation drill must be followed:

- cease further attempts at intubation
- call for help
- maintain cricoid pressure
- insert an oral airway
- hand-ventilate via bag and mask using 100% oxygen
- await return of spontaneous respiration
- once spontaneous ventilation has returned, turn the patient into the lateral position with head tilted down and await return of consciousness.

A decision to abandon further attempts at intubation must be made early and certainly before arterial desaturation supervenes. The prime concern of the anaesthetist is patient safety. The safest option following failed intubation is to wake the patient. Once the effects of the intravenous induction agent and muscle relaxant have worn off, consideration must be given to how to proceed. This requires consultation with a senior anaesthetist and may involve an awake intubation technique.

Inhalational induction

Gas induction, controversially, is often used as a means of inducing anaesthesia (particularly in a child) without having to site an intravenous cannula first. However, in the event of difficulties (e.g. laryngospasm, arrhythmias) instant intravenous access should be available, because otherwise the anaesthetist controlling the airway will be unable to attempt rapid cannulation. For this reason, some anaesthetists seldom perform gas induction; others permit gas induction if a second anaesthetist is present to assist with intravenous cannulation. Gas induction of children and adults has taken place without intravenous access for over 150 years, in most cases safely and without incident.

Indications: gas induction (with intravenous access) is indicated for patients in whom airway difficulties are expected. In these cases, the patient continues to breathe spontaneously throughout and apnoea is avoided, since it may then be impossible to manually ventilate the lungs with bag and mask.

Upper airway obstruction is an important indication for inhalation induction, and in these circumstances fibre-optic techniques for intubating the trachea are contraindicated for fear of producing complete airway obstruction. However, in patients with an unobstructed 'difficult' airway, the increasing availability of fibre-optic intubation equipment and the growing skill of anaesthetists in awake intubation techniques may reduce the need for gas induction. The difficult airway may best be secured even before anaesthesia is induced.

Technique: there is controversy over whether to induce in 100% oxygen or to use nitrous oxide as well.

- Concurrent use of volatile and nitrous oxide exploits the second-gas effect for a cumulatively more rapid induction. The rapid absorption of the second gas (nitrous oxide) has the effect of increasing the alveolar concentration of the first agent. The partial pressure of anaesthetic gas in the alveolus reflects the partial pressure of anaesthetic in the brain and hence the anaesthetic effect.
- 'Pre-induction', with 33% oxygen and 66% nitrous oxide only, may render a child sleepy enough not to resist when the odour of the volatile agent is added. Clearly the more nitrous oxide is used the more anaesthetic effect is achieved; but likewise the less reserve there is against desaturation. A minimum of 30% oxygen should be given.
- Induction in 100% oxygen is least smooth, but should laryngospasm occur, it is an advantage to have as much of the lung FRC filled with oxygen as possible. This maximizes oxygen stores and thus delays the onset of hypoxaemia.

Conventional practice for inhalational induction with halothane is to start with a low inspired concentration of 0.5%, and to increase it by 0.5% every four breaths up to 4%.

Sevoflurane has greatly enhanced gas induction, because it is faster, better tolerated by patients, and is less arrhythmogenic than halothane. It has been suggested that the lower incidence of arrhythmias has contributed to a decrease in dental anaesthetic deaths in recent years. The high blood-gas solubility of sevoflurane accounts for its rapid onset and offset. Because sevoflurane is less pungent it is often used in high concentrations (maximum 8% on most vaporizers) for faster induction.

Enflurane is seldom used for gas inductions because it is slow; isoflurane and desflurane are almost never used because they are pungent and irritating to the airway.

The last-minute checks before inhalational induction are the same as those for the intravenous route. Monitoring should be established; some children make this difficult, but ECG should be the minimum monitoring instituted. Induction should ideally take place via a tight-fitting face mask (even small leaks may significantly delay induction). However, the use of a cupped hand may be less threatening to a small child in the first instance.

'Single-breath induction' has been described with halothane and sevoflurane. A Mapleson A breathing system containing a 4-litre reservoir bag is filled with a maximum concentration of volatile anaesthetic (4% halothane or 8% sevoflurane) in 66% nitrous oxide and 33% oxygen. The patient is asked to exhale to residual volume, then, via a tight-fitting mask, to inhale a full vital-capacity breath of gas, and then to hold their breath for as long as possible. This technique produces a faster induction than conventional tidal volume inhalational induction in cooperative adults. In the case of single-breath 8% sevoflurane, the speed of induction is comparable with induction with intravenous propofol. It may be a useful technique to use in cooperative needle-phobic adults, but it offers few other advantages.

Four main variables determine the speed of inhalational anaesthetic induction.

- The inspired partial pressure of the anaesthetic agent relative to its minimum alveolar concentration (MAC) alters the speed of induction. MAC is the partial pressure of the agent, expressed in volumes %, which at equilibrium prevents gross muscle movement in response to a skin incision in 50% of patients. It is thus the effective dose in 50% of patients and is a measure of anaesthetic potency.
- The faster the patient breathes, or the greater the alveolar ventilation, the faster the alveolar partial pressure of the agent approaches the inspired partial pressure. In a child, crying speeds up gas induction by increasing minute ventilation.
- The higher the cardiac output the more anaesthetic agent is removed from the alveoli and hence the slower the partial pressure rises in the alveoli. Thus, an anxious, hyperdynamic patient is slow to induce, whereas a shocked patient with a low cardiac output is quicker.
- The higher the solubility of an agent (i.e. a high blood-gas solubility coefficient), the more the agent will dissolve in blood and thus a lower partial pressure will be generated. Agents with a low solubility (e.g. sevoflurane) result in more rapid induction.

During a gas induction, most patients pass briefly through a phase of excitability during which they may be agitated and at increased risk of laryngospasm or, more rarely, arrhythmias. If a child is being induced, it is useful to warn the parents of this disinhibition in advance. The disinhibition is not remembered by the patient.

Once the patient is unconscious, anaesthesia should be deepened, assisting the ventilation by hand, using bag and mask if necessary. If not already obtained, intravenous access should be secured, which requires the help of an assistant. Muscle relaxants may then be given intravenously to assist in securing the airway. If the patient is sufficiently deeply anaesthetized, as evidenced by a regular respiratory pattern and a forward gaze in eyes with small pupils, the airway may be secured (even by intubation) purely under inhalational anaesthesia. Nevertheless, it is valuable to have intravenous access before attempting to manipulate the airway, in case any untoward airway reflexes are produced (e.g. arrhythmias, laryngospasm). With the airway secured, the remainder of the induction sequence proceeds as above.

Historical note

In 1937, Arthur Guedel published *'Inhalational Anaesthesia – a Fundamental Guide',* three chapters of which were devoted to his observations of premedicated patients' responses to gas inductions with nitrous oxide, the ethers, chloroform and cyclopropane

Guedel's stages of anaesthesia

Stage	Definition	Features
1 Analgesia	From beginning to loss of consciousness	Sedation Loss of eyelash reflex[1]
2 Delirium	Loss of consciousness to onset of rhythmic breathing	Agitation, vomiting, arrhythmias Eyes deviated
3 Surgical		
• 1st plane	Onset of rhythmic breathing to loss of eyeball movement	Loss of eyelid reflex Loss of conjunctival reflex[1]
• 2nd plane	Loss of eyeball movement to onset of intercostal paralysis	Loss of laryngeal and gag reflexes Loss of corneal reflex[1]
• 3rd plane	Onset to completion of intercostal paralysis	
• 4th plane	Complete intercostal paralysis to respiratory arrest	Dilated pupils Loss of carinal reflex[1]
4 Respiratory paralysis	Respiratory arrest to death	Loss of anal reflex

[1] Not described in Guedel's original monograph

Induction in children

Children from about 3 months of age until the teenage years are generally more anxious, or less able to control their anxiety, than adults. The preoperative visit is important in children because meeting the anaesthetist and having the procedure explained calms the fears of children and parents. If the child is old enough, address your conversation to him or her. Explain in detail what will happen, and invite the parents and child to ask questions. Where possible, bring relevant equipment, particularly a face mask for gas induction, for the child to become familiar with.

Topical local anaesthetic cream such as EMLA (a eutectic mixture of lignocaine and prilocaine) or amethocaine gel is desirable if awake intravenous access is planned. Marking visible veins in advance helps the nurse to cover the right spots. Both preparations are similarly effective in clinical practice though onset and duration of action differ (Figure 4).

It has become common for parents to accompany children to the anaesthetic room, and this is generally helpful. Smaller children may best be anaesthetized on a parent's lap – a well-positioned hug serves to comfort the child and to restrain them during intravenous cannulation or gas induction. Strapping for the cannula, and the induction drugs, should be on hand for swift application once access has been obtained.

- For gas induction, a sideways hug helps to immobilize all the limbs, while the anaesthetist's hands control the head.
- For intravenous cannulation, a 'face-to-face' hug (Figure 5), with the child's arm under the parent's arm, helps to immobilize the arm and restrict the child's view of cannulation.
- The older child may prefer or need to be anaesthetized on the trolley. If the trolley permits, it is useful to raise the back until just before (or even during) induction itself. This more upright position allows the child a better view of their surroundings, and hence a feeling of more control and less anxiety.

Children should be treated with respect at all times. They should be spoken to in non-condescending language they can understand – if something is going to be unpleasant, it should be acknowledged. The alternative is for the child to become suspicious and uncooperative for even the most innocuous procedure. There is no formula that will ensure every paediatric induction is smooth and trouble-free; some children will be understandably fractious despite all efforts to calm them.

Comparison of EMLA cream and amethocaine gel

	EMLA cream	Amethocaine gel
Constituents	Lignocaine 2.5%, prilocaine 2.5% as an oil/water emulsion	Amethocaine 4%
Presentation	White cream, 5 g per tube	Clear gel, 1.5 g per tube
Application	2 g minimum 1 hour before venepuncture, maximum 5 hours	1 g 30–45 minutes before venepuncture. Remove after 45 minutes
Duration	Efficacy declines soon after cream is removed	Efficacy remains 4–6 hours after application
Skin effects	Usually transient paleness May produce redness and oedema	Usually transient redness May produce itching and oedema
Contra-indications	Not for children < 1 year	Not for children < 1 month

4

5 Hugging the child face to face helps to immobilize the arms.

Further Reading

Association of Anaesthetists of Great Britain and Northern Ireland.*Recommendations for Standards of Monitoring During Anaesthesia and Recovery.* 1994.
Sear J W. Induction of Anaesthesia. In: Aitkenhead A R, Jones R M, eds. *Clinical Anaesthesia.* London: Churchill Livingstone, 1996: 155–72.

Induction of Anaesthesia in Special Circumstances

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A full stomach

The pulmonary aspiration of acid gastric contents has long been recognized as a major risk of anaesthesia. Patients are normally asked to fast preoperatively to allow sufficient time for gastric emptying. However, induction of anaesthesia in the presence of a full stomach may be unavoidable when normal gastric emptying is impaired, or when the urgency of surgical intervention overrides the requirement for a patient to have fasted adequately. Gastric stasis, ileus and reverse peristalsis may accompany obstruction or perforation of the gastrointestinal tract. Trauma, pain and its treatment with opioids delays gastric emptying. Gastric motility may also be abnormal in the presence of diabetes mellitus or obesity and in these circumstances no period of fasting may be considered to be safe. The hazards of induction of anaesthesia in these circumstances are listed in Figure 1.

If the patient has a full stomach an attempt to reduce intragastric volume and acidity before anaesthetic induction is desirable. Gastric fluid may be removed through a gastric tube, or if there is time and no contraindications by giving a prokinetic agent (e.g. metoclopramide, 10 mg i.v.). The pH of the gastric contents may be increased by the ingestion before induction of a non-particulate alkali, usually 30 ml of a 0.3 molar solution of sodium bicarbonate.

Induction of anaesthesia in the presence of a full stomach

Hazards	Management
Pulmonary aspiration of gastric contents	Reduce gastric volume Raise intragastric pH with alkali Use of cricoid pressure Rapid sequence induction
Unanticipated failure to intubate	Preoxygenation Rapid sequence induction Failed intubation drill

1

Rapid sequence induction

Rapid sequence induction is the anaesthetic technique indicated in the presence of a full stomach (Figure 2). It aims to reduce to a minimum the period during which the airway is unprotected after induction of anaesthesia and before inflation of the cuff of a correctly placed tracheal tube.

During preparation for rapid sequence induction, a skilled assistant should carefully identify and hold the cricoid cartilage between the thumb and forefinger, ready to apply cricoid pressure as anaesthesia is induced. Cricoid pressure (Sellick's manoeuvre) correctly applied with adequate, but not excessive, force compresses and occludes the upper oesophagus between the flat posterior surface of the cricoid cartilage and the body of the sixth cervical vertebra, preventing reflux of gastric contents without distorting the view at laryngoscopy. If a gastric tube is already in place, it should not be removed but should be allowed to act as a gastric vent.

The main risk of rapid sequence induction is that there is no prior opportunity to ensure that intubation or mask ventilation will be possible after induction. Good preparation for intubation is vital and it is essential that all equipment is checked, suction equipment and aids to oxygenation are ready and the patient is in an optimum intubating position.

The patient's lungs should be preoxygenated. This is achieved by allowing the patient to breathe 100% oxygen through a tightly fitting mask and anaesthetic circuit for about 3 minutes. When apnoea occurs at induction, the lung rests at end tidal volume where there is equilibrium between the elastic recoil of the lungs and the chest wall. Arterial oxygen desaturation follows when the oxygen content within the functional residual capacity (FRC) of the lungs is exhausted. During preoxygenation, the nitrogen in the FRC will be displaced, increasing the oxygen content of this reservoir substantially and delaying the onset of cyanosis after induction of apnoea. Despite these measures, arterial oxygen desaturation is accelerated by the presence of a reduced FRC (e.g. obesity), a raised metabolic oxygen demand (e.g. sepsis) or a combination of the two (e.g. late pregnancy).

Rapid sequence induction requires the use of rapidly acting induction and paralysing agents injected intravenously in quick succession. Most intravenous induction agents cause loss of consciousness within one arm–brain circulation time in the following doses: thiopental (thiopentone), 2–4 mg/kg, etomidate 0.2–0.3 mg/kg, propofol 2–3 mg/kg. In UK practice, suxamethonium, 1.5 mg/kg, remains the neuromuscular blocking agent of choice because it provides optimum intubation conditions in the shortest time.

Once the correct position of the tracheal tube is verified clinically and by capnography and after the cuff has been inflated, cricoid pressure can be released.

In case of failure to intubate, the duration of action of the induction and paralysing agents is critical. Despite the additional time made available by preoxygenation, it may be impossible to see the larynx or intubate the patient. It is then essential to revert to a well-rehearsed failed intubation drill. The effects of the common induction agents wear off in a few minutes and the choice of suxamethonium is reinforced by its short duration of action. The temptation to give a second dose of the drugs and prolong attempts at intubation should be resisted. At this point, resumption of patient oxygenation is the priority.

Rapid sequence induction

- Selection of intubation aids and equipment for cricothyroid puncture
- Skilled assistant applying cricoid pressure
- Patient on surface that can be tipped head down
- Suction switched on with catheter under pillow
- Optimal patient intubating position
- Good quality venous access with running intravenous infusion
- Preoxygenation with 100% oxygen through close fitting face mask
- Single sleep dose of intravenous induction agent
- Single adequate intravenous dose of suxamethonium (e.g. 1.5 mg/kg)
- Failed intubation drill

2

After head injury

Induction of anaesthesia and tracheal intubation after head injury (Figure 3) is indicated when:

- the patient's airway or oxygenation is compromised
- the patient has a depressed level of consciousness (Glasgow Coma Score of 8 or less)
- in the presence of agitation
- before emergency surgery
- in preparation for safe transfer to either CT scanner or to a neurosurgical centre.

It is vital to prevent secondary brain injury due to hypoxia, hypotension, hypercapnia or uncontrolled rises in intracranial pressure. The patient is assumed to have a full stomach so a rapid sequence induction with preoxygenation and cricoid pressure is indicated. In addition, patients presenting with a severe head injury must be assumed to have suffered a cervical spine injury. Cricoid pressure is applied using a two-handed technique, the second hand supporting the back of the cervical spine. Another assistant is required to provide manual in line stabilization of the spine during induction because any cervical collar has to be temporarily removed to facilitate intubation. Coexisting facial injuries need to be assessed carefully because they may affect intubation by displacing, distorting or obstructing the airway.

Careful monitoring of cardiovascular status is required. It may not be practical to monitor blood pressure invasively before induction, but non-invasive measurements should be made frequently. Suppression of the hypertensive response to intubation requires an intravenous induction agent, though the dose may have to be reduced in the presence of depressed consciousness. Lidocaine (lignocaine), 1 mg/kg, may also be given for this purpose. After induction there should be a smooth transition to maintenance sedation, which may include opiates, to avoid fluctuations in blood pressure.

Suxamethonium is associated with a transient rise in intracranial pressure, but this potential for harm is outweighed by its advantage of rapidly producing optimal intubating con-ditions and thereby reducing the risk of hypoxia. A peripheral nerve stimulator will help to ensure adequate neuromuscular blockade before intubation, and that a non-depolarizing agent is given in time to prevent coughing and facilitate controlled ventilation as the effect of suxamethonium wears off.

Tracheal and gastric tubes should not be placed nasally, for fear of breaching a skull base fracture. Constriction or distortion of neck veins that could result in cerebral venous hypertension should be avoided when securing the tracheal tube and applying a cervical collar. Arterial hypotension must be actively investigated and treated, while moderate hypertension should be tolerated because this may be a normal response to intracranial hypertension, preserving cerebral perfusion pressure.

Induction in head injury

Hazards	Management
Full stomach	See Figure 1
Cervical spine injury assumed	In line stabilization of neck Two-handed Sellick manoeuvre
Rising intracranial pressure	Adequate dose of induction agent Adequate neuromuscular blockade Smooth transition to maintenance sedation and paralysis
Reduced cerebral perfusion pressure	Avoid hypotension
Facial injuries	Intubation facilitated or made more difficult
Skull base fracture	Avoid nasal intubation

3

Upper airway obstruction

The management of the patient with obstruction of the upper airway, including the larynx, is a vital skill for anaesthetists (Figure 4). Adequate diagnosis of the airway pathology and the derangement of normal anatomy should precede discussion of the management plan between senior anaesthetic and ENT staff. An alternative strategy must also be agreed so that there is a back-up plan before proceeding. The management plan should be explained clearly to the patient, whose cooperation will be required.

Induction in airway obstruction

Hazards	Management
Potential for airway obstruction in expert hands	Senior help present
Abnormal anatomy	Information from imaging or endoscopy
Loss of muscle tone in upper air-way at induction may precipitate complete obstruction	Inhalation induction or awake tracheostomy
Obstruction during inhalation induction	Back-up plan in place with scrubbed ENT surgeon for surgical airway

4

Assessment of the patient may elicit stridor (inspiratory noise) at rest, which suggests that the airway is more than 50% narrowed. Results of radiographs, CT or MRI scans or nasendoscopy should be available. In their absence it may be appropriate to perform endoscopic examination by fibrescope via a topicalized and vasoconstricted nasal passage. The site of obstruction must not be approached with the fibrescope because attempted fibre-optic intubation may be impossible and may be hazardous, but endoscopy may provide important reconnaissance information. If there is doubt about the feasibility of intubation, then an awake surgical tracheostomy under local anaesthesia should be considered.

If intubation is likely to be possible, an alternative strategy must be in place before embarking on induction of anaesthesia. A scrubbed ENT surgeon must be present ready for immediate intervention and opening of a surgical airway.

The usual technique for induction of anaesthesia in the presence of upper airway obstruction is an inhalation induction. Most experience has been obtained with halothane although use of sevoflurane is growing. Gradual induction of anaesthesia while maintaining spontaneous ventilation and airway muscle tone may allow adequate depth of anaesthesia for intubation without airway closure. Should there be no obstruction, no manipulation of the airway or laryngoscopy is allowed before adequate depth of anaesthesia is achieved as judged by the pupils coming to lie centrally. It is vital that no neuromuscular blockade or intravenous sedation is used before the airway is safely secured.

Obstruction of the airway during inhalation induction prevents further uptake of anaesthetic agent, therefore allowing anaesthetic depth to lighten and the patency of the upper airway to be restored. An awake surgical tracheostomy should then be performed under local anaesthesia.

FURTHER READING

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Maintenance of Anaesthesia

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This contribution is an overview of what is meant, and required, by maintenance of anaesthesia. Many of the topics are covered in greater detail in separate contributions; the aim here is to put these topics in context.

Maintenance of general anaesthesia involves four priorities:

- keeping the patient safe
- keeping the patient comfortable
- presenting the best possible operating conditions for the surgeon
- preparing the patient for the postoperative period.

Keeping the patient safe

There are several aspects involved in keeping the patient safe:

- airway, breathing and circulation
- temperature control
- monitoring
- positioning.

Airway: this will usually have been established at the time of induction. However, it should not be assumed that this remains secure. Airway disconnection or obstruction may occur and the anaesthetist must be able to detect and correct these incidents promptly, assisted by monitors such as the capnograph, pulse oximeter, disconnect alarm and airway pressure monitor. Movement of the tracheal tube (either towards the right main bronchus or withdrawal from the trachea) or dislodgement of the laryngeal mask airway (LMA) are particularly likely to occur when patients are transferred to the operating table or when changes are made to patient position. These periods require increased vigilance by the anaesthetist. The integrity of the airway should be rechecked both clinically and by monitoring after each patient movement.

Tracheostomy, rigid bronchoscopy or 'one-lung' thoracic surgery may require intraoperative changes to the airway. The anaesthetist must be prepared for such changes and, if necessary, should formulate a plan with the surgeon in advance as to how the airway will be managed.

Breathing will often depend on whether muscle relaxants are being employed as part of the anaesthetic technique. Although the use of muscle relaxants is not essential for controlled ventilation, they are usually employed for ventilated patients. Surgical factors often influence the decision to use muscle relaxants. For example, abdominal surgery is greatly facilitated by muscle relaxation. In specialized surgery, such as ophthalmic surgery or neurosurgery, where the slightest move or cough may have disastrous consequences and carbon dioxide must be controlled, paralysis is ideal. Otherwise, anaesthetists have widely differing views as to whether breathing should be controlled. Some anaesthetists use muscle relaxants almost routinely for any operation lasting longer than about 30 minutes, on the basis that carbon dioxide retention is avoided, potent short-acting opioids can be used without fear of respiratory depression, and good lung aeration with avoidance of atelectasis may be easier to achieve. Others control ventilation less often unless indicated for reasons of airway management or the requirements of surgery. Some advantages and disadvantages of paralysis and ventilation are listed in Figure 1.

The technique of 'paralysing and ventilating' may be preferred when a tracheal tube is present. It is likely that a relaxant will already have been given to enable intubation. Also, the presence of a tube within the trachea is a potent stimulus, and unless local anaesthesia has been applied to the respiratory tract, a deeper level of anaesthesia may otherwise be needed for the patient to breathe spontaneously without coughing. Lighter planes can be tolerated when a laryngeal mask or oropharyngeal airway are employed, because these devices are less stimulating to the patient. Paralysing and ventilating may also be used for longer operations, where carbon dioxide control and prevention of atelectasis is important.

However, avoiding relaxants wherever possible can reduce two important complications of general anaesthesia:

- unrecognized awareness – patient movement usually warns of light anaesthesia before the patient becomes aware
- accidental hypoxia – the spontaneously breathing patient may maintain oxygenation even in the event of circuit disconnection.

Use of muscle relaxants and controlled ventilation

Advantages	Disadvantages
• May allow 'lighter' anaesthesia because reflex activity is abolished by neuromuscular blockade	• May allow unrecognized awareness as a result of inadequate anaesthesia
• Facilitates abdominal surgery by relaxation of abdominal muscles	• Reliance on ventilation equipment and circuit integrity to maintain alveolar ventilation
• Intracranial and intraocular pressure control by regulation of $PaCO_2$	• Possible side-effects of muscle relaxant drugs (e.g. histamine release, vagal blockade, malignant hyperpyrexia)
• Allows effective ventilation during, for example, thoracic surgery, prone positioning or long procedures	• Need for reversal of neuromuscular blockade
• Allows use of potent opioids to reduce the surgical stress response in major surgery	• Possible contraindication in patients with a difficult airway. Absence of spontaneous respiration may render ventilation impossible
• May improve surgical conditions by facilitating a hypotensive technique and lowered $PaCO_2$	• When there is requirement to monitor neuromuscular function (e.g. facial nerve during surgery on the parotid gland or acoustic neuroma)
• Decreases intraoperative atelectasis	
• Decreases energy requirements and tissue carbon dioxide production	• Contraindicated in some myopathies

1

Ventilator settings – most anaesthesia ventilators are time-cycled and volume- or flow-driven. A rate, usually with a ratio of inspiratory time to expiratory time (I:E), and a tidal volume or flow need to be set. Most adults have a minute volume of 80–100 ml/kg, therefore a tidal volume of 8 ml/kg (e.g. 500–600 ml) and a rate of 10 breaths/minute is a good starting point; this can be adjusted according to the observed end-tidal partial pressure of carbon dioxide ($P_{E'CO_2}$). For routine surgery, a $P_{E'CO_2}$ of about 4.5 kPa should be aimed for. If metabolic rate and cardiac output (and hence pulmonary perfusion) are assumed to be constant, then $P_{E'CO_2}$ varies inversely with the alveolar ventilation.

In general, an I:E ratio of 1:2 is often the best compromise between maintaining low inflation pressures (e.g. 15–20 cm H_2O), satisfactory oxygenation (Sp_{O_2} > 95%) and adequate carbon dioxide removal ($P_{E'CO_2}$ 4.5 kPa). However, this can be decreased to 1:1.5 or even 1:1 to prolong inspiratory time. This may be useful in some patients to help decrease high airway pressures (e.g. > 25–30 cm H_2O) or improve oxygenation (e.g. in the obese). Some patients with asthma or chronic airway disease may benefit from a longer expiratory time to allow the lungs to empty, and an I:E ratio of 1:3 or 1:4 may be preferable.

Children have a proportionately higher minute ventilation than adults – up to 200 ml/kg in infancy, approaching adult values weight-for-weight by about age 10 years. Given that their tidal volume is slightly less weight-for-weight than adults (7 ml/kg), this increased minute volume must be provided for by an increase in rate. For example, in a 5 kg infant, a minute volume of 1000 ml might be provided by 30 breaths each of about 33 ml/minute.

However, paediatric ventilation is complicated by the obligatory leak around the uncuffed tube. Volume control is unlikely to inflate the lungs to the set volume (especially if a Newton valve is used with T-piece ventilation). This is usually overcome by increasing the tidal volume by titrating against inflation pressure and/or $P_{E'CO_2}$. Some modern anaesthesia ventilators have pressure control capabilities (e.g. the *Draeger Julian*). Specific compliance varies little with age, therefore pressure control mode can be used to deliver an inflation pressure of 15–20 cm H_2O. This provides an adequate tidal volume for any age, despite small to moderate leaks, as long as lung compliance is normal.

Regardless of the mode of ventilation, a fresh gas flow must be selected. This depends on the breathing system in use as well as the size of the patient. A high flow should be used initially (e.g. 6 litres/minute), regardless of the circuit being used. This allows time for denitrogenation and equilibration of inhaled anaesthetic agent during this early period of rapid anaesthetic uptake. After about 10 minutes, flows can be reduced considerably if the system permits. The circle system with carbon dioxide absorber is widely used, and modern lightweight valves and low-resistance tubing make it suitable for paediatric use well below the traditional lower patient weight limit of 20 kg. With appropriate monitoring of gas concentrations within the circle, this permits total fresh gas flows of 1 litre/minute or less. Higher flows are required for T-pieces such as the Bain and Jackson Rees systems. Formulae exist for each of these circuits to predict the flow of fresh gas required per kilogram patient weight to eliminate rebreathing for controlled and spontaneous respiration. However, a more practical approach is to reduce the fresh gas flow gradually, stopping when rebreathing of carbon dioxide begins to appear on the capnograph.

General anaesthesia, particularly when using volatile anaesthetic agents, causes the development of atelectasis in the dependent parts of the lung and impairs the pulmonary vascular response to hypoxia (hypoxic pulmonary vasoconstriction). These two factors produce a small but noticeable degree of shunt, usually about 10%. This can be corrected by giving anaesthetized patients higher inspired oxygen than the 21% present in air; 30% is usually given, though this can be titrated against observed oxygen saturation.

Circulation: appropriate fluid management is an important component of anaesthetic maintenance. Intravenous fluid requirements may range from none in short and relatively non-invasive procedures, to many times the circulating volume in long and traumatic procedures. Fluid requirement consists of:

- replacement of existing deficit – crystalloid or blood
- metabolic maintenance requirements – crystalloid
- replacing additional ongoing losses – crystalloid, colloid or blood.

Existing deficit – in the adult elective surgical patient, who has been starved for at least 4 hours preoperatively (and sometimes much longer), a deficit of 500 ml of crystalloid can be assumed. This deficit is generally well tolerated and does not necessarily need replacing, but it decreases the patient's margin of reserve against any further losses, or against ongoing postoperative dehydration as a result of nausea or vomiting. Many anaesthetists routinely administer 500–1000 ml of crystalloid in all patients except those at risk from fluid overload (e.g. those with renal or cardiac failure). There is evidence to suggest that this may improve the quality of early recovery and help to decrease postoperative nausea.

In the emergency patient, fluid deficit may be considerable, as a result of either trauma-related blood loss, or anorexia, vomiting and/or interstitial (third-space) fluid loss from surgical pathology. In either case, the deficit should be assessed and replaced with the appropriate fluid. The larger the deficit, the more important that it be replaced before induction, whenever circumstances permit. The exception to this rule is during major ongoing blood loss, such as a ruptured aortic aneurysm or major trauma, where the priority is stopping the bleeding rather than prolonging attempts to normalize the circulation preoperatively.

Maintenance – for many patients this is the least important component of intraoperative fluid management – the average adult requirement of about 100 ml/hour is negligible in the context of a short procedure and other fluid losses. However, in small children, maintenance requirements are proportionately larger and more significant. Paediatric maintenance fluid is usually calculated according to: 4 ml/kg/hour for the first 10 kg, plus 2 ml/kg/hour for the next 10 kg, plus 1 ml/kg/hour for the remainder. Thus, a 25 kg child would have a maintenance requirement of 40 + 20 + 5 = 65 ml/hour. The smaller the child, the less reserve there is for managing without ongoing maintenance fluids, and the greater the impact of preoperative starvation.

Infants have small glycogen reserves, and therefore need intravenous dextrose (e.g. as 5% dextrose in 0.18% saline) as maintenance to sustain their blood sugar levels. For longer procedures, careful attention must be paid to electrolyte balance, because infants have less ability to correct excessive salt loads or water loads.

Ongoing losses – the most significant aspect of intraoperative fluid management can be the most difficult to estimate.

Losses from extravascular spaces (e.g. gastrointestinal, evaporative, third-space fluid losses) are usually crystalloid losses. Evaporative losses can be large – an adult may lose in excess of 1 litre/hour from a laparotomy or thoracotomy wound, and even larger amounts from extensive open skin wounds such as burns or large graft sites. There is no way of measuring these losses directly, and measures such as blood pressure, pulse rate or central venous pressure (CVP) provide only an indirect measure of total body water. Urine output may be the most useful clinical measure. Blood tests such as plasma urea, sodium and haematocrit may provide information regarding the hydration state, and plasma electrolytes and haematocrit are now commonly available from blood gas machines.

Losses also occur from the intravascular space (i.e. blood). Losses in suction bottles may be complicated by wash, faeces, urine or amniotic fluid. Visual estimates of blood loss on swabs are often inaccurate – weighing of swabs is more precise, but still neglects losses on drapes, gloves and instruments. A dilutional technique relies on washing all swabs, instruments and gloves in a fixed volume of water, which can then be measured colorimetrically to give an accurate measure of blood loss. Such instruments are not widely available. Intravascular loss may be estimated indirectly from clinical measures such as blood pressure, pulse rate or CVP, though other anaesthetic factors such as the balance between surgical stimulation and depth of anaesthesia complicate these measures. Estimation of haemoglobin is useful only when adequate intravascular volume has been replaced. Blood losses may initially be replaced by colloid solution (e.g. a gelatin solution or hydroxyethyl starch), but larger losses (> 20% blood volume) may require replacement by packed-cell blood. Very large losses (> 1 blood volume) may require supplementation with fresh frozen plasma and/or platelets to maintain clotting function.

In practice, it is likely that fluid losses are under-replaced in many patients. This is offset by the hormonal 'stress response' to surgery: aldosterone, cortisol and antidiuretic hormone levels rise and atrial natriuretic peptide falls; all contribute to postoperative water retention.

Temperature control: there is now good evidence that the maintenance of a physiological body temperature reduces postoperative morbidity. Patients suffering from head injury or undergoing certain neurosurgical procedures are possible exceptions. Shivering increases oxygen consumption, and predisposes to myocardial ischaemia, dysrhythmias, hypotension and acidosis. Hypothermia also increases susceptibility to infection and tends to lengthen hospital stay.

Temperature control is of particular importance in patients at the extremes of age (who have less intrinsic control over body temperature and a larger surface area-to-volume ratio through which to lose heat), in operations involving open body cavities, and in all patients undergoing lengthy procedures. About 20% of trauma patients who arrive at hospital are hypothermic (core temperature < 35°C).

A change in core temperature as a result of general anaesthesia is a three-phase response.

- The first phase is a brisk fall in core temperature as a result of vasodilatation, caused by redistribution of heat to the peripheries. Core temperature may be as low as 35.5°C in some patients after transfer to the operating theatre from the anaesthetic room.
- The second phase is a slower but more sustained fall as a result of accelerated loss of heat to the environment from the warmer peripheries.
- The third phase is a stable equilibrium at a lower core temperature.

It is important to note that the anaesthetic itself brings about these changes, which are independent of the nature of the surgery, though surgery may modify the pattern. The use of spinal or epidural anaesthesia instead of general anaesthesia reduces, but does not abolish, the three-phase response described above.

Passive rewarming is the prevention of heat loss, typically by raising the temperature of the environment. Passive rewarming can serve to modify only the second phase of the heat loss response. Covering with blankets or the use of foil 'space' blankets decreases heat loss by reduced transfer of heat by convection, conduction, evaporation and radiation.

Dry inspired anaesthetic gases need to be humidified, and a heat and moisture exchange filter in the breathing system reduces heat loss by evaporation from the respiratory tract (latent heat). Low flows in a circle system (e.g. 1 litre/minute) further reduce the quantity of dry gas needing to be humidified and help retain heat and moisture within the breathing system.

A 'normal' operating room temperature of 21°C is a compromise between that which is warm enough for the patient, but cool enough for the comfort of theatre personnel. An increase in theatre temperature (e.g. to 25°C) helps to reduce the gradient for heat loss in patients at high risk (e.g. young children, patients with extensive burns).

Active rewarming is the addition of heat into the patient. It may be used to prevent or reverse the first phase of the temperature drop. The local environmental temperature can be raised so much that the transfer of heat is reversed. Warm air convection blankets (e.g. the *Bair Hugger*) are considered as active rewarming.

Intravenous fluid warmers play an increasingly important role the greater the volume of intravenous fluid given. A fluid-warming device should be used in all at-risk patients and especially when stored blood is administered. Ventilatory gases may be warmed using a heated humidifier. Overhead radiant heaters may be used when a large area of the body needs to be exposed, and neonates may undergo surgery on an open incubator such as the *Resuscitaire*.

Cardiopulmonary bypass represents the ultimate in active rewarming, but is practical only in cardiothoracic surgery or in uncommon resuscitation situations.

Care is needed not to overheat the patient and temperature monitoring is necessary when active rewarming methods are used. Monitoring probes are available for a variety of body cavities, including nasopharynx, oesophagus, rectum, bladder and tympanic membrane. In routine clinical practice, core temperature is usually measured by nasopharyngeal or rectal temperature probes. Surface temperature monitors do not reflect core temperature, but the core–peripheral gradient may provide a useful measure of peripheral vasodilatation. A gradient of less than 2°C implies good peripheral perfusion.

Monitoring: the Association of Anaesthetists has published recommendations on standards of monitoring. A summary is given in Figure 2.

Blood sugar should be monitored in infants and diabetic patients. The blood sugar of diabetic patients should be known before anaesthesia is given, and should be estimated every 1–2 hours during routine surgery.

The Association of Anaesthetists summary of standards of monitoring

- The Association of Anaesthetists of Great Britain and Ireland strongly recommends that the standard of monitoring used during general anaesthesia should be uniform in all circumstances irrespective of the duration of anaesthesia or the location of administration
- An anaesthetist must be present throughout the conduct of general anaesthesia
- Monitoring should be commenced before induction and continued until the patient has recovered from the effects of anaesthesia
- These recommendations also apply to the administration of local anaesthesia, regional analgesia or sedation where there is a risk of unconsciousness or cardiovascular or respiratory complications
- The anaesthetist should check all equipment before use. Monitoring of anaesthetic machine function during the administration of anaesthesia should include an oxygen analyser with alarms. During spontaneous ventilation, clinical observation and a capnometer should be used to detect leaks, disconnection, and rebreathing and high pressure in the breathing system. Measurement of airway pressure, expired volume and carbon dioxide concentration is strongly recommended when mechanical ventilation is employed
- A pulse oximeter and capnometer must be available for every patient
- It is strongly recommended that clinical observation of the patient should be supplemented by continuous monitoring devices displaying heart rate, pulse volume or arterial pressure, oxygen saturation, the electrocardiogram and expired carbon dioxide concentration. Devices for measuring intravascular pressures, body temperature and other parameters should be used when appropriate. It is useful to have both waveform and numerical displays
- Intermittent non-invasive arterial pressure measurement must be recorded regularly if invasive monitoring is not indicated. If neuromuscular blocking drugs are used, a means of assessing neuromuscular function should be available
- Additional monitoring may be required in certain situations. These recommendations may be extended at any time on the judgement of the anaesthetist

2

Positioning: an unconscious patient cannot move to relieve an uncomfortable position, and it is the anaesthetist's responsibility to prevent discomfort from becoming damage. The anaesthetist is also responsible for protecting the patient during movement on and off the operating table, and during changes of position. Traditionally, the anaesthetist has particular responsibility for the head and airway. It must be ensured that all members of the team are working to a common agenda and with coordinated timing. It is usually easiest and safest to disconnect as much equipment as possible before moving the patient.

Prophylaxis against venous thromboembolism – the thrombotic process often starts intraoperatively. It is difficult to identify patients at high risk, though coexisting medical illness, major surgery, malignancy, trauma (especially hip and pelvis), obesity, high-dose oestrogen therapy and age greater than 40 years are well-known risk factors. Thromboprophylaxis should commence before anaesthesia; gradated compression stockings and low-dose unfractionated heparin, 5000 IU s.c. twice daily, continued until full mobilization, is popular and effective. When positioning for surgery, raising the heels on foam pads prevents venous stasis in the calves. Intermittent pneumatic compression pumps assist venous return, but it is not known whether this reduces the incidence of postoperative pulmonary embolism.

Keeping the patient comfortable

Traditionally, the main components of anaesthetic maintenance are unconsciousness (hypnosis), analgesia and absence of movement. Some advantages and disadvantages of using muscle relaxants have been discussed. Keeping the patient unconscious and relieving the pain of surgery are now considered.

Maintenance of unconsciousness is usually achieved by anaesthetic drug delivery via the inhalational or intravenous route, or both. The intramuscular route is seldom used in hospital practice owing to the relatively slow onset of drug action, unpredictable duration and delayed recovery. Ketamine, 10 mg/kg, is the only useful intramuscular agent, with an onset of 5–10 minutes producing up to 30 minutes of anaesthesia. It has a role in the provision of emergency anaesthesia in difficult locations.

Inhalational route – this is the most widely used technique, using a volatile anaesthetic agent with or without nitrous oxide. It therefore requires a supply of compressed gas, a vaporizer and a breathing system for drug delivery. Compressed gas may not be required if a 'drawover' type vaporizer is used.

The potency of an inhaled anaesthetic agent may be described in terms of its minimum alveolar concentration (MAC). MAC is defined as the alveolar concentration of the anaesthetic agent which at equilibrium is required to prevent gross reflex muscular movement in response to a standardized skin incision in 50% of healthy, unpremedicated patients. It is therefore a measure of anaesthetic potency, and is the effective dose in 50% of the population (ED_{50}). It should be borne in mind that not all operations are 'a standardized skin incision'. The amount of anaesthetic needed to remove a foreign body from the nose is very different from that needed for an anal stretch. It is important to know the MAC of individual inhalational agents and the factors on which they depend (Figures 3 and 4).

Of any given inhalational anaesthetic, 0.7–1.3 MAC will anaesthetize 95% of the population. MACs are also additive: 0.5 MAC of nitrous oxide (52%) plus 0.5 MAC of isoflurane (0.6%) is equivalent to 1 MAC of any other inhalational agent given alone.

The principle of MAC acts as a useful guide. It allows the anaesthetist to select a vapour concentration that is likely to maintain unconsciousness. The state of anaesthesia is related to the partial pressure of anaesthetic within the brain, which is taken to be equivalent to the alveolar partial pressure. This can be measured by analysis of the end-tidal partial pressure of the anaesthetic agent. What is dialled on the vaporizer or the nitrous flowmeter is not necessarily what is in the patient's alveoli – the fresh gas flow takes time to equilibrate both with the dead space of the circuit and with the uptake by the patient. Observing how the ratio of end-tidal to inspired partial pressure varies with time can assess this rate of uptake (or 'wash-in').

MAC is useful to estimate the amount of anaesthetic required. In clinical practice this must be adjusted against indicators such as pulse rate, blood pressure, respiratory rate, patient movement, pupillary size, lacrimation and sweating. Many of these variables may be abolished by factors other than anaesthetic depth. Tachycardia may be prevented by co-administered β-blockers, hypertension masked by hypovolaemia, respiratory rate and patient movement abolished by paralysing drugs, and pupillary size altered by use of opioids or anti-muscarinic drugs. Thus, lacrimation and sweating, though crude indicators of inadequate anaesthesia, reflect the need for clinical observation in addition to monitoring.

Minimum alveolar concentration (MAC) of inhalational anaesthetic agents

Anaesthetic agent	MAC in oxygen (%)	MAC in 70% nitrous oxide
• Halothane	0.75	0.29
• Enflurane	1.68	0.57
• Isoflurane	1.15	0.50
• Sevoflurane	2.0	0.8
• Desflurane	6–9	2.5–3.5

3

Factors affecting minimum alveolar concentration

Decrease	Increase	No change
• Increasing age	• Decreasing age	• Gender
• Alcohol (acute ingestion)	• Alcohol	• Duration of anaesthesia (chronic ingestion)
• Nitrous oxide	• Hyperthermia	• Time of day
• Analgesics	• Hyperthyroidism	• Hypercarbia
• Sedatives and hypnotics	• Hypocarbia	
• Hypotension		
• Hypothermia		
• Hypothyroidism		
• Hypoxia		

4

Intravenous route – a popular alternative to inhalational anaesthesia is total intravenous anaesthesia (TIVA). Many intravenous anaesthetics have been used for TIVA, including barbiturates, ketamine, etomidate and propofol. The pharmaco-kinetic profile of propofol makes this drug the most commonly used for TIVA. It has a high clearance (1300–1900 ml/minute), short metabolic half-life (60–100 minutes) and inactive metabolites. For short procedures, propofol may be administered following initial intravenous induction by intermittent bolus with no special infusion equipment (e.g. 50 mg as required every 3–5 minutes).

For longer procedures, the advent of reliable electronic syringe pumps, and in particular the development of target-controlled infusion (TCI) software, have contributed to the widespread use of TIVA techniques. Some advantages and disadvantages of inhalational or TIVA maintenance are shown in Figure 5.

Consider a three-compartment model: vascular space, richly perfused organs, and poorly perfused organs plus clearance. A large initial bolus of propofol is needed to fill the vascular compartment, namely the induction dose. Thereafter an initially high rate of infusion is needed to keep up with losses to the richly perfused compartment until it approaches saturation. Then a slower rate is required to keep up with losses to the poorly perfused but difficult to saturate compartment, and with metabolic clearance.

The 'Bristol regimen' reflects these kinetics. This regimen aims to maintain a plasma propofol concentration of about 3 μg/ml by giving patients receiving 67% nitrous oxide an initial bolus of 1 mg/kg, followed immediately by infusion at 10 mg/kg/hour for 10 minutes, then 8 mg/kg/hour for 10 minutes, then 6 mg/kg/hour thereafter. A dose of 10 mg/kg/hour is equal to the patient's weight (in kg) as ml/ hour of 1% propofol – hence a 60 kg patient will initially receive 60 ml/hour of 1% propofol. At the end of the operation, switching off the propofol allows rapid redistribution from the vascular compartment (and therefore from the richly perfused compartment also) to the still unsaturated third compartment. It is this rapid redistribution that allows a prompt wake-up even after a long period of TIVA.

TCI microprocessor-controlled technology (e.g. as incorporated in the Graseby 3500 'Diprifusor' syringe pump) requires manual input of patient age, weight and desired plasma concentration. The pump then administers propofol according to the three-compartment pharmacokinetic model incorporated into its software. Change to a higher propofol concentration is achieved by a rapid zero-order infusion, and the plasma concentration is calculated until the new predicted value is reached. Change to a lower concentration is achieved by temporary cessation of drug infusion until the predicted plasma level falls to the required level, followed by continuation of infusion at a lower rate. The system is used in a similar fashion to adjusting the vaporizer setting during inhalational anaesthesia; the predicted plasma concentration of drug is analogous to the end-tidal concentration of the inhalational agent. Maintenance of satisfactory anaesthesia requires a plasma concentration of propofol of 2–6 mg/ml, depending on patient fitness, coexisting drug therapy and degree of surgical stimulation.

Comparison of inhalational anaesthesia and total intravenous anaesthesia (TIVA) maintenance techniques

Inhalational maintenance

Advantages
- Cost-effective (especially when used with low-flow circle systems)
- Predictable population pharmacokinetics and confidence in anaesthetic depth achieved
- Ease of measurement of end-tidal partial pressure
- Minimal metabolism of modern agents, no accumulation and clearance independent of patient hepatic and renal function

Disadvantages
- Requires conventional tidal ventilation for drug delivery
- Requires specialized equipment (e.g. vaporizer, anaesthetic machine, agent analyser)
- Concern regarding tissue and organ toxicity (especially hepatotoxicity following repeat halothane exposure)
- All volatile anaesthetics are known triggers for malignant hyperpyrexia
- Environmental pollution

TIVA

Advantages
- Independent of airway for drug delivery. May be advantage in, for example, jet ventilation techniques
- No specialized equipment is essential. More suitable technique for patient transport and difficult locations
- Rapid increase in anaesthetic depth possible by administration of intravenous bolus
- Low incidence of postoperative nausea and vomiting and better quality of early recovery (especially for propofol)
- No contraindication in malignant hyperpyrexia

Disadvantages
- Requires patent and dependable intravenous access. Undetected failure may result in awareness
- Drug accumulation with prolonged infusion
- Inability to measure plasma concentration directly has led to concerns about possibility of awareness

5

Analgesia: modern inhalational or intravenous anaesthetic drugs possess little analgesic activity, with the exception of ketamine. For all but the simplest procedures, analgesia must be provided by systemic analgesics (usually opioids) or by local anaesthetics. Analgesia has several effects.

- It reduces the required MAC (or plasma concentration) of co-administered anaesthetic drugs. Analgesia is an important component of the balanced anaesthetic technique.
- It reduces the immediate autonomic activity in response to pain. Sympathetic stimulation otherwise results in cardiovascular and respiratory responses that may lead to myocardial ischaemia and dysrhythmias.
- It reduces the neuroendocrine 'stress response' caused by surgery.

Opioid analgesics such as fentanyl, 15 μg/kg, reduce circulating concentrations of the stress hormones that increase after moderate and major surgery (e.g. noradrenaline, adrenaline, cortisol, growth hormone, glucagon, antidiuretic hormone). The stress response is largely detrimental and leads to increased catabolism, metabolic rate and oxygen consumption. This response is not significant in minor surgery.

The short-acting synthetic opioid drugs such as fentanyl and alfentanil are widely used to provide intraoperative analgesia. Fentanyl, a synthetic opioid structurally related to pethidine, is the most popular (1–2 μg/kg for minor procedures, onset 1–2 minutes, duration 30 minutes). Its potency and minimal effect on pulse and blood pressure make it commonly used for the provision of intense analgesia during surgery. These drugs are unsuitable for routine use in postoperative analgesia because of their short duration of action and their tendency to produce marked respiratory depression. They are commonly substituted by longer-acting analgesics (e.g. morphine 0.1–0.2 mg/kg i.v.) towards the end of the procedure to provide pain relief following surgery.

Pre-emptive analgesia – laboratory work suggests that noxious stimuli produce hypersensitivity in the pain pathways both centrally and peripherally. Larger doses of analgesics are then required to have an effect. If systemic analgesia or local anaesthetics are used to prevent the initial pain, this hypersensitivity is reduced. This is the basis of pre-emptive analgesia, but its clinical significance is disappointing.

Providing the best possible operating conditions

The surgeon hopes for two things from his patient during the operation: not to move, and not to bleed. If the anaesthetist has succeeded in keeping the patient safe and comfortable as described, then the patient is unlikely to move. The anaesthetist can also help to minimize bleeding.

Tourniquets are ideal for extremity surgery. Traditionally, a 90-minute time limit is imposed on upper limb tourniquets (usually at 250 mm Hg), and a 120-minute limit on lower limb tourniquets (usually at 300 mm Hg). This is arbitrary; the longer the tourniquet is on, the greater the potential for damage. The main risk is ischaemic damage to nerves directly under the tourniquet; distal ischaemia is likely to take 4–6 hours to become significant. If antibiotics are necessary, they should be given at least a few minutes before exsanguination.

Sickle-cell disease is an absolute contraindication to tourniquet use, because sickling of haemoglobin S may be induced by the local hypoxia and acidosis.

Positioning – adequate venous drainage from the operative site is ensured by careful attention to patient positioning. Raising the operative site above heart level decreases arterial and venous pressures. Arterial pressure falls by 2 mm Hg for each 2.5 cm vertical height. Head-up tilt is commonly used in head and neck surgery to decrease bleeding, but there is a risk of venous air embolism.

Hypotensive anaesthesia – moderate reduction of systolic blood pressure (e.g. to 70–80 mm Hg) in otherwise fit patients may greatly improve the operative field. It must be used with caution in patients with coronary, cerebral, renal or peripheral vascular diseases who are at risk from ischaemic events. Techniques for deliberate hypotension are outside the scope of this contribution.

Non-steroidal anti-inflammatory drugs used intraoperatively may increase blood loss during surgery.

Blood gases – carbon dioxide is a local vasodilator, and moderate hypocapnia (e.g. P_{CO_2} 4.0–4.5 kPa) contributes to a dry surgical field.

Preparing the patient for the postoperative perio

The maintenance period is often a convenient time to complete the necessary anaesthetic record and drug prescription charts. During anaesthesia, it should be considered what else may be done while the patient is unconscious to enhance his or her postoperative course. This includes the following.

Venous access must be sufficient for postoperative requirements. A central venous line should be sited if access is likely to be difficult or prolonged, or to enable central venous monitoring. A subcutaneous cannula for analgesic administration may avoid the need for injections, especially in children.

A nasogastric tube is more comfortably inserted while the patient is asleep, and its position can be checked during laparotomy.

Analgesia – ideally, the plan for postoperative pain control should be formulated before anaesthesia, and discussed with the patient. 'Balanced analgesia' is the concept of using several analgesics with differing modes of action, thus reducing dose-related side-effects and enhancing overall analgesic effect. Typically this may involve local or regional analgesia in combination with opioids, non-steroidal anti-inflammatory drugs and simple analgesics (e.g. paracetamol).

Antiemetics should be given in particular to patients receiving opioids, and those at high risk of postoperative nausea and vomiting (PONV). High risk includes patients with a history of previous PONV or motion sickness, certain operations (e.g. gynaecological, middle ear or strabismus surgery) and female gender.

Oxygen – all anaesthetics (with the exception of ketamine) induce about 10% shunt. Atelectasis, impaired hypoxic pulmonary vasoconstriction, diffusion hypoxia from nitrous oxide use, opioid-mediated hypoventilation and other factors contribute to making the postoperative patient prone to hypoxia. Added oxygen (e.g. 30–40% via a simple face mask) should be administered in the immediate recovery period to all patients for about 15 minutes, guided by pulse oximetry. Subsequently, the need for added oxygen must be determined for each patient depending on factors such as age, pre-existing disease and the nature of anaesthesia and surgery.

Fluids – there must be clear instructions for postoperative fluid intake. Elective day-surgery patients will drink when ready, but in-patients and those undergoing major procedures require intravenous fluids to replace continuing fluid losses and provide maintenance. How far in advance fluids can be prescribed depends on the accuracy of prediction of future needs.

Thromboprophylaxis – stockings for prevention of thrombo-embolic disease and/or regular heparin should be prescribed where indicated by local policy.

Antibiotics – should be prescribed at the surgeon's discretion.

Monitoring – the anaesthetist should understand the routine standard of monitoring on the postoperative ward and ensure that it meets the needs of the patient. Specific requirements must be clearly communicated, such as hourly urine output, hourly blood pressure, overnight Sp_{O_2} or any other observ-ations in an at-risk patient. Action that should be taken if the observation deviates from the desired targets should be documented.

Medical Gas Storage, Suction Devices and Humidifiers

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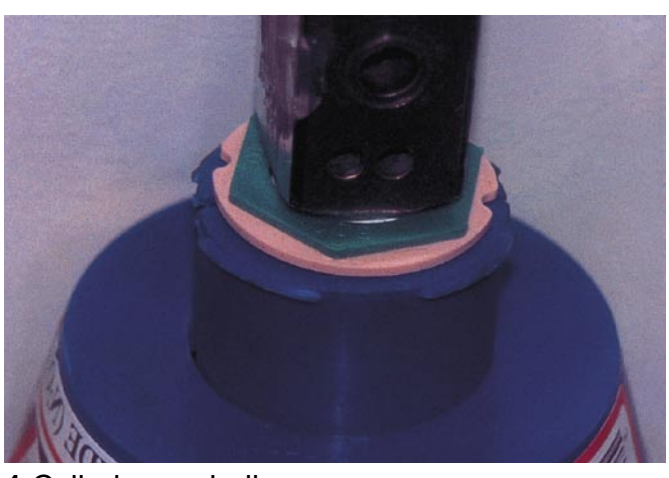
Cylinders

Medical gas cylinders are made of molybdenum steel to ensure they are strong and able to withstand high pressures, but are also relatively light in weight. They are constructed as a seamless tube and consist of a body, shoulder and neck. They are colour coded according to British and International Standards (BS1319C and ISO32) to identify their gas contents (see Figure 7, page 109). Cylinders are manufactured in different sizes from A, the smallest, to J, the largest. Size E cylinders are usually attached to the anaesthetic machine and size J cylinders make up manifolds.

The cylinder valve fits into the cylinder neck by a screw thread mechanism, to permit safe, controlled use of its contents. The junction between the cylinder and valve melts in the presence of intense heat, thus allowing escape of gas and minimizing the risk of explosions. Between the neck and cylinder valve is a plastic disc, the colour and shape of which denotes the year in which the cylinder was last examined (Figure 1).



1 Cylinder neck disc.

Cylinder body
The cylinder body is colour coded and engraved with:
- test pressure
- date of last test performed
- chemical symbol of contents
- tare weight (i.e. weight of empty cylinder).

It is also labelled (Figure 2) with the name and symbol of the gas it contains, its volume, pressure and minimum purity (Figure 3). The label gives additional information relating to storage, use (in conjunction with the Medical Gases Data Sheet) and safety matters. The safety points highlighted are:
- compressed gas
- flammability status
- avoidance of oil or grease because spontaneous combustion can occur with high-pressure gases.

2 Cylinder label.

Cylinder size, volume, pressure and purity of contents

Gas	Cylinder size (litres)	Volume of gas at 15°C	Pressure (kPa)	Purity (%)
Oxygen	E	680	13700	99.5
Nitrous oxide	E	1800	4400	98.0
Air	E	640	13700	21.0 (oxygen)
Carbon dioxide	C	450	5000	99.0

3

Storage
- Cylinders must be stored under cover, in a dry, clean and well-ventilated area, away from extremes of temperature.
- Smoking or the use of a naked flame in the storage area is prohibited.
- Moisture or exposure to chemicals can lead to the corrosion of the cylinder or its valve.
- Cylinders should be kept in the upright position or horizontal on shelves to avoid direct damage to the valves.
- Cylinders should be used in a sequential manner to ensure that no cylinder remains in storage for too long.
- Full and empty cylinders should be kept apart.

Testing
During manufacture, one in every 100 cylinders is cut into strips and tested for tensile strength. Cylinders in circulation are tested on a 5-yearly basis by:
- exposure to hydraulic pressure of about 22,000 kPa (far in excess of the pressures encountered in daily use)
- filling with water under pressure to assess expansion and elastic recoil
- internal endoscopic inspection.

Test date details are recorded on the plastic disc between the cylinder valve and the neck and engraved on to the cylinder body.

Filling
Medical gases are stored either in the gaseous state (oxygen and air) or as a mixture of the liquid and vapour (nitrous oxide and carbon dioxide). Cylinders that contain liquid should be used only in the upright position. Gases and vapours stored in cylinders must be free of water vapour to avoid the formation of ice (secondary to a fall in temperature on cylinder opening), which may block the exit valve. For cylinders containing gas alone, the contents can be assessed directly by measuring the pressure using a Bourdon gauge (see *Anaesthesia and Intensive Care Medicine* **1:2:** 65). In the case of cylinders containing both the liquid and vapour phases the situation is more complex. The contents of these can be determined only by subtraction of the tare weight from the cylinder weight because the pressure within will not fall until the liquid has completely vaporized, assuming the temperature stays constant.

During nitrous oxide use, the liquid within the cylinders cools owing to the uptake of latent heat of vaporization. Condensation or ice may form on the outside of the cylinder. In such circumstances, the cylinder gauge pressure may fall despite there being liquid nitrous oxide in the cylinder owing to the fall in saturated vapour pressure of nitrous oxide following the drop in temperature of the liquid. However, once the gas flow is turned off the temperature returns to that of the atmosphere and the gauge pressure returns to that at the beginning of use. Carbon dioxide is used at low flows so the chances of ice forming are low. Liquid is less compressible than gas, therefore cylinders containing nitrous oxide or carbon dioxide are only partially filled with liquid. Any change in pressure within the cylinder is minimized, thus reducing the chance of cylinder rupture should the temperature rise.

The filling ratio is that between the mass of liquid contained in the cylinder and the mass of water that it could contain if filled to the top. The filling ratios for nitrous oxide and carbon dioxide are both 0.75 in temperate climates and 0.67 in the tropics.

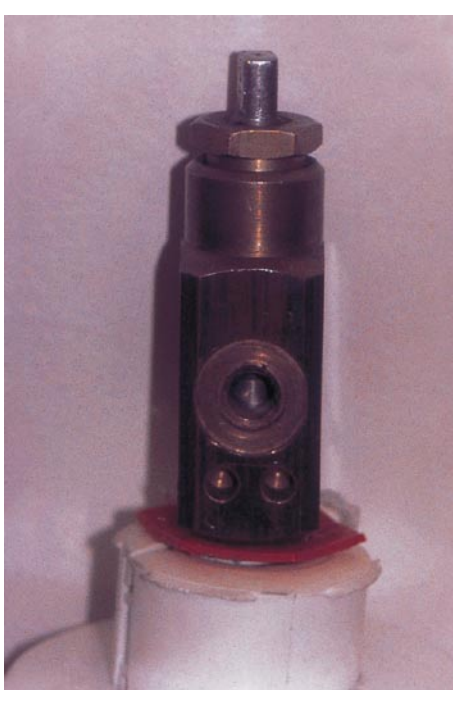
$$\text{Filling ratio} = \frac{\text{Mass of liquid}}{\text{Mass of water}}$$

Cylinder valve
Cylinder valves are made of brass and screw into the cylinder neck. There are four types of valve:
- pin-index valve block
- bull-nose valve
- hand-wheel valve
- star valve.

A pin-index valve is used on all cylinders that are to be attached to an anaesthetic machine. It is an international system (ISO2407) designed to prevent the fitting of the incorrect gas to the yoke and is fully detailed in the British Standard BS1319.

The system is made up of two components.
- Two pins projecting from the yoke, which are arranged in a gas-specific configuration in relation to the valve outlet
- Two holes within the valve block on the cylinder with a corresponding pattern for the designated gas (Figure 4).

This arrangement ensures that it is impossible to fit the incorrect cylinder to the yoke. The pin-index valve block on the cylinder is engraved with:
- tare weight
- chemical symbol for contents
- cylinder owner
- pressure of hydraulic test.



4 Pin-index valve holes on the cylinder.

Cylinder use
New or refilled cylinders are supplied from the manufacturer with a plastic dust cover over the valve to avoid dirt contamination. Before use, this cover should be removed and the valve transiently opened to expel any dirt or grease from the outlet. This reduces the chance of debris entering the anaesthetic machine and is known as 'cracking' the cylinder.

The cylinder is mounted on to the anaesthetic machine by engaging the pins on the yoke with the holes in the valve block. It is secured by tightening the wing nut.

Before use, the cylinder should be opened gently to ensure that there are no leaks, either from the cylinder valve itself or at the point of attachment to the yoke on the anaesthetic machine. A possible reason for gas leakage at the pin-index junction is the absence of the Bodok seal. This is an aluminium-rimmed neoprene washer that sits between the outlet on the valve block and the yoke on the anaesthetic machine. Gentle opening of cylinders minimizes sudden surges of high-pressure gas that may damage the pressure gauge or regulator.

Suction systems

Suction systems form part of the piped medical gases and vacuum systems (see page 107) and must comply with specifications detailed in BS4957. Portable and fixed suction systems are available to accommodate the differing circumstances of use. General operating principles are the same for both systems. Outlets from the central piped vacuum system must have the capability of maintaining a vacuum of at least 53 kPa below atmospheric pressure (101.3 kPa) and supporting a flow of 40 litres/minute.

Suction apparatus and nozzle: suction nozzles are made of either firm plastic (e.g. Yankauer) or metal. They should have a smooth tip to prevent damage to the soft tissues of the oropharynx. The tip often has more than one hole to allow continuation of suction should one hole become blocked. Suction tubing is constructed of semi-rigid plastic to minimize kinking, with a smooth internal surface to limit resistance to flow. The tubing must be of sufficient length to be practical to use, but it should be remembered that the length and width of a tube influences the laminar flow within it, according to the Hagen–Poiseuille equation:

$$\text{laminar flow} = \frac{\Delta P \pi r^4}{8 \eta L}$$

where: ΔP = pressure gradient along tube, r = tube radius, L = tube length, η = viscosity of liquid.

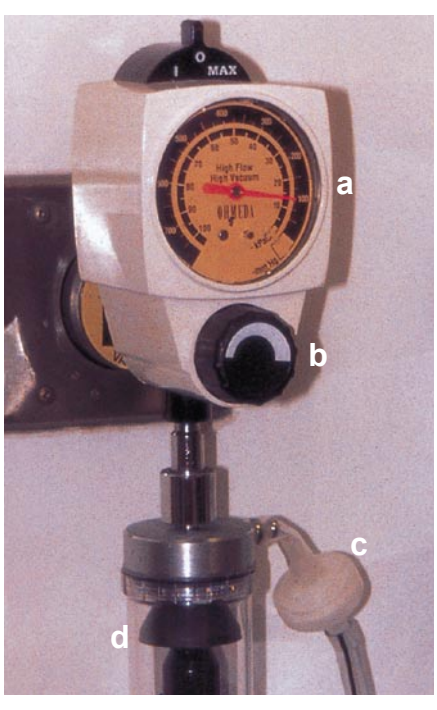
Thus, short, wide tubing maximizes laminar flow.

Reservoir: the reservoir must be of sufficient size to contain the estimated volume of suctioned material, but not so large that it increases the time taken for the vacuum to build up. Most reservoir vessels are constructed of clear material to allow the contents to be visualized and are graduated to permit accurate assessment of aspirate volume. Disposable liners are commonly used to reduce staff exposure to potentially infective material. A floating ball valve within the collection vessel prevents material from entering the control unit and the vacuum source if the container overfills.

Vacuum control regulator unit: this unit is usually situated between the reservoir and the vacuum source (Figure 5). Its function is to allow adjustment of the degree of vacuum applied to the distal suction tubing. The vacuum control adjuster acts as a variable orifice (either directly or by way of a spring acting on a diaphragm) to adjust the force of vacuum, which is indicated on a gauge. Within the unit is a filter and some form of float valve to provide protection from particulate matter.

Distribution pipeline network: between the terminal outlet and the control unit there is a colour-coded (yellow) flexible hose with a specific Schrader probe connection, as for piped medical gases.

Terminal outlet: the terminal outlet of the vacuum pipeline consists of a labelled, self-sealing valve, fronted in yellow, that accepts a probe with indexing collar to prevent misconnection.



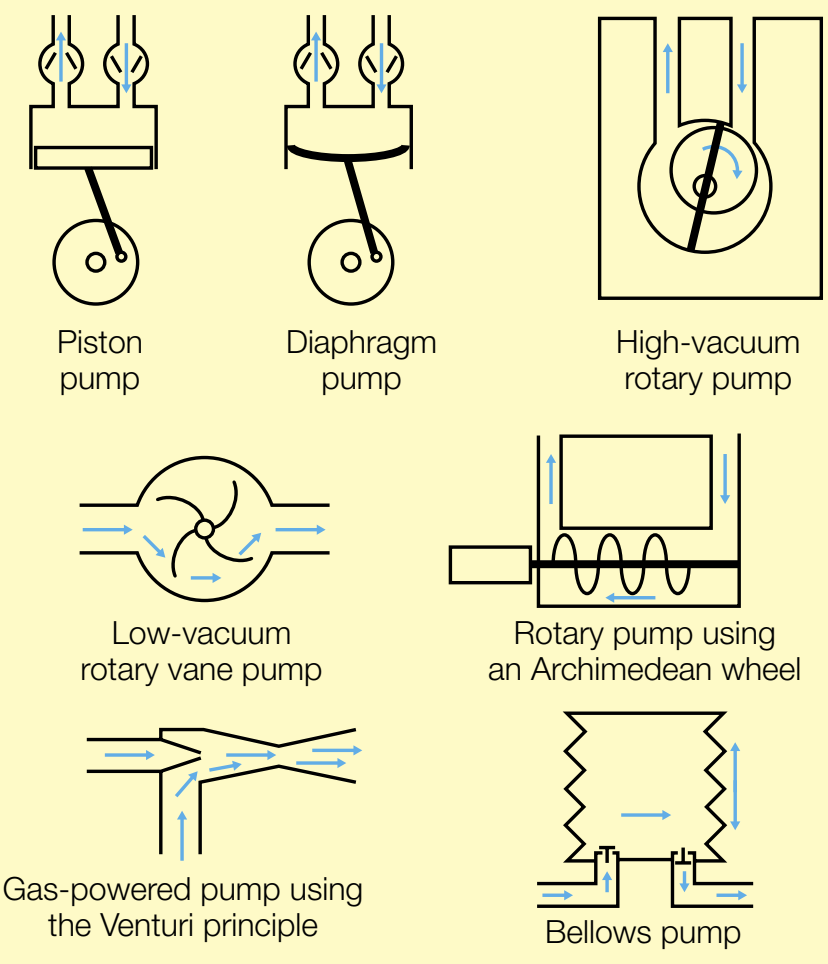
5 Vacuum control regulation unit.
a vacuum gauge, **b** vacuum control, **c** filter, **d** float valve.

Filter unit: filters are sited within the control unit, but also in the case of piped medical gases and vacuum systems between the terminal outlet and the central vacuum source. They remove particulate matter and bacteria from the system to prevent blockage and contamination.

Central pump: the role of the pump is to generate subatmospheric pressure within the system. Pumps are commonly driven by electrical, pneumatic or manual means (Figure 6). The piston, diaphragm and rotary devices shown in Figure 6 all require some form of energy source (usually electricity) to drive mechanical pumps. In contrast to these, the gas-powered pump works on the Venturi principle and the bellows require manual input to generate subatmospheric pressure.

The type of pump is determined by the specific requirements of the suction unit. For example, most portable units use a manual pump, whereas a rotary-driven pump may be used when a large volume of aspirate is anticipated. The pump expels its exhaust gases, via a silencer, to the atmosphere at a suitable site, such that staff and patients are not exposed to the pollution.

Vacuum pumps



Adapted from: Moyle J T B, Davey A. *Ward's Anaesthetic Equipment.* 4th ed. London: WB Saunders, 1998. By courtesy of the publisher.

6

Humidification devices

Humidification strictly refers to the addition of water vapour to air. Humidification of dry, cold anaesthetic gases as they enter the patient's airway is important because dry gases result in drying of the mucosal surfaces, abnormal ciliary function and increase in the viscosity of respiratory tract secretions. Loss of these protective mechanisms can cause mucus plugging, atelectasis, reduction in gas exchange and an increased susceptibility to infection. Also, heat energy due to latent heat of vaporization is lost by the patient in warming and humidifying dry, cold anaesthetic gases.

Aims: under normal circumstances, the upper respiratory tract warms and humidifies the air to an absolute humidity (i.e. mass of water vapour in a given volume of air at specified temperature and pressure) of 34 g/m^3 at 34°C in the trachea and 44 g/m^3 at 37°C in the alveoli. These values equate to fully saturated air whereby the air contains the maximum possible water vapour at specified temperature and pressure. Achievement of these values is the 'gold standard' for humidification. The different efficiencies of various humidifiers are shown in Figure 7.

Approximate efficiency of humidifiers

The exact values depend on the model of humidifier used.

Adapted from: Davis P D, Parbrook G D, Kenny G N C. *Basic Physics and Measurement in Anaesthesia.* 4th ed. Oxford: Butterworth-Heinemann, 1995. By courtesy of the publisher.

7

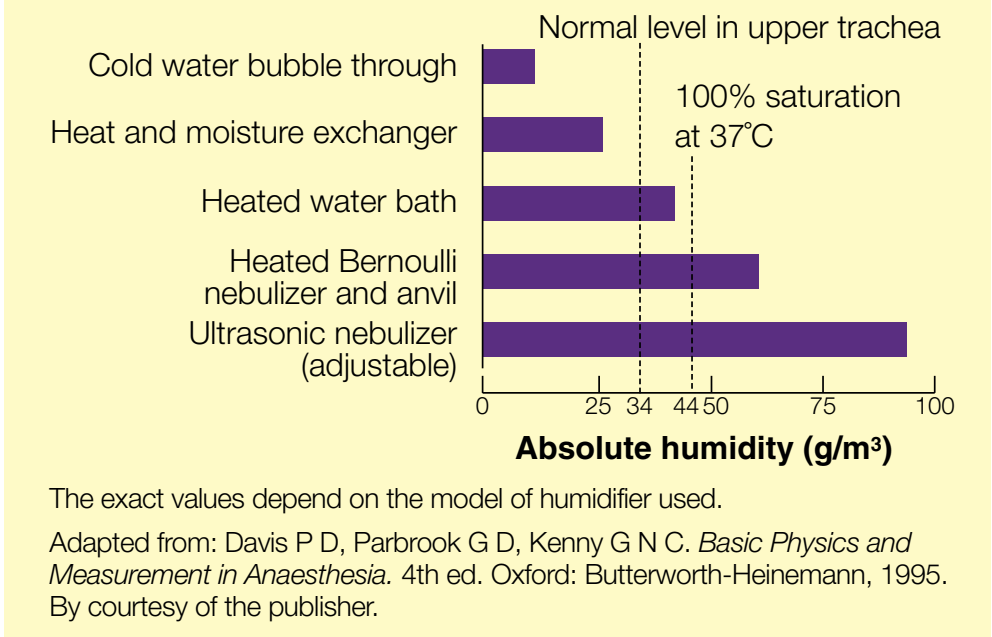
Types of humidifiers

Heat and moisture exchanger (HME) is the most commonly employed humidifier in day-to-day anaesthetic practice (Figure 8). It consists of a sealed unit that is placed within the breathing circuit. The exchanger contains a structure usually of either sponge or mesh, of large surface area, on to which water is absorbed. Absorption is maximized if the mesh is made of a hygroscopic material such as paper coated with calcium chloride or glass fibre. An additional role of some devices is to act as bacterial filters because over 99.99% of bacteria will not pass through pores of less than 0.2 microns. HMEs work on the principle that the moisture from expired gas condenses on to the mesh material within the device as it cools. The mesh is also warmed as the cooling moisture emits latent heat. As gas is inhaled it is warmed and humidified, thus exchanging heat and moisture. The advantages of the system are that it is:

- lightweight
- compact
- disposable
- efficient (60–70% relative humidity at 30–34°C, equating to absolute humidity of about 25–35 g/m^3)
- passive (requires no external power source)
- inexpensive.

The disadvantages are:

- increased dead space
- increased resistance to breathing
- single-patient use.



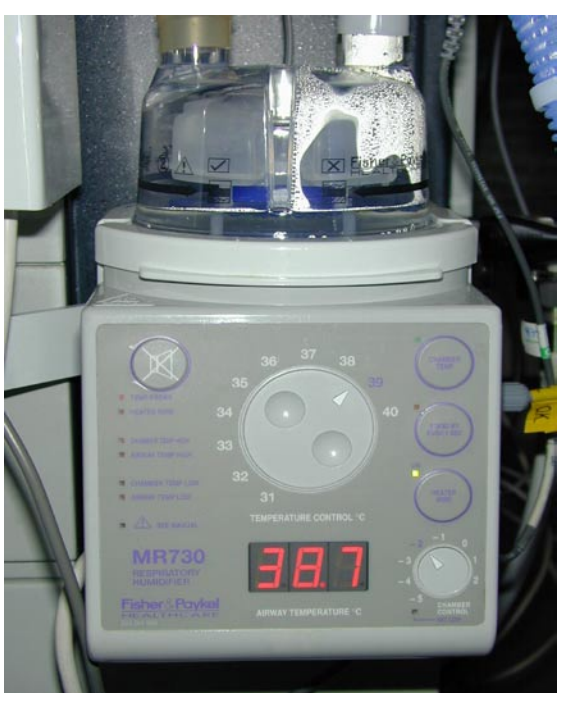
8 Heat and moisture exchanger.

Cold water bath humidifier (Figure 9): this operates by bubbling inspiratory gas through or over a cold water bath. The advantages are it is simple and safe. The disadvantage is that it is inefficient.

Hot water bath humidifier (Figure 10): inspiratory gases are bubbled through, or pass over, a warm water reservoir. The contact surface area is increased in some devices by the use of wicks or multiple bubble holes. The water temperature must be rigidly regulated to attain a balance between maximum humidification, bactericidal activity and heating, with the risk of thermal injury to the patient. This is achieved by the use of a thermostatic control and temperature monitoring within the circuit close to the patient. A water trap must be included on the patient side of the system and the whole apparatus must be below patient level to limit the risk of condensed water in the tubing entering the breathing circuit directly. The system is efficient but the disadvantages are:

- risk of scalding
- bacterial growth if temperature falls below 60°C
- condensation of water within tubing.

9 Cold water bath humidifier.



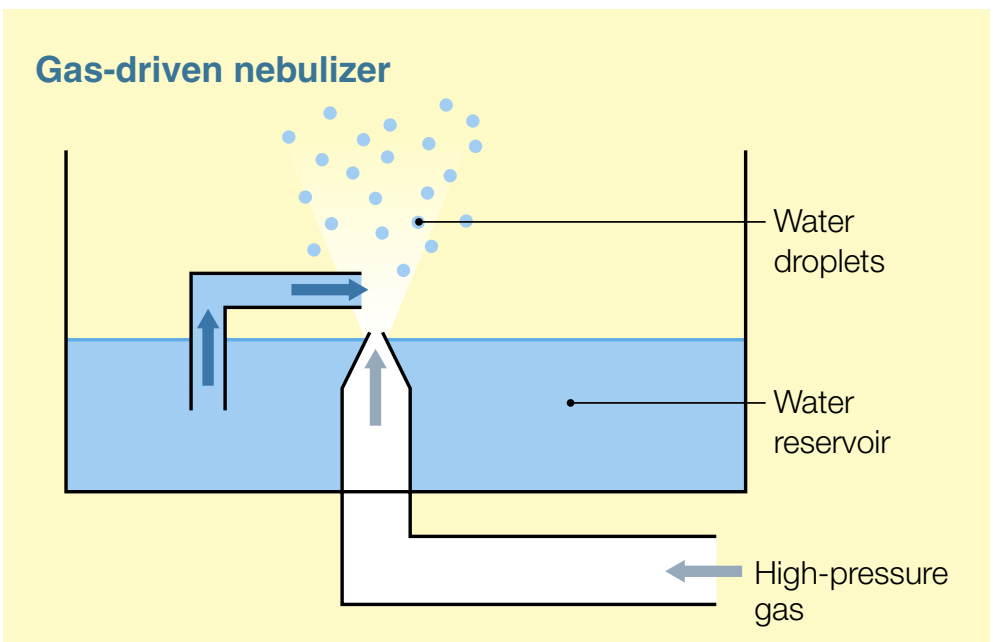
10 Hot water bath humidifier.

Nebulizers: the principle of nebulizers is to add tiny droplets of water to the inspired gas. Strictly speaking nebulizers are not humidifiers because they add water droplets not vapour to the gas. Nebulizers have the potential to produce water droplets of varying sizes. The result of this is that very small droplets pass into the alveoli and thus risk fluid overload, whereas large droplets risk being deposited in the breathing circuit or upper airway. Ideal droplet size is 1–5 microns. Nebulizers are highly efficient but they can be expensive and water overload may occur, especially in ultrasonic devices. There are three commonly encountered methods by which nebulizers produce water droplets.

Venturi principle – water is entrained into a jet of gas that breaks it into droplets (Figure 11). Some systems also contain a solid object (anvil) into which the droplets are propelled, thus further reducing their size. Droplet size averages 2–4 microns. Back pressure from a breathing system can affect the efficiency of the device by reducing water entrainment. Some nebulizers incorporate a heater to increase their efficiency.

Spinning disc – a rapidly rotating disc that throws off tiny water droplets.

Ultrasonic – high-frequency ultrasound waves fragment water into tiny droplets. The water may be dropped on to a vibrating surface or the device may be immersed in a water bath. Droplets 1–2 microns in size are produced.



11

FURTHER READING

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Al-Shaikh B, Stacey S. *Essentials of Anaesthetic Equipment.* Edinburgh: Churchill Livingstone, 1995.
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Medical Gases and their Delivery

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Medical gas

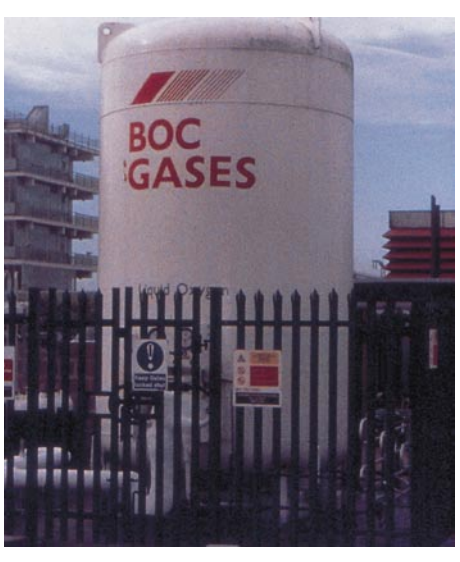
In the UK, most hospitals have piped medical gases and vacuum systems (PMGV) for convenience and economic reasons. The vacuum component of this system is discussed on page 114.

The pipeline network carries medical gases from central bulk storage sites to hose outlets in the walls of anaesthetic rooms, theatres and wards. The responsibility for this section of the PMGV is principally that of the hospital pharmacy, supplies and engineering departments. Anaesthetists have responsibility for the section of pipeline between the terminal outlet and the anaesthetic machine. The bulk store for medical gases is usually a series of cylinder manifolds (Figure 1). In the case of oxygen, the cylinder manifold is often used as a reserve because most hospitals store oxygen in a vacuum-insulated evaporator (VIE) (Figure 2). The cylinder manifold is divided into a primary unit, which is in use, and a secondary unit in reserve. As the pressure in the primary unit falls, the supply is automatically switched to the secondary unit and an alarm sounds to alert the staff to replace the empty cylinders. When there is actual or impending supply failure the alarm usually sounds in the switchboard area of the hospital.

The pipes are constructed of high-grade copper alloy to prevent degradation of gases and are de-greased to reduce the risk of combustion or explosion. They are labelled at regular intervals along their length and are separated from other pipelines within the hospital to avoid confusion. Within the network of pipes there are valves to control the supply to individual theatres or a complete department, in the event of fire or pipeline damage. These are lever-operated, non-lubricated valves housed in clearly accessible units usually behind a breakable glass cover (Figure 3).

The pressure within the pipelines is regulated at about 400 kPa.

1 Cylinder manifolds.



2 Vacuum-insulated evaporator.

3 Pipeline lever safety valve.

Terminal outlet connection

Outlet points (Figure 4) for each of the piped medical gases have specifically labelled, shaped, colour-coded and non-interchangeable Schrader sockets to prevent connection of the incorrect gas supply to the flexible hoses supplying the anaesthetic machine. These must comply with the British Standard codes (BS5682) and be labelled as such. Each terminal outlet is a self-sealing valve unit of specific size to receive the corresponding collar-indexed probe of the flexible hose.

To ensure correct connection and function of the outlet valve, the probe is firmly inserted and a sharp tug applied to ensure full engagement and opening of the valve. This simple procedure is known as the 'tug test'.

4 Terminal gas outlets.

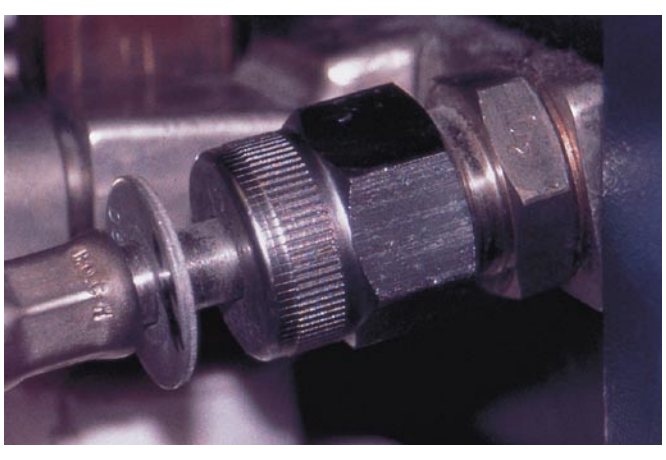
Flexible pipeline

A flexible pipeline carries medical gases from the terminal outlet to the anaesthetic machine. The terminal outlet probe (Schrader probe; Figure 5) is fitted with an indexing collar of a specific diameter for each gas, which will fit only the corresponding gas socket on the terminal outlet valve. In addition, each collar has a notch that fits over a pin within the socket to prevent rotation of the hose once installed. The entire assembly is constructed so that rapid probe insertion or withdrawal can be performed single-handedly and that once withdrawn the terminal outlet unit is self-sealing.

The flexible hose is made of a high-quality copper alloy with antistatic and bacteriostatic properties. It is colour coded and labelled in accordance with the gas it carries.

The hoses are connected to the anaesthetic machine by a non-interchangeable screw thread unit. This unit consists of a probe unique to each gas and a nut to screw the assembly on to the machine. A stainless-steel ferrule is crimped over the whole unit to seal the connection and prevent its removal (Figure 6).

5 Schrader probe.



6 Non-interchangeable screw thread.

Safety

Pipelines and flexible hoses: guidance for manufacturers, installers and maintenance engineers is in accordance with BS5682 (1987) and Health Technical Memorandum 2022 (1994). Pipelines for each of the medical gases are manufactured in different locations within the factory to prevent accidentally mixing up their unique features, for example, connection of the wrong terminal probe, non-interchangeable screw thread fitting or incorrect colour coding.

Pipelines and flexible hoses are steam cleaned, dried and sealed at both ends after internal inspection before being transported to their installation site. This is to prevent contamination and particulate matter from entering the gas supply. In the event of damage to, or technical failure of any part of the pipeline, it must be returned directly to the manufacturer for repair or replacement.

The pharmacy, supplies and engineering departments within each hospital are responsible for the pipeline supply. This includes testing of gases for purity and identity after installation of new pipelines.

The anaesthetist is responsible for ensuring that the flexible hoses are correctly engaged and that the corresponding gas passes into the anaesthetic machine. Correct engagement is checked by using the 'tug test' and the identity of the gas by using the 'single-hose test'. This is done by attaching the oxygen pipeline to the anaesthetic machine, turning on all the flowmeters and ensuring that gas flows only through the oxygen flowmeter and that it is detected by an oxygen analyser fitted at the common gas outlet.

Cylinder gas supply: cylinders and their use in conjunction with the anaesthetic machine are covered elsewhere in *Anaesthesia and intensive care medicine*.

Medical gas pressure

Working pressures within cylinder and piped medical gas supplies are outlined in Figure 7.

Pressure monitoring and display of both pipeline and cylinder gases is performed by Bourdon gauges. The Bourdon gauge is an aneroid (i.e. without liquid) gauge consisting of a coiled tube, attached at one end to the gas supply and at the other end to a pointer. The pressure of the gas causes straightening of the coil and thus causes movement of the pointer over the colour-coded, labelled and calibrated dial. The gauge is faced with heavy glass and designed such that leaks vent from the back of the valve casing and do not blow out the glass.

Cylinder and pipeline colour coding and pressures

	Body colour	Shoulder colour	Pressure (kPa) at 15°C
Cylinder			
• Oxygen	Black	White	13700
• Nitrous oxide	Blue	Blue	4400
• Carbon dioxide	Grey	Grey	5000
• Air	Grey	White/black	13700
Pipeline			
• Oxygen	White		400
• Nitrous oxide	Blue		400
• Air (clinical use)	Black		400
• Air (power tool use)	Black		700

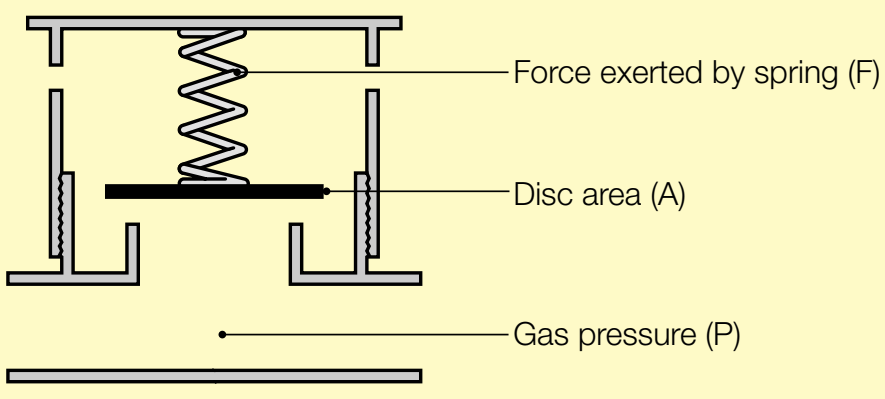
7

Pressure regulators: throughout the medical gas supply network the pressure within the system is closely regulated. This is vital for the protection of both equipment and patient. Measures to maintain a near-constant pressure are found in many sites and usually take the form of a pressure relief valve or a pressure regulator (see *Anaesthesia and Intensive Care Medicine* **1:2:** 66). Both devices are also present within the anaesthetic machine.

Pressure relief valves are designed to allow escape of gas above a certain set pressure. In the case of the VIE this protects the oxygen storage equipment from damage from pressure above 1690 kPa. Similar valves are positioned downstream of pressure regulators within the pipeline supply in case of regulator failure. These are set slightly above 400 kPa.

The principle on which the valve works relates to an equilibrium between two opposing forces: that exerted by the spring and that generated by the gas itself (Figure 8).

Pressure relief valve



$F = P \times A$

As the disc area is constant, and the force exerted by the spring to close the valve is pre-set, once the gas pressure within the system exceeds this closing force, the valve opens and gas escapes

Adapted from: Aitkenhead A R, Smith G, eds. *Textbook of Anaesthesia.* 3rd ed. London: Churchill Livingstone, 1998. By courtesy of the publisher.

8

Medical gases

Oxygen

Manufacture: industrial manufacture is by the fractional distillation of liquid air. This involves the removal of carbon dioxide and then the separation of oxygen and nitrogen by means of their different boiling points.

Oxygen may also be produced by oxygen concentrators, which extract oxygen from air. This process involves the passing of air through a sieve of zeolite (aluminium silicate), which absorbs the nitrogen, leaving oxygen and a trace of argon. The equipment for this process used to be bulky, but recently smaller units suitable for home use have been developed. A maximum concentration of 95% pure oxygen can be produced using these devices.

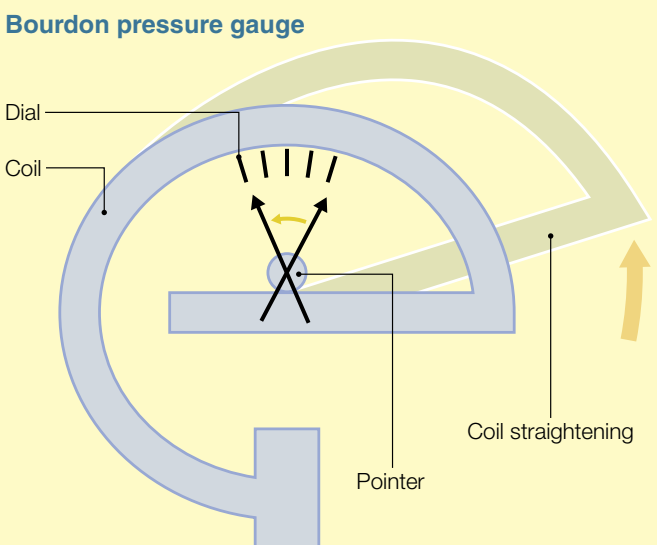
Storage: oxygen is stored either as a gas in cylinders or as a liquid in a VIE. In the UK, cylinders used for oxygen storage are black with a white shoulder (Figure 9); in the USA they are green. The oxygen is stored at a pressure of 13700 kPa at 15°C. Where piped medical gases are used, oxygen is also stored in cylinder manifolds. In cylinders, oxygen is a gas and the volume of oxygen remaining in the cylinder is directly related to the measured pressure, according to Boyle's law.

9 Cylinders. From left: oxygen, nitrous oxide, air, carbon dioxide.

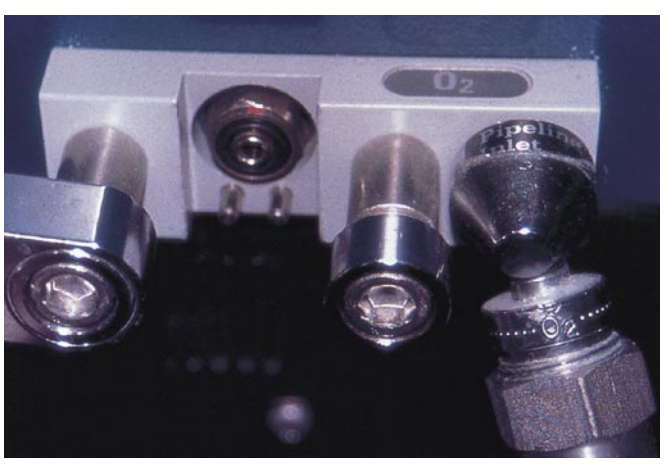
The VIE (Figure 10) is a thermally insulated device similar to a large vacuum flask. Oxygen is stored within this vessel at about –160°C and at a pressure of 5–10 atmospheres (500–1000 kPa). The low temperature is maintained by the vacuum surrounding the main chamber and by heat energy being lost from the liquid oxygen as it evaporates (latent heat of vaporization). Under normal working conditions, oxygen evaporates and passes through the pressure regulator to reduce its pressure to 400 kPa, and then enters the pipeline supply. If demand for oxygen is low, the internal pressure gradually rises until a safety valve opens at 1690 kPa to release gas to the atmosphere. When demand for oxygen is great, the control valve opens allowing liquid oxygen to pass through the pressure-raising superheater and vaporizer, evaporate and enter the pipeline supply. The superheater is a coil of uninsulated copper pipe.

The VIE (Figure 2) can be found outside all hospitals that use piped gases and may be supported by a tripod structure. Two of these legs support the weight of the evaporator, while the third is a weighing device to allow the mass of liquid contained to be measured. Modern designs stand on four legs and the contents are calculated by measuring the pressure difference between the top and bottom of the vessel.

Bourdon pressure gauge



10



11 Cylinder yoke.

Delivery: oxygen is delivered from a central supply (i.e. a manifold or VIE) or directly from cylinders. Central oxygen supply is via the pipeline system described above. Direct cylinder supply of oxygen to the anaesthetic machine involves the connection of the cylinder valve to the cylinder yoke (Figure 11) on the back of the machine.

Carbon dioxide

Manufacture: carbon dioxide is manufactured by heating calcium or magnesium carbonate in the presence of their oxides. Other sources are as a by-product of the manufacture of hydrogen, fermentation of beer or the combustion of fuel.

Storage: in the UK, carbon dioxide is stored in grey cylinders (Figure 9) at a pressure of 5000 kPa at 15°C, as a liquid in equilibrium with its vapour.

Distribution: unlike the other medical gases, carbon dioxide is not distributed via a central pipeline. The attachment of carbon dioxide cylinders to anaesthetic machines has declined in recent years to minimize the risk of accidental administration during anaesthesia. The present guidelines issued by the Association of Anaesthetists of Great Britain and Ireland state that carbon dioxide cylinders should not be routinely fitted to the anaesthetic machine.

Air

Manufacture: air for medical use is compressed, cleaned and filtered before use.

Storage: compressed air for anaesthetic use is stored in grey cylinders with black and white shoulders (Figure 9) at a pressure of 13,700 kPa at 15°C. In the USA, the cylinders are yellow.

Distribution: pipeline air is sourced from either a manifold (Figure 1) or, more economically, from an air compressor. It is important to know that air for clinical use is regulated to a pressure of 400 kPa, whereas that for the use of surgical power tools is supplied at 700 kPa. The terminal outlet for compressed air is colour coded black and white, labelled and has a non-interchangeable connection (Figure 4).

Cylinders are attached directly to the anaesthetic machine by connection of the cylinder valves to the cylinder yoke. A larger portable cylinder may be attached via a flexible hose.

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Perioperative Fluids

E Anne Thornberry

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Any surgery under anaesthesia can upset the patient's normal fluid status through preoperative restriction of oral intake of fluids. The degree of disruption depends on the patient's medical condition, the nature of the surgery and the choice of anaesthetic. Factors to consider when planning perioperative fluid management are listed in Figure 1.

Maintenance requirements: normal values for daily fluid and electrolyte requirements are shown in Figure 2. Dextrose 4% with saline 0.18% contains 30 mmol/litre of sodium and is often used for basal fluid therapy.

Determinants of perioperative fluid requirements

- Maintenance requirements
- Preoperative deficits
- Blood loss
- Third-space losses
- Transcellular fluid losses
- Effects of anaesthetic agents and technique

1

Maintenance fluid and electrolytes

Adults
- 40 ml/kg/day

Children
- 100 ml/kg/day for first 10 kg
- 50 ml/kg/day for second 10 kg
- 25 ml/kg/day for each subsequent kg

Na^+ = 1–1.5 mmol/kg/day
K^+ = 1 mmol/kg/day

2

Preoperative deficits

Preoperative assessment of the fluid status of the patient requires an appropriate history, examination and investigations.

History and examination

The following questions should be asked.
- How long has the patient been starved?
- Do they have an intravenous infusion in progress?
- Have they any reason to expect excessive losses?
- Are they taking diuretics?
- Are they pyrexic?
- Have they been vomiting or do they have a nasogastric tube *in situ*?
- Have they got diarrhoea or had a bowel preparation?
- Could they have third-space losses or occult bleeding?
- Have they any symptoms of fluid overload?

The physical examination includes evaluation of the mucous membranes and skin turgor, and measurement of the vital signs, including orthostatic changes. Ascites, pulmonary oedema and pleural effusions should be sought. Measurement of urine output may be useful.

Investigations

A normal haematocrit value may indicate that the patient has a normal fluid status or it may reflect someone with anaemia who is also dehydrated. A raised serum urea with a normal creatinine level may indicate dehydration. Raised urinary sodium levels, specific gravity and osmolality all reflect the normal homeostatic response to water depletion and can be used to monitor progress with resuscitation. The signs and symptoms of water depletion are described in Figure 3.

Estimation of total body water deficit

Deficit of body weight	For example in a 70 kg man	Signs and symptoms
Up to 5%	3.5 litres	Thirst Dry mouth
5–10%	3.5–7 litres	Decreased skin turgor Decreased intraocular pressure Tachycardia Orthostatic hypotension Tachypnoea Oliguria Skeletal muscle weakness Drowsiness
10–15%	7–10.5 litres	Severe hypotension Tachycardia Anuria Confusion/coma

3

Signs and symptoms of uncorrected acute blood loss

Volume lost	For example in a 70 kg male	Signs and symptoms
10%	490 ml	Thirst Venoconstriction
20%	980 ml	Mild increase in heart rate Systolic blood pressure normal Slight rise in diastolic pressure Decreased urine output
30%	1470 ml	Tachycardia > 120/minute Moderate hypotension Tachypnoea Cool, clammy, pale Anxious/aggressive Oliguria
40%	1960 ml	Severe hypotension and tachycardia Tachypnoea Anuria Mental confusion
50%	2450 ml	Coma

4

Fluid losses

Blood loss: the signs and symptoms of unreplaced blood loss (Figure 4) can help to estimate acute losses if accurate measurements cannot be made. Estimates of intraoperative blood losses are derived from measuring or estimating observed losses. Prediction of postoperative losses requires knowledge of the type of surgery and expected postoperative bleeding, combined with measurement of losses in the drains, vital signs, and haemoglobin and haematocrit levels.

Third-space losses are caused by sequestration of extracellular fluid into the tissues. The composition of this fluid is the same as that of interstitial fluid and losses after major bowel resection may be as great as 8 ml/kg/hour. The extent of third-space losses depends on the severity of injury to the tissues.

Transcellular fluid losses: nasogastric aspirate can be measured but pleural effusions and ascites must be estimated. Losses from evaporation occur from the surgical site and during a laparotomy these can be as much as 10 ml/kg/hour.

Effects of anaesthetic agents and techniques

Ventilation with dry anaesthetic gases increases the pulmonary losses from evaporation. General and regional anaesthesia tend to decrease the patient's blood pressure by a reduction in sympathetic tone, vasodilatation or myocardial depression. Vasopressors and intravenous fluids are used to minimize these effects, complicating the assessment of perioperative fluid status. Central venous pressure monitoring can be invaluable in helping to manage more complex cases.

Choosing perioperative fluids

Crystalloids

Dextrose solutions disperse through all the body fluid com-partments and are required to replace combined intracellular plus extracellular water depletion. Once any deficit has been replaced, dextrose is used only perioperatively as part of the basal water requirements or in a diabetic regimen.

Physiological saline disperses throughout the extracellular fluid compartments and is commonly used perioperatively to replace blood loss, transcellular losses, evaporation and third-space losses. Only one-third remains in the intravascular compartment and therefore three times the volume of the blood loss must be given if saline is used as a replacement. When large volumes of saline are administered there is a risk of developing hyperchloraemic acidosis.

Ringer's lactate (Hartmann's solution) behaves as normal saline in distribution. It is often used as the first-choice replacement fluid because the electrolyte content more accurately mimics the extracellular fluid. Its constitution varies between laboratories but in general it contains 137 mmol/litre sodium, 4 mmol/litre potassium, 3 mmol/litre calcium and 142 mmol/litre chloride. There are fewer risks of electrolyte disturbances if large volumes are administered but it is hypotonic and large volumes reduce plasma osmolality.

Colloids

The contents of the commonly used colloids are listed in Figure 5.

Properties of commonly used colloids

	Average molecular weight	Sodium (mmol/litre)	Potassium (mmol/litre)	Chloride (mmol/litre)	Calcium (mmol/litre)
Haemaccel	35,000	145	5.1	145	6.2
Gelofusine	35,000	154	0.4	154	0.4
Hetastarch	450,000	154	0	154	0
Dextran 70 in saline	70,000	150	0	150	0
Albumin 4.5%	70,000	150	2	120	0

5

Colloids used for intravenous therapy have an increased osmolality with respect to plasma and can increase plasma volume by more than the volume infused by attracting water from the interstitial fluid compartment. Consequently they are used predominantly to replace intravascular losses and are unsuitable for the treatment of dehydration. The length of time a colloid stays in the intravascular compartment depends on the shape, size and charge of the molecules suspended and the porosity of the capillary endothelium.

Gelatins are colloid solutions derived from animal gelatin. They have an average molecular weight of 35,000 but there is a wide variation in molecule size. The two commonly used gelatins are *Haemaccel*, which is urea linked, and *Gelofusine*, which is a succinylated gelatin. Their intravascular persistence is low, about 2–3 hours with *Gelofusine* and less for *Haemaccel*. Gelatins are the colloids most likely to induce an anaphylactoid reaction. Cross-matching is unaffected by the use of gelatins. *In vitro* studies suggest they interfere with clotting and platelet aggregation but in clinical practice little effect is seen.

Hydroxyethyl starches (HES) are modified natural polymers of amylopectin, which are metabolized by amylase. They are divided into high, medium and low molecular weight starches according to the range of molecular weights in the solution. *Hetastarch* is a 6% solution with an average molecular weight of 450,000 and a mean molecular weight of 70,000. The intravascular persistence of *Hetastarch* is over 24 hours. Some enters the interstitial space and is taken up by the reticulo-endothelial system where it can persist for years. Hexastarch and pentastarch are lower metabolic weight starch solutions. High molecular weight HES solutions can cause a coagulopathy by reducing factor VIII and von Willibrand factor. The lower the average molecular weight of the solution the less effect it has on coagulation. The maximum recommended dose is 33 ml/kg/day, though this has often been exceeded without any adverse effects. Anaphylactic reactions have been reported, but the incidence is low.

Dextrans are branched polysaccharides produced by the action of bacteria on a sucrose medium. Dextran solutions are divided by their average molecular weight into 10% Dextran 40 (molecular weight 40,000) and 6% Dextran 70 (molecular weight 70,000). Dextran reduces blood viscosity, reduces platelet adhesiveness and increases fibrinolysis. Doses higher than 1.5 g/kg can increase bleeding. Only Dextran 70 is used for short-term plasma expansion. Severe anaphylaxis is uncommon but has been reported.

Albumin has a molecular weight of 69,000 and is a naturally occurring plasma protein that contributes significantly to the maintenance of plasma oncotic pressure. It has been used as a colloid to treat critically ill patients with hypoalbuminaemia but there is no evidence that this improves outcome. Recent research has suggested it may worsen outcome but this is not proven. The increasing cost of production of albumin has significantly reduced its use in clinical practice.

Crystalloid–colloid controversy
It has been argued that colloids are more appropriate than crystalloids for the replacement of intravascular losses because they stay in the intravascular compartment longer, necessitating a smaller volume of replacement and a more rapid result. As stated above, the intravascular persistence varies significantly between the different colloids, while this argument holds for hydroxyethyl starches it is not so strong for the gelatins.

Opponents of colloids emphasize the incidence of ana-phylaxis with colloids, which does not exist with crystalloids. The pragmatists suggest that the normal physiological response to an acute intravascular deficit is to draw water in from the interstitial fluid compartment and therefore it makes sense to initiate resuscitation with a crystalloid and then to continue with a colloid if the loss becomes significant.

Blood and blood products
Red cell transfusions: the indication for a red cell transfusion is to increase the oxygen-carrying capacity of the blood by raising the haemoglobin concentration of patients with acute or chronic anaemia. The extent to which it should be raised depends on the balance between oxygen consumption and supply, with the aim of avoiding tissue hypoxia. Factors that affect perioperative oxygen consumption are body temperature, sympathetic activity, metabolic activity, heart rate and drug therapy.

New safety requirements are making blood products more complex and expensive to produce. Recent research suggests the traditional trigger of a haemoglobin concentration of 10 g/dl for perioperative transfusion is too high. The rate of blood loss also needs to be taken into consideration when deciding to transfuse. Suggested British Society for Haematology guidelines are summarized in Figures 6 and 7.

Need to transfuse based on an estimate of lost circulating volume

Volume lost	Indication for transfusion
15%	Only if superimposed on existing anaemia or Patient unable to compensate because of severe cardiac or respiratory disease
15–30%	As above or In the presence of continuing blood loss
30–40%	Transfusion should be considered
> 40%	Transfuse

6

Need to transfuse based on consideration of haemoglobin concentration

Haemoglobin concentration	Indication for transfusion
< 7 g/dl	Transfuse
7–10 g/dl	Transfuse patients who would tolerate anaemia poorly (e.g. those with cardiac or respiratory disease, those over 65 years of age)
> 10 g/dl	No indication

7

Concerns about the safety of transfusion have encouraged the development of alternative strategies to minimize the need for homologous transfusions. These include the use of autologous pre-donation of blood, acute normovolaemic haemodilution, intraoperative cell salvage, preoperative administration of erythropoietin and the development of blood substitutes.

Fresh frozen plasma is valuable because it contains all the clotting factors. It is used to correct a coagulopathy due to a concurrent illness, the use of anticoagulants or a dilutional coagulopathy. A coagulation screen should be requested to establish the need for fresh frozen plasma, although in the presence of a massive haemorrhage, fresh frozen plasma may be given before laboratory results are available if there are clinical signs of impaired coagulation.

Platelets should be given only if there is clinical and laboratory evidence of abnormal coagulation.

Blood substitutes
There are three different areas of research in progress: free haemoglobin solutions, encapsulated haemoglobin cells, and perfluorocarbon emulsions.

Haemoglobin-based oxygen carriers: free haemoglobin has been used as a red blood cell substitute for decades but initially there were many adverse effects including hypertension, bradycardia, renal dysfunction and a short intravascular retention time. A problem was the lack of 2,3-diphosphoglycerate (2,3-DPG) and the higher pH of plasma compared with that inside the red blood cell. There is also an increase in oncotic activity which limits the concentration of free haemoglobin that can be used to about 5–7 g/dl.

Some of the adverse effects of free haemoglobin have been reduced by a variety of modifications including polymerization and conjugation to increase the intravascular retention time and the introduction of haemoglobin into cell-like structures, using stable, porous membranes that allow molecules such as glucose to enter. Some products have reached the stage of clinical trials.

Perfluorocarbon emulsions: perfluorocarbons are synthetic carbon–fluorine compounds. They dissolve gases including oxygen and carbon dioxide. They are not metabolized *in vivo* and most are excreted unchanged via the lungs. A small amount is taken up by the reticulo-endothelial system and excreted later. They are immiscible in water and have to be emulsified. Initial emulsifiers caused numerous adverse effects. Second-generation perfluorocarbons have reduced the complications, but high doses can still interfere with coagulation, elevate liver enzymes and produce a febrile response. They are in phase III trials as a blood substitute. ◆

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Positioning the Surgical Patient

Jonathan Warwick

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The correct positioning of a patient for surgery is a balance between optimizing surgical exposure and minimizing complications for the patient. The surgeon may request a particular position and it is often the role of the anaesthetist to ensure that this is accomplished safely. The anaesthetist must consider the limits of position that may be tolerated and ensure access to the airway, monitoring and vascular devices as far as possible. In general, complications may arise from physiological consequences of the position and the effects of direct pressure on soft tissue structures.

Supine position

Indications: the supine position is the standard for most surgical procedures. The orthopaedic fracture table is a modification that enables traction to be maintained on a lower limb and provides access for an image intensifier.

Physiological consequences: when an individual is upright, ventilation per unit lung volume is greater in the lower part of the lung, because here the weight of the lung makes the intrapleural pressure–volume curve steeper (see Figure 2). The apex of the lung is on a flatter part of this curve, representing a relatively larger change in pressure for a given change in lung volume, and hence a lower compliance. The lower part of the lung is better perfused as a result of gravity.

When an individual is supine, ventilation and perfusion become more uniform and the effects of gravity less marked. The differences between base and apex are then replaced by differences between dependent and non-dependent parts of the lung. Stroke volume and cardiac output may increase as a result of the increase in central venous pressure. Baroreceptors sense an increase in arterial pressure, leading to a fall in heart rate and systemic vascular resistance.

The physiological effects of a change of posture when anaesthetized depend on additional factors:

- pharmacological effects
- circulating blood volume
- method of ventilation.

The functional residual capacity (FRC) decreases by about 20% following induction, though closing capacity remains unchanged. Anaesthetized patients are vasodilated and have diminished compensatory cardiovascular reflexes. Therefore, all positioning movements must be made slowly. The basic supine position is generally well tolerated and has no additional physiological effects in healthy patients.

Pregnant patients may suffer from the supine hypotensive syndrome, where the weight of the gravid uterus reduces venous return by compression of the inferior vena cava (IVC). This can be avoided by a lateral tilt of the operating table, usually to the left side.

Direct pressure complications: the eyes should be taped closed to prevent corneal drying or injury from scratching. Limbs must be fully supported and moved with care to prevent joint dislocation or even fracture. The arms can be secured in the drawsheet, or by the use of padded arm supports.

Skin overlying all bony points is prone to pressure damage, especially the occiput, elbows, knees, greater trochanter of the femur and sacrum. As little as 2 hours of unrelieved pressure may result in a pressure sore; the duration of pressure is considered to be more important than its intensity. The ankles should be placed in soft foam-rubber boots to avoid pressure necrosis of the heel skin.

Injury to peripheral nerves (Figure 1) is often a consequence of the way in which the patient is positioned during surgery. Nerve injury is most likely to occur with the combination of muscle relaxation, an extreme position and prolonged surgery. Peripheral nerves are damaged by local ischaemia caused by compression or stretching. This produces segmental demyelination. Complete clinical recovery usually occurs within 6–8 weeks, but may take several months. Severe damage may be associated with permanent injury. Electromyography studies may aid the prognosis.

Supine position – nerve injuries

Nerve injury	Comments
• Supraorbital	Compression by catheter mount, trachael tube connectors
• Nerves to the eye	Compression from face mask
• Facial (VIIth)	Compression by anaesthetist's fingers against ramus of mandible, face mask harness
• Brachial plexus	Stretching injury, especially when arm is abducted > 90°, externally rotated, elbow extended and forearm supinated
• Ulnar	Most common nerve injury occurring during anaesthesia. Compression between the medial epicondyle of the humerus and the edge of the operating table. Pronation of the forearm may place the nerve more at risk than supination
• Radial	Compression between the edge of the operating table or armboard and the shaft of the humerus, compression from a head-screen support
• Pudendal	Compression from the post of an orthopaedic fracture table may cause pudendal nerve injury or genital trauma
• Sciatic	Direct compression in thin patients undergoing prolonged surgery on a hard table

1

Lateral ('lateral decubitus') position

Indications:

- thoracic surgery
- lateral approach to the kidney
- surgery to the hip.

Reference to the right or left lateral position indicates the side on which the patient is lying.

Physiological consequences: when lying awake in the lateral position, ventilation to the upper and lower lungs behaves in a similar fashion to the ventilation of lung apex and base when upright. The lower lung lies on the steeper, more compliant part of the intrapleural pressure–volume curve (see Figure 2, page 12). The weight of the abdominal contents pushes the lower lung diaphragm higher than the diaphragm of the upper lung, so that it is also able to generate a higher force of contraction. The lower lung is therefore better ventilated than the upper lung. Perfusion of the lower lung is also greater as a result of gravity.

Following anaesthesia, the distribution of blood flow remains unchanged but there are significant changes to the distribution of ventilation. Muscle tone is greatly reduced or absent and the FRC of each lung falls, especially in the lower lung as a result of the weight of the mediastinum pushing down from above and the weight of the abdominal contents below. This has the effect of moving the upper lung down to a more favourable (i.e. steeper and more compliant) part of the intrapleural pressure–volume curve. The lower lung moves down to a flatter, less compliant part of the curve. Therefore the upper lung becomes the better ventilated, but because it receives less of the pulmonary blood flow, ventilation–perfusion mismatch increases.

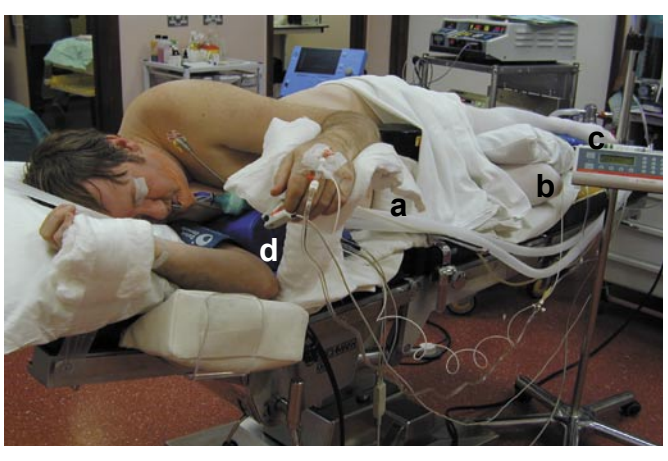
To expose the flank during the lateral approach to the kidney, the lateral flexed position over a support ('kidney position') may be necessary. Significant hypotension may result when the patient is positioned on the right side for a left kidney operation. Reduced venous return occurs as a result of partial obstruction of the IVC from the support. Hepatic encroachment on the IVC may also contribute. This problem is less common when the patient is in the left lateral position.

Direct pressure complications: the pelvis and shoulders must be well supported to prevent the patient from rolling backwards off the table, or forwards into the recovery position. The lower leg should be flexed and the upper leg extended, with a pillow between the two (Figure 2).

An axillary roll places the weight of the chest on to the ribcage and prevents direct compression injury to the shoulder and axilla, thus avoiding deltoid muscle ischaemia or neurovascular damage to the lower arm.

The lower leg is at risk from pressure damage, especially in obese patients. Compartment syndrome, myoglobinuria and acute renal failure have been reported.

Nerve injuries that may result from the lateral position are listed in Figure 3.



2 The lateral position.
a Padded supports to prevent patient rolling over – anteriorly next to iliac crests; posteriorly next to lumbar spine.
b Lower leg flexed and pillow between knees.
c Heel supported.
d An axillary roll places the weight of the chest on to the ribcage.

Lateral position – nerve injuries

Nerve injury	Comments
• Cervical spine	Lateral flexion may stretch cervical spinal nerves and make arthritic joint pain worse. May cause Horner's syndrome
• Brachial plexus	Stretching injury when the neck is extended and in lateral flexion. May occur when the arm is suspended from a bar or gutter and is inadequately supported
• Common peroneal	Compression between the operating table and the head of the fibula

3

Trendelenburg ('head-down') position

Indications:

- pelvic surgery
- insertion of central venous lines.

Friedrich Trendelenburg first described the 45° supine head-down position in 1890. This position facilitates access to the pelvis. Most head-down positions are now about 20° or less with acceptable results. The steep head-down position is now avoided because it is unnecessary and has too many disadvantages. A corrugated or non-slip mattress helps prevent patient movement.

Physiological consequences: there is a greater reduction in FRC than in the basic supine position as a result of pressure of the abdominal contents on the diaphragm. Usually ventilation is little impaired, especially in fit patients and for short periods. For longer operations and in obese patients, there is increased work of breathing against the weight of the abdominal contents, therefore controlled ventilation is preferable.

Central venous pressure rises, and cardiac output may increase. This may precipitate acute heart failure in patients with poor cardiac reserve. The position is not generally effective in improving the circulation during shock and can increase venous pooling in the upper half of the body. A prolonged head-down position will cause venous congestion and oedema in the head and neck.

Barrier pressure is the difference in intraluminal pressures either side of the gastro-oesophageal junction. The pressure within the oesophagus is normally 15–25 mm Hg higher than gastric pressure and gastro-oesophageal reflux is prevented. Barrier pressure is maintained by the action of the smooth muscle cells of the lower oesophageal sphincter and the skeletal muscle of the surrounding crural diaphragm. The head-down position may raise intragastric pressure, reduce barrier pressure and encourage reflux to occur.

There is an increase in intracranial and intraocular pressure. While inserting central venous lines in patients with head injury, care should be taken to limit the head-down tilt to the minimum necessary so as not to worsen cerebral perfusion pressure.

Direct pressure complications: injury to the brachial plexus was common when the steep 45° head-down position was used and patient movement was prevented by shoulder supports or wrist straps. Patient movement is prevented by the non-slip mattress when lesser degrees of head-down tilt are used (e.g. 20°). Brachial plexus injury is now uncommon.

Reverse Trendelenburg ('head-up') position

Indications:
- operations on the head and neck; this position reduces venous pressure and helps reduce bleeding
- surgical access to the gall bladder and proximal gastrointestinal tract, especially during laparoscopic surgery
- operations on the shoulder joint.

Usually, 15–20° head-up tilt is sufficient.

Physiological consequences: there is a small decrease in arterial pressure; but less of a decrease in FRC than in the basic supine position because less pressure is exerted on the diaphragm by the abdominal contents. There is a reduction in intraocular and intracranial pressure, mainly as a result of improved venous drainage.

Any open vein or sinus above the level of the right atrium can cause venous air embolism.

Direct pressure complications: injury to the brachial plexus may be caused by excessive rotation and lateral flexion of the neck away from the operative site.

Lithotomy position

Indications:
- urological procedures
- operations on the perineum, anus and rectum.

The patient is positioned in the supine position, with both hips and knees flexed and the thighs abducted. The ankles and feet may be supported by lithotomy poles using stirrups or calf supports, or by strapping into padded boots. The position is usually combined with some head-down tilt to aid surgical access.

Physiological consequences: the lithotomy position is generally well tolerated. There is a reduction in vital capacity and FRC as a result of diaphragmatic splinting from upward displacement of abdominal contents. This may cause difficulty with spontaneous ventilation in obese patients and controlled ventilation may be preferable. Care should be taken when the legs are lowered because this may reveal previously unrecognized hypovolaemia and cause sudden hypotension.

Direct pressure complications: backache is common and may be reduced by providing a support to maintain the normal lumbar lordosis. The sacrum must be supported and should not hang free over the end of the table. Marked flexion of the hips and knees may cause sacroiliac strain, and the legs must be moved together to avoid pelvic asymmetry. Slippage of the lithotomy poles once the legs are positioned can cause hip dislocation. Moving the thighs too far apart may strain the adductor muscles.

Compartment syndrome in the lower leg may be initiated by pressure of the calf muscles on the stirrup pole. 'Breaking' or raising the lower end of the table when the fingers have been inadvertently trapped in the gap has caused crush injury.

Anaesthesia should not be induced with the legs elevated because raised intra-abdominal pressure may predispose to regurgitation, and turning the patient will be difficult.

Nerve injuries that may occur with the lithotomy position are shown in Figure 4.

Lithotomy position – nerve injuries

Nerve injury	Comments
• Sciatic	Stretching as a result of maximum external rotation of the flexed thigh
• Common peroneal	Compression between lithotomy pole and the head of the fibula
• Tibial	Compression if the legs are supported by stirrups behind the knees
• Femoral	Compression beneath the inguinal ligament when the thighs are fully flexed on the abdomen
• Obturator	Compression at the obturator foramen when the thighs are fully flexed on the abdomen
• Saphenous	Compression between the medial condyle of the tibia and lithotomy post or stirrup

Prone position

Indications:
- operations on the spine and posterior cranial fossa
- operations on the buttocks and natal cleft
- percutaneous extraction of renal calculi.

Physiological consequences: there is often an improvement in gas exchange in the prone position. This may be as a result of the greater inspiratory pressures required to maintain the tidal volume, which decreases atelectasis, increases FRC and improves oxygenation. Pulmonary barotrauma caused by excessive inspiratory pressures should be avoided by correct positioning of the pelvis and upper chest.

The pelvis and the upper chest must be supported so that the abdomen is not compressed and the diaphragm can descend freely during respiration. This may be particularly difficult to achieve in obese patients. Patients may be positioned by using pillows, supporting the iliac crests with cushioned props, or by the use of a specialized hollowed mattress. Controlled ventilation is preferable in most patients.

There are no significant cardiovascular changes. Pulmonary blood flow is essentially unchanged from the supine position. Poor positioning and high inspiratory pressures may decrease venous return. Patients with previous coronary artery bypass grafting may be at risk from graft occlusion.

Direct pressure complications: turning the supine patient prone requires a team of four people. Great care must be taken with the head and neck to avoid twisting or hyperextension injury to the cervical spine. The face should rest on a cushioned horseshoe with the weight of the head evenly distributed. The eyes are naturally protected within their bony sockets, but exophthalmos or a flattened nasal bridge may allow transmission of pressure to the globe. Prolonged compression may result in central retinal vein thrombosis and blindness.

The tracheal tube must be securely fixed and its position checked after the turn. Some experienced anaesthetists may use the laryngeal mask for airway maintenance in prone patients, though the use of a reinforced tracheal tube is likely to be safer for the trainee. Excessive pressure on the breasts may cause ischaemic damage to the nipples, interstitial bleeding or rupture of breast implants. In men, the penis or scrotum may become trapped and compressed.

Possible nerve injuries are shown in Figure 5.

Prone position – nerve injuries

Nerve injury	Comments
• Cervical spinal cord	Stretching injury caused by overextensio plane
• Nerves to the eye	Compression from face support
• Facial (VIIth)	Compression from face support
• Brachial plexus	Stretching injury caused by extreme abduction of the arms. Limit abduction to 90°
• Ulnar	Compression between the medial epicondyle of the humerus and the mattress
• Lateral cutaneous nerve	Compression between iliac crest of the thigh and the positioning prop. If used, props should be angulated and positioned so that the patient is unable to slip sideways
• Anterior tibial	Stretching injury caused by forced plantar flexion of the foot

The sitting position

Indications:
- operations on the posterior cranial fossa and cervical spine
- dental chair anaesthesia.

The sitting position enables the surgeon to gain clear access, with optimal venous drainage, low arterial pressure and reduced bleeding. CSF drainage is good and brain swelling is minimized.

Dental chair anaesthesia in the sitting position is now uncommon.

Physiological consequences: the patient is anaesthetized in the standard supine position and the neurosurgical pins and head frame are applied. On the operating table, the patient is progressively sat upright with the neck flexed; the knees are slightly flexed and the legs are lowered. The arms rest in the lap on a pillow, with the elbows flexed.

A small fall in systolic blood pressure of 20 mm Hg usually occurs; this can be offset by prior volume loading with 500 ml of colloid solution. Occasionally, persistent instability of blood pressure can occur that may cause the position to be abandoned despite the use of vasopressors. Controlled ventilation is the method of choice, to enable control of Pa_{CO_2} and intracranial pressure. It maintains a higher mean intrathoracic pressure and reduces the likelihood of air embolus.

Air embolus is the major complication. All patients must be considered to be at risk throughout the procedure. For this reason, many neurosurgeons seldom use this position. It is still used when insufficient access is provided by the alternative prone or semi-prone positions.

Dysrhythmias, especially bradycardia, and blood pressure instability may occur following surgical manipulation in the region of the brain stem. This is a result of direct pressure effects on the autonomic control centres of the medulla.

Direct pressure complications: nerve injuries that may result from the sitting position are shown in Figure 6.

The sitting position – nerve injuries

Nerve injury	Comments
• Cervical spinal cord	Stretching injury and spinal cord ischaemia following excessive neck flexion. A two-finger breadth gap between chin and chest is recommended
• Brachial plexus	Stretching injury if the arms are unsupported
• Ulnar	Compression between the medial epicondyle of the humerus and the arm supports
• Sciatic	Stretching injury if thighs are flexed and knees extended. Maintain adequate knee flexion

Premedication

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Premedication involves the prescription of drugs before the induction of anaesthesia in order to alleviate the apprehension associated with surgery, to counteract the side-effects of anaesthetic agents or to reduce the risks of pre-existing pathology (Figure 1). When choosing a premedicant drug the anaesthetist must consider which of its properties are appropriate for the individual patient, the possible side-effects and its potential effect on the proposed anaesthetic technique. The ideal premedicant is:

- painless to administer
- highly reliable and specific
- of rapid onset and rapidly cleared
- free of side-effects and interactions with other drugs.

Premedicant drugs entered anaesthetic practice in the late 19th century. Early anaesthetic agents were delivered by open systems and induced unconsciousness slowly. Ether caused an increase in pharyngeal and bronchial secretions, which interfered with smooth gaseous induction. Chloroform caused marked vagal stimulation of the heart leading to bradycardia. Atropine was first used in premedication in 1890. Hyoscine, which combined anticholinergic effects with antiemesis and sedation, was often combined with an opioid (e.g. papaveretum) to produce ‘twilight sleep’. Opioids were prescribed to aid the induction of anaesthesia before the development of more potent anaesthetic induction agents.

The routine use of drugs for premedication is now in decline. There are several reasons for this.

- Modern anaesthetic agents are potent and have a rapid, smooth onset.
- The increased use of day-care surgery requires rapid patient recovery.
- In-patients are often admitted on the day of surgery and the time available between preoperative assessment and induction of anaesthesia is short.
- Pressures of high patient turnover and staffing constraints can make premedication difficult to deliver in practice.

Rationale of premedication

- Reduction of anxiety and fear
- Sedation
- Amnesia
- Antiemesis
- Reduction in volume and acidity of gastric secretions
- Attenuation of autonomic reflexes
- Maintenance of cardiovascular stability
- Reduction of airway secretions
- Provision of analgesia

1

Anxiolysis, sedation and amnesia

The preoperative visit: anxiety is common in preoperative patients. As well as being unpleasant, this anxiety is part of a stress response that may worsen coexisting pathology such as hypertension or angina. A preoperative visit by the anaesthetist is the most effective way to allay the fears and anxieties of forthcoming surgery. This visit can be used to establish rapport with the patient, to discuss the proposed anaesthetic technique in terms that they can understand and to address their worries in a sympathetic manner. Older children will benefit from inclusion in preoperative discussions and it is becoming usual for parents to stay with children during induction of anaesthesia.

For some patients, the preoperative visit alone is insufficient to allay anxiety and pharmacological methods are required. The nature of the surgical procedure, coexisting pathology or the need for a rapid recovery from anaesthesia may dictate extreme caution before the prescription of sedating premedication (Figure 2). Co-administration of an opioid and a benzodiazepine has a potent respiratory depressant effect.

Relative contraindications to sedative premedication

- Airway obstruction or airway surgery
- Poor ventilatory reserve
- Sleep apnoea
- Intracranial pathology
- Severe hepatic or renal disease
- Rapid-sequence induction
- Obstetric anaesthesia
- Day-case anaesthesia (delayed discharge)
- Extremes of age

2

Benzodiazepines
Benzodiazepines are the most commonly used premedication. They are safe and have a broad therapeutic index though they can cause unpredictable psychological effects at the extremes of age. Those that are suitable premedicants can usually be given by mouth about 1 hour before induction, have a short duration of action and produce inactive metabolites (Figure 3).

Benzodiazepines are agonists of γ-aminobutyric acid (GABA) receptors within the CNS. GABA is an important inhibitory neurotransmitter, which hyperpolarizes the neuron by causing an influx of chloride ion. Benzodiazepines also produce sedation and amnesia by their action on the limbic system. Both these effects are variable and depend on the drug used and the dose given.

Temazepam is an effective anxiolytic and is available in elixir or tablet form. It has a sufficiently short duration of action to allow its use in day-case surgery. Midazolam is presented in 2 mg/ml or 5 mg/ml glass vials. Unlike the other benzodiazepines it is water soluble at acid pH but becomes highly lipophilic at physiological pH. It can be given orally or nasally, which makes it an attractive premedicant for children in doses of 0.2–0.5 mg/kg. Lorazepam, 0.05 mg/kg (max. 4 mg), produces intense anterograde amnesia within 30 minutes, often lasting over 3 hours. Amnesia may be viewed as an advantageous property of a premedicant but some patients find the sensation unpleasant.

Benzodiazepines commonly used as premedication

Drug	Usual adult dose	Half-life of parent drug (hours)	Half-life of active metabolites (hours)
• Diazepam	5–10 mg p.o.	24–48	4–10
• Temazepam	10–30 mg p.o.	4–10	None
• Lorazepam	2–4 mg p.o.	10–20	None
• Midazolam	5–10 mg i.m. 0.5 mg/kg (maximum 20 mg) p.o. in children	1–3	None

3

Other anxiolytics and sedatives
Phenothiazines are major tranquillizers that have sedative and anticholinergic actions. They are histamine antagonists (via H_1-receptors) and have antidopaminergic and α-adrenoceptor blocking properties. They may cause pallor and restlessness in the presence of pain and hypotension. Trimeprazine elixir is sedating and is used for children in doses of 1.5–2 mg/kg, up to 2 hours before surgery. It is not licensed for use in children less than 2 years of age.

Droperidol is the only commonly used butyrophenone in current anaesthetic practice. It has antiemetic and sedating properties. Antidopaminergic side-effects such as dystonic reactions and agitation limit its routine use at sedating doses (e.g. 10 mg orally for adults).

Antiemesis

Postoperative nausea and vomiting (PONV) is a common problem, which is distressing for the patient. There are several risk factors:

- gender (incidence is three times higher in women than in men)
- patients undergoing operations on the ear, squint surgery, gynaecological procedures and laparoscopy
- previous history of PONV or motion sickness
- use of morphine
- anaesthetic technique (volatile anaesthetic maintenance is more emetic than intravenous propofol maintenance).

The vomiting reflex is coordinated by the vomiting centre within the dorsolateral reticular formation of the medulla. It receives multiple afferent pathways from peripheral and central chemoreceptors, nociceptors, the vestibular system and the cerebral cortex. The synapses in these pathways are predominantly muscarinic. The vomiting centre also receives stimuli from the chemoreceptor trigger zone in the area postrema on the floor of the fourth ventricle, but outside the blood–brain barrier. This structure is rich in dopamine (D_2) and serotonin (5-HT_3) receptors. The antiemetics commonly used in anaesthetic practice involve inhibition at one or more of these receptor sites.

Muscarinic antagonists: hyoscine (adults, 300 μg; children 4–10 years, 75–150 μg orally) is a more effective antiemetic and is more sedating than atropine. Antihistamines, including cyclizine, 50 mg orally, i.v. or i.m., and promethazine, children 2–5 years, 5–15 mg, 5–10 years, 10–25 mg orally; adults, 25–50 mg orally or intramuscularly, also have antiemetic properties, largely as a result of their antimuscarinic activity. Antimuscarinics cause dry mouth, blurred vision, and bowel and bladder dysfunction.

Dopamine antagonists are powerful antiemetics but extra-pyramidal side-effects, such as dystonia, dyskinesia, tremor and oculogyric crisis are not uncommon.

Prochlorperazine, 12.5 mg i.m., is the most widely used phenothiazine because it is less sedating and has fewer antidopaminergic and α-blockade side-effects than others of the same group.

Droperidol is an effective antiemetic at low dose, 0.625–1.25 mg, reducing the risk of unpleasant dopaminergic or psychological effects. It is usually given intravenously at induction.

Metoclopramide, 0.1 mg/kg i.v., i.m. or orally, is a dopamine antagonist with peripheral as well as central effects. Its prokinetic effects are more marked than its antiemetic properties and comparative studies have raised doubt about its effectiveness as a prophylactic antiemetic.

5-HT antagonists are powerful new antiemetics that are relatively free of side-effects. The most widely used agent is ondansetron, 4 mg i.v., given immediately before or at the end of surgery. Their relative expense has resulted in the cost-effectiveness of their prophylactic use being questioned.

Non-pharmacological measures including acupunture and acupressure have been explored. There is some evidence that these techniques are weakly effective.

Reduction in volume and acidity of gastric secretions

The potential for lung damage from the aspiration of gastric contents increases with the volume and the acidity of the aspirate. Risk of aspiration accompanies late pregnancy, emergency or trauma surgery, symptomatic oesophageal reflux, and obesity.

Acid secretion by gastric parietal cells can be reduced by the use of H_2-histamine antagonists such as ranitidine, 150 mg p.o. Proton pump inhibitors such as omeprazole, 20 mg p.o., are more powerful in reducing acid secretion but inhibit the metabolism of other drugs such as warfarin, phenytoin and diazepam.

A 0.3 molar solution of sodium citrate, 30 ml, will raise gastric pH and is less irritant to the airway should aspiration occur. The routine use of the prokinetic agent metoclopramide, 10 mg, is common practice but of no proven value in the prevention of gastric aspiration.

Attenuation of autonomic reflexes

Parasympathetic stimulation can lead to hypotension, bradycardia or even asystole mediated via the vagus nerve. Triggers include:

- traction on the extraocular muscles during squint surgery
- surgical dilatation of the cervix or of the anal sphincter
- repeated doses of suxamethonium
- laryngoscopy in children (especially on lifting the epiglottis with a straight-bladed laryngoscope)
- opioid analgesics, propofol and halothane.

Glycopyrronium, 0.2 mg i.v. at induction, provides prophylaxis without the discomfort of a dry mouth before surgery. It does not penetrate the blood–brain barrier and lacks the central side-effects of atropine.

An increase in circulating catecholamines may be caused by several factors:

- laryngoscopy and tracheal intubation
- surgical stimulation and pain
- drugs such as ketamine, cocaine and adrenaline (epinephrine) in local anaesthetics.

This increase may cause hypertension and increased myocardial oxygen demand. It may result in myocardial ischaemia in susceptible patients. A balanced anaesthetic technique reduces these risks, and β-blocker premedication (atenolol, 50 mg p.o.) may be of benefit.

There has been recent interest in the use of α_2-adrenoceptor agonists such as clonidine, 3 µg/kg p.o., as premedicants. They reduce sympathetic activity, cause sedation, a reduction in anaesthetic requirement (decreased minimum alveolar concentration) and reduce pressor responses including that of laryngoscopy. However, there appears to be a narrow therapeutic window with the potential for development of hypotension and bradycardia.

Reduction in airway secretions

Antisialogogues are occasionally prescribed as premedicants though their use in modern-day practice is uncommon. Glycopyrronium, 0.2 mg i.v. or i.m., may be used to improve conditions before fibre-optic intubation.

Analgesia

Opioids (e.g. morphine, 0.1–0.2 mg/kg i.v. or i.m.) should be used to relieve acute preoperative pain. However, in the absence of any preoperative distress and with the development of new potent opioid analgesics with a rapid onset given at induction, such as fentanyl, alfentanil and remifentanil, an opioid premedicant is seldom indicated.

Non-steroidal anti-inflammatory drugs decrease the requirement for opioid analgesia during and after a surgical procedure. Typically, ibuprofen, 400 mg p.o., or diclofenac, 50–100 mg p.o., p.r. or i.v., may be given. They should be avoided in patients with a history of peptic ulceration or renal impairment and used with caution in asthmatic patients. Other simple analgesics such as paracetamol, 1 g, can also be given p.o. or p.r.

The concept of pre-emptive analgesia is that nociception can be modulated at the level of the spinal cord by analgesia given before surgery, thereby reducing total postoperative analgesic requirements. While this concept is attractive and has been demonstrated in animal models, clinical studies have yet to prove its value.

Topical anaesthetics such as eutectic mixture of local anaesthetic (*Emla* cream) or amethocaine gel applied to the site of venepuncture, reduce the fear of intravenous anaesthetic induction in children and many adults.

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Principles of Anaesthetic Vaporizers

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Gases, liquids and vapours

Substances can exist in the solid, liquid or gaseous state. Below a certain temperature, known as the critical temperature, it is possible to liquefy gases by compressing them. When a gas is below this critical temperature it is referred to as a vapour.

Vapours consist of molecules that have left the surface of a liquid below the critical temperature. Vapour molecules have had sufficient energy to break away from the attraction of the molecules left behind in the liquid and are therefore the more energetic molecules. Molecules leave the surface of the liquid and return to it randomly. When the vapour is in equilibrium with the liquid, the number of molecules leaving the liquid is equal to the number returning to it, and the vapour is said to be saturated. If there is insufficient liquid for there to be a reservoir from which molecules can evaporate and to which they can return, then the vapour is unsaturated and behaves as a gas.

The pressure of a vapour in equilibrium with a liquid is known as the saturated vapour pressure (SVP).

Variation of SVP with temperature

As the temperature of the liquid increases, more molecules have sufficient energy to escape from the surface and therefore the SVP rises. When the boiling point is reached, all the molecules evaporate and the SVP is equal to atmospheric pressure. Figure 1 shows the variation of SVP with temperature for halothane, enflurane and isoflurane. Unsaturated vapours behave as gases so that the pressure is inversely proportional to the volume (Boyle's law).

Cooling due to vaporization

If molecules that have left the surface of a liquid are not allowed to return to it (e.g. if they are swept away by a stream of fresh gas) then the liquid cools. This is because the evaporating molecules are more energetic than those left behind, therefore there is a net loss of energy from the liquid, which causes a drop in temperature. The latent heat of vaporization is the heat required to convert a unit mass of liquid into its vapour phase at a constant temperature. Cooling may be prevented or reduced if the liquid is in contact with a surface that can supply heat by conduction. The amount of heat that a body can supply at a given temperature depends on its specific heat and its mass, or, in other words, on its thermal capacity. Heat is also supplied by conduction from the surroundings and the rate at which this occurs is determined by the thermal conductivity of the body.

The specific heat of a substance is defined as the amount of heat (or energy) required to raise the temperature of a unit mass of the substance through 1 deg C. The units of specific heat are joules per kilogram per Kelvin change in temperature (J/(kg.K)).

The thermal capacity of a body is the heat required to raise its temperature through 1 deg C (this is also equivalent to the amount of energy the body loses when cooled by 1 deg C). The units of thermal capacity are joules per kilogram (J/kg). The thermal capacity of a body is equal to the product of its mass and specific heat.

The thermal conductivity of a material is the rate of heat transfer per unit area when a temperature difference of 1 deg C is maintained across an insulated block of the material 1 m thick. The units of thermal conductivity are Watts per metre per Kelvin (W/(m.K)).

Values of specific heat, density and thermal conductivity for copper, aluminium, glass and stainless steel are shown in Figure 2. It can be seen from this table that copper has the highest thermal conductivity of these materials so that vaporizers made of copper are the most efficient at conducting heat from the atmosphere to replace the energy that the liquid agent loses due to evaporation. Copper has the lowest specific heat of these substances; however, since it is much denser than aluminium or glass, the thermal capacity of a given volume of copper is higher than that of either of these materials. A given volume of stainless steel has the highest heat capacity of these materials. In practice, most vaporizers are made of stainless steel because it is readily available. However, copper is thermally more suitable because its much higher thermal conductivity more than compensates for the lower heat capacity.

Anaesthetic vaporizers

The SVP of most anaesthetic agents at room temperature is too high for them to be delivered to a patient without dilution (Figure 1). For example, the SVP of isoflurane at 20°C is 236.5 mm Hg (i.e. 31% v/v if atmospheric pressure is 760 mm Hg). In general, concentrations below 2% v/v are required for maintenance of anaesthesia. An anaesthetic vaporizer is a device that dilutes the vapour to give a known concentration of the agent.

Fresh gas enters the vaporizer and is split into two portions (Figure 3). One portion flows through an area known as the vaporizing chamber, where it comes into contact with the anaesthetic vapour; the remainder of the gas bypasses this chamber. The two flows then recombine and the vapour is diluted. By varying the flow rate in the two paths the resultant vapour concentration can be varied. The concentration of agent depends on the flow through the vaporizing chamber, the total fresh gas flow and the saturated vapour pressure of the anaesthetic agent. The way in which the gas flow is split between the bypass and vaporizing chamber depends on the relative resistance of each pathway. If the total fresh gas flow (F) is split into a bypass flow (F_b) and a vaporizing chamber flow (F_v) then:

$F_v + F_b = F$

The flow rate emerging from the vaporizing chamber (F_e) will be greater than that entering it, due to the volume of vapour added:

$F_e = F_v + F_e \times SVP/100$

where SVP is expressed as a percentage.

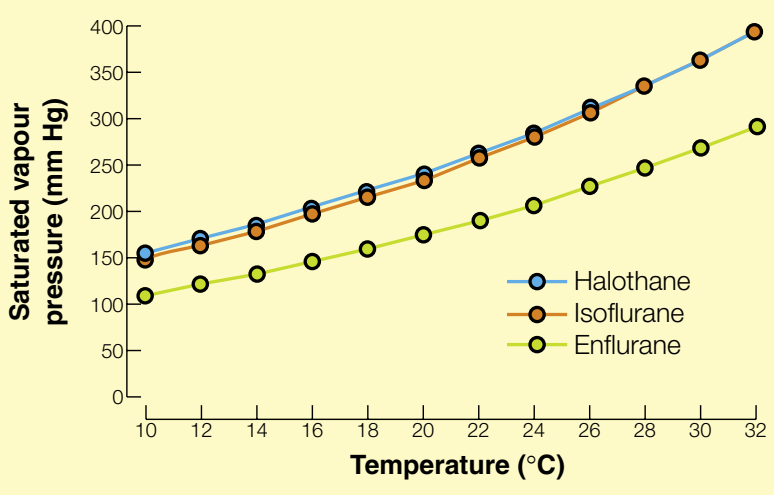
Therefore $F_e = F_v/[1-(SVP/100)]$

The concentration (C) of the vapour in the gas emerging from the vaporizer will be given by:

$C = F_e \times SVP/(F_b + F_e)$

This calculation assumes that the gas emerging from the vaporizing chamber is fully saturated with vapour. To ensure that this is the case, manufacturers increase the surface area of liquid that the gas passes over by introducing wicks made of cloth or metal into the vaporizing chamber. In many cases the gas is forced to take a long pathway through the chamber, which also helps to ensure saturation.

Variation of saturated vapour pressure with temperature



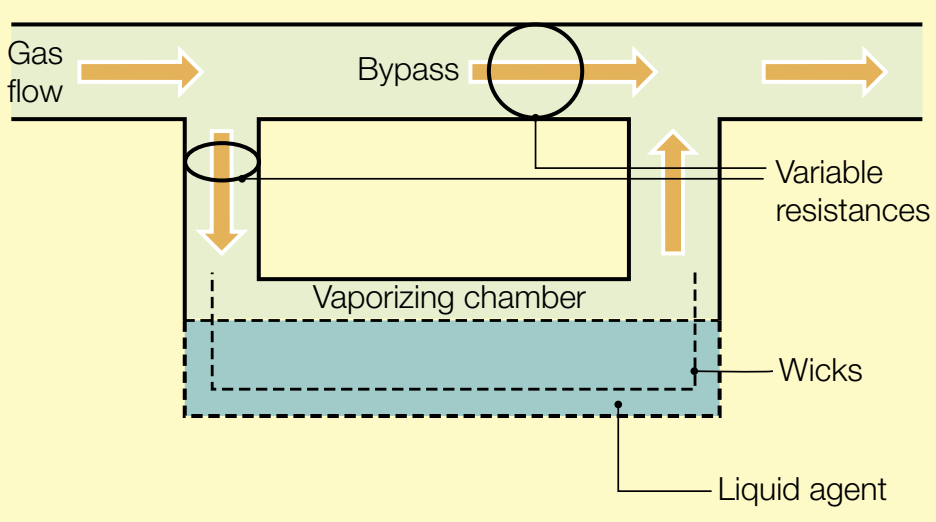
1

Physical properties of some common materials at 293K

	Specific heat (J/(kg.K))	Thermal conductivity (W/(m.K))	Density (kg/m³)
Copper	385	385	8930
Aluminium	913	201	2710
Glass	670	1	2600
Stainless steel	510	150	7930

2

An anaesthetic vaporizer



3

Temperature compensation

As liquid evaporates from the vaporizing chamber the temperature drops, and unless there is some means of compensating for this, the output of the vaporizer also drops. The temperature drop, and hence the fall in output, is lower if the vaporizer has a large heat capacity and can therefore supply energy to the liquid to compensate for that which it has lost. For this reason most vaporizers contain a large mass of metal that can also conduct heat from the surroundings into the liquid. In addition, most vaporizers incorporate some kind of temperature compensation, which reduces the resistance of the vaporizing chamber relative to that of the bypass as the temperature drops. As a result, more gas flows through the vaporizing chamber so that the vapour concentration is maintained.

Effect of intermittent positive-pressure ventilation (IPPV)

During IPPV, the pressure at the outlet of a vaporizer is not constant. When the pressure is high, flow emerging from the vaporizer reduces and the pressure in the vaporizing chamber builds up. As the pressure drops, the excess of vapour, which has accumulated in the vaporizing chamber at this time, emerges not only from the normal outlet of the vaporizing chamber but also from the inlet. This means that the bypass gas contains vapour and therefore the concentration rises. Manufacturers have compensated for this by introducing a long inlet tube into the vaporizing chamber. When the pressure inside the vaporizing chamber drops, the vapour enters this tube, but its volume is not enough to emerge into the bypass.

Effect of flow rate on vaporizer output

The vaporizer output is dependent on the resistance of the vaporizing chamber relative to that of the bypass. With varying flows the vaporizer output remains constant only if this does not change. In practice, this is difficult to achieve over the wide range of flows used in anaesthetic practice. Only if laminar flow is maintained in each pathway throughout the flow range will this be the case. Another factor influencing the output at high flows is the increased cooling, which occurs as a result of the large amount of evaporation taking place.

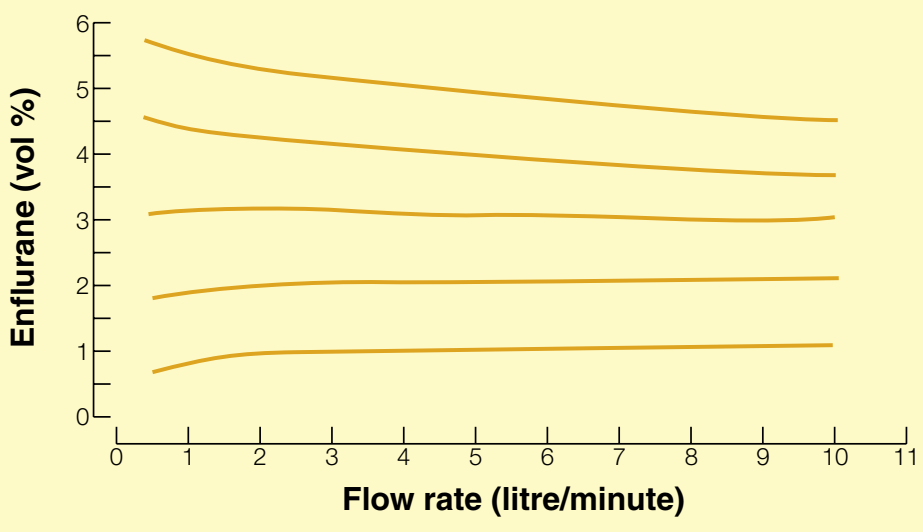
Figure 4 shows the variation of output with flow for a Penlon plenum enflurane vaporizer. It can be seen that the output of this vaporizer at high settings drops as the flow rate increases. However, at the lower settings more commonly in use, the output remains reasonably constant. This indicates that the temperature compensator in the Penlon plenum vaporizer (PPV) can adjust adequately for cooling due to evaporation except at the highest dial settings and flow rates.

Effect of gas composition

The relative flow rates through the bypass and vaporizing chamber at a given dial setting remain constant only if laminar flow is maintained in both pathways. As soon as the flow in one pathway becomes turbulent, its resistance rises causing less gas to flow through it, unless it is matched by a proportional rise in the resistance of the other pathway.

Nitrous oxide has different physical characteristics from oxygen (Figure 5); in particular, the ratio of viscosity to density, which determines the flow rate at which turbulence sets in, is much lower. The effect that this has on the output of the vaporizer depends on its design. In some vaporizers, output drops when the carrier gas contains nitrous oxide whereas in others it increases.

Variation of output with flow for the Penlon plenum vaporizer



Courtesy of Penlon Ltd.

4

Physical properties of oxygen and nitrous oxide

Gas	Density (kg/m^3)	Viscosity ($\mu N.second/m^2$)	Kinematic viscosity ($m^2/second$)
Oxygen	1.43	18.9	10.3×10^{-5}
Nitrous oxide	1.96	13.5	6.9×10^{-5}

5

Types of vaporizer

Vaporizers fall into two broad categories.

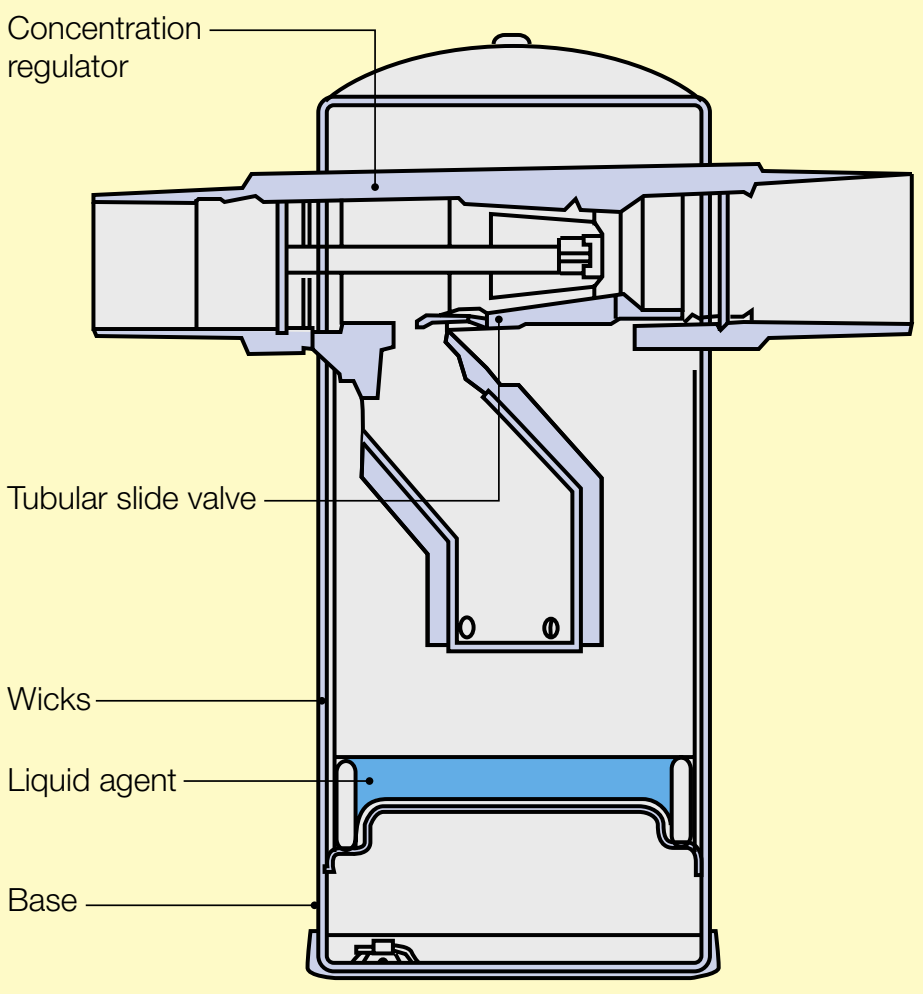
Drawover vaporizers – in a drawover vaporizer, gas is pulled through as the patient inspires (expiration is to atmosphere via a non-rebreathing valve). The flow rate of gas through the vaporizer is therefore not constant and it is necessary for the vaporizer to have a low resistance.

Plenum vaporizers – in a plenum vaporizer, gas is driven through under positive pressure. The term plenum is derived from the plenum system of ventilation where gas is forced into the system. Plenum vaporizers may have a higher resistance than drawover vaporizers though some vaporizers are designed to be used in either mode (e.g. the Oxford miniature vaporizer).

Oxford miniature vaporizer

The Oxford miniature vaporizer (Figure 6) is designed as a low resistance drawover vaporizer. It does not have any temperature compensation, but it has a water-filled jacket to increase its heat capacity.

Oxford miniature vaporizer



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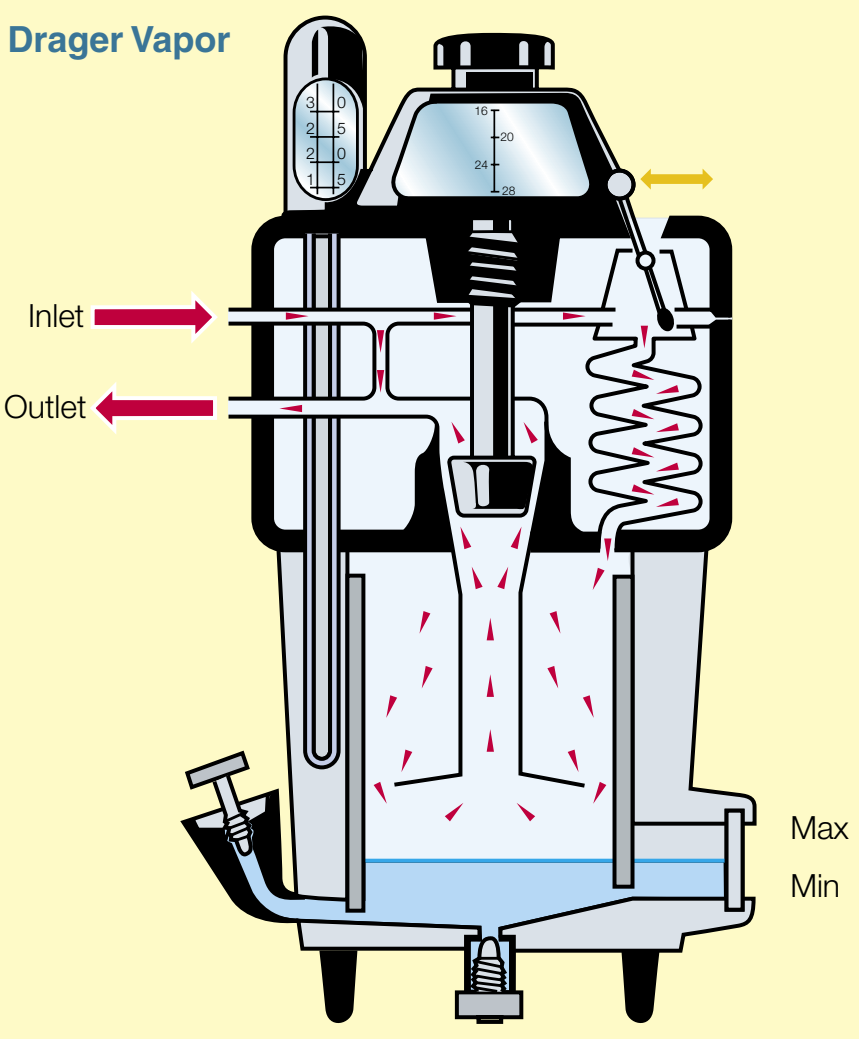
Drager Vapor

The Drager Vapor (Figure 7) is constructed from a large block of copper and is therefore thermally stable. It has a built-in thermometer so that the temperature of the liquid agent may be read and the position of the concentration dial is adjusted according to this temperature. In this vaporizer, the gas flow through the bypass and the vaporizing chamber is controlled by a pair of needle valves, which are carefully manufactured to ensure that gas flow is laminar in both pathways over a large range of flow rates. There is therefore little variation of output with flow rate for this vaporizer.

Drager Vapor



7

PPV

In the PPV (Figure 8), when the control dial is in the zero position the vaporizing chamber is isolated by means of a spring-loaded valve attached to the push rod, which is aligned with the control knob. When the control knob zero lock button is pressed the push rod opens the valve and as the control knob is rotated the vapour control orifice opens to allow more gas to flow through the vaporizing chamber.

Temperature compensation is achieved by a moving needle valve within the bypass orifice, which increases the bypass resistance as the temperature drops, thus forcing more gas to flow through the vaporizing chamber. The movement of the valve is controlled by a push rod attached to an ether-filled metal bellows unit. As the liquid agent changes temperature, the ether in the bellows expands or contracts causing the bellows to expand or contract linearly. Compensation for fluctuating back pressure is achieved by the inclusion of a long narrow tube in the vaporizing chamber.

Penlon plenum vaporizer

8

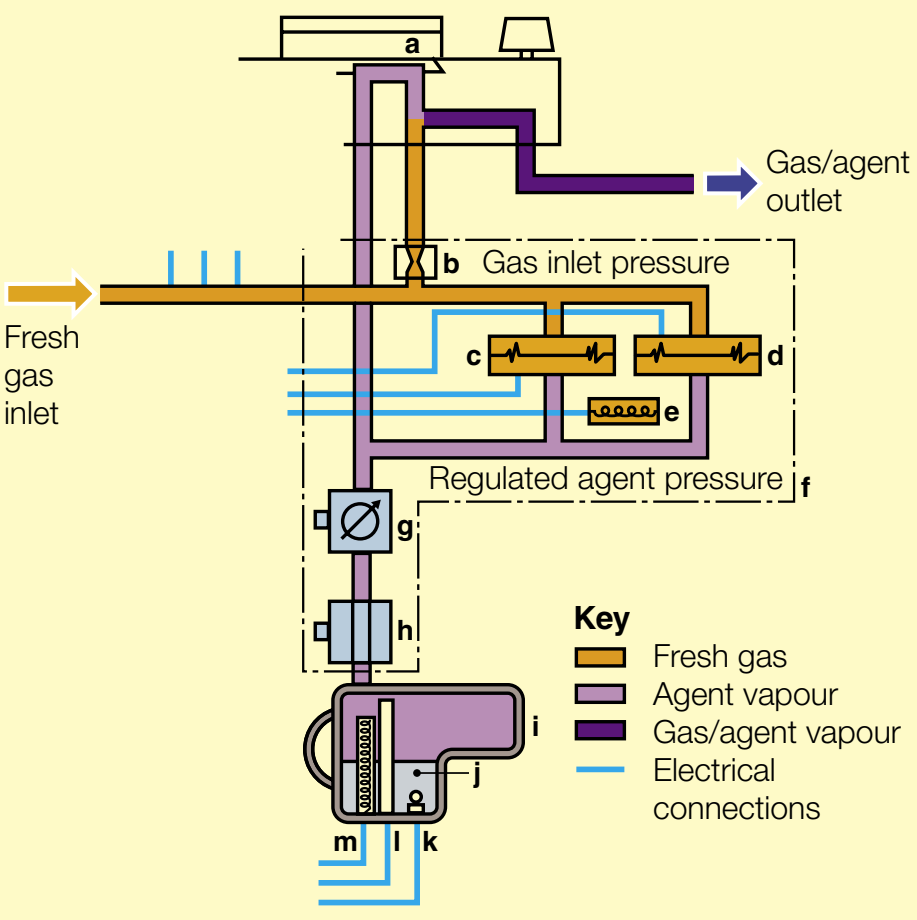
Tec 6 vaporizer

The Tec 6 vaporizer (Figure 9) varies from most other conventional vaporizers because it incorporates a heater element. This is necessary because desflurane concentrations up to 18% v/v may be required. The concentration knob has an interlock system, which means that it cannot be turned until the liquid agent has been heated to the correct temperature. When the control dial is turned, an electronic signal opens the shut-off valve. The pressure transducer measures the difference between the gas inlet pressure and the regulated agent pressure. The agent pressure is controlled electronically by opening or closing the pressure-regulating valve to balance the pressures. When the pressures are correctly balanced the vaporizer functions correctly.

Calibration of vaporizers

Anaesthetic vaporizers are calibrated in the factory using a refractometer (an accurate optical device) in a temperature-controlled room. In general, either oxygen or air at a medium flow rate is used for the carrier gas. The output of a vaporizer may vary under different conditions of temperature, flow or carrier gas – this is not surprising, considering the wide range of flow rates and concentrations over which a vaporizer is used. It has been said that one should expect vaporizers to produce concentrations only within 20% of their dial settings. While this is a wide margin, it is not at all unusual for concentrations to differ by 10% of the dial setting and as conditions become more extreme this difference may approach 20%. It is important that anaesthetists recognize the problems faced by manufacturers when designing vaporizers and that they do not always expect vapour concentration and dial setting to coincide.

Tec 6 vaporizer



a Dial and rotary valve, **b** fixed restrictor, **c** pressure control transducer, **d** pressure monitor transducer, **e** heater in vapour control manifold, **f** vapour control manifold assembly, **g** pressure-regulating valve, **h** shut-off valve, **i** sump assembly, **j** agent, **k** level switch, **l** level sensor, **m** sump heaters

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Recognition and Management of Anaphylactic and Anaphylactoid Reactions

Andrew McIndoe

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The term anaphylaxis was coined by Charles Richet in 1902 to describe the reaction of dogs to a second, and often fatal, injection of foreign protein (sea anemone toxin). The term was introduced to distinguish this later injection from the first 'prophylactic' injection that induced sensitization.

Anaphylaxis is now recognized to be an immediate hypersensitivity or type I immune reaction mediated by immunoglobulin E (IgE) and resulting in mast cell degranulation and basophil activation. It is not dose related and can occur in response to minute exposure to an allergen. Typically, the severity of the response worsens on re-exposure owing to progressive sensitization of the subject. The true incidence of anaphylaxis is unknown but is estimated to be 1/6000–20,000 anaesthetics or 1/10,000 of the general population/year. Women are more likely to suffer an anaphylactic reaction than men, with a quoted increase in risk of 3–10:1. Intravenous administration of the antigen is more likely to precipitate a severe generalized reaction. Cross-sensitivities with non-steroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants makes previous exposure unnecessary. Up to 80% of neuromuscular blocking agent reactions are not associated with known prior exposure.

Anaphylactoid reactions may present with a similar clinical picture, but do not result from hypersensitivity and are not mediated by IgE. Drugs such as opioids can directly stimulate mast cell degranulation with histamine release causing pruritus, rash and hypotension. They should be managed as potential anaphylactic reactions because confusion over the diagnosis merely delays effective treatment.

Pathophysiology

Primary exposure to an antigen results in the synthesis of specific IgE antibodies by lymphocytes and plasma cells. The Fc portions of these antibodies are able to fix themselves to the surface of tissue mast cells and circulating basophils. The antigen binding sites are thus presented externally. Subsequent contact with antigen causes IgE antibody:antigen cross-binding and triggers immediate degranulation of the host mast cell or basophil. Release of histamine and serotonin results in an acute inflammatory reaction, smooth muscle constriction, vasodilatation and increased capillary permeability. The clinical picture depends on the mode of exposure.

- Skin – urticaria, flare and weal reaction (hence the use of skin prick testing).
- Eyes – conjunctivitis.
- Mouth/airway – perioral and laryngeal oedema, broncho-spasm.
- Parenteral – generalized cardiovascular collapse.
- Eosinophils are mobilized by chemotaxis, attracted by histamine and other substances, they produce histaminase, helping to terminate the reaction.

History and examination

Anaphylaxis may present with a spectrum of clinical signs including hypotension, tachycardia, dysrhythmias, dyspnoea, laryngeal oedema, bronchospasm, angio-oedema, flushing, urticaria, conjunctivitis, rhinitis, abdominal pain and diarrhoea. It can therefore mimic a variety of other conditions. Diagnosis is further complicated by a variable time for exposure until symptoms develop, varying from a few seconds to several hours. 5% of patients show a biphasic response with symptoms recurring from 1–72 hours after the initial attack. Many patients do not develop all the classic signs (Figure 1).

Differential diagnoses are vasovagal faint with hypotension, bradycardia and pale, sweaty skin and panic attack with hyperventilation, tachycardia and an erythematous rash.

Percentage of patients presenting with classic signs of anaphylaxis

Signs	Patients (%)
• Cardiovascular collapse	88
• Erythema	45
• Bronchospasm	36
• Angio-oedema	24
• Rash	13
• Urticaria	8.5

1

Management

The management of anaphylaxis is summarized in Figure 2.

Management of anaphylaxis

Condition
IgE mediated immediate hypersensitivity reaction to an antigen resulting in histamine and serotonin release from mast cells and basophils

Presentation
- Cardiovascular collapse
- Erythema
- Bronchospasm
- Oedema
- Rash

Immediate action
- Remove trigger
- 100% oxygen
- Elevate legs
- Adrenaline (epinephrine) 500 μg i.m. or 50 μg increments i.v. titrated to effect
- 20 ml/kg i.v. fluid challenge

Follow-up action
- Chlorphenamine (chlorpheniramine), 10–20 mg i.v.
- Hydrocortisone, 100–300 mg i.v.
- Arterial blood gases

Investigations
- Plasma tryptase
- Urinary methylhistamine

Also consider
- Primary myocardial/cardiovascular problem
- Latex sensitivity
- Airway obstruction
- Asthma
- Tension pneumothorax
- Panic attack

2

Immediate management
- Check the airway, breathing and circulation. Stop the administration of or exposure to any potential triggers, particularly intravenous agents. Muscle relaxants, antibiotics and NSAIDs (and increasingly latex) are the most common triggers in an anaesthetic environment. Outside the operating theatre, foods (especially nuts, fish, shellfish, eggs and milk), insect venom, drugs (antibiotics, NSAIDs, contrast media, opioids) and latex are the most common precipitants.
- Call for help.
- Maintain the airway and give 100% oxygen. Reassess airway patency frequently and regularly, especially in known asthmatics and in those exposed to the allergen via the airway or mouth. If in doubt and the reaction is severe, intubate early because it may be impossible to do so later in the presence of increased oedema.
- Cardiovascular collapse is most likely following parenteral exposure to the allergen. Lay the patient flat with the legs elevated to increase central venous return.
- If the patient has a continuous ECG monitor attached, give adrenaline (epinephrine) in 50 μg i.v. increments (0.5 ml of a 1:10,000 solution) at a rate of 100 μg/minute until the blood pressure or bronchospasm improves. Alternatively, give adrenaline (epinephrine) 0.5–1 mg i.m. as 0.5–1.0 ml of a 1:1000 solution (repeated after 10 minutes if necessary). Adrenaline (epinephrine) stabilizes mast cell membranes, increases myocardial contractility, causes bronchodilatation and reverses vasodilatation; it therefore treats both cause and effect.
- Give intravenous fluid (colloid or suitable crystalloid), 20 ml/kg.
- Latex allergy may take up to 30 minutes to manifest itself. Removal of all latex triggers can then be a complex process. Allergen is more readily absorbed across mucous membranes (e.g. from surgical gloves or a urinary catheter, which should be removed immediately and hands should be re-washed to remove latex-impregnated starch granules). Inhalation of aerosolized particles within the breathing circuit is minimized by the use of an airway filter. Ensure that rubber 'corings' are not introduced intravenously (e.g. ampoule bungs and injection sets). Laryngeal mask airways are made of silicone and do not contain latex. *Diprivan* syringe bungs are also latex free.

Subsequent management
- Give an antihistamine (H_1-blocker) such as chlorphenamine (chlorpheniramine, *Piriton*), 10–20 mg by slow i.v. or i.m. injection. Consider H_2-antagonists, such as ranitidine, 50 mg slow i.v. injection.
- Give corticosteroids such as hydrocortisone, 100–300 mg by slow i.v. or i.m. injection, to inhibit later relapses.
- Give a catecholamine infusion because cardiovascular instability may last for several hours. Consider adrenaline (epinephrine) 0.05–0.1 μg/kg/minute (e.g. 4 ml/hour of 1:10,000 for a 70 kg adult) or noradrenaline (norepinephrine) 0.05–0.1 μg/kg/minute (e.g. 4 ml/hour of a solution of 4 mg made up to 40 ml in 5% dextrose for a 70 kg adult).
- Check arterial blood gases for acidosis and consider giving bicarbonate, 0.5–1.0 mmol/kg (8.4% solution = 1 mmol/ml).
- Check for the presence of airway oedema by letting down the tracheal cuff and confirming a leak before extubation.
- Consider bronchodilators for persistent bronchospasm (e.g. salbutamol, 5 mg by nebulizer or 250 μg slow i.v. injection, aminophylline 250–500 mg slow i.v. injection).

Complications

Hospital mortality to anaesthetic drug-induced anaphylaxis is 4%, despite the presence of good resuscitation facilities. Over half of those who die of anaphylaxis do so within the first hour. The deaths are related to asphyxia, from severe bronchospasm or upper airway obstruction, and from refractory hypotension.

The early use of adrenaline (epinephrine) is advisable but advice differs over the safest and most appropriate mode of administration. Adrenaline (epinephrine) is best administered by intramuscular injection (0.5 mg – usually 0.5 ml of 1:1000 solution) by first responders because it is a reliable means of achieving therapeutic plasma concentrations quickly and safely. The subcutaneous route is slow and unpredictable and is inappropriate during an acute life-threatening reaction. Anaesthetists often opt for intravenous administration of a 1:10,000 solution in incremental doses (of 50–100 μg). The intravenous route, while rapidly effective, can result in tachydysrhythmias. Cardiac complications are more common in the presence of hypoxia, hypercapnoea, and in patients taking tricyclic antidepressants or cocaine.

Patients taking β-blockers are likely to suffer more severe reactions and may be resistant to treatment with adrenaline (epinephrine). However, β-blockers are competitive antagonists and careful but continued titration of adrenaline (by sequential doubling of the initial dose in severe cases) should achieve a clinical effect.

Late diagnosis may be complicated by severe compromise of the airway and difficulty intubating the trachea.

Investigations

Investigations should be carried out when the patient has been stabilized.

Plasma tryptase: at least one 10 ml clotted blood sample should be taken 1–6 hours after the start of the reaction to perform a tryptase assay. The specimen must be spun down as soon as possible and the serum stored at –20°C, to stabilize the protein for later analysis. Tryptase is the main protein released during mast cell degranulation and is a specific marker of histamine release due to anaphylaxis or anaphylactoid reaction. Normal basal levels of serum tryptase are less than 1 ng/ml. However, unlike histamine, which is rapidly eliminated, tryptase levels remain elevated for up to 6 hours after an anaphylactic reaction. It is not a protein that is produced by RBCs or WBCs and is therefore not raised by haemolysis. Levels over 20 ng/ml may accompany an anaphylactic reaction.

Elevated metabolites in the form of urinary methylhistamine may also be measured. The value measured has to be corrected for urinary creatinine but levels in excess of 15–20 ng/ml/mmol creatinine/litre are considered higher than normal, and may indicate anaphylaxis.

Radio allergosorbent testing (RAST) is a means of searching for antigen-specific IgE in the serum. Tests are limited to specific allergens. At present only a few anaesthetic RASTs are available (e.g. suxamethonium). Fluoroimmunoassay is an alternative (*CAP System*, Pharmacia).

Follow-up and prognosis

The anaesthetist should follow up the investigation, report reactions to the Committee on Safety of Medicines via the 'yellow card' reporting scheme, and arrange skin prick testing in consultation with an immunologist. Having identified allergens, the patient should be advised to wear an alert bracelet at all times. Those who have suffered a severe reaction, especially anaphylaxis to allergens that are commonly encountered in everyday life, may be advised on how to carry and when to administer their own adrenaline (epinephrine). The *Epipen* syringe is preloaded with adrenaline (epinephrine) and will deliver a fixed intramuscular injection of 300 µg (0.3 ml of 1:1000) for adults or 150 µg for children.

Desensitization is a process that attempts to stimulate the production of IgG or IgA antibodies that competitively bind to the antigen and help block the IgE antibody–antigen hypersensitivity reaction that precipitates anaphylaxis. It is not without risk because it involves repeated inoculation with small doses of antigen.

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Recognition of Correct Placement of Tracheal Tubes

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The technique of tracheal intubation is fundamental to anaesthetic practice. Critical incident reporting indicates that oesophageal intubation is a relatively common problem. Misplacement of a tracheal tube is not in itself harmful if the diagnosis is made promptly and corrective action taken. However, tracheal tube misplacement still accounts for a large proportion of anaesthetic deaths. It should be considered in any hypoxic intubated patient. Failure to detect incorrect tube placement is equally common for trainees and consultants. It is as likely with routine as with difficult intubation.

Methods of confirming correct tube placement

Clinical signs are often unhelpful in detecting tube misplacement and intubation should be confirmed by:

- direct visualization of the tube passing through the vocal cords
- auscultation over both axillae, lung bases and the epi-gastrium
- capnography
- oesophageal detector device or colorimetric detector if capnography is not readily available.

Visualization of larynx

The larynx is usually visualized and the tracheal tube is observed passing between the vocal cords into the trachea. However, a view of the larynx is not always possible. In routine laryngoscopy, an anaesthetist may become distracted at the moment of intubation, allowing the tube to slide past into the oesophagus. Occasionally the oesophagus may be mistakenly identified as the trachea or the tube may become displaced during fixation. Direct visualization is thus not totally reliable and may even delay a diagnosis of tube misplacement by promoting a false sense of security.

Repeat laryngoscopy is essential if a tube problem is suspected; oesophageal intubation, extubation or a kinked tube can all be identified and remedial action taken.

Chest movement

Bilateral symmetrical chest wall expansion should occur coincident with inspiration. It may be difficult to discern in the obese patient, in those with a rigid chest wall, or in chronic lung disease (e.g. emphysema). Oesophageal ventilation may imitate chest movement by expansion of the mediastinum, while gastric distension can simulate diaphragmatic and lower chest wall ventilation, especially in infants.

Auscultation

The combination of auscultation over each axilla, lung base and epigastrium achieves the most reliable results. Direct auscultation over the trachea may be of additional benefit; more obvious breath sounds can be heard, which are less likely to be confused with oesophageal ventilation.

Breath sounds over the chest wall do not always exclude oesophageal intubation. Air ventilating the oesophagus can be transmitted through the lungs to resemble convincing breath sounds. Conversely, breath sounds may be inaudible in the obese patient.

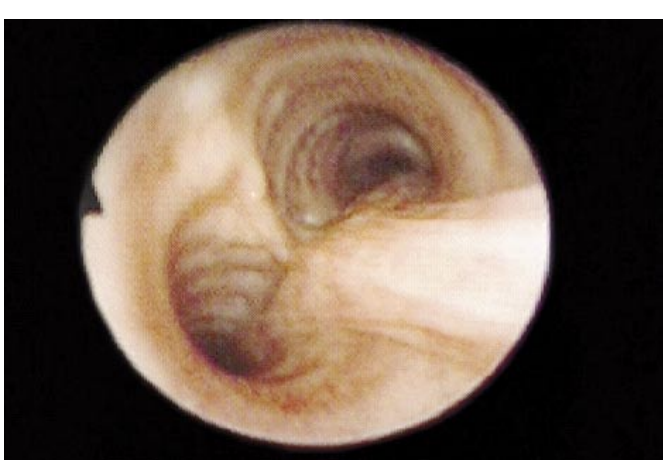
Breathing circuit

The ability to ventilate the lungs via the reservoir bag together with its typical compliance characteristics is a useful sign for the anaesthetist. In a spontaneously breathing patient the bag should empty and refill synchronously with the patient's breathing pattern. However, small movements (cardiac oscillations) can be demonstrated with oesophageal tube placement.

In contrast, it may be difficult to ventilate a morbidly obese patient via the reservoir bag or to differentiate between oesophageal intubation and partial or complete bronchospasm.

Fibre-optic laryngoscopy

The fibre-optic bronchoscope or laryngoscope can reliably confirm tracheal tube placement by identification of the tracheal rings and carina under direct vision (Figure 1). The technique requires operator experience and the equipment must be readily available.



1 View of the carina via a fibrescope, confirming the correct placement of the tracheal tube.

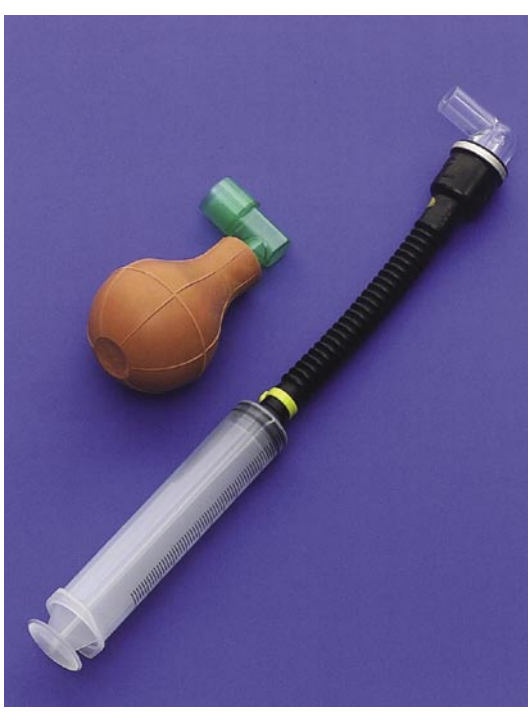
Oesophageal detector device

The Wee oesophageal detector device (ODD) consists of a 60 ml bladder syringe connected to a catheter mount. This is attached to the tracheal tube following intubation. The syringe freely aspirates gas from the patient's lungs if the tube is in the trachea (negative result). However, if this negative pressure is applied to a tube within the oesophagus, the oesophageal wall collapses and no air can be aspirated (positive result).

As a modification, the syringe has been replaced by a large rubber bulb (Ellick's evacuator) to enable the device to be used one-handed (Figure 2). In this case the bulb is first emptied and then failure to refill indicates oesophageal intubation.

The ODD is cheap, simple to construct, easy to use and reliable. It has been validated in several studies with only a small incidence of false-positive results, possibly related to endobronchial intubation or secretions blocking the lumen of the tracheal tube; there are no reported false-negative results.

It has been used successfully with uncuffed tubes in older children but is unreliable in those under 2 years of age.



2 Oesophageal detector device with Ellick's evacuator modification.

Capnography

Capnography is the real-time detection of carbon dioxide in the breathing gases and its display as a waveform that plots concentration versus time. Carbon dioxide is detected by infrared spectroscopy. It is the gold standard for verifying tracheal intubation. The guidelines of the Association of Anaesthetists state that during induction of anaesthesia, capnography is 'essential to the safe conduct of anaesthesia'.

For carbon dioxide to be detected, it must be produced in the tissues, then transported to the lungs, and finally exhaled in the expiratory gas. The capnograph is therefore an important monitor that gives information about:

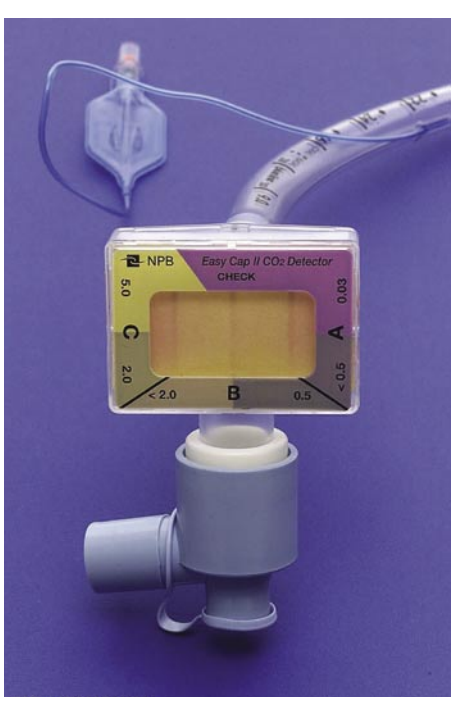
- metabolic rate
- pulmonary perfusion
- alveolar ventilation.

If metabolic rate and pulmonary perfusion (or cardiac output) are constant, then changes in the capnograph trace reflect the adequacy of alveolar ventilation.

Deceptively low values may result from a large leak around the tube. Gas arising from the stomach and oesophagus usually contains only a trace of carbon dioxide, but false-positive results occur if expired alveolar gas is introduced into the stomach from mask ventilation. Significant concentrations of carbon dioxide have been reported following ingestion of carbonated drinks ('cola complication'). In these circumstances, capnography following oesophageal intubation initially resembles the normal waveform for end-tidal carbon dioxide. This initial value rapidly diminishes towards zero as the carbon dioxide is washed out. It has been suggested that the waveform should be observed for a minimum of six breaths.

Colorimetric carbon dioxide detector

This small disposable device contains a pH-sensitive indicator that displays a colour change (e.g. from purple to yellow) when exposed to carbon dioxide (Figure 3). The colour change is rapid and the detector can be left in the breathing circuit for several hours allowing continuous ventilatory monitoring. The device is about the same size and weight as a heat/moisture exchange filter and requires no power source for operation. This portability makes it useful during cardiopulmonary resuscitation or in emergency situations when capnography may not be available. Reduced carbon dioxide concentrations often present in these clinical situations, which may reduce its sensitivity.



3 Colorimetric carbon dioxide detector.

Complications of oesophageal and endobronchial tube placement

Oesophageal intubation

Undetected oesophageal intubation is a major anaesthetic cause of permanent neurological damage and death. There should be a high index of suspicion in any situation in which hypoxia develops following intubation; the onset may be delayed if preoxygenation has occurred. Difficulty in ventilation, poor or absent chest movement, inaudible breath sounds and increasing abdominal distension should all alert the anaesthetist to the possibility of tube misplacement. In practice, clinical signs are not always obvious.

Progressive gastric distension may cause regurgitation and subsequent aspiration. Splinting of the diaphragm impairs ventilation even after the patient has been correctly intubated unless the stomach is actively decompressed using a nasogastric or orogastric tube.

If there is any doubt as to correct tube placement, it is essential to remove the tube and recommence mask ventilation.

Endobronchial intubation

Endobronchial intubation is more common in children owing to the smaller length of the trachea. Flexion or extension of the neck can move the tube a significant amount within the trachea (up to 5 cm in adults), leading to endobronchial intubation or inadvertent extubation. The right main bronchus is more commonly intubated than the left side because it arises at a straighter angle from the trachea.

One-lung ventilation causes hypoxaemia due to the shunt effect that failure to ventilate the opposite lung produces. Progressive lung collapse of this unventilated side occurs. There is a reduced uptake of volatile anaesthetic agent and bronchospasm is a common occurrence, probably as a result of vagal stimulation from irritation of the carina.

The diagnosis may be obvious with asymmetric chest movement and absent breath sounds on one side of the chest, but clinical signs are often unreliable. With an uncuffed tube, breath sounds can easily be transmitted to the non-ventilated lung. A chest radiograph confirms the diagnosis and provides an estimate of the distance that the tube needs to be withdrawn. Fibre-optic bronchoscopy can also be useful.

The chances of endobronchial intubation can be lessened by cutting tracheal tubes to an appropriate size (e.g. 22–24 cm in the adult) preceding intubation. The black marker line present at the distal end of some tracheal tubes can also serve as a guide to the length of the tube to be passed through the vocal cords.

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Regurgitation, Vomiting and Aspiration

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Regurgitation is the passive movement of gastric contents into the pharynx. The lower oesophageal sphincter normally prevents regurgitation. The sphincter is a physiological, rather than a distinct anatomical structure. Reflux is prevented because the lower oesophageal pressure is greater than the gastric pressure. This is referred to as the barrier pressure.

Vomiting is an active reflex usually occurring in the lighter planes of anaesthesia (i.e. induction and emergence). It is the forceful ejection of the contents of the upper gastrointestinal tract through the mouth. It is often secondary to stimulation from inappropriate airway manipulation.

The afferent limb of the reflex arc is composed of fibres from the gastrointestinal tract, the vestibular system, or from the chemoreceptor trigger zone in the brain stem. The vomiting centre' in the brain stem coordinates the reflex. The efferent limb involves autonomic outflow to the gastro-intestinal tract and also produces widespread effects such as pupillary dilation, sweating, salivation, vasoconstriction and tachycardia.

Pulmonary aspiration of gastric contents into the lungs is a serious, though infrequent, complication of modern anaesthesia. Mendleson first described it in detail in 1946 in 66 obstetric patients. Aspiration occurs following gastro-oesophageal regurgitation or vomiting when protective laryngeal reflexes are depressed or absent. Prevention of pulmonary aspiration is by measures aimed at reducing the incidence of regurgitation and vomiting.

Although silent regurgitation is thought to occur in up to 25% of patients under anaesthesia, the incidence of significant pulmonary aspiration in the general surgical population is much less at 1–6/10,000. For obstetric general anaesthesia the incidence is doubled. The mortality following aspiration is about 5%.

Pathophysiology

The adverse effects of pulmonary aspiration occur by three mechanisms.

Particle related – this could result in acute airway obstruction.

Acid related – the traditional view is that patients are 'at risk' if the gastric contents consist of a critical volume of more than 25 ml and have a pH of less than 2.5; there is little clinical evidence to support this. pH is the more critical factor for lung injury sustained following aspiration though there may not be an exact cut-off value. Significant morbidity can occur following inhalation of material with a very low pH even in small volumes due to chemical pneumonitis, and following large volumes of neutral fluid due to a 'near drowning' effect.

Bacterial related – aspirated fluid is not sterile and lung infection may result. Damaged lung is also more prone to secondary infection.

Risk factors

Predisposing factors for pulmonary aspiration are shown in Figure 1. Vomiting and regurgitation during induction of anaesthesia occur most often in emergency cases with acute abdominal pathology or following trauma. Pain, fear, anxiety and opioid administration all delay gastric emptying. These patients should be regarded as at high risk and appropriate precautions taken. The interval between last oral intake and time of injury in trauma patients is said to give a better guide to gastric emptying than the duration of fasting. In practice this is unreliable and it is often best to assume patients have a full stomach.

Risk factors for aspiration

Condition	Examples
Full stomach	Inadequate preoperative fasting Gastrointestinal obstruction, bleeding or ileus Trauma, burns, pain, anxiety Pregnancy Drugs (e.g. opioids)
Reduced lower oesophageal sphincter function	Hiatus hernia Drugs (e.g. opioids, atropine) Pregnancy Raised intra-abdominal pressure Obesity Lithotomy position
Material in oesophagus/ pharynx	Achalasia, scleroderma Strictures, carcinoma Pharyngeal pouch
Depressed laryngeal reflexes	Reduced consciousness (e.g. general anaesthesia, drug or alcohol intoxication, cerebrovascular accident, head injury, seizures or postictal state) Topical anaesthesia Neurological disease (e.g. myasthenia, multiple sclerosis, Parkinson's disease, Guillain–Barré syndrome) Muscular dystrophies
Others	Inexperienced anaesthetist Night-time surgery Emergency surgery Extremes of age

Obstetrics
In the third trimester, the enlarged uterus increases intra-abdominal pressure and therefore intra-gastric pressure. Before this, there is an increased risk of aspiration due to the production of:

- gastrin from the placenta, which increases gastric acid secretion
- progesterone, which relaxes smooth muscle and reduces gastrointestinal motility.

Anatomical changes in late pregnancy may increase the incidence of airway difficulties and thus of aspiration (e.g. increased body weight, large breasts, upper airway oedema). Surgery often occurs 'out of hours' as an emergency. Risks may be increased further during labour from the effects of pain, anxiety and opioid administration. Pregnant patients should be assumed to have a full stomach from the end of the first trimester until at least 18 hours post-partum. Regional anaesthesia should be used whenever possible to reduce the aspiration risks.

Prevention

Methods to prevent pulmonary aspiration are directed towards reducing the volume and increasing the pH of the stomach contents. The technique of cricoid pressure and induction of anaesthesia in the patient with a full stomach is elsewhere.

Fasting requirements
Traditionally, patients were fasted overnight before elective surgery. More recently it has been shown that the administration of clear fluids (e.g. water, non-particulate juice) up to 2–3 hours preoperatively does not increase residual gastric volume or alter pH. This increases patient comfort and reduces dehydration and hypoglycaemia in infants. An example of current fasting guidelines for elective, nonobstetric patients is shown in Figure 2.

Fasting requirements are less straightforward for emergency surgery. It is often necessary to provide anaesthesia to patients suspected of having a full stomach. Delaying urgent surgery to reduce the possibility of aspiration is usually of no benefit and may be detrimental. Patients requiring emergency surgery should be assumed to have a full stomach, irrespective of the duration of fasting, because gastric emptying is likely to be delayed. Following painful trauma, a significant gastric residue can be present after 24 hours. It is not currently recommended that emergency patients be allowed to drink clear fluids before surgery. Intravenous therapy should be used to prevent dehydration. At present there is no consensus regarding fasting during labour.

Preoperative fasting guidelines for patients undergoing elective surgery

	Length of fast (hours)
Adults	
• Solid food	6
• Clear fluid	2–3
Children	
• Solid food	6
• Formula milk	4
• Breast milk	3
• Clear fluid	2

Regional anaesthesia
Avoiding general anaesthesia reduces the risk of pulmonary aspiration. Both the proposed surgery and the patient must be amenable to the technique. The patient should be fasted because an inadequate or failed regional block, or adverse reaction, may make general anaesthesia necessary.

Gastric decompression
The insertion of a nasogastric tube to decompress the stomach may be useful. Liquid, but not solid, gastric contents can be aspirated via the tube. It is not usually possible to empty the stomach completely by this means, so the possibility of aspiration remains. If a nasogastric tube has been passed before surgery, it should be aspirated before induction. Effective cricoid pressure can be performed with the tube *in situ*.

Pharmacotherapy
Antacids: prophylactic administration of antacids to high-risk patients is recommended. These drugs neutralize gastric acid and raise gastric luminal pH. Neutral pH aspirate causes less lung damage than fluid of acidic pH. Antacids should be non-particulate to reduce the potential for lung damage if inhaled. 0.3 M sodium citrate, 30 ml, is effective in elevating the pH of gastric contents if given 15–20 minutes preoperatively; it remains effective for 1–3 hours. Antacids are used routinely in elective and emergency obstetric anaesthesia, but less often in the general surgical population.

H_2-receptor antagonists reduce the volume and acidity of gastric contents by the inhibition of hydrochloric acid secretion from gastric parietal cells. Cimetidine, 400 mg orally 90–120 minutes before induction, and ranitidine, 150 mg orally 120 minutes before induction, 50 mg intramuscularly or slow intravenous administration 45 minutes before induction, are commonly used H_2-antagonists. Ranitidine has a duration of action of at least 8 hours; about twice as long as cimetidine. It is also associated with fewer side-effects. Side-effects with cimetidine, though infrequent, include sedation and confusion, and the potentiation of other drugs through inhibition of hepatic enzymes. Hypotension, bradycardia and even cardiac arrest can follow rapid intravenous injection of cimetidine, and also of ranitidine, though ranitidine has a much lower incidence.

Prokinetics: metoclopramide, 10 mg orally 1–4 hours before surgery or intravenously shortly before induction, acts centrally and peripherally to stimulate gastric emptying, increases lower oesophageal sphincter pressure and is anti-emetic. Its central action is due to its antidopaminergic properties whereas peripherally it stimulates acetylcholine release, resulting in increased gastrointestinal motility.

Proton pump inhibitors: omeprazole, 40 mg orally at night and on the morning of surgery, inhibits the proton pump in the parietal cells of the gastric mucosa, resulting in prolonged suppression of acid secretion. It elevates gastric pH. Combining omeprazole with metoclopramide reduces gastric volume. It is seldom used in the UK despite proven effectiveness.

Anticholinergics (e.g. atropine, glycopyrollate) can decrease gastric acid secretion, but have an adverse effect on barrier pressure by decreasing lower oesophageal pressure. They are not used for aspiration prophylaxis.

Induction of anaesthesia
If general anaesthesia is chosen, a cuffed tube in the trachea should secure the patient's airway. The airway should be assessed to predict whether this is likely to be difficult. The laryngeal mask airway has become popular in modern anaesthetic practice, however, it does not protect the airway from aspiration of gastric contents as efficiently as a cuffed tube and should not be used routinely in patients at high risk.

Uncuffed tubes are used in children because the paediatric airway narrows at the cricoid ring. Uncuffed tubes prevent tracheal mucosal damage by excessive cuff pressure, and may allow passage of a slightly larger tube size permitting improved gas flow. There is no precise age or size at which cuffed tubes are chosen, but use of uncuffed tubes in children below 8–10 years is usual. The absence of a cuff may imply the theoretical risk that aspiration can still occur, although satisfactory airway protection still occurs in clinical practice.

Position:there is controversy regarding the optimum position for induction of anaesthesia in the patient at risk of pulmonary aspiration. Some anaesthetists argue in favour of a head-up (reverse Trendelenburg) or semi-sitting position, because this may reduce the incidence of reflux in patients prone to passive regurgitation. Others favour a head-down (Trendelenburg) position with the patient on their side, because this may decrease the likelihood of aspiration should regurgitation occur.

Patient safety is paramount and therefore clinicians should induce anaesthesia in the position in which they have the most experience and confidence. This will usually be a rapid sequence induction in the supine position.

Rapid sequence induction: if the anaesthetist is confident that tracheal intubation will be straightforward then an intravenous rapid sequence induction performed with cricoid pressure is indicated. Aspiration is most likely to occur in the time from loss of consciousness to intubation with a cuffed tracheal tube. Rapid sequence induction reduces this time to a minimum.

Awake intubation: if a difficult intubation is anticipated consideration should be given to securing the airway before induction. In modern practice this involves topical local anaesthesia to the airway, and intubation via a flexible fibre-optic laryngoscope. A 'blind nasal' technique used to be popular, but the arrival of modern fibre-optic instruments has allowed awake intubation to be performed under direct vision.

Inhalational (gaseous) induction may be indicated in a patient considered at risk from aspiration, in whom conventional laryngoscopy and intubation is predicted to be difficult and where awake intubation attempts may be hazardous (e.g. acute stridor, maxillofacial trauma). There is a trade-off between taking steps to prevent aspiration during induction, and maintaining and securing the airway. A senior anaesthetist should manage these cases and patient safety is paramount.

Extubation should be performed with the patient awake and following the return of upper airway protective reflexes. It is often safest to position the patient on their side with head-down tilt to facilitate clearance of the upper airway using suction, should regurgitation occur.

Diagnosis

Clinical signs and symptoms of aspiration are variable (Figure 3) and it is sometimes difficult to make a definitive diagnosis. 'Silent' aspiration may occur, and may not be diagnosed until after surgery when the patient has returned to the ward. The initial and most reliable sign of aspiration is hypoxia, which occurs following even mild cases. Wheezing is also common. In severe cases an acute respiratory distress syndrome can result. In such patients there is increased intrapulmonary shunting, ventilation–perfusion (V/Q) mismatch, increased lung water, increased airway resistance and reduced lung compliance. Although aspiration classically affects the posterior aspect of the right lower lobe, radiographic changes are variable, nonspecific and may be absent, particularly in the first few hours. The most usual findings are irregular fluffy den-sities, frequently bilaterally, collapse or pulmonary oedema (Figure 4).

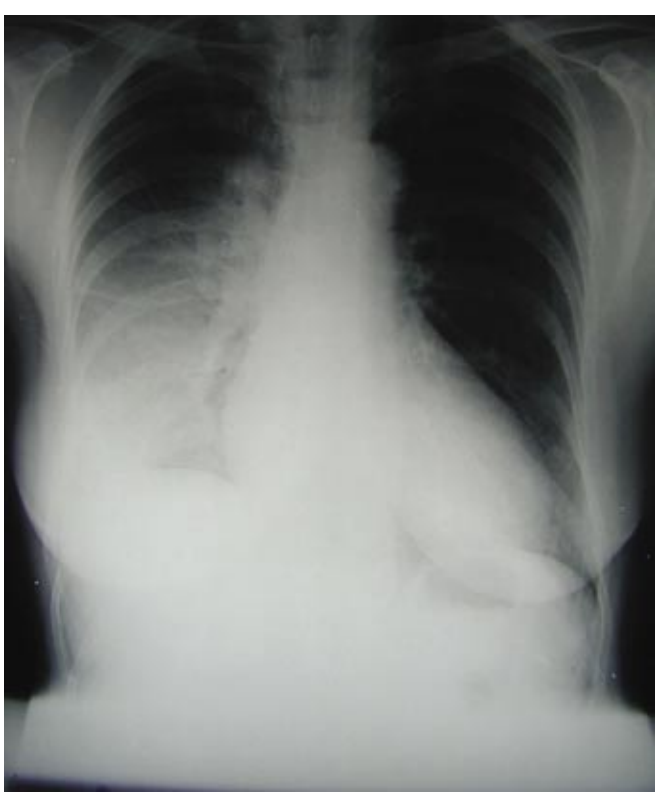
Differential diagnoses include anaphylaxis, cardiac failure, pulmonary embolism, fat embolism, sepsis and, in obstetric patients, amniotic fluid embolism.

Signs and symptoms of pulmonary aspiration

Symptoms
- Cough
- Breathlessness

Signs
- Stomach contents in oropharynx
- Tachypnoea
- Wheeze, crackles (mainly coarse)
- Cyanosis
- Tachycardia
- Pulmonary oedema
- Increased airway pressure
- Radiographic changes

3



4 Typical radiographic appearance of the chest in a patient with aspiration.

Management

If acute aspiration occurs the following procedure should be carried out.
- Place the patient in a head-down position, with head turned to one side.
- Suction material from the oropharynx.
- Administer 100% oxygen.
- Intubate the trachea if:

– adequate oxygenation cannot be maintained with spontaneous ventilation
– further tracheobronchial suction is required
– the patient is unable to protect their own airway.

The decision to continue with surgery depends on the severity of the aspiration and the urgency of surgery.

The management of established aspiration is largely supportive. Treatment is described in Figure 5.

Management of established aspiration

Oxygen therapy
- Guided by blood gas estimations or pulse oximetry

Ventilatory support
- Spontaneous ventilation may be adequate in mild cases
- Continuous positive airway pressure can be used for more severe cases, but requires alert, cooperative patient at no further risk of aspiration
- For severe cases, or those who cannot maintain a patent airway, mechanical ventilation via a tracheal tube is indicated
- Positive end-expiratory pressure is applied to increase functional residual capacity of the lung and minimize intrapulmonary shunting

Removal of aspirate
- Regular suctioning and physiotherapy are needed
- Bronchoscopy is required in more severe cases

Bronchodilators
- Given regularly by nebulizer

Antibiotics
- No proven benefit from prophylactic use
- Antibiotics often prescribed before identification of any pathogens

Fluid balance
- Shifts of fluid from the circulation to the lungs can result in pulmonary oedema
- Central venous pressure and urine output monitoring help guide fluid management
- A positive fluid balance worsens gas exchange and should be avoided

Corticosteroid therapy
- Routine use of corticosteroids is not indicated – no current evidence has shown benefit from their use

5

FURTHER READING

Engelhardt T, Webster N R. Pulmonary Aspiration of Gastric Contents in Anaesthesia. *Br J Anaesth* 1999; **83:** 415–21.
Kallar S K, Everett L L. Potential Risks and Preventive Measures for Pulmonary Aspiration: New Concepts in Perioperative Fasting Guidelines. *Anaesth Analg* 1993; **77:** 171–82.

Surgical Diathermy: Mechanisms, Use and Abuse

Andrew D Farmery

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The application of heat to wounds is evident in unearthed Neolithic skulls. Thermal cautery to ulcers and tumours of the breast was described in a papyrus from about 3000 BC, and later described by Hippocrates in 300 BC. Electrical diathermy is at least 250 years old, predating the practice of anaesthesia by a century.

Diathermy (*dia*, through; *thermy*, heat) strictly applies to the uniform heating of tissues by radiofrequency current or radiation. As a surgical tool, uniform heating is not required, but rather discrete and destructive heating in a specific area. This application is called 'electrosurgery' in the USA, and 'surgical diathermy' in the UK, but the term diathermy has remained.

Basic electrical principles

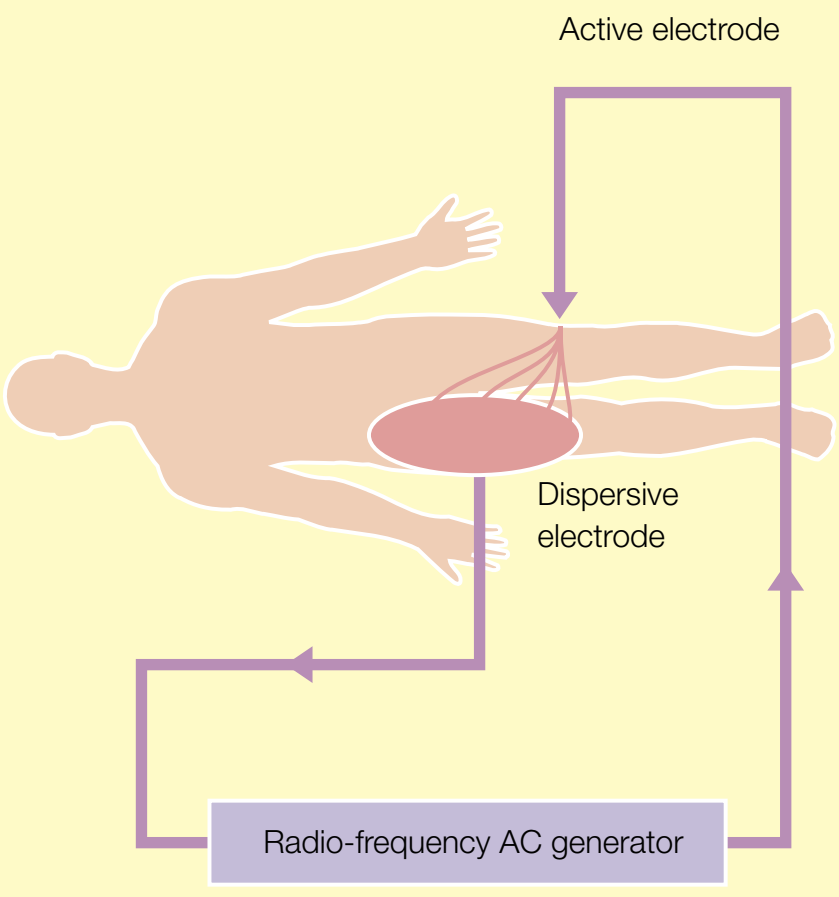
Forcing current through a resistance liberates heat

The power to heat, cut or vaporize tissues is derived from passing an electrical current through it. At any point in an electric circuit, the power dissipated is given by the formula:

$$\text{Power} = \text{Current}^2 \times \text{Resistance} \qquad (P = I^2 \times R) \quad 1$$

Current forced through regions of high resistance produces more heat than the same current passed through regions of low resistance. Figure 1 shows how the current density (and resistance) at the tip of a diathermy probe is many orders of magnitude higher than the current density elsewhere in the circuit, namely the patient's body and the large 'dispersive' electrode. This is analogous to a large crowd of people moving along a wide walkway to gain access to a football stadium. The flow is ordered and comfortable at the rear of the walkway, but when the same 'flow' is forced through a narrow turnstile, the 'power' of the crowd will be liberated (destructively) at this high resistance, high flow-density point.

Current density



The tiny active electrode/tissue contact has a high resistance, therefore a high power is liberated ($P = I^2 \times R$). Because this power is delivered to a small area, the power density, and ability to heat the tissue, is great. By contrast, the dispersive electrode, with its larger area of contact, has a low resistance and thus little power is liberated and it is distributed over a wide area, therefore the heating effect is negligible.

1

Using high-frequency alternating current prevents 'electrocution'

In Equation 1, both direct current (DC; e.g from a large battery) or alternating current (AC; e.g. from the mains supply) produce the same amount of heat for the same mean current. However, DC polarizes a tissue such that tissue connected to the anode becomes 'positive', and that connected to the cathode, 'negative'. This triggers ion channel opening and depolarizes important excitable tissues such as nerves, striated muscle and myocardium. The same is true of moderately low-frequency AC (e.g. 50 Hz), in which the tissue is alternately polarized and depolarized because the polarity of the applied voltage changes sinusoidally. This can result in convulsions, tetanic muscle twitch and ventricular fibrillation (i.e. electrocution).

High-frequency current is less prone to causing these phenomena because voltage-sensitive ion channels in excitable tissues do not respond instantly to an applied depolarizing voltage, but have a finite response time. An analogy is when the rudder of a tanker is turned suddenly, there is a delay before it slowly starts to change direction. If the rudder is turned from left to right with a low frequency, the tanker steers a course veering from left to right sinusoidally. However, if the rudder is oscillated from left to right with a high frequency, the ship steers a straight course because it does not have enough time to respond to a rudder movement in one direction before being directed to move in the opposite direction.

In the same way, a high-frequency AC voltage applied to the myocardium will neither polarize nor depolarize the membrane, because the ion channels will not have time to open or close before the polarity of the applied voltage is reversed and so the tissue will continue to function normally. Electrosurgical generators typically operate at frequencies of 0.5–4 MHz.

Surgical effects of diathermy

There are three main diathermy modes: desiccation, cutting and coagulation.

Desiccation

To cause desiccation (drying out), a low power current is passed through the tissues, as in Figure 1. The aim is to increase tissue temperature at the site of contact with the active electrode. Intracellular water is slowly driven off as steam and the tissue is dried out. This produces a blanching of tissue. Because the current is of low power, it is effective only in delicate tissues and small vessels (e.g. it is often used to blanch the fallopian tube before surgical division in laparoscopic sterilization). When tissue has been desiccated, its resistance to current flow becomes very high and current flow effectively ceases, thus terminating the heating process. It is impossible to 'cut' tissue in this mode. The current waveform is not important in this application.

Cutting

In the cutting mode, the aim is to make a discrete cut through the tissue. Initial contact with the electrode heats the tissue rapidly so that cells explode and their contents are instantly vaporized. Heat is not conducted very far from the site of contact because most of the liberated power is used to vaporize water (i.e. is consumed as latent heat of vaporization). The heating effect is therefore concentrated and neighbouring tissue is undamaged. Unlike desiccation, 'sparking' is a key feature.

The vaporized desiccated tissue is a poor electrical conductor and therefore breaks the circuit so that current flow ceases through this pathway. However, if the voltage (the driving force for current) is high enough, air around the electrode is ionized. Ionized air is a better conductor than desiccated tissue, and so current will now flow as a spark jumps to the nearest region of moist tissue. Tissue heating is produced by:

- current delivered by the spark ($I^2 \times R$)
- radiant heat from the spark
- collision of electrons bombarding the tissue.

This causes intense local heating, vaporization and thermal destruction. Cells are torn apart. The current waveform used is a continuous radiofrequency sinewave (Figure 2a).

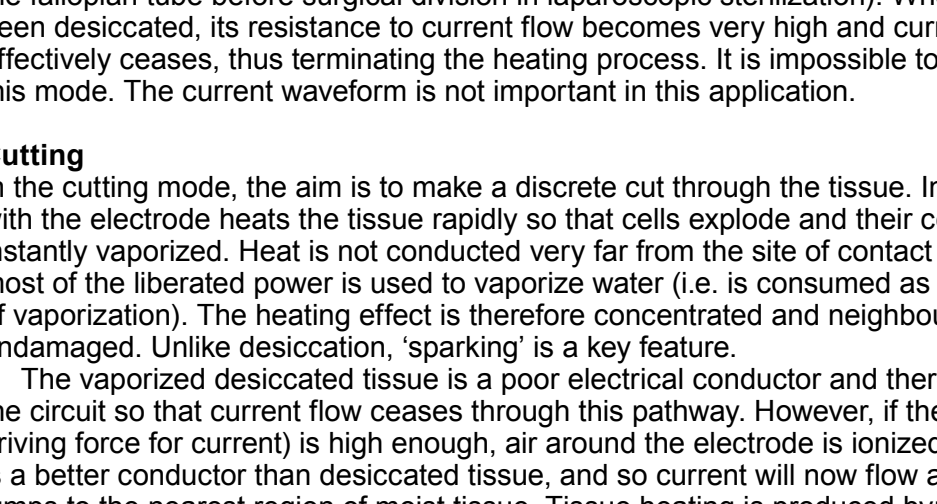
Coagulation

In coagulation mode (Figure 2b), the current waveform comprises short bursts of radiofrequency sinewaves (about 1 MHz), with bursts occurring about 20,000 times per second (burst frequency 20 kHz). The coagulation waveform can cause sparking to tissues. However, the radiofrequency current is delivered in intermittent bursts and therefore the ion cloud generated at each spark has a chance to disappear between bursts. Therefore, with each current burst, ionization occurs afresh, and because this is a random process sparking occurs more randomly and over a wider area than it does in cutting mode. This reduces the concentration of the sparking power and allows effective coagulation of vessels without tissue cutting. Peak voltages are much higher in the coagulation mode than in the cut mode because the current is zero for most of the time and so in order to deliver the same average power, the coagulation waveform generator has to deliver more power in the short periods when current is switched on.

Waveforms

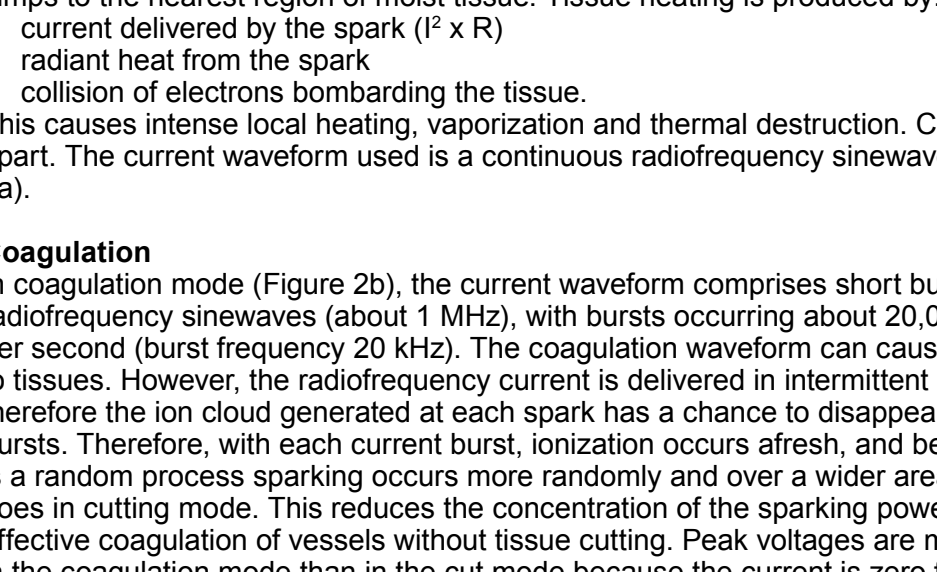
a Cutting waveform

A continuous radiofrequency sinewave of about 1 MHz



b Coagulation waveform

A 1 MHz sinewave delivered in bursts (20,000/second)



2

Monopolar and bipolar systems

Monopolar

The system described in Figure 1 is monopolar. Current is delivered via a pinpoint active electrode, which then passes through the patient (in a low-density path) to return via the dispersive electrode. This is the most widely used system because it is most effective in producing cutting as well as coagulation.

Bipolar
In a bipolar system, current is delivered via one arm of a pair of insulated forceps. It passes through any tissue grasped between the arms of the forceps and returns via the opposite arm. With a bipolar system, only desiccation can be achieved. The system is of limited power, and sparking does not occur. If the arms of the forceps are allowed to make contact with each other directly, despite there being some tissue in the path, current will be 'shorted-out', and diathermy will be less effective. Bipolar diathermy is indicated where it is undesirable to pass current through the patient's body to a distant dispersive electrode; some examples are given below.

Narrow current conduits to extremities (e.g. testicle surgery) – if a monopolar system were used, with the dispersive electrode placed on the abdominal wall, current would be forced to pass from the testicle along the vas deferens (the path of least resistance) to the trunk. Because the vas deferens is a narrow tube, current density would be high within it, and thermal injury might result.

Metal prostheses – if a metal prosthesis lies between the dispersive and active electrode, current preferentially passes through this low resistance route, producing a high current density and heating in narrow points such as a cortical screw. This may necrose bone or conduct heat to neighbouring soft tissue or vessels, sufficient to perforate an artery.

Cardiac pacemakers – the cable connecting a pacemaker generator box (implanted in the anterior chest) to the electrode in the right ventricle and/or atrium constitutes a low impedance pathway for radiofrequency current if it lies between the active and dispersive diathermy electrodes. This may result in a high current density at the point of pacemaker electrode insertion into the myocardium. Tissue desiccation may occur at this point, increasing the resistance of the contact. The 'threshold' potential may increase, such that the pacing pulse fails to trigger the heart.

More sophisticated pacemakers are capable of detecting intrinsic cardiac activity and withholding activation of the pacemaker. It is possible that stray radiofrequency current may be detected by the pacemaker, and interpreted as intrinsic cardiac activity, resulting in inappropriate inactivation of the pacemaker. For this reason, it is advisable, if possible, to have the pacemaker programmed so that this function is disabled. The safest precaution, however, is to avoid monopolar diathermy.

Patient safety

The principal issues are:
- avoidance of inadvertent thermal burns from stray diathermy current
- avoidance of inadvertent electrocution from stray 50 Hz mains current.

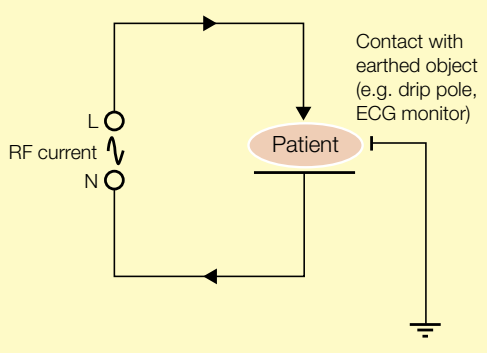
Isolated (unearthed) dispersive electrode system
Figure 3a shows a simple circuit in which neither live nor neutral terminals of the radiofrequency current generator are connected to earth.

A fundamental law of electricity is that all the current leaving the live terminal is returned to the neutral terminal. Therefore, if the patient makes contact with an earthed object (e.g. lithotomy pole, drip stand or faulty low impedance ECG electrode) none of the radiofrequency diathermy current should pass via this contact to earth because such a stray current would not be able to return to the neutral terminal. All the current should pass to the neutral terminal via the large dispersive electrode, thereby eliminating the potential for burns. This might seem a safe system but it is possible to burn patients inadvertently with isolated systems because of the phenomenon of 'capacitive coupling'. It is difficult to confine very high-frequency currents to wires, and currents tend to pass out of the cables like a radio transmitter because a wire and another conductor (e.g. earth) can behave like the two plates of a capacitor. Capacitors can conduct high-frequency current, even though insulation and a few feet of air separate the wire and earth. Radiofrequency leakage current flows only if there is a route for it to return to the neutral terminal; Figure 3b shows how this might happen. A certain amount of current from the active lead is leaked to earth via this capacitive coupling. This can return to the patient via any small, grounded contact point and potentially cause a burn at this site. From this point, the leakage current joins the main current and returns to the neutral terminal via the dispersive electrode.

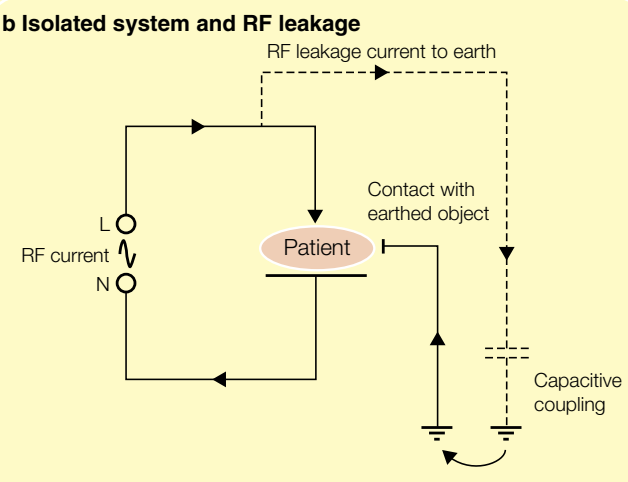
Early electrosurgical generators were not truly isolated. There was usually some connection of the neutral terminal and dispersive electrode cable to earth because of capacitive coupling between them, in a similar way to that described above. Figure 3c shows how this allows current to flow to earth through grounded contact points and complete the circuit to the neutral terminal via the 'virtual' earth connection. The amount of stray current passing through the grounded contact points depends on the relative impedance of the pathways. Given that one cannot avoid some current passing to ground, the best way to prevent this passing through unwanted pathways is to provide a route to ground via the dispersive electrode which is more 'attractive' than the alternative routes. This is done by physically earthing the dispersive plate and making the impedance of this connection as low as possible.

Isolated and earthed systems

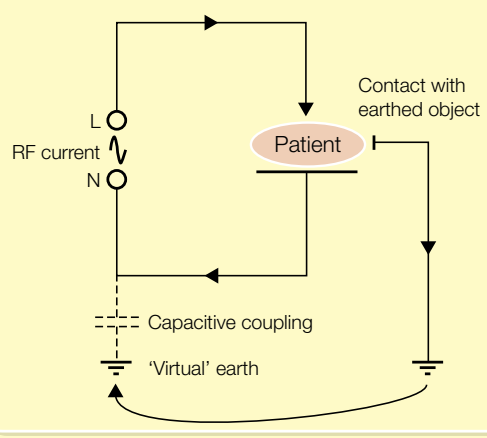
a Isolated system



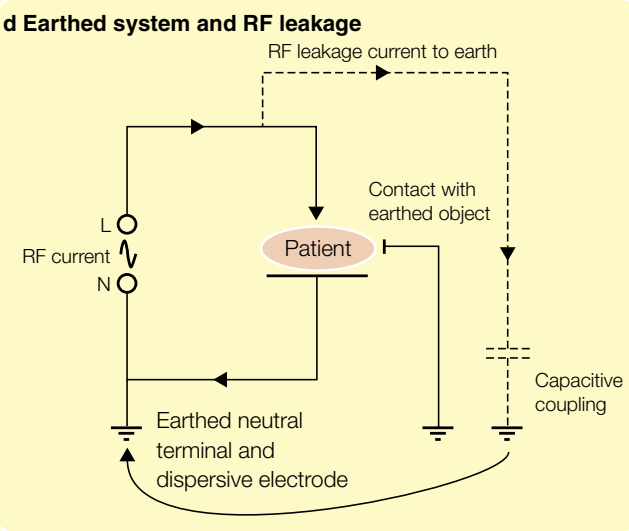
b Isolated system and RF leakage



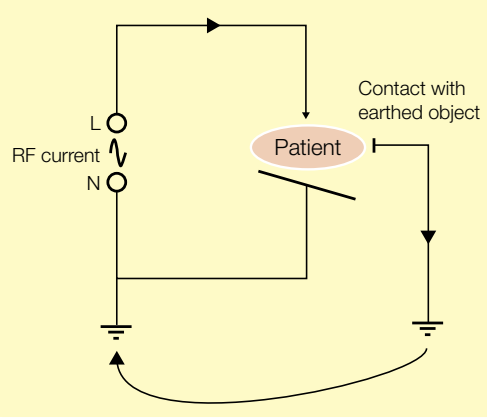
c Isolated system and 'virtual' earthing of dispersive electrode



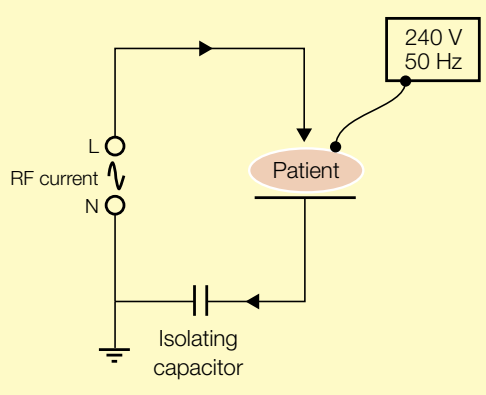
d Earthed system and RF leakage



e Earthed system and poor dispersive electrode contact



f Earthed system and isolating capacitor



L, live; N, neutral; RF, radiofrequency

Earthed dispersive electrode system
Earthing the dispersive electrode overcomes both the 'virtual' earth problem (Figure 3c) and the radiofrequency leakage problem (Figure 3b). Figure 3d shows how if the dispersive electrode and neutral terminal are earthed, any radiofrequency leakage current can return to the neutral terminal via a direct low impedance earth route that bypasses the patient. However, earthing poses other problems.

Dispersive electrode detachment: the dispersive electrode is an attractive route for ground-seeking radiofrequency current only if its impedance is many orders of magnitude lower than unwanted stray routes. If the dispersive electrode becomes detached or makes poor contact, all of the radiofrequency current can pass to earth (and hence return to the neutral terminal) via unwanted grounded contact point, as shown in Figure 3e, thus causing burns.

Mains electrocution: if the patient is exposed to a live mains voltage (e.g. via a faulty monitor lead) the earthed dispersive electrode provides a low impedance pathway for this dangerous 50 Hz current to pass through the patient to earth, thus causing electrocution. This is because mains voltage is ground seeking. This problem can be overcome by placing a capacitor in the circuit as in Figure 3f. This is capable of passing radio-frequency current, but does not conduct low frequency (50 Hz) current. Even though the patient is exposed to a live mains cable, no 50 Hz current will flow through the patient to the ground.

Techniques of Cricoid Pressure

Richard Vanner

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In 1956, the Association of Anaesthetists had collected 1000 reports of anaesthetic deaths; 110 from pulmonary aspiration of stomach contents. This often occurred during induction of general anaesthesia especially when muscle-relaxant drugs were used. Anaesthetic techniques were developed to prevent aspiration in patients at risk and included:

- emptying the stomach before induction
- intravenous induction with head-up tilt position
- inhalational induction in the lateral and head-down position.

In 1961, Sellick described cricoid pressure as a technique used to prevent regurgitation of stomach contents during the induction of general anaesthesia. It was brought into widespread practice in the UK by 1970 and largely replaced the other techniques, despite no randomized controlled trials demonstrating its benefit. It has become a routine part of anaesthetic practice for patients at risk of aspiration in combination with pre-oxygenation, an intravenous induction and tracheal intubation. All UK maternity units routinely apply cricoid pressure during induction of general anaesthesia.

Before the introduction of cricoid pressure, the incidence of aspiration pneumonitis in obstetric general anaesthetics was about 0.15%. If cricoid pressure prevents aspiration, the number needed to treat to prevent one case of aspiration would be 666. A controlled trial would be difficult because of the large numbers of patients needed and the difficulty of obtaining ethical approval.

Indications

In a patient who has been prepared for elective surgery and has not eaten for 6 hours or drunk for 2 hours, regurgitation of stomach contents during the induction of anaesthesia is unusual even when muscle-relaxant drugs are used, which relax the upper oesophageal sphincter. In these patients, cricoid pressure is unnecessary, because its benefits have to outweigh the risk of complications. However, cricoid pressure is indicated if:

- surgery is necessary before the patient is fasted
- gastric emptying is delayed
- the lower oesophageal sphincter is incompetent (e.g. in the last half of pregnancy or in reflux oesophagitis). With a full stomach from any cause, distention of the fundus causes reflex relaxation of the lower oesophageal sphincter.

Mechanism of action

Regurgitation is the flow of fluid from the oesophagus into the pharynx and is a passive process. When patients are awake the upper oesophageal sphincter prevents regurgitation. The pressure that this sphincter exerts is about 40 mm Hg and it relaxes during swallowing and during sudden distension of the oesophagus (e.g. belching, vomiting). The sphincter is mainly the cricopharyngeus muscle, a skeletal muscle, which is attached to the lateral aspects of the cricoid cartilage and is positioned behind it like a sling. The lumen of the hypopharynx within the cricopharyngeus is therefore crescent shaped. The oesophagus begins below the level of the cricoid cartilage.

The upper oesophageal sphincter relaxes during intravenous induction with thiopental (thiopentone), with heavy sedation, during deep sleep or following muscle-relaxant drugs. In all of these situations the sphincter pressure is reduced to less than 10 mm Hg, which is low enough to allow regurgitation. Following thiopental (thiopentone) the sphincter starts to relax just before loss of consciousness but is not fully relaxed until 30 seconds later. Ketamine does not relax the upper oesophageal sphincter, nor does an inhalational induction. Coughing during an inhalational induction increases upper oesophageal sphincter pressure to over 100 mm Hg.

Cricoid pressure prevents regurgitation by replacing the function of the upper oesophageal sphincter by compressing the hypopharynx against the prevertebral fascia muscles and vertebrae behind. The convex cricoid is pressed against the convex body of either the 5th or 6th cervical vertebrae. Inevitably the cricoid cartilage is deviated slightly laterally (Figures 1 and 2). Part of the crescent-shaped lumen is compressed against the vertebral body and the rest of it is less well compressed against the longus colli muscle to one side. A nasogastric tube is squeezed laterally towards the less well compressed part of the lumen and makes the occlusion of the hypopharynx more complete and therefore cricoid pressure more efficient.

A study of women undergoing emergency caesarean section under general anaesthesia with muscle relaxation showed that gastric pressure is likely to be less than 25 mm Hg in 99%. Oesophageal pressure can rise to equal gastric pressure during gastro-oesophageal reflux as the lower oesophageal sphincter relaxes to create a common cavity. A study of ten cadavers showed that 20 Newtons (N) of force applied to the cricoid cartilage prevented the regurgitation of oesophageal fluid at a pressure of 25 mm Hg in all cases and 30 N prevented regurgitation at a pressure of 40 mm Hg in all cases. Therefore, 20 N of cricoid pressure is probably sufficient and 30 N is more than enough to prevent regurgitation into the pharynx. Anaesthetic assistants can be trained to apply the correct force by practising on weighing scales and by doing this they can apply a range of forces between 5 N above or below the target force. A reasonable recommendation is to apply 30 N (3 kg).

Correct technique

Although cricoid pressure is apparently a simple technique there is growing evidence that incorrect application can cause serious problems during induction of anaesthesia. The anaesthetic assistant should practise the correct forces on weighing scales. The anaesthetist should be confident that the anaesthetic assistant knows the anatomical landmarks of the cricoid cartilage. Although Sellick suggested that the patient's head should be extended, the author recommends that it should rest on a pillow because intubation is easier and cricoid pressure is just as effective in this position. After pre-oxygenation, but before intravenous induction, lightly applied cricoid pressure should be started with a force of 10 N (1 kg), after loss of consciousness the force is increased to 30 N (3 kg). Forces of 20 N or more are not tolerated by awake patients and may cause them to retch and vomit. Normally the assistant applies cricoid pressure with their dominant hand because this can be maintained more accurately and for longer (3–5 minutes). There is no evidence that a bimanual technique, with the assistant's other hand supporting the patient's neck, improves the view at laryngoscopy when the correct forces are applied. The assistant's other hand is best kept free to assist with a difficult intubation if necessary.

Patients with small bowel obstruction should have a nasogastric tube inserted preoperatively. This should be aspirated before induction and left in place during induction. This does not make cricoid pressure less efficient and may improve it. As the tube is not compressed, it is possible, by leaving it open to atmospheric pressure, to vent liquid and gas remaining in the stomach, minimizing any increase in gastric pressure.

Sellick described the application of cricoid pressure with three fingers, thumb and middle finger on each side of the cartilage with the pressure applied with the forefinger. However, with the head on a pillow it is more comfortable to apply it with two fingers, forefinger and thumb on each side of the cartilage. This gives flexibility to apply upward and backward cricoid pressure, which improves the view at laryngoscopy if this becomes necessary. As the cricoid inevitably moves slightly laterally during cricoid pressure, it is better to ensure that it moves to the patient's right rather than to the left because this also makes intubation easier with a Macintosh laryngoscope.

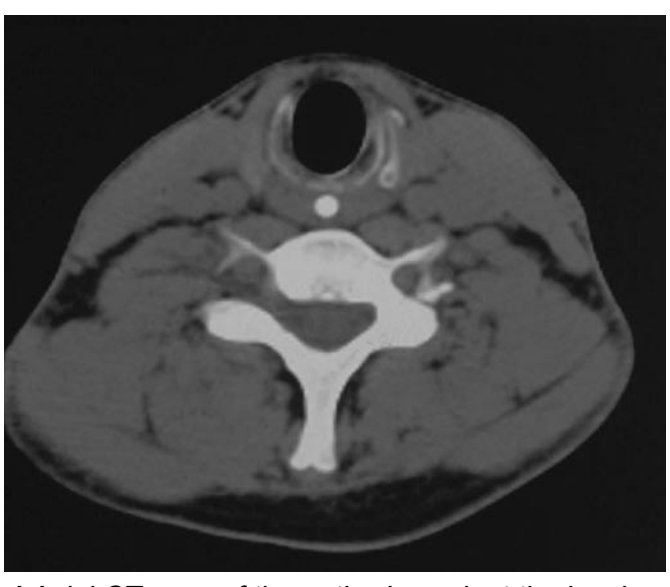
Complications

Excess force applied to the awake patient has caused retching and death from aspiration and ruptured oesophagus.

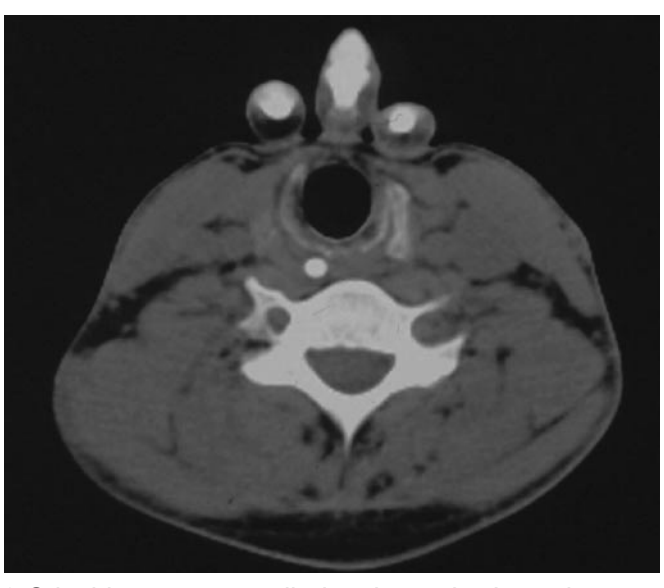
Difficult intubation can be caused by cricoid pressure if the force is applied to the thyroid cartilage or if the larynx is pushed laterally to the left or if too much force is used, which compresses the airway. When cricoid pressure is applied properly with a force of 30 N (3 kg) the view at laryngoscopy is improved compared with the situation when no cricoid pressure is used. However, if only the epiglottis can be seen, then the slight lateral displacement of the larynx, which is inevitable, will make the passage of a gum elastic bougie more difficult because this is normally passed in the midline.

The so-called 'cricoid yoke', a force transducer applied to the neck, is not ideal, because it may not be applied accurately to the cricoid cartilage and may cause tracheal compression or extreme lateral displacement of the larynx, resulting in difficulty with tracheal intubation.

Difficult ventilation – cricoid pressure can obstruct the airway and prevent ventilation of the lungs with a face mask and Guedel airway. This is proportional to the force applied; 30 N causes complete obstruction in 2% of patients and 40 N does in 35%. Upward and backward cricoid pressure at a force of 30 N causes airway obstruction in 56% possibly because it tilts the cricoid cartilage and opposes the vocal cords. Following a failed intubation in a patient with a full stomach when the lungs cannot be ventilated, the force of cricoid pressure should be reduced by half. If this does not allow ventilation, cricoid pressure should be released completely to allow ventilation, with laryngoscope and suction immediately available. Further airways that may then be necessary (e.g. laryngeal mask, *Combitube*, cricothyrotomy cannula) are all better placed without cricoid pressure applied.



1 Axial CT scan of the author's neck at the level of the cricoid cartilage showing a nasogastric tube filled with radio-opaque contrast media.



2 Cricoid pressure applied to the author's neck showing the slight lateral displacement of the cricoid and the lateral position of the nasogastric tube.

FURTHER READING

Brimaccombe J R, Berry A M. Cricoid Pressure. *Can J Anaesthesia* 1997; **44:** 414–25.
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Tracheal Intubation: Management of Difficult and Failed Intubation

Stuart W Benham

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Securing the airway with a tracheal tube is a core skill for anaesthetists. The technique may be required during anaesthesia, resuscitation or intensive care. The ability to manage patients when laryngoscopy is predicted to be difficult, or when intubation has previously failed, requires a methodical approach and a workable back-up plan. Indications for tracheal intubation are given in Figure 1.

Patients with depressed conscious levels (e.g. following head injury, self-poisoning, vascular accident, infections) need careful assessment. If there is any concern that airway reflexes are diminished, the airway must be secured with a tracheal tube. A low Glasgow Coma Score (e.g. GCS < 9) should not be relied on as the sole indication of airway compromise.

Intermittent positive-pressure ventilation can be achieved by non-invasive means without tracheal intubation. In the operating theatre this is often performed with the laryngeal mask airway (LMA), and in the ICU with a secure fitting face mask with head strapping.

Indications for tracheal intubation

Surgical indications
- Shared airway surgery
- Requirement for one lung ventilation
- Prone or sitting position for surgery
- Open abdominal or thoracic surgical procedures
- Major head and neck surgery
- Prolonged surgery

Emergency indications
- Prevention of aspiration in unfasted patients requiring general anaesthesia
- Impending airway obstruction (e.g. epiglottitis, airway burns)
- Maxillofacial trauma (blood in the airway)
- Depressed conscious level with poor airway reflexes

Ventilatory failure indications
- For intermittent positive-pressure ventilation
- Prevent aspiration of gastric contents
- Advanced ventilation strategies (e.g. partial liquid ventilation, high frequency jet ventilation)
- Prone ventilation strategies
- Ventilatory failure unresponsive to non-invasive positive- pressure ventilation

1

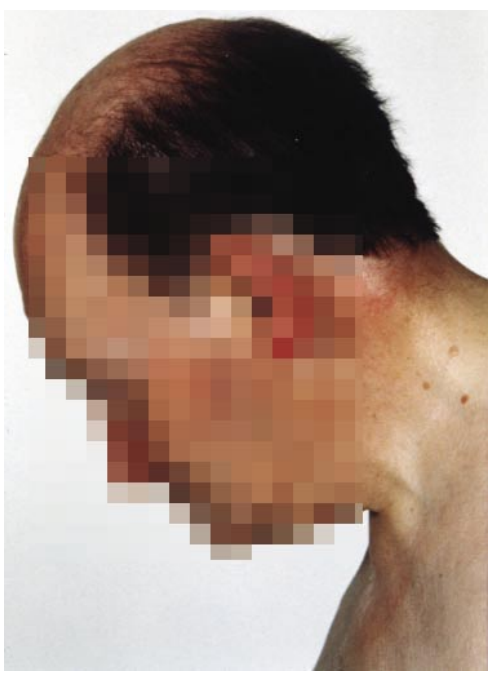
Management of difficult airway and failed intubation

The maintenance of alveolar ventilation is the most important aspect of difficult airway management. Patients in whom intubation is difficult or has failed, and in whom mask ventilation is also difficult are uncommon (about 1:10,000 routine anaesthetics). The anaesthetic plan must not render an awake patient who can maintain a patent airway into an unconscious patient with an unsafe and obstructed one. Preoperative assessment aims to identify patients in whom laryngoscopy and/or airway maintenance are likely to be difficult when consciousness is lost. Patients generally fall into one of three categories:
- anticipated difficult laryngoscopy
- elective unanticipated difficult laryngoscopy
- emergency unanticipated difficult laryngoscopy or failed intubation.

Anticipated difficult laryngoscopy
A comprehensive plan is required involving a primary plan and a secondary plan to be used if the primary plan fails. Two common pitfalls are:
- the operator is inexperienced in the technique chosen (e.g. flexible fibre-optic laryngoscopy – FFL)
- the back-up plan involves staff, skills and equipment that are not readily available at the time of induction (e.g. tracheostomy).

Anaesthetists have to develop plans with their own skill levels in mind, incorporating available equipment and supporting staff. Patient safety is of paramount importance. Generally, less invasive, atraumatic techniques should be preferred to surgical airway control, especially in elective patients. However, the emergency anticipated difficult airway (e.g. patients with severe maxillofacial trauma, or enlarging wound haematoma and stridor following head and neck surgery) may require a surgical airway as the primary plan.

Patients with bony abnormalities may have restricted mouth opening due to temporo-mandibular joint disease, or a cervical spine with limited neck flexion or extension (Figure 2). There is an expectation that the oropharynx and periglottic regions will be normal. In these patients, direct laryngoscopy may be impossible, but the normal oropharyngeal anatomy allows the passage of an FFL under general anaesthesia and assisted ventilation should be possible. If the primary plan fails during this elective surgery, the patient may be woken before implementing the secondary plan.



2 Restricted neck extension in ankylosing spondylitis.

Patients with obstruction in the supraglottic region include those with previous major oral surgery or radiotherapy. If there is evidence of stridor, the patient should be treated with extreme caution and one of the plans outlined below for periglottic or infraglottic obstruction should be considered. Stridor implies 50% airway narrowing. These patients may develop complete airway obstruction when anaesthetized and a surgical airway should be included in the management plan. Depending on the anaesthetist's skill, two options for the non-stridulous patient are:
- an awake fibre-optic endoscopy and intubation, before any relaxant or induction agent is given
- an inhalational induction and direct laryngoscopy to define the anatomical situation, and the feasibility of passing a tracheal tube.

Patients with obstruction in the periglottic region (including obstructing laryngeal tumours) require a thorough preoperative evaluation (e.g. CT, MRI) to assess the degree of obstruction and clinical assessment of the degree of stridor. Indirect laryngoscopy and flexible fibre-optic nasendoscopy are necessary to determine the extent of the obstruction and the feasibility of passing a tracheal tube, which should be performed by an experienced ENT surgeon. Non-stridulous lesions can be managed similarly to lesions causing supraglottic obstruction. Stridulous lesions are the most difficult to manage because neither awake fibre-optic endoscopy nor inhalational induction guarantees success. The choice of technique depends on the degree of stridor, the general condition of the patient and the experience of the anaesthetist. Severe cases may best be managed by awake tracheostomy under local anaesthesia. Depending on the level of the lesion, particularly with infraglottic obstruction, even emergency tracheostomy may not be realistic. For the most severe lesions it may be necessary to consider extracorporeal oxygenation as part of the secondary plan.

Elective unanticipated difficult laryngoscopy
Elective unanticipated difficult laryngoscopy is best managed using a stepwise approach.
- Reconfirm that assisted bag and mask ventilation is possible.
- Consider repositioning the head and neck and the use of a bougie.
- Avoid prolonged attempts at direct laryngoscopy. Change the length of laryngoscope blade once and the type of blade once to achieve the optimum view.
- Call for help and for the FFL if competent in its use.
- Consider the use of the LMA or the intubating LMA (ILMA) for ventilation.
- Consider using the LMA/ILMA as a conduit for intubation (see below).
- Consider abandoning anaesthesia, and performing an awake intubation.

Emergency unanticipated difficult laryngoscopy and failed intubation
This is a failure to secure the airway with a tracheal tube following a rapid sequence induction. Remember that it is failure of oxygenation, rather than a failure of intubation, that accounts for morbidity and mortality. The same stepwise approach as that for the elective unanticipated difficult laryngoscopy should be followed. All departments of anaesthesia should have a failed intubation drill for these circumstances, and clinicians should be familiar with their local protocols (see *Anaesthesia and Intensive Care Medicine* **2:6:** 221). It should be noted that in these situations the removal of cricoid pressure may help ventilation attempts, especially through the LMA. The risks of aspiration are small in comparison to the potential for morbidity and mortality caused by hypoxia from failed ventilation.

Techniques to overcome difficult intubation

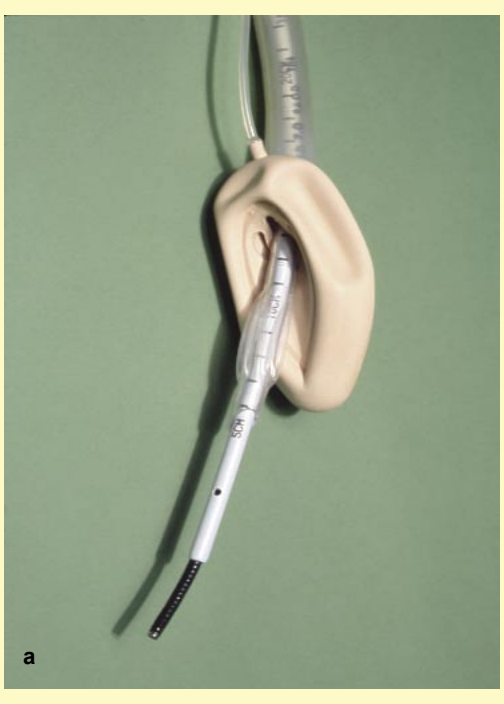
Many devices have been developed to improve the chances of securing the airway with a tracheal tube. Some of those used by practising clinicians are described below.

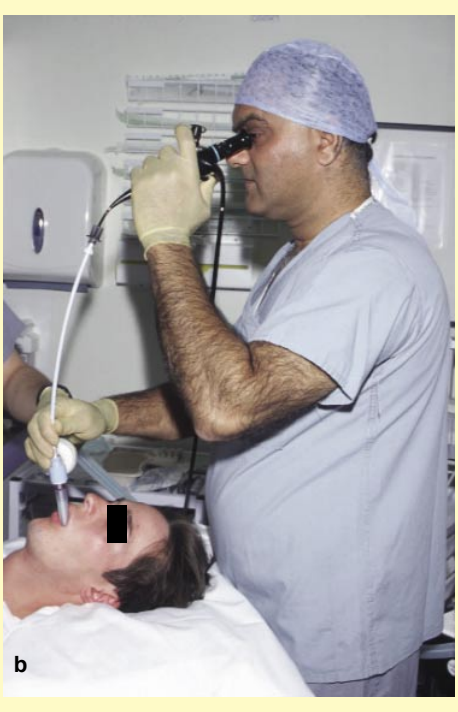
Position and simple manoeuvres
Optimizing the patient's position (flexion of the cervical spine and head extension at the atlanto-occipital joint – the 'sniffing the morning air' position) is the first step to improve the view at direct laryngoscopy. Simple manoeuvres such as external laryngeal manipulation, especially backwards, upwards and rightwards pressure on the larynx can improve the view by more closely aligning the visual axis with the laryngeal inlet.

Laryngoscopes
There is a range of curved and straight blades, as well as blades with movable hinged tips (McCoy), that may improve the view at direct laryngoscopy (see *Anaesthesia and Intensive Care Medicine* **1:1** 34). Many experienced anaesthetists, however, tend to use the same type of laryngoscope blade for all their patients. Skills in the use of different blades are best acquired during routine intubations. The McCoy, or the angled Belscope laryngoscope, may be able to convert a Cormack/Lehane grade 3 view to a grade 2 view, though familiarization with the technique is required.

Simple props and aids
Gum elastic bougies should be used when:
- direct laryngoscopy allows visualization of the epiglottis but not the larynx (a grade 3 view)
- visualization of the larynx is possible but direct passage of the tracheal tube is prevented by awkward oral anatomy or teeth
- a reinforced or flexible tracheal tube cannot be directed into the visualized larynx.

Aintree intubation catheter (Cook©) (Figure 3) can be used like a gum elastic bougie, or in combination with other airway and intubating devices such as the LMA or FFL. It is sufficiently long and thin to allow a tracheal tube to be railroaded over it. It is hollow and has a detachable tube connector/adaptor that allows ventilation during the intubation process. An FFL can also be passed through it if required.





a Flexible fibre-optic laryngoscope and Aintree intubation catheter passed through the laryngeal mask airway (LMA).
b Fibre-optic endoscopy through the LMA with the Aintree exchange catheter.

3

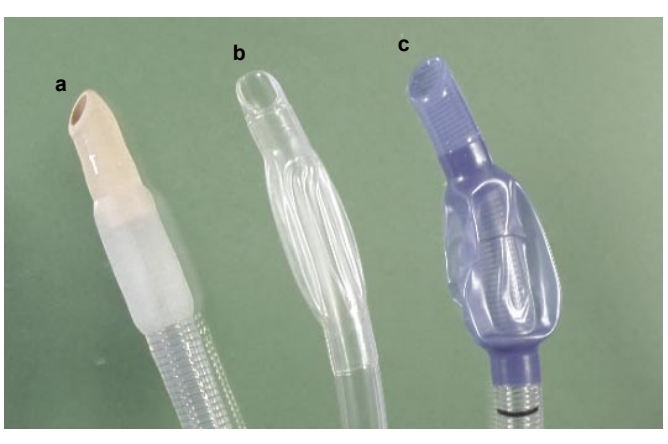
LMA and ILMA
Most anaesthetists use the LMA regularly for patients not requiring intubation. The ability to insert an LMA to allow spontaneous or assisted ventilation is a core skill for anaesthetists. It also provides a route guide for intubation, either blind or guided by an FFL. The LMA may help to achieve ventilation in patients who are otherwise difficult to intubate and ventilate.

The ILMA is modified to improve the chances of passing a tube blindly through the mask into the trachea. There is an initial short learning curve for the operator, and the clinician should practise using the ILMA in patients with normal airways before it is used in those with difficult or abnormal ones.

The main limitation on both devices is that there has to be enough mouth opening to permit inserting the device. Intubation can be blind, but both devices can be used with an FFL to visualize laryngeal anatomy and aid intubation.

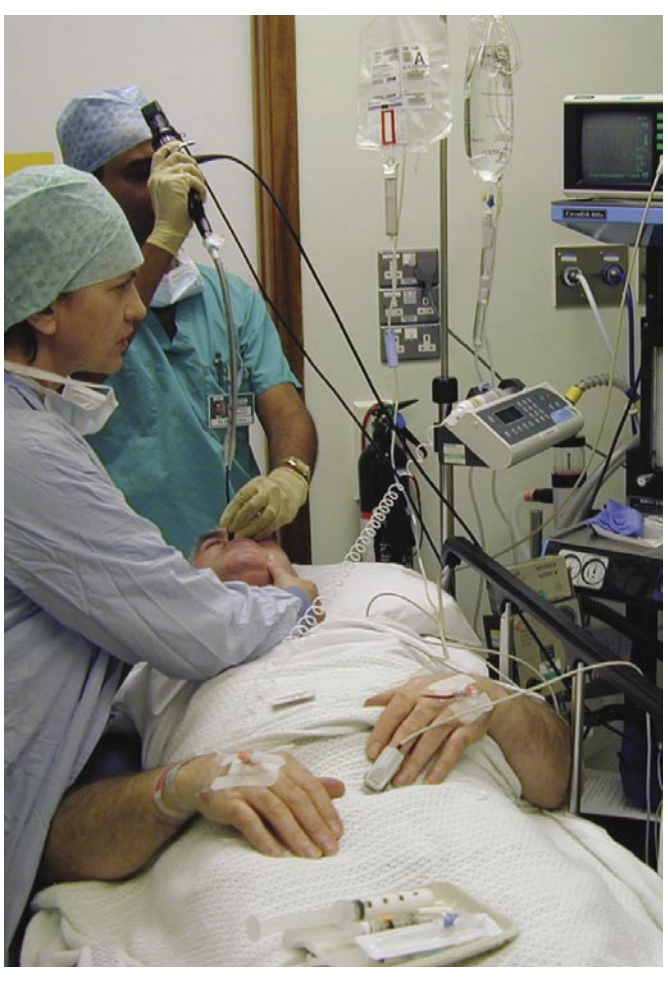
Railroading the tracheal tube
The need to railroad the tracheal tube over the guide is the final step in intubation. Two manoeuvres to increase its success rate and minimize laryngeal trauma are choice of tracheal tube and bevel direction.

- The ILMA tube (softer tip) or reinforced tracheal tube (less acute bevel and softer tip) has a higher chance of passing through the vocal cords (Figure 4).
- The bevel of the standard tracheal tube is directed to lie in the right or left lateral position as it reaches the vocal cords. It is then rotated 90° as it is pushed gently through the cords. If this is unsuccessful, the tube is rotated through 360° continuously with gentle pressure to slip through the cords. If still unsuccessful, direct laryngoscopy can be performed to check the position of the route guide, and to lift the epiglottis to facilitate tube railroading.



4 Tracheal tube tips. **a** The intubating laryngeal mask airway tube, **b** standard tube, and **c** the flexometallic tube

FFL and intubation
FFL and intubation can be performed with the patient awake or anaesthetized. Awake fibre-optic intubation performed by a competent endoscopist is safe (Figure 5). The patient remains awake and self-ventilating with maintained pharyngeal muscle tone.



5 Awake fibre-optic intubation. Note the use of propofol sedation and jaw thrust.

Suggested procedure for awake fibre-optic intubation
1 Premedication of morphine, 0.1–0.15 mg/kg i.m., and hyoscine (scopolamine), 200 µg i.m., 1 hour before procedure.
2 The patient should lie semi-reclined on a trolley in the anaesthetic room, facing the anaesthetist.
3 Intravenous sedation should be administered cautiously. Target-controlled infusion with propofol (plasma concentration 0.5–1.5 µg/ml) is well tolerated.
4 Topical anaesthesia of the upper airway should be provided:

- Nasal mucosa; mixture of 5% cocaine, 2 ml, and 8.4% bicarbonate, 2 ml, as topical spray, with the patient taking deep breaths in with each spray. If the patient requires orotracheal intubation the oropharynx can be anaesthetized with lidocaine (lignocaine) spray or gel. Oropharyngeal route guides (e.g. *Ovassapian* or *Berman* airway) can be used to aid orotracheal intubation. These allow the operator to pass the FFL and tracheal tube through them. They prevent soft tissue collapse and are sized to guide the FFL through the mouth, and emerge at the epiglottis, where it can be directed into the larynx.
- Spray as you go (SAYGO) with 4% lidocaine (lignocaine) through the working channel of the FFL. Insertion of an epidural catheter through the working channel to the tip of the scope, with the catheter end trimmed to produce one end-hole, can facilitate accurate delivery of the local anaesthetic injection. Inject 1 ml solution with 4–5 ml air to help disperse the anaesthetic. Before the first attempt to pass the FFL, and before each subsequent attempt, oropharyngeal suctioning with a Yankaur sucker may be required.
- Administer supplemental oxygen. This can be delivered conveniently via a flexible suction catheter passed into the opposite nostril.

5 Allow adequate time (at least 30 seconds) after topicalization before the FFL is advanced. Avoid passing the FFL blindly. If the view ahead becomes obscured, gently withdraw the insertion cord until airway anatomy is again identified. Ask the patient to take deep breaths when advancing towards the laryngeal inlet. This opens the airway and abducts the vocal cords. If visualization of the larynx is difficult, performing a gentle jaw thrust manoeuvre on the patient can help.
6 Once the scope has been advanced through the cords it should be advanced to just proximal to the carina. A common error is to allow the FFL to withdraw, or even become displaced from the trachea while the tube is railroaded into place. This happens more often if the patient coughs at this time. The operator should attempt to keep the FFL in the centre of the airspace at all times. This minimizes trauma to the delicate tracheal mucosa and reduces the amount of blood in the airway.
7 Railroading the tracheal tube is described above. It is helpful for the assistant to hold the FFL stationary allowing the operator to railroad the tube into place using both hands.
8 A final useful check to estimate the distance from the end of the tracheal tube to carina can be performed as follows. Once intubation has been performed, the FFL is passed down just proximal to the carina. The assistant lightly pinches the FFL as it enters the proximal end of the tracheal tube. The FFL is then withdrawn slowly until the distal end of the tracheal tube comes into view. As soon as this is seen, the distance from the assistant's fingers to the tube connector of the tracheal tube is noted. This is the distance from tip of tube to carina.
9 The breathing system with capnograph is connected. The patient may then be anaesthetized and laid flat. Satisfactory ventilation is confirmed, and muscle relaxant can be given if required.

Problems with flexible fibre-optic intubation: the FFL is an intubating tool, not a ventilation device. Oxygenation and ventilation must be maintained throughout the intubation procedure.

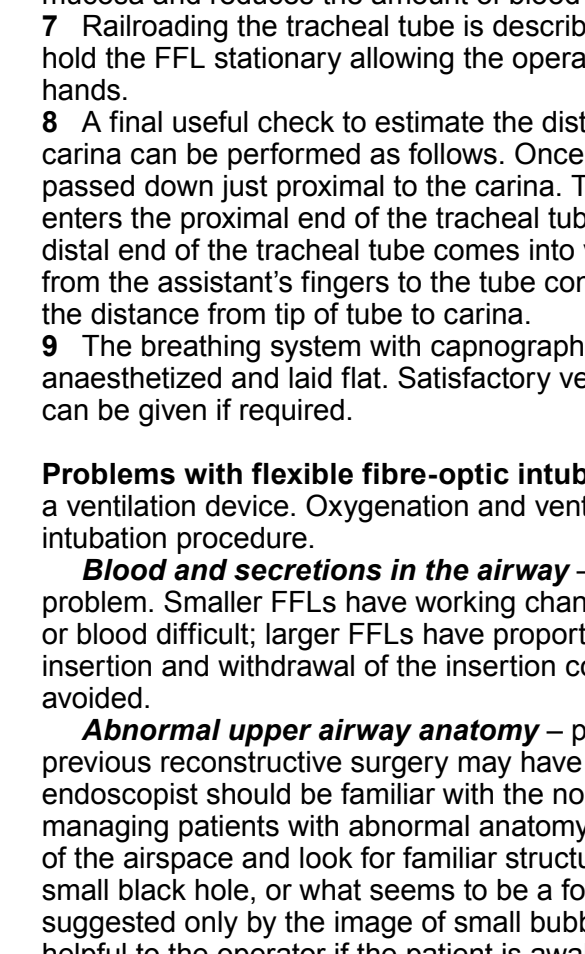
Blood and secretions in the airway – a poor view is the endoscopist's main problem. Smaller FFLs have working channels that make suctioning of sticky secretions or blood difficult; larger FFLs have proportionally larger suction channels. Repeated insertion and withdrawal of the insertion cord may precipitate bleeding and should be avoided.

Abnormal upper airway anatomy – patients with oro-pharyngeal lesions or previous reconstructive surgery may have abnormal upper airway anatomy. The endoscopist should be familiar with the normal appearances through the FFL before managing patients with abnormal anatomy. In all patients, keep the FFL in the centre of the airspace and look for familiar structures. Often the larynx is identified only as a small black hole, or what seems to be a fold in the mucosa. Identification is sometimes suggested only by the image of small bubbles appearing from a dark crevice. It is helpful to the operator if the patient is awake, semi-recumbent, and cooperating by taking deep breaths.

Equipment problems – the FFL should be checked and cleaned before use.

- The tracheal tube should be loaded on the FFL before endoscopy; forgetting to do this is a common mistake.
- Ensure that the light is on and working with white balance and focus optimal before commencing endoscopy.
- Lubricating jelly should be applied to the outside of the scope, and the tracheal tube, to facilitate easy nasal passage and tracheal intubation.
- Difficulties in railroading the tracheal tube can sometimes result from a large difference in the external diameter of the scope and internal diameter of the tracheal tube. This may be overcome by use of the Aintree intubation catheter. The intubation catheter can be railroaded over the scope, and then the tracheal tube railroaded over this.

Lack of hand–eye coordination can be remedied by practice on simulators, manikins and learning models such as an artificial bronchial tree or the Oxford 'hit-the-hole' box (Figure 6). It is indefensible to acquire these basic skills at the expense of the patient's mucosa.



6 The Oxford 'hit-the-hole' training box.

An inability to recognize anatomy is easily addressed by experience gained from instructional videos, clinical teaching and supervision. The case for using an FFL to aid routine nasal intubation is robust. In addition to the excellent learning opportunity afforded by routine use of the FFL, it assists in the selection of the best nostril and largest airspace, and identifies vulnerable nasal pathology such as polyps.

Transtracheal access

The final route for rescuing an obstructed airway is direct transtracheal access. This can be through the cricothyroid membrane, or through the upper trachea. Most anaesthetists never need to resort to this. Elective procedures, such as cricothyroid puncture used to inject local anaesthetic, or performing percutaneous tracheostomies in the ICU, provide valuable experience in tracheal access. The ability to identify the cricothyroid membrane and to insert a cricothyroid airway catheter rapidly may be a life-saving procedure. See Anaesthesia and Intensive Care Medicine issue 2:7: 268 for discussion of emergency tracheal access.

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Clinical assessment

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Assessment of Gastrointestinal Problems

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Anaesthetists encounter patients with gastrointestinal problems in two contexts.

- As critical care physicians caring for patients with gastro-intestinal problems that occur as a cause of and a consequence of critical illness.
- As perioperative physicians caring for patients undergoing elective and emergency gastrointestinal surgery. The importance of this role was emphasized by the CEPOD and NCEPOD reports, and is considered in this article.

Primary problems

Bleeding into a viscus may arise from the upper gastrointestinal tract. Bleeding from duodenal ulcers, gastric erosions, gastric ulcers and oesophagitis accounts for almost 75% of cases; other causes such as gastritis and oesophageal varices are less common. Patients commonly present with haematemesis, melaena, with or without pain, and varying degrees of shock. Physical examination aims to assess the degree of shock and primary cause of the bleeding, which may be elucidated only by upper gastrointestinal endoscopy or mesenteric angiography. Lower gastrointestinal haemorrhage, most commonly encountered in the elderly, is often a result of colorectal carcinoma, colonic polyps, ischaemic colitis, inflammatory bowel disease or diverticular disease. The clinical presentation varies with the cause, often with few symptoms.

Perforation of a viscus is characterized by sudden onset of acute abdominal pain and peritonitis, with the patient lying still with a rigid abdomen and absent bowel sounds. Common causes include perforations of peptic ulcer, appendix or diverticulum. Malignant and inflammatory bowel diseases may also present in this way. An erect plain chest radiograph looking for free gas under the diaphragm may confirm the diagnosis.

Obstruction of a viscus is suggested by colicky abdominal pain, vomiting, constipation and abdominal distension. Common causes include intra-abdominal adhesions, hernias, inflammatory bowel disease and malignancies. Plain and contrast-enhanced abdominal radiographs aid diagnosis.

Infarction of a viscus may be secondary to torsion or strangulation of a viscus, thromboembolic occlusion of its arterial inflow or venous outflow or vasculitis. Pain and peritonitis are common clinical features.

Inflammation of a viscus – the history, onset of pain and site of maximal tenderness help to determine the origin of the inflamed viscus. Common conditions include appendicitis and diverticulitis. Crohn's disease and Meckel's diverticulitis are less common causes. Other intra-abdominal structures can present in a similar way (e.g. salpingitis, cholecystitis, adenitis, pancreatitis, cystitis, pyelonephritis).

Gastrointestinal emergencies may be complicated by hypovolaemic shock or endotoxaemia/bacteraemia, culminating in the development of a systemic inflammatory response syndrome and multi-organ dysfunction.

The urgency of the surgery is usually defined by the degree of acute systemic disturbance. Surgery and anaesthesia for gastro-intestinal problems carry a high risk of complications, principally affecting the respiratory, cardiovascular and renal systems. The mortality rate for elective intra-abdominal procedures is up to 5%. Patients having upper abdominal procedures have a higher risk of complications and are twice as likely to die postoperatively as those having lower abdominal procedures. Factors increasing the risk of an adverse postoperative outcome include the site of surgery, its urgency and patient co-morbidities such as cardiac failure, physical status, those rated as ASA III or IV, and age over 50 years. This emphasizes the need for careful preoperative patient assessment, so that informed decisions can be made about the appropriateness of surgery and what measures can be taken to achieve the best outcome for the patient.

Secondary problems

Water and electrolyte depletion: the magnitude of any water and electrolyte deficit reflects the duration of the primary problem and the site of the fluid loss. Gastrointestinal fluid and electrolyte losses (Figure 1) may lead to severe hypovolaemia and acid–base and electrolyte imbalances. Clinical estimation of the volume of fluid lost is difficult and often underestimated.

Daily volume and electrolyte content of gastrointestinal secretions

Secretion	Volume (litres)	Na^+ (mmol/litre)	K^+ (mmol/litre)	Cl^- (mmol/litre)	HCO_3^- (mmol/litre)
Saliva	1.5	15	30	10	30
Gastric	2.0	50	15	120	0
Small bowel	3.0	140	10	100	30
Bile	0.6	140	5	100	35
Pancreatic	0.7	140	5	70	100
Total	7.8	725	112	764	226

1

Water – extracellular volume deficit is a common problem before any gastrointestinal surgery. It is caused by preoperative water deprivation, extracorporeal water losses (e.g. vomiting, diarrhoea, fistulae, nasogastric suction), sequestration of water into bowel lumen, bowel wall and peritoneum and preoperative bowel purgation. The clinical features are outlined in Figure 2 and depend on the severity of the water deficit and factors affecting cardiovascular reflexes (e.g. age).

Clinical features of water loss

Percentage body weight lost as water	Clinical signs
> 4%	• Thirst • Reduced skin turgor • Dry tongue • Reduced sweating
> 6%	• All above • Orthostatic hypotension • Reduced peripheral venous filling • Oliguria • Apathy • Low central venous pressure • Haemoconcentration • Raised serum urea out of proportion to raised serum creatinine (pre-renal pattern) • Low urinary sodium concentration (0–15 mmol/litre) • High urinary osmolality (800–1400 mosmol/kg)
> 8%	• All above • Hypotension • Thready pulse • Cool peripheries
> 10%	• Coma • Shock

2

Electrolytes and acid–base – significant loss of oral and pharyngeal secretions predominantly affects water balance, with minimal effects on serum electrolyte concentrations, whereas significant loss of gastric secretions can result in hypochloraemic alkalosis (caused by loss of hydrochloric acid) with hypovolaemia (caused by sodium and water loss) and hypokalaemia. In the early stages of this problem, the urine is alkaline in an attempt to maintain a normal pH. As the condition worsens, the kidneys attempt to preserve sodium ions, therefore hydrogen and potassium ions are preferentially excreted, producing a paradoxically acid urine, thereby exacerbating the alkalosis and the hypokalaemia. Hypocalcaemia can also occur as a consequence of calcium lost in the vomitus and a reduction of the serum concentration of ionized calcium owing to alkalosis (increased protein binding). Loss of lower gastrointestinal secretions from massive diarrhoea, duodenal, jejunal and pancreatic fistulae is more commonly associated with hypovolaemia and metabolic hyperchloraemic (normal anion gap) acidosis, due to the loss of bicarbonate. Hypomagnesaemia has been associated with loss of upper and lower gastrointestinal secretions and malnutrition.

Abnormalities of serum phosphate can also be associated with gastrointestinal disease. Hypophosphataemia may occur secondary to dietary deficiency and systemic alkalosis.

Haemorrhage: bleeding into the gastrointestinal tract sufficient to cause intravascular volume depletion is a common cause of emergency hospital admission (Figure 3). It is seldom possible to estimate the magnitude of gastrointestinal blood losses from the patient's history or by measuring overt blood losses. A better estimation is gained from clinical assessment of the patient's intravascular volume, bearing in mind that age and co-morbidities significantly affect the clinical cardiovascular signs of hypovolaemia.

Clinical signs of hypovolaemia

Grade of hypovolaemia	Clinical signs[1]
1 10% IVBV lost	• HR normal • SAP normal • Urine output normal • Peripheral circulation 1 ml/kg/hour • Normal sensorium
2 20% IVBV lost	• HR 100–120 • SAP orthostatic hypotension • Urine output < 1 ml/kg/hour • Peripheral circulation cool and pale • Normal sensorium
3 30% IVBV lost	• HR 120–140 • SAP systolic pressure < 100 • Urine output < 1 ml/kg/hour • Peripheral circulation cold, pale with slow capillary refill • Restless
4 > 40% IVBV lost	• HR > 140 • SAP systolic pressure < 80 • Urine output nil • Peripheral circulation cold and clammy with peripheral cyanosis • Impaired consciousness

[1] Typical signs in a young healthy adult with normal cardiovascular reflexes.
IVBV, intravascular blood volume; HR, heart rate (beats/minute); SAP, systemic arterial pressure (mm Hg)

3

Pulmonary problems: respiratory dysfunction commonly arises from factors such as diaphragmatic compression by an intra-abdominal process that decreases functional residual capacity (FRC) and may lead to atelectasis. Pleural effusions, mediast-inal emphysema, pneumothorax, and acute respiratory distress syndrome also occur. Loss of muscle mass and weakness from malnutrition, accumulation of thick bronchial secretions in dehydrated patients, and high metabolic demands resulting from sepsis may cause functional and mechanical respiratory dysfunction. Such patients often breathe shallowly, at higher than normal rates, and are often hypoxaemic. Chest radiographs help to exclude pneumonia in these patients.

Aspiration of gastric contents can cause pulmonary damage including fulminant aspiration pneumonitis. Fasting before anaesthesia reduces this risk (Figure 4). Some clinical situations are always associated with an increased risk of aspiration:

- reduced gastrointestinal motility secondary to metabolic causes (e.g. diabetes mellitus, renal failure), peritonitis, head injury, trauma, pain, drugs (e.g. opioids)
- gastrointestinal obstruction of pylorus or small bowel
- reduced lower oesophageal function secondary to raised intra-abdominal pressure (e.g. pregnancy, gastro-oesophageal reflux disease) and hiatus hernia.

The interval between the last oral intake and the injury is the fasting period. The American Society of Anesthesiologists (ASA) has recommended preoperative fasting times for healthy patients undergoing elective surgery (Figure 4).

Preoperative fasting times for healthy patients undergoing elective surgery

Ingested material	Minimum fast (hours)
Clear fluids	2
Breast milk	4
Formula milk	4–6
Non-human milk	6
Light meal	6

4

Sepsis is associated with the gastrointestinal tract; it divides broadly into primary and secondary types. Primary acute intestinal infections (e.g. gastroenteritis) can be confused with inflammatory bowel disease and are caused by a variety of pathogens. Secondary acute intestinal infections cause inflammation of a viscus and are usually associated with obstruction (e.g. appendicitis, diverticulitis) or another abnormality (e.g. trauma, adenitis, peritonitis). The causative bacteria are usually the commensals (e.g. *Escherichia coli*, enterococci, *Streptococcus milleri*, *Bacterioides fragilis*). Peritonitis is often secondary to another intra-abdominal process (e.g. perforation of a viscus). These infections are often polymicrobial, requiring broad-spectrum antibiotics until the causative organism is isolated.

Patients with severe sepsis secondary to an intra-abdominal cause usually present with abdominal symptoms (pain, vomiting, diarrhoea) and signs of peritonism (abdominal tenderness, rigidity, guarding) together with signs of a systemic response to the inflammatory process, the so-called ‘systemic inflammatory response syndrome’ characterized by fever, raised white cell count and insidious multiple organ dysfunction.

Nutritional deficiencies: malnutrition is commonly caused by failure to absorb multiple nutritional components (protein, fat, carbohydrate, vitamins, minerals). It often occurs in association with chronic disease states. In normal individuals, a 30–40% weight loss due to starvation may be fatal. During starvation, metabolic adaptation aims to conserve essential tissues. Once glycogen stores are exhausted as a source of glucose (in about 24 hours in normal individuals) protein and fat are broken down to provide energy. Protein is initially catabolized, with the resultant urinary loss of urea, sodium, potassium, magnesium and calcium, followed by fat as the chief source of energy once the metabolic pathways are established with reduction of protein catabolism. Once fat reserves are exhausted, protein catabolism begins. The physical result is a decrease in basal metabolic rate due to decreasing lean body mass, decreased physical activity and reduced thyroxine production. The co-existence of severe illness may compound the rate of decline and cause fatality sooner. Starvation and malnutrition are prevalent on surgical wards (notably following major abdominal surgery), in long-term hospitalized patients and cancer patients. They occur through poor appetite, impairment in digestion and absorption, and the increased metabolic demands of acute illness. Nutritional support in malnourished patients undergoing major surgery reduces their postoperative morbidity and mortality.

General assessment

Any clinician approaching a patient for the first time should rapidly assess the life-threatening conditions that, if left unrecognized and unmanaged, can be lethal. When problems associated with the airway, breathing and circulation are solved, a definitive diagnosis can be sought and a management plan instigated.

Airway problems are uncommon unless consciousness is obtunded. Immediate attempts to secure a patent, protected airway should ensue.

Breathing – if vomiting is a significant feature, the risk of pulmonary aspiration of gastric contents should be borne in mind; a nasogastric tube to drain fluid and gas from the stomach may reduce this risk. Clinical features of respiratory dysfunction (e.g. dyspnoea, tachypnoea, hypoxia) may occur for a variety of reasons, including diaphragmatic splinting secondary to pain with or without abdominal distension causing raised intra-abdominal pressure. Respiratory distress may be a sign of shock or sepsis. Kussmaul’s respiration (tachypnoea with deep inspiratory excursions) is associated with acidaemia from metabolic causes. Immediate steps should be taken to ensure adequate oxygenation and ventilation, with interventions ranging from providing supplemental oxygen to mechanical ventilation of the lungs.

Circulation – hypotension is the most common circulatory problem asssociated with gastrointestinal problems. Occult bleeding can occur in the gut lumen, peritoneal cavity or retroperitoneum. Patients with septic shock are classically vasodilated and warm, with hypotension and a fever, but many (particularly if presenting late) are peripherally vasoconstricted and have a normal or even low body temperature. Atrial fibrillation in the elderly patient with abdominal pain means that mesenteric artery embolism should be considered in the differential diagnosis. Two large-bore peripheral intravenous cannulae should be inserted and venous blood taken for a full blood count, biochemistry (including amylase) and blood cross-match, and a coagulation screen, blood cultures, pregnancy test and sickle screen if appropriate. Suspected hypovolaemia should be treated by fluid resuscitation, septic shock with fluid resuscitation and intravenous broad-spectrum antibiotics.

A portable ultrasound scan (if available) may confirm the cause of hypovolaemic shock (e.g. a leaking aortic aneurysm, free intraperitoneal fluid, an ectopic pregnancy).

Anaesthetic assessment

Items of interest in the history include the presence and nature of pain, other gastrointestinal symptoms (e.g. anorexia, dyspepsia, nausea, vomiting, haematemesis, melaena, diarrhoea, constipation), previous abdominal surgery and recent drug ingestion.

Physical examination should concentrate on the general appearance of the patient, in particular their posture, pigment-ation, pallor and pattern of respiration. The following should be specifically examined:

- cardiovascular system – particularly signs of intravascular and extracellular fluid volume deficits
- respiratory systems – particularly signs of respiratory distress or areas of lung collapse
- signs of sepsis.

This is followed by a review of all appropriate investigations to help estimate the magnitude of the secondary effects of the gastro-intestinal problem. Haematological, blood chemistry, arterial blood gases and imaging techniques should be ordered only if the result is likely to alter the management of the patient.

Preoperative management

When surgery is necessary and the secondary anaesthetic assessment is completed, preoperative management should begin.

Analgesia: early judicious analgesia is advocated for the patient with acute abdominal pain. If opioid analgesia is given as a dilute solution by slow intravenous injection, the dose can be titrated against the patient’s pain. Adequate analgesia reduces the patient’s suffering and may allow them to give a clearer history and be easier to examine.

Anti-emetic and nasogastric tube: the ASA recommend physical and pharmacological methods to reduce the risk of regurgitation and aspiration. They do not recommend routine use of these agents in healthy, elective patients. Physical methods involve nasogastric drainage of gastric contents. For most laparotomies a PVC/polyurethane 16 FG Ryles or Salem tube is adequate.

Pharmacological methods include antacids, which neutralize acid in the stomach, to reduce the risk of damage should aspiration occur. Particulate antacids are not recommended. Sodium citrate solution administered shortly before induction is the agent of choice in high-risk cases (e.g. pregnancy) but this results in an increase in gastric volume. Additionally, antihistamines (e.g. ranitidine and proton-pump inhibitors such as omeprazole) decrease acid secretion in the stomach and should be used for high-risk patients. Ideally, they should be administered on the evening before surgery (or early morning for an afternoon list) and a second dose given 2 hours preoperatively. Gastric prokinetic agents (e.g. metoclopramide) increase gastric emptying in healthy patients, but a clear benefit in trauma patients has not been demonstrated. Anticholinergic agents do not have a significant effect and are not routinely recommended.

Fluid and electrolyte replacement: signs of intravascular and extracellular volume depletion require immediate correction with intravenous fluids, and the response to fluid resuscitation should be monitored. Fluid and electrolyte deficits should be replaced with an appropriate crystalloid solution; haemorrhage with clear colloid until red cells are available for transfusion. Central venous pressure monitoring is often required to manage fluid replacement in the elderly or those with cardiac disease.

Preoperative ‘optimization’ of cardiovascular and respiratory function reduces mortality, morbidity and length of stay in the ICU and hospital. High-risk patients include those with severe cardiovascular and/or severe respiratory diseases; those having aortic surgery, major surgery for malignancy or surgery for abdominal sepsis; and those with haemodynamic instability due to an acute intra-abdominal catastrophe. It has been suggested that haemodynamic monitoring should start in the preoperative period, using a pulmonary artery catheter to assess fluid requirement and cardiac output. Patients in studies by Boyd and colleagues were given blood if anaemic and oxygen if hypoxaemic and subsequently colloid with or without an inotrope until a predetermined level of pulmonary capillary wedge pressure and oxygen delivery were achieved. Such an approach makes heavy demands on staff and resources. In emergencies, a balance has to be struck between the benefits of optimization before surgery and commencing surgery. If bleeding is the main problem, surgery may be part of the resuscitation process, and time should not be wasted preoperatively.

Antibiotics are needed for localized infection or if clinical sepsis is thought to have an intra-abdominal source (e.g. perforation of the colon in an elderly patient). Patients who are septicaemic should start treatment with a broad-spectrum intravenous antibiotic without waiting for the result of blood cultures. ◆

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Clinical Aspects of Hepatic Problems

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Advanced liver disease is a classic example of multisystem failure resulting from a single organ disease. Historically, even minor surgery on cirrhotic patients resulted in high mortality. Liver transplantation has dramatically improved the prognosis for these patients. It is important for clinicians to appreciate the multisystem sequelae of end-stage liver disease, to assess risk and manage patients appropriately. Recognition of severe disease is crucial; improved perioperative care has not significantly reduced operative mortality. These patients should be referred for transplant assessment or, if surgery for unrelated conditions is considered, should be managed in specialist centres.

Risk assessment
The Child–Pugh classification of liver disease (Figure 1) was originally described to assess operative risk in cirrhotic patients undergoing surgery for variceal bleeding. Its use has extended to predict outcome in cirrhotic patients for all types of surgery.

Pugh's modification of the Child classification of severity of liver disease

Clinical and biochemical measurements	Points scored for increasing abnormality		
	1	2	3
Encephalopathy	None	Grade 1–2	Grade 3–4
Ascites	None	Slight	Moderate
Bilirubin (μmol/litre)	< 35	35–60	> 60
Prothrombin (seconds prolonged)	1–4	4–10	> 10
Albumin (g/litre)	> 35	28–35	< 28

The points for the five variables are added to give a score ranging from 5 to 15. Patients with scores 5–6 are Grade A, 7–9 are Grade B and 10–15 are Grade C. Grade A represents 'good' risk with 5% mortality, Grade B represents 'moderate' risk with 10% mortality, Grade C represents poor risk with mortality > 50%

1

Others have studied the effects of systems failure on outcome in patients with severe liver disease (Figure 2). Optimizing treatable complications (e.g. ascites) may decrease mortality significantly. Causes of death in these patients are sepsis, renal failure, bleeding, hepatic failure and encephalopathy. Poor nutrition, portal hypertension with ascites and encephalopathy herald poor prognosis for any surgery in these patients. However, recent work suggests that cirrhotic patients with good function who are well compensated (i.e. Child–Pugh Grade A) are good candidates for certain types of surgery (e.g. liver resection for hepatocellular carcinoma or portosystemic shunt surgery).

Preoperative variable and mortality in cirrhotic patients

Variable	Mortality if present (%)
Pulmonary failure	100
Cardiac failure	92
Gastrointestinal bleeding	86
More than two antibiotics	82
Second operation required	81
Renal failure	73
More than 2 units of blood required	69
Hepatic decompensation	66
Positive blood/urine culture	61
Albumin < 30 g/litre	58
Ascites	58
Less than 2 units of blood required	22

2

Extrahepatic effects of end-stage liver disease

Cardiovascular system: in end-stage liver disease the systemic circulation is characterized by various pathological changes. Peripheral vasodilatation and shunting (cutaneous, intrapul-monary, portopulmonary and pleural) result in increased cardiac output. This can mimic the hyperdynamic picture of a septic state. Activation of the renin–aldosterone–angiotensin (RAA) system causes an increase in plasma and extracellular fluid volume, though effective circulating volume is reduced. Cirrhotic cardiomyopathy may be masked by the reduction in afterload, and is difficult to detect by non-invasive preoperative investigations. Pulmonary hypertension is also seen and is a rare cause (< 1%) of right ventricular failure. Cardiac arrhythmias also occur, associated with cardiomyopathy or electrolyte abnormalities such as hypomagnesaemia and hypokalaemia. The responsiveness to catecholamines is reduced.

Respiratory system: respiratory compromise may result from restrictive lung disease caused by ascites or pleural effusions, the hepatopulmonary syndrome, pulmonary hypertension, defects in alveolar oxygen diffusion or pulmonary manifestations of systemic disease (e.g. α_1-antitrypsin deficiency, autoimmune disease). Several factors dispose the cirrhotic patient towards hypoxaemia: a rightward shift in the oxygen-dissociation curve (due to decreased levels of 2,3-diphosphoglycerate (2,3-DPG)), intrapulmonary shunting due to capillary vasodilatation and restrictive defects due to large volume ascites and pleural effusions. These effects are compensated for by the raised mixed venous oxygen saturation consequent on poor oxygen extraction and the raised resting cardiac output. All patients with end-stage liver disease and a partial pressure of oxygen (pO_2) less than 9 kPa should be considered hypoxic. In patients with the hepato-pulmonary syndrome (chronic liver disease, increased alveolar–arterial gradient while breathing room air, and evidence of intrapulmonary vasodilatation) transplantation is associated with a good outcome and improvement of hypoxia as vascular remodelling occurs. By contrast, in patients who have porto-pulmonary hypertension and an increase in pulmonary vascular resistance, transplantation does not result in improvement. Severe pulmonary hypertension (mean pulmonary arterial pressure > 50 mm Hg) is associated with right ventricular failure and sudden cardiac death; mortality is 100% in this group. Preoperative therapy with prostacyclin and nitric oxide may improve outcome in this group though treatment needs to continue long term, suggesting that the benefit is obtained from vascular remodelling not just a decrease in pulmonary pressures. Large volume ascites also increases the risk of pulmonary aspiration.

Renal and endocrine system: some renal dysfunction is common in patients with cirrhosis, portal hypertension and ascites. Compensatory mechanisms to restore mean arterial pressure in cirrhotic patients result in activation of the RAA system with sodium and water retention and the development of ascites. Non-osmotic hypersecretion of vasopressin occurs due to the relative decrease in central blood volume due to splanchnic pooling. As the severity of the disease progresses, disproportionate water retention occurs and dilutional hyponatraemia results. At its most severe this can lead to the 'hepatorenal syndrome'. This represents severe renal vasoconstriction. Renal angiography in this setting demonstrates absent cortical blood flow. Hepatorenal syndrome is characterized by a rapid deterioration in renal function associated with low urinary sodium excretion. Strategies to improve renal function in this setting include the use of splanchnic vasopressors (e.g. terlipressin) with volume resuscitation, transjugular intrahepatic portosystemic stent (TIPSS) placement to reduce portal hypertension, and liver transplantation. Prognosis is poor for hepatorenal syndrome. Renal function is difficult to assess in end-stage liver disease because reduced muscle mass and hepatic synthesis of creatine reduce serum creatinine inappropriately. Creatinine clearance overestimates glomerular filtration rate, and inulin or ^{51}Cr EDTA clearance remain the gold standard.

Endocrine dysfunction is common in end-stage liver disease, due to inappropriate activation of some systems (RAA system, vasopressin release), abnormal responses (insulin resistance), over-secretion of growth hormone and glucagon, and abnormal metabolism (steroid hormones). This leads to clinical syndromes of insulin resistance and impaired glucose metabolism, a shift towards lipid utilization as a preferred energy substrate, and depletion of glycogen stores. Hypoglycaemia in cirrhosis is uncommon and a poor sign. The abnormal metabolism of sex hormones leads to feminization, gonadal atrophy and gynaecomastia in men, and amenorrhoea in women.

Gastrointestinal system: advanced cirrhosis is characterized by portal hypertension and portosystemic shunting, typically resulting in oesophageal varices, which can cause massive gastro-intestinal haemorrhage. Varices may also be present on the anterior abdominal wall and may cause severe blood loss during laparotomy. Ascites develops due to a combination of portal hypertension, poor synthetic function with hypoalbuminaemia and the pathophysiological activation of the RAA system. The volume of ascites may be such that intra-abdominal pressure exceeds renal perfusion pressure causing deterioration in renal function. For this reason, draining ascites (especially if intra-abdominal pressure is > 25 mm Hg) is regaining popularity, especially in those resistant to diuretic treatment. Nutritional abnormalities are common in these patients and associated with peripheral and hepatic insulin resistance and a poor outcome. Glucose utilization is impaired and lipid utilization is increased in fasting and fed conditions. Hypermetabolism seems to predate the malnutrition seen with increasing severity of cirrhosis and in contrast to earlier regimens a high-protein, high-calorie intake, taken little and often, seems to prevent the catabolic state without increasing the incidence of hepatic encephalopathy.

Haematological system: the liver has a central role in the control of coagulation. Impairment of haemostasis is common in liver disease, bleeding is a leading cause of death in cirrhotic patients. The liver is the main site of synthesis of all coagulation factors except von Willebrand's factor. It is also the key site for clearance of activated clotting factors and plasminogen activators; the coagulation state depends on the balance of hepatic synthesis of clotting factors and clearance of activated clotting factors, their inhibitors and fibrinolytic proteins. Failure of bile salt secretion results in poor absorption of vitamin K and low levels of the vitamin K-dependent clotting factors (II, VII, IX, X), but inactive prothrombin complexes are present in liver disease without vitamin K deficiency suggesting an acquired defect in activation.

Many platelet abnormalities occur in patients with liver disease.

Thrombocytopenia may result from hypersplenism secondary to portal hypertension in cirrhotic patients, bone marrow suppression, abnormalities in platelet metabolism or autoimmune causes. In alcohol-related liver disease thrombocytopenia may result from folic acid deficiency. Qualitative platelet dysfunction is also seen in liver disease, with impaired aggregation and clot retraction.

CNS: hepatic encephalopathy is the decrease in conscious level seen in association with severe liver disease. In the early stages a reversal of the sleep–wake cycle is seen with patients sleeping during the day. As encephalopathy advances, subtle changes in intellectual function occur with confusion, memory loss and irritability being common. Finally, changes in conscious level are observed. Work in liver failure shows intracranial hypertension, brain oedema and herniation with altered perfusion. Encephalopathy can be precipitated by a variety of factors including hypovolaemia, sepsis, gastrointestinal haemorrhage and hypoglycaemia. The final common pathway in the aetiology of brain oedema may be increased cerebral blood flow with consequent increased ammonia uptake across the blood–brain barrier. Hyperventilation and consequent alkalosis increase the ammonia available to cross the blood–brain barrier.

Immune system: patients with advanced cirrhosis are relatively immunocompromised. Low complement levels, loss of effective white cell opsonization and dysfunctional macrophage phagocytosis contribute to anergy, leading to high levels of bacteraemia. Spontaneous bacterial peritonitis is common in end-stage liver disease. Increasingly, Gram-positive bacteria, which may be multiresistant, are being cultured in these patients. ◆

Laboratory Tests in Hepatic and Renal Failure

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Laboratory tests of liver function are of little use unless combined with a thorough history and examination. In this situation they may be used to pursue a diagnosis, to assess degrees of acute or chronic liver failure, or as trends to map disease progression or response to treatment. With the advent of automated serum multi-channel analysis the most common indication for 'liver function' testing is as a screening test (often mistakenly performed to exclude a problem). Normal values for tests are defined around 95% confidence intervals, therefore multiple tests commonly produce false-positive results. True abnormal results usually represent liver dysfunction. The most common profiles include bilirubin, aminotransferases, alkaline phosphatase and γ-glutamyl transpeptidase (GGT).

True liver function tests
True liver function tests include tests of synthetic function such as estimation of serum albumin, clotting factors or dynamic tests that estimate the liver's capacity to metabolize drugs or endogenous substances.

Albumin is the most abundant plasma protein and is largely synthesized by the liver. In stable chronic liver disease, monitoring serum albumin is a valuable indicator of hepatic synthetic function and as such is incorporated in many prognostic scoring systems (e.g. the Child–Pugh (see page 42) and Mayo End-stage Liver Disease (MELD) score). Albumin has a long half-life of 20 days; this, combined with the possibility of regulation of albumin synthesis in liver disease, can make interpretation of serum albumin levels difficult in an acute situation. Peri-operative albumin levels may change as a result of supplementation, changes in vascular permeability and in volume of distribution. In these situations, measurement of albumin is an unreliable measure of liver function.

Prothrombin time (PT): in the acute situation, assessment of the coagulation factors of the extrinsic cascade (with their much shorter half-lives) are a more reliable monitor of liver failure than albumin. Failure of a prolonged PT to correct with parenteral vitamin K supplementation defines hepatocellular failure, and is one of the most reliable prognostic indicators of survival in acute liver failure. Inter-laboratory variations can occur with different thromboplastin reagents. This may also occur when the PT is expressed as the international normalized ratio (INR). Therefore, trends in prothrombin time measured in a single laboratory are more useful than isolated values.

Blood lactate concentration reflects the balance between production and elimination. Under normal conditions, the liver removes 40–60% of lactate. Hypoperfusion, hypoxia and severe ischaemic damage convert the liver from a lactate-consuming to a lactate-producing system. In acute liver failure, hyperlactacidaemia may be used as a marker of hepatic injury and the accompanying multiple organ failure. Assuming adequate oxygen delivery, blood lactate levels have been shown to correlate with survival in paracetamol-induced liver failure.

'Dynamic' tests of liver function
'Dynamic' tests measure the ability of the liver to clear or metab-olize an infused substance.

Formation of monoethyleneglycine (MEGX): this lidocaine (lignocaine) metabolite can be measured 15–30 minutes after injection of lidocaine (lignocaine), 1 mg/kg. Theoretically, it can be used to quantify the hepatic cytochrome P450 family metabolism. However, lidocaine (lignocaine) is a flow-limited rather than capacity-limited drug. Although MEGX measurements have been shown to correlate with survival in chronic liver disease, they probably reveal more about liver blood flow than functional capacity. Inevitably there is a delay while assay results are obtained.

Indocyanine green (ICG) clearance: the elimination of injected ICG, 0.5 mg/kg, has been used to assess liver function. Interest in this method was fuelled by the introduction of a bedside non-invasive monitor of ICG clearance. ICG has a high hepatic extraction ratio and measurements reflect changes in liver blood flow. Reports suggest it is useful for assessing donor livers for transplantation and following liver resection.

Conventional tests of liver dysfunction
Bilirubin is the by-product of haem metabolism. Unconjugated bilirubin is water insoluble and transported bound to serum albumin. Hepatic conjugation produces a water-soluble compound, normally excreted in the bile. Total bilirubin levels therefore represent the balance between production metabolism and excretion. Excessive production may result from disease processes resulting in increased red cell turnover leading to unconjugated hyperbilirubinaemia. Conjugated hyperbilirubinaemia results from leakage of bilirubin into the blood directly from the hepatocytes or distal to the liver in the case of biliary obstruction. Conjugated bilirubin released into the blood stream tends to be excreted and can be measured in the urine, however, because some of the conjugated bilirubin can covalently bind to serum albumin, bilirubin is not always detected in the urine. The presence of bilirubin in the urine (as tested by a Diazo impregnated test strip) is sensitive and may detect liver dysfunction before overt jaundice is detected.

Aminotransferases: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are released into the blood stream as a result of cell damage or necrosis. AST is a sensitive but nonspecific marker of hepatocellular damage. AST can be released from a number of damaged organs including liver, heart muscle, kidney, pancreas and red blood cells. ALT is slightly more specific for liver damage with less extrahepatic production, but may be elevated in conditions such as myositis. High (> 1000 IU/litre) levels of AST usually represent hepatitis of viral, drug or ischaemic origin. Intermediate levels (200–400 IU/litre) may be seen in acute alcoholic hepatitis with more severe clinical dysfunction. Absolute levels of transaminases do not correlate with outcome.

Glutathione-S-transferase (GST): one problem with AST and ALT as measures of hepatocellular damage and necrosis is that these enzymes are not uniformly distributed throughout the liver, being predominantly concentrated in periportal hepatocytes. Centrilobular hepatocytes are most prone to hypoxia and are relatively deficient in AST and ALT, this may explain some of the difficulties when correlating absolute values of transaminases with outcome. GST is more evenly distributed throughout the liver. In addition, its relatively small molecular weight encourages rapid release following hepatocellular damage. A short half-life of 90 minutes means that acute changes can be tracked rapidly but that peak effects may be missed, depending on the sampling time after injury. GST is increasingly used as a sensitive marker for changes in hepatocellular function following surgery and anaesthesia.

Alkaline phosphatase (AP): this family of enzymes is located in liver, bone, placenta and intestine. In healthy individuals, circulating AP is derived from bone or liver. In pregnancy, AP is often twice the upper range of normal. Elevations also occur in peri-pubertal children. The wide distribution of the enzyme can cause confusion in the assessment of liver function, and extrahepatic elevation may occur as a result of hyperthyroidism, cardiac failure, hypernephroma and Paget's bone disease. In the liver, AP is located in the microvilli of the biliary canaliculi and on the sinusoidal surface of the hepatocyte. Classically, AP levels in liver disease are elevated when there is intra- or extrahepatic obstruction to biliary drainage or due to space-occupying lesions such as tumours. The raised levels in the blood seem to be due to increased synthesis in the canalicular membrane rather than failure of excretion. The diversity of AP families makes isoenzyme determination desirable, but this assay is not widely available and other markers of biliary obstruction, such as GGT, are often monitored.

GGT is a membrane-bound glycoprotein found in cells with a high secretory or absorptive activity (e.g. liver, kidney, pancreas intestine, prostate). 90% of patients with hepatobiliary disease have raised GGT, but specificity is low. Its main value is in combination with AP to convey additional liver specificity. Raised levels of GGT have been associated with obesity, alcohol use and raised cholesterol levels. In non-drinking, obese individuals the most common cause of raised GGT is a fatty liver.

Tests of renal failure
In perioperative care, laboratory tests are commonly requested to aid in the diagnosis and management of acute renal failure. This brief review concentrates on tests of function rather than those requested to confirm or refute a specific diagnosis. Classically, renal impairment (Figure 1) is classified as:

- pre-renal (poor perfusion), often correctable with volume resuscitation
- renal (intrinsic renal disease)
- post-renal (obstruction).

Urinary measurements in pre-renal and renal failure

Indices	Pre-renal	Renal
Urinary sodium (mmol/litre)	< 20 (low)	> 40 (high)
Urine osmolarity (mosmol/litre)	> 500 (high serum +100)	< 350 (low)
Urine/plasma urea	> 8 (high)	< 3 (low)
Specific gravity	High 1.020	Fixed 1.010–1.020

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Post-renal failure is common and is often excluded by ultrasound. Clinical acumen is vital for the detection of hypovolaemia and low cardiac output states. Laboratory examination of the urine can sometimes be useful in the differentiation of pre-renal and 'true' renal failure.

Measuring urinary biochemical indices has limitations because typical values are seldom present and concomitant diuretic therapy often confuses estimates of urinary sodium in pre-renal failure. Hepatorenal failure mimics pre-renal failure with extremely low urinary sodium levels, but fails to respond to volume loading.

Urine analysis is an important, but often neglected, investigation. A normal urine analysis in the presence of impending acute failure supports the presence of pre-renal or obstructive patterns. Abnormal results may help to discriminate tubular and glomerular problems. Red blood cells suggest the presence of glomerular or vascular inflammatory disease. Urine protein excretion can occur as a result of glomerular damage (increased loss) or tubular failure of absorption.

Blood urea is often measured automatically when concentrations of sodium and potassium are requested. There is a common misconception that plasma urea usefully relates to glomerular filtration rate (GFR), however it is altered by diet, fever, gastro-intestinal haemorrhage, renal blood flow, urine flow rates and in liver disease. Some laboratories no longer offer it as a routine assay. It still has a place in assessing the effect of compliance or alterations to diet in patients with stable chronic renal failure or in assessing the need for, or effects of, renal replacement therapy.

GFR, classically measured by inulin clearance, would be the ideal measurement to detect alterations in renal function, but in early renal disease, GFR is normal or increased. Inulin clearance is seldom measured in clinical practice and the serum creatinine and the creatinine clearance are used as estimates of GFR.

Serum creatinine is the most commonly used indirect estimate of GFR. The exponential rise in serum creatinine with falling GFR limits its use in assessing patients with low clearances. With low concentrations of creatinine, cross-reaction in the assay may overestimate the creatinine concentration and consequently underestimate creatinine clearance. Also, creatinine secretion by the tubules occurs and creatinine production is determined by muscle mass. Wasted patients have low levels of creatinine, which underestimate deterioration in renal function. Serum creatinine is also affected by age as muscle mass falls.

Attempts to correct for age and muscle mass have resulted in formulae that attempt to compensate for these changes.

$$\text{Creatinine clearance} = \frac{1.22 \times (140 - \text{age}) \times \text{Weight}}{\text{Serum creatinine } (\mu\text{mol/litre})}$$

Creatinine clearance can be calculated by combining a timed urine collection with estimations of plasma and urine creatinine concentration.

$$\text{Creatinine clearance} = \frac{\text{Urine concentration } (\mu\text{mol/litre}) \times \text{Urine volume (ml/minute)}}{\text{Serum concentration } (\mu\text{mol/litre})}$$

Measuring creatinine clearance removes some of the problems associated with the use of isolated creatinine values, but it necessitates a 24-hour urine collection and assumes that serum creatinine is constant over 24 hours.

Measuring GFR using radioactive indicators: labelled chromium ethylenediamine tetraacetic acid (^{51}Cr EDTA) is the most widely used indicator. Clearance of this agent is almost identical to inulin even down to a GFR of 3–15 ml/minute. Following a single injection of 2 MBq ^{51}Cr EDTA, clearance can be calculated by serial blood sampling over 5 hours. ◆

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Clinical measurement

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Cardiac Output Measurement

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The cardiac output is the volume of blood in litres pumped by the left ventricle per minute and is the product of heart rate and stroke volume. It changes with heart rate as well as with preload, afterload and contractility (the three determinants of stroke volume).

Cardiac output is measured primarily because it is thought to reflect the adequacy of global blood flow. However, poor tissue perfusion and cellular hypoxia can exist despite normal blood oxygen content and cardiac output. Therefore, the clinician must be wary of relying on absolute values and should concentrate on trends and their physiological effect on the patient. Numerical data should be evaluated frequently in the context of clinical and laboratory findings rather than relying on accepted normal values. The values obtained should also be considered in the context of the patient's age, sex, weight, pre-morbid condition and current disease process. Cardiac output measurements are used to determine myocardial performance, oxygen delivery, derived variables (e.g. systemic vascular resistance), to calculate shunt, and as a measure of therapeutic intervention.

In laboratory animals, cannulation of the aorta and pulmonary artery allows direct measurement of output with flowmeters, but such invasive practices are unacceptable in human medicine. The essence of clinical cardiac output measurement is to quantify end-organ perfusion and therefore clinical examination should be the cornerstone of good practice. Level of consciousness, unprovoked urine output and examination of the skin for colour, temperature and capillary refill are good indicators of circulating volume and the adequacy of cardiac output. Blood pressure measurement provides a poor guide to pump function, and may be maintained despite a failing myocardium by increased systemic vascular resistance. In critical illness or its recovery phase, simple assessment of organ function may be difficult to interpret owing to the disease process, associated medical interventions and the combined effects on normal physiology.

The ideal method of measuring cardiac output would be non-invasive, continuous, accurate over the range of cardiovascular function encountered in intensive care, operator independent and labour free. In the absence of this ideal method, the 'gold standard' for cardiac output measurement in intensive care remains the indirect thermodilution technique using the highly invasive, balloon-tipped, flow-directed, pulmonary artery catheter. Earlier methods employed the Fick principle and dye dilution, based on the theory of volume displacement.

The Fick method

The Fick principle states that the total uptake or release of a substance by an organ is the product of the blood flow through that organ and the arteriovenous concentration difference of the substance in question. Applying the Fick principle to cardiac output measurement, the pulmonary blood flow over 1 minute may be determined by measuring the arteriovenous concentration difference of oxygen across the lungs and the rate of oxygen uptake. In the absence of intracardiac or intrapulmonary shunts, the pulmonary blood flow is equal to systemic blood flow and thus cardiac output.

The Fick principle will not give a dynamic measure of output and the procedure is time-consuming, with blood sampling and the need for steady-state haemodynamic, respiratory and metabolic conditions over the period of measurement. For these reasons, and the development of the pulmonary artery catheter, the Fick method has remained largely a laboratory tool, despite its accuracy, especially in low-output states.

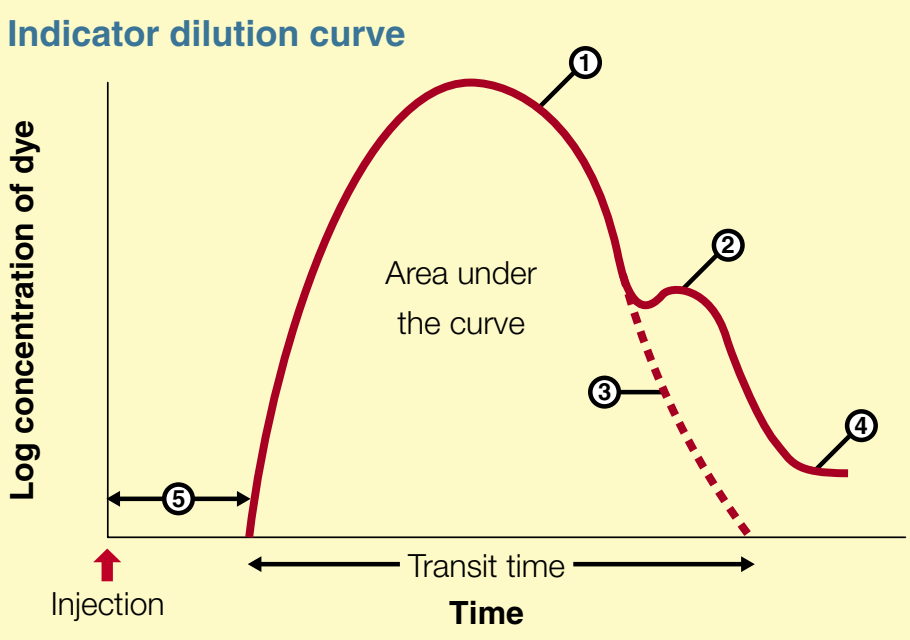
Indicator dilution methods

An indicator mixed into a flowing volume of blood can be used to determine the position of that volume in time and space, provided that the following conditions are met:

- the indicator remains in the system between the points of injection and measurement
- complete mixing of the indicator and the blood occurs
- blood flow is constant during the measurement phase.

Dye dilution

Classically, the non-toxic dye, indocyanine green is injected into the pulmonary artery and its transit time through the systemic circulation monitored by aspirating peripheral arterial blood through a densitometer. A washout curve is then plotted on semi-logarithmic paper to describe the changing concentration of dye from injection through to steady state. The cardiac output can be derived from this curve, by dividing the dose of dye injected by the area under the washout curve. Recirculation of the dye distorts the time–concentration curve and therefore the downslope to point zero has to be extrapolated from the primary curve and an exponential decay assumed (Figure 1). Furthermore, steady-state conditions are assumed over the 40-second measurement period. Errors may occur in the mixing and administration of the dye, which is photosensitive and unstable with time. The technique is invalidated by intracardiac shunts owing to inadequate mixing and severe valve regurgitation and shock, because the first-pass curve is so prolonged that recirculation occurs before the downstroke is fully inscribed. For these reasons, as well as the elevation of the baseline concentration with repeated injection and the need for referenced controls, this method has been superseded by thermodilution.



Indicator dilution curve

① Primary curve
② Recirculation peak
③ Extrapolation of primary decay curve
④ Elevation of baseline secondary to circulation of dye
⑤ Appearance time

Source: Hinds CJ, Watson D. *Intensive Care.* Philadelphia: WB Saunders, 1997.

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Thermodilution

Heat can also be used as a detectable indicator in the blood and has the advantage of rapid dissipation into the tissues and consequently no recirculation peak or elevation of the indicator baseline. As a result, cardiac output measurements can be repeated at frequent intervals and thermodilution is therefore the established method of measuring cardiac output.

Using a pulmonary artery catheter, a 10 ml bolus of ice-cold saline is injected into the right atrium and the ensuing temperature change recorded by a thermistor at the catheter tip located in the pulmonary artery. A plot of temperature against time gives a washout curve, from which cardiac output can be calculated using a modification of the Stewart–Hamilton conservation of heat equation:

$$Q = \frac{V \times Di \times Si[Tb - Ti] \times 60}{dT \times t \times Db \times Sb \times 1000}$$

where: V = volume of injectate; Di and Db = densities of injectate and patient's blood; Si and Sb = specific heats; Ti and Tb = temperatures; dT = mean temperature change; t = duration of temperature change in seconds. To convert cardiac output to litres/minute a scaling factor of 60/1000 is used.

In current practice, a microprocessor system measures the area under the curve and calculates cardiac output. The manufacturers of the sensors add correction factors to account for the mixture of cold indicator with warm residual fluid in the catheter injection lumen and heat transfer from the catheter walls to the cold indicator.

Sources of error include any circumstances that affect the temperature versus time graph. For example, intracardiac shunts and severe tricuspid and mitral regurgitation.

- The presence of thrombus on the thermistor can delay cooling and rewarming, and therefore overestimate the area under the curve.
- Distal migration of the catheter can lead to disproportionate blood flow with variability in the volume of cold bolus reaching the thermistor.
- The volume, temperature and rate of delivery of the injectate are important variables. For example, the cold saline bolus has been associated with bradycardias and supraventricular tachyarrhythmias.
- Alteration in ventricular performance owing to an arrhythmia also affects the thermal dilution washout curve.

It is possible to 'lose' the thermal indicator, especially in low cardiac output states if the baseline temperature is variable, for example during large-volume transfusion or rewarming following cardiopulmonary bypass. The temperature of pulmonary artery blood changes with respiration, owing to the different contributions of blood from the superior and inferior venae cavae at different stages of the respiratory cycle, which is exacerbated by mechanical ventilation.

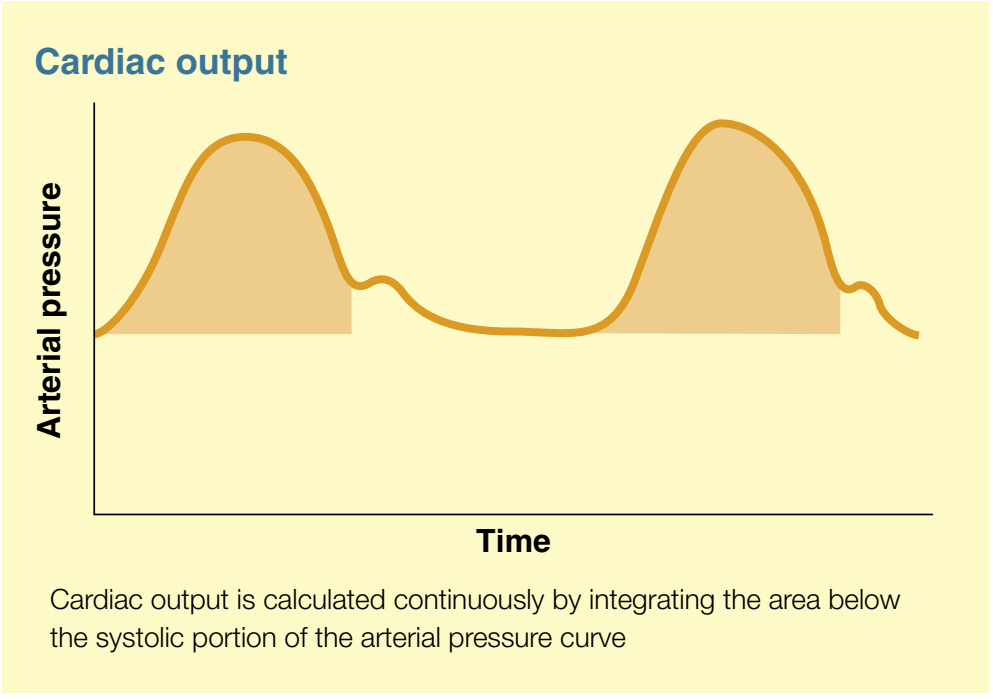
Modified pulmonary artery catheter: this apparatus was developed to address the intermittent nature of the thermodilution method. A thermal filament placed in the right atrium and ventricle gives 15 W pulses, which are recorded by a thermistor at the catheter tip to generate washout curves and 'continuous' cardiac output measurements. Since bolus injections are not required, this system avoids what can be a considerable volume load to the patient with the attendant risk of infection. Described as a continuous output monitor, this apparatus has a lag time of about 10 minutes. It has the potential to detect changes in myocardial function more rapidly than traditional thermodilution, but it does not give beat-to-beat output data. Concerns about thermal damage to the myocardium and red blood cells appear unfounded, but this technique suffers from many of the limitations of the bolus method.

Future developments: although the pulmonary artery catheter is well established, derangements in the normal physiological function of the heart and lungs make errors in interpretation likely. Furthermore, it is an invasive tool and is associated with risks regarding initial central venous access, floating the catheter and its residence in the right heart and pulmonary circulation. As a result of these problems, there is a reluctance to initiate early invasive monitoring, which may delay appropriate therapeutic intervention. For these reasons, and the desire to obtain continuous cardiac output data, a number of non-invasive or minimally invasive monitors have been developed, though they have not received universal acceptance.

Oesophageal probes have been developed to determine cardiac output from measurements of blood velocity. Doppler devices derive flow in the descending aorta from integrals of the systolic velocity versus time curve, the aortic cross-sectional area and the heart rate. Transoesophageal echocardiography generates outputs from flow through the mitral valve, multiplied by the calculated valve area, a computation constant and the heart rate. These devices have the advantage of giving anatomical information about ventricular function, but they require constant repositioning. There are also questions about their safety, related to bleeding and unrecognized oesophageal rupture. The greatest restriction to their use, however, is that the patient has to be intubated, ventilated and sedated to tolerate the probe which offsets the benefits of avoiding invasive vascular monitoring.

Recently, transpulmonary thermodilution with pulse contour analysis has been advocated as a 'minimally invasive' means of continuous (30 seconds) cardiac output measurement. Left ventricular stroke volume is computed by measuring the area under the systolic part of the arterial pressure waveform (Figure 2) and dividing by aortic impedance. When multiplied by the heart rate, this gives the cardiac output. Initial studies suggested that cannulation of a central artery was necessary for accurate measurement, however, the radial artery has been found to be satisfactory. Before using pulse contour analysis, cardiac output has to be measured by an alternative method to derive the aortic impedance used in the pulse contour equation. Traditionally, thermodilution using a pulmonary artery catheter would have been used, but now a less invasive transcardiopulmonary method is applied. A cold fluid bolus (0.2 ml/kg) is injected into the right atrium via a central venous line and a temperature washout curve recorded by a thermistor located in a peripheral artery. When the aortic impedance is known, further cardiac outputs are recorded 'continuously' by pulse contour analysis, with calibration by thermodilution as required. Under steady-state conditions, this can be as infrequent as 8 hourly, but when changes in systemic vascular resistance are anticipated, calibration should be more frequent.

The technique uses central venous and peripheral arterial lines, and its advocates suggest that it is no more invasive than standard intensive care monitoring. It is not affected by the respiratory cycle, because the washout curve is at least 20 seconds long, but it is subject to thermal baseline drifts, with inadequate volumes of injectate or too warm a solution giving inaccurate dilution curves. Errors can also be generated by air in the manometer lines, giving dampened arterial waveforms and therefore inaccurate pulse contour analysis.



Cardiac output is calculated continuously by integrating the area below the systolic portion of the arterial pressure curve

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Measurement of Pressure: Direct and Indirect Methods of Measuring Blood Pressure and Pulmonary Artery Pressure

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Pressure is defined as force per unit area. In clinical practice, the units commonly used to measure pressure are mm Hg and kPa. The SI unit of pressure is Newton per square metre (N/m^2) or Pascal (Pa).

Instruments used for measuring pressure

Liquid manometers
There are two types of liquid manometers (Figure 1).

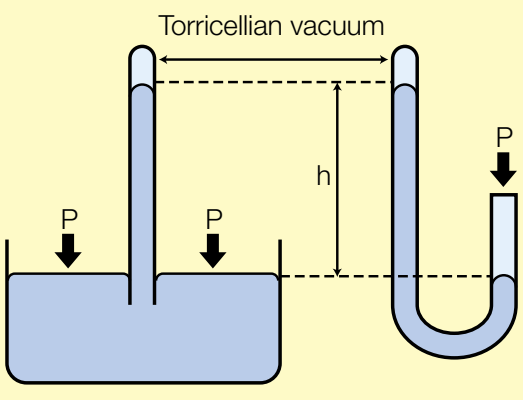
- In the 'closed' mercury manometer (e.g. barometer) there is a virtual vacuum (Torricellian vacuum) above the mercury, such that the height of the mercury column indicates absolute pressure.
- In the 'open' mercury manometer (e.g. sphygmomanometer), the tube is opened at both ends and thus the height of the fluid column indicates the amount by which the pressure exceeds atmospheric or gauge pressure. The force exerted by a column of fluid is equal to:

height x density x acceleration due to gravity.

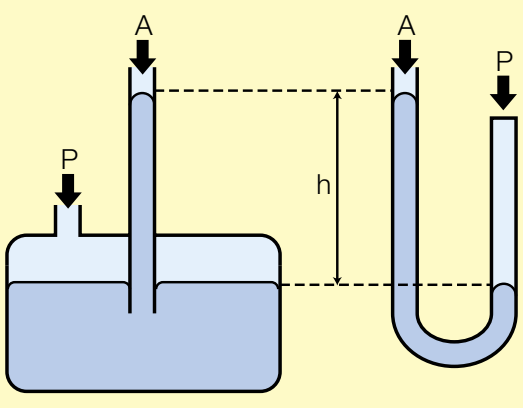
Thus, pressure is independent of the width of the fluid column and of the shape of the liquid column. In single tube manometers, pressure is defined by the height of the fluid column as measured from the meniscus in the reservoir. One source of error is that the level of the meniscus in the reservoir falls as fluid is forced up the tube so that a fixed graduated scale does not accurately reflect the true difference between the two menisci. This error can be minimized either by making the cross-sectional area of the reservoir large compared with the cross-sectional area of the tube or shortening the scale length to allow for the fall in reservoir level. Another potential source of error is caused by the surface tension of the liquid. Most liquids have a meniscus that is concave upwards, and surface tension causes the position of the meniscus to appear to be higher than it is. However, in mercury manometers, the meniscus is concave downwards and this causes a negative error in the reading.

Liquid manometers

Mercury manometer giving measurement for absolute pressure



Mercury manometer giving gauge pressure



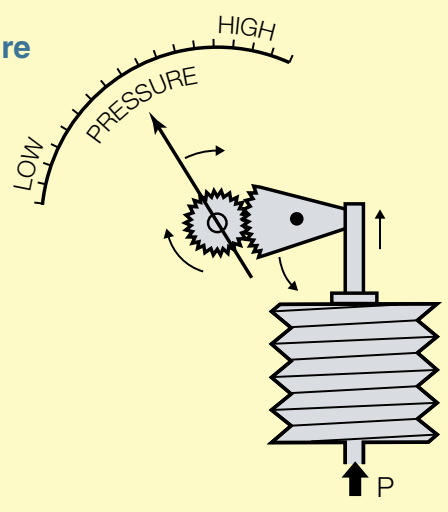
P, applied pressure; A, atmospheric pressure; h, measured pressure

1

Mechanical pressure gauges
Aneroid gauge is used to sense and measure small pressures (Figure 2). Expansion of a small metal bellows is detected by a lever mechanism, which amplifies the movement and drives a pointer on a scale.

Bourdon gauge is used for measuring high pressure. It consists of a coiled tube, flattened in cross-section. One end of the coil is anchored to the case and connected to the pressure source, while the other end is closed and attached to a mechanism that drives a pointer across a dial. Application of pressure causes the cross-section to become more circular, thus causing the coiled tube to straighten and, with one end fixed, the pointer moves across the dial.

Aneroid pressure gauge



P, pressure

2

Measuring blood pressure

Indirect measurement of arterial pressure
Most indirect methods of measuring blood pressure are based on the occlusion of a major artery by a cuff. In clinical practice, systolic and diastolic end points are detected by auscultation of the Korotkoff sounds. The systolic point is marked by the sudden appearance of tapping sounds (phase I) synchronous with the heart beat. The sounds then become quieter (phase II) and as the cuff pressure decreases further the sounds become louder with a tapping quality (phase III), then the sounds become muffled (phase IV) and disappear (phase V). Errors may occur related to the site of the measurement, because arterial blood pressure is not identical in every artery. Pulse pressure is greater in peripheral arteries because the velocity of the pulse wave increases as it travels from the heart to the artery. Blood pressure may also differ in the limbs. Indirect methods are intermittent, with systolic and diastolic readings reflecting conditions in the artery at two instants at which they are measured. The end point of diastolic blood pressure measurement is also the subject of controversy; there is a difference of 5–10 mm Hg between Korotkoff phases IV and V. This is not important in clinical practice but may affect epidemiological studies. A short or narrow cuff may cause readings to be too high, while a wide cuff gives a low reading. The cuff should cover about two-thirds of the length of the upper arm, or its width should be 20% greater than the diameter of the arm. Zero and calibration errors in aneroid manometers also occur.

Oscillometric measurement of blood pressure depends on the principle that blood pressure can be estimated by analysing the pressure oscillations in the cuff as it is slowly deflated. Most instruments use a single pressure cuff applied to the arm, which is inflated to about 30 mm Hg above systolic blood pressure. During slow deflation, each pulse wave leads to a pressure transient in the cuff, which is transmitted to the connecting tube, where a transducer detects it. Above systolic blood pressure, the transients are small and, at the systolic point, they quickly increase in magnitude. As the cuff pressure decreases, the transients reach a peak amplitude and then decrease. The mean arterial pressure is the lowest cuff pressure where the peak amplitude is maintained and at diastolic blood pressure is the point where the transients abruptly decrease in amplitude.

This oscillometric principle is used in the *Dinamap* (a non-invasive, automatic method of measuring blood pressure) where at each pressure plateau point, successive pulses are compared and accepted only if their amplitude is similar. With this device, systolic blood pressure shows good correlation with direct pressure measurement with a bias towards overestimation at low blood pressure and underestimation at high blood pressures. Newer devices operate in a similar fashion, but cuff deflation is continuous, rather than in steps, leading to shorter measurement time. However, all these devices rely heavily on a regular cardiac cycle with no great difference between successive pulses.

Continuous non-invasive blood pressure measurement is based on the Penaz technique, which makes use of the principle that the force exerted by a body may be measured by determining the counterforce needed to stop the original force from causing physical disruption. This principle works only if the counterforce can be measured accurately and the detection does not need to be linear because it should be capable of detecting the null condition only.

A small cuff is placed round a finger and can be inflated or deflated at high speed. Inside the cuff is a light-emitting diode, which transilluminates the finger, and on the other side is a photodiode that detects light intensity after it has passed through the finger (using the same principle as a pulse oximeter). The detected light intensity is a crude measure of the blood volume in the finger, but is a precise indicator of any change in volume. The system inflates the cuff rapidly to above systolic blood pressure and then deflates. As soon as the optical detector senses the pulse wave, the pressure in the cuff is increased such that flow is decreased to maintain a constant volume of blood in the finger, thus maintaining a constant signal. The pressure waveform applied to the finger by the cuff closely mirrors the pressure waveform within the arteries. This device not only measures systolic and diastolic blood pressure but also reproduces the actual arterial waveform. These devices are highly accurate in the normal or vasodilated finger but less effective in patients with poor peripheral perfusion or in hypotensive patients. They show marked variability between patients, and small differences in the positioning and tightness of the cuff produce significant differences in recorded blood pressures.

Direct methods of monitoring blood pressure
Continuous monitoring of arterial blood pressure using intra-arterial cannulation, pressure transduction and display is particularly useful during cardiovascular instability, massive fluid shifts, drug-induced manipulation of blood pressure and when non-invasive blood pressure measurement is inaccurate (e.g. with obesity, cardiopulmonary bypass, arrhythmias). Intra-arterial cannulation also allows repeated sampling of arterial blood for blood gas analysis.

The ability to provide a continuous, accurate, beat-to-beat reproduction of the arterial waveform depends on a structured pressure transducer system. The lumen of the vessel is connected to the pressure transducer by a fluid-filled catheter. The components of the system include a short, parallel-sided, *Teflon* or polyurethane cannula inserted into one of the peripheral arteries; a catheter (a short length of narrow-bore, stiff, non-compliant tubing containing saline or heparinized saline); a flush system to prevent occlusion of the cannula with clots by flushing with saline at the rate of 1–4 ml/hour; and a pressure transducer. A transducer is any device that converts energy from one form to another. Most physiological pressure measurements are made by sensing the movement of a flexible diaphragm, which can be converted into an electrical signal for processing and display. The most common method of pressure transduction uses a strain gauge (an electrically conductive elastic material that responds reversibly to deformation by a change in its electrical resistance). Silicon strain gauges are more sensitive, but they are affected by temperature and are non-linear. In a silicon strain gauge, a thin slice of silicon crystal is bonded on to the back of the diaphragm. The movement of the diaphragm causes a change in the resistance of the crystal, which can be converted into an output signal using a Wheatstone bridge circuit. The movement of the diaphragm may also be sensed optically by reflecting a beam of light off the silver back of the diaphragm on to a photoelectric cell, which measures changes in electrical output. These transducers have a high-frequency response and eliminate the risk of microshock.

The sensing element of the diaphragm may rely on capacitance. The diaphragm forms one plate of the capacitor, the second plate being fixed. The capacitor is part of a bridge circuit that is energized by an alternating current source. The impedance of the transducer changes with the displacement of the plates of the capacitor. The output is an alternating signal with an amplitude that varies with pressure. Inductance may also be used, in which case the diaphragm moves a soft iron core between the primary and secondary coils of a transformer. An alternating current energizes the primary coil. The movement of the soft iron core modulates the voltage in the secondary coil. The voltage is then rectified, filtered and amplified.

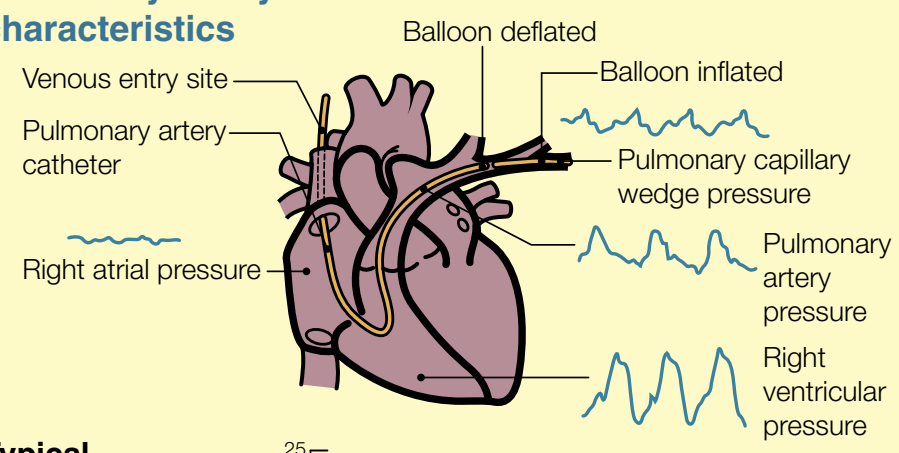
Pulmonary artery catheter pressure measurements

Pulmonary artery catheterization was introduced into clinical practice in the early 1970s for the treatment of patients with cardiac diseases. While many physicians believe that a pulmonary artery catheter is useful in guiding intravascular volume expansion and pharmacological intervention in selected critically ill patients, its use is controversial.

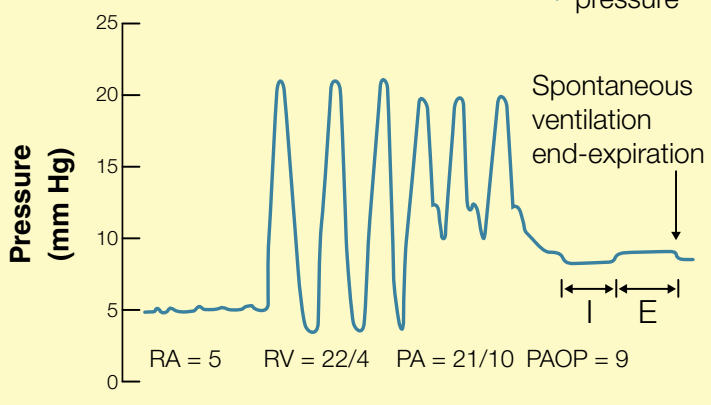
The balloon-tipped, flow-directed, pulmonary artery catheter (Swan–Ganz) is commonly used to measure pulmonary artery pressure and pulmonary capillary wedge pressure (PCWP) or pulmonary artery occlusion pressure (PAOP) as a means of assessing left ventricular filling pressures. It also allows the measurement of cardiac output by a thermodilution technique and the measurement of mixed venous oxyhaemoglobin saturation. A pulmonary artery catheter should be inserted by a physician who knows about the complications, and is capable of interpreting and using the data obtained (Figure 3). Figure 4 gives normal values for pulmonary artery measurement.

PCWP or PAOP reflect mean left atrial pressure, which reflects left ventricular end-diastolic filling, which reflects left ventricular preload. However, preload is the stretch placed on the left ventricle by the end-diastolic volume. Assuming changes in left ventricular end-diastolic pressure are predictive of changes in left ventricular end-diastolic volume implies that the compliance of the left ventricle is constant, which may not always be the case. Therefore PCWP is not a perfect reflection of left heart preload, because changes in the myocardium may alter left ventricular compliance (i.e. during myocardial ischaemia). Other factors that may adversely affect the accuracy of PCWP measurements include significant mitral valve stenosis and pulmonary venous resistance (as may be seen in patients with chronic obstructive airways disease).

The insertion path of a balloon-tipped, flow-directed, pulmonary artery catheter with its waveform characteristics



Typical pressure waveforms



Typical pressure waveforms of a pulmonary artery (PA) catheter as it travels through the right atrium (RA), right ventricle (RV), and PA where it is wedged to give the pulmonary capillary wedge pressure (PCWP) or pulmonary artery occlusion pressure (PAOP). I, inspiration; E, expiration. The diastolic PA pressure is usually significantly higher than RV diastolic pressure and the PAOP is necessarily lower than PA diastolic pressure. To record otherwise suggests that blood is flowing from the left heart to the right heart. It is essential to read the PAOP at the end-expiration

3

Normal values of physiological measurement obtained using a pulmonary artery catheter

Value	Normal range
• Right atrial pressure (RAP)	2–8 mm Hg
• Right ventricular pressure	Systolic: 20–30 mm Hg; diastolic RAP less or equal to RAP
• Pulmonary artery pressure (PAP)	Systolic: 20–30 mm Hg; diastolic: 5–15 mm Hg
• Pulmonary capillary wedge pressure (pulmonary artery occlusion pressure)	2–12 mm Hg; must be less than diastolic PAP
• Cardiac output	4–6 litres/minute (adult)
• Mixed venous oxyhaemoglobin saturation	65–75%

4

FURTHER READING

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Principles of Cardiac Pacemakers and Defibrillators

Richard Griffiths

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A patient presenting for surgery with a permanent cardiac pacemaker is a common occurrence. The anaesthetist must be familiar with the type of pacemaker that has been inserted and the potential malfunctions that can occur during surgery. Over 1 million pacemakers have been implanted worldwide and in 1994 the estimated new implant rate was 295/1 million population.

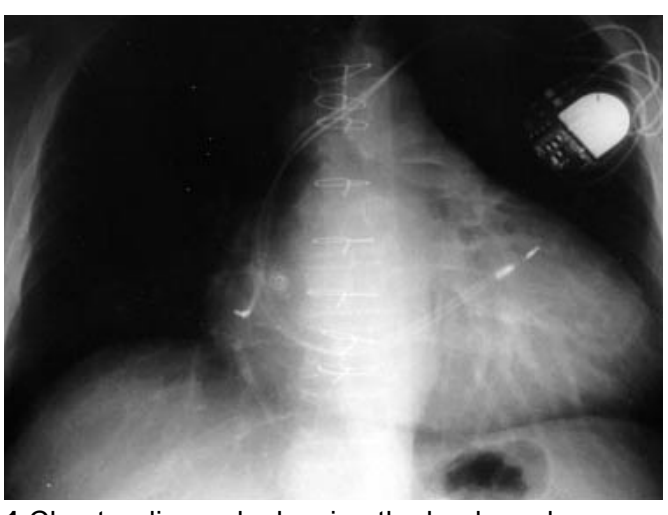
The pacemaker system

The system consists of a generator and one or two leads. The pulse generator has three basic components, a power source, an electrical impulse former and a timer. The early pacemakers had a fixed rate, but most new devices are demand units. The life of the battery is 8–15 years, and the units are checked regularly for battery life and performance. The circuitry and battery are contained in a titanium or stainless-steel box attached to a block that contains the electrode connections through which the pacemaker leads interface with the generator circuit.

The leads are non-thrombogenic, resistant to fracture and have to be insulated. The wire is made of metal alloy covered by an insulating layer of silicone or polyurethane. The pacing lead can be connected to the epicardial or endocardial surface of the heart. The endocardial surface is used if the unit is inserted via a subcostal approach or if inserted at the time of cardiac surgery. The epicardial surface is most commonly used and is reached transvenously either through the internal jugular or subclavian veins. The femoral and antecubital veins have also been used. Electrical impulses are formed in the pulse generator and are transmitted to the myocardium by the lead, resulting in mechanical contraction of the heart (Figure 1).

The distal end of the pacing lead is attached to the myo-cardium. The lead can be anchored by passive or active fixation. Passive fixing is achieved using a system of fins, which become entangled in the myocardium. Active fixation is used in patients with dilated right ventricles and involves insertion of the lead into the myocardium with a screw mechanism.

Cathodal stimulation is used in permanent pacing systems because the thresholds are lower and the risk of induced arrhythmias is reduced. The electrode has a small surface area to enhance current density and thus reduce the stimulation threshold. Permanent pacing systems are able to cause myocardial contraction (capture) and can sense the intrinsic electrical activity. The minimum stimulation needed to cause capture is the pacing threshold. The voltage is set at twice the threshold level to ensure reliable capture. The sensing threshold is the voltage at which the pacemaker is able to detect the intrinsic signal in the chamber being sensed. The current returning via blood to the anode completes the circuit. The anode is just proximal to the tip in a bipolar system and is part of the pacemaker unit in a unipolar system.



1 Chest radiograph showing the leads and generator unit of a dual-chamber system.

Types of pacemakers

In the 1960s, pacemakers were introduced to treat bradycardias, but now they can also be used to treat tachycardias. Pacemakers can pace both cardiac chambers to improve the physiological performance of the heart. They can also respond to the patient's activity and enable heart rate to alter with exercise. A common nomenclature has been described by the NASPE (North American Society of Pacing and Electrophysiology) and BPEG (British Pacing and Electrophysiology Group) known as the NBG pacemaker code (Figure 2).

In fixed-rate modes, the pacemaker paces but does not sense the myocardium. The NBG codes for these pacemakers are VOO, AOO or DOO. Fixed-rate pacing can interfere with the intrinsic cardiac rhythm and may lead to other arrhythmias. Owing to the risk of spontaneous cardiac activity, demand units have superseded fixed-rate pacemakers.

Demand mode pacemakers sense the electrical activity of the atria (P wave) or the ventricle (R wave). When spontaneous ventricular activity is sensed, the output of the pacemaker is suppressed (R wave inhibited) or the unit is made to discharge instantly (R wave triggered) so that the impulse will occur within the safe period of the QRS complex.

Most pacemakers are on-demand units with a single pacing lead passing to the right ventricle. In cases where there is sinus node disease and normal atrioventricular (AV) conduction, the lead may be located in the right atrium to maintain the normal sequence of atrial and ventricular depolarization.

The NASPE/BPEG Generic (NBG) Pacemaker Code

Letter position	I	II	III	IV	V
Category	Chamber paced	Chamber sensed	Response to sensing	Programmability rate modulation	Anti-tachycardia functions
	O = none A = atrium V = ventricle D = dual	O = none A = atrium V = ventricle D = dual	O = none T = triggered I = inhibited D = dual R = reverse	O = none P = simple programmable M = multiprogrammable C = communicating R = rate modulation	O = none P = pacing S = shock D = dual

The code is a five-letter system in which the first three letters describe the basic anti-bradycardia functions and the last two letters describe programmability and anti-tachycardia functions. Clinically the first three letters are often used alone if the last two letters have no function (e.g. fixed-rate modes are VOO, AOO or DOO)

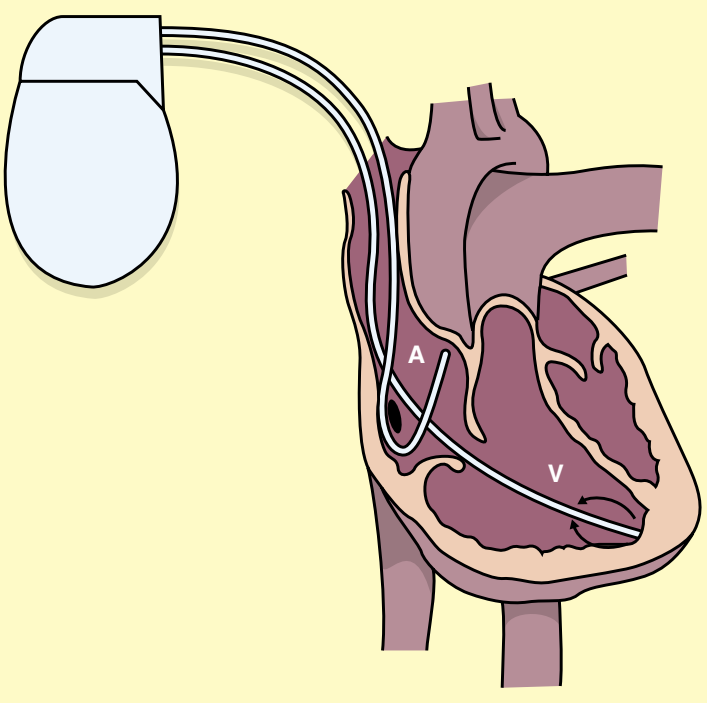
2

Atrial only: the NBG codes for these pacemakers are AAI or AAT. The atrium is paced and sensed, and is either inhibited or triggered. These modes are used for sinus node dysfunction when the AV conduction system is normal.

Ventricular only: the NBG codes for these pacemakers are VVI or VVT. The ventricle is sensed and paced, and either inhibited or triggered. However, there is no AV synchrony and these modes are not used for patients who rely on coordinated atrial contraction to improve end-diastolic filling of the left ventricle. A single ventricular lead is shown in Figure 3.

Dual chamber pacemakers have pacing electrodes in both the right atrium and ventricle (Figure 3). They are designated VAT, VDD, DVI or DDD. AV synchronous pacing is provided with VAT and VDD modes, and the ventricle is paced after sensing atrial activity. These modes are useful in patients with abnormal sinus node function who have an intact AV conduction system. Atrial synchronous pacemakers enable the heart rate to increasein response to an increase in sinus rate during exercise. These modes also maintain the physiological relationship between the atria and ventricles.

Position of leads in single and dual pacemaker systems



In the single chamber system, the lead is implanted in the ventricle only (V). In the dual system, one lead is implanted in the ventricle (V) and the other in the atrium (A)

3

Rate-responsive pacemakers can sense other stimuli as well as atrial and ventricular activity and can increase the basic pacemaker rate. Dual-chamber pacemakers are unable to increase heart rate during exercise in patients with severe sinus node disease, because the node fails to respond to stimuli. There may also be a need to increase heart rate and cardiac output during physiological stimuli other than exercise. Various sensors are used to detect muscle activity, movement and an increase in minute ventilation, temperature and mixed venous oxygen saturation. Rate-responsive modes include VVIR, DVIR and DDDR. Most modern implanted pacemakers have some programmable features.

Implantable cardioverter defibrillators are used in patients who have sustained ventricular tachycardia (VT) and syncope caused by VT. They are described according to a separate NASPE/BPEG code – the defibrillator code (Figure 4). The typical code is VVEV. Early models could deliver countershocks only, but now the pacemakers can cardiovert episodes of VT with anti-tachycardia pacing.

The NASPE/BPEG Defibrillator Code

Letter position	I	II	III	IV
Category	Shock chambe	Anti-tachycardia pacing	Tachycardia detection chamber	Anti-bradycardia pacing
	O = none A = atrium V = ventricle D = dual	O = none A = atrium V = ventricle D = dual	E = electrogram H = haemodynamic O = none	A = atrium V = ventricle D = dual

4

Surgery for patients with a pacemaker

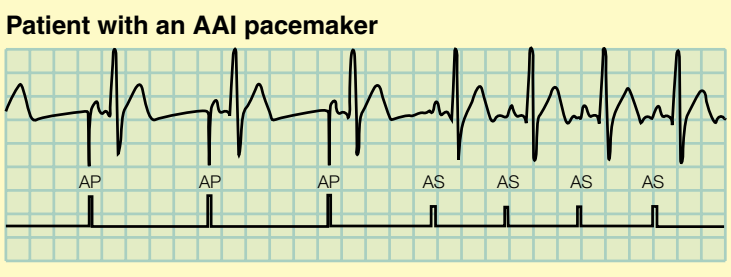
The two primary concerns during anaesthesia in patients with a pacemaker are whether the unit will continue to function and the consequences of using diathermy.

Preoperative assessment

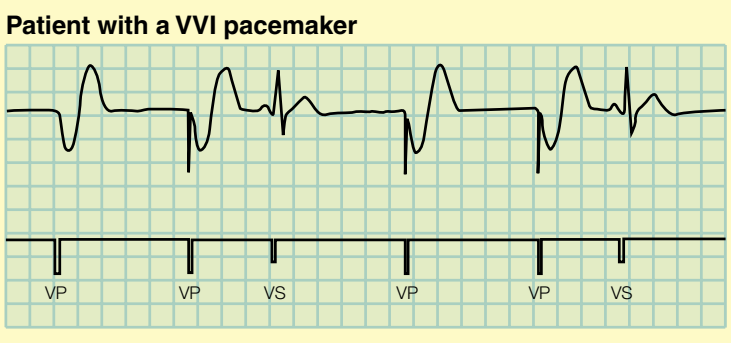
Full preoperative assessment must be undertaken. Of particular note in the history is the initial indication for pacemaker insertion and an assessment of the present function of the unit. The type and mode of pacemaker can be obtained from the patient's pacemaker identity card. The date of the most recent check should be noted with specific reference to the state of the battery. The ECG should be examined for evidence of sensing, pacing and capture (Figure 5). If the intrinsic heart rate is greater than the preset rate of the pacemaker, applying a magnet over the unit can check the correct functioning of the unit. This converts the unit to an asynchronous mode and captured beats should appear on the ECG. A chest radiograph should be taken to confirm the position of the leads. The potassium level should be determined because hypokalaemia increases the resting membrane potential and may lead to loss of capture. Acute hyperkalaemia decreases the resting membrane potential and thus increases ventricular irritability.

ECGs of patients with pacemakers

Patient with an AAI pacemaker



Patient with a VVI pacemaker



AP, atrium paced; AS atrium sensed; VP, ventricle paced; VS, ventricle sensed

Anaesthetic technique

The anaesthetic technique should avoid suxamethonium because muscle fasciculations can inhibit demand pacemakers (myopotential inhibition). The pacemaker senses skeletal muscle electrical activity, which can be caused by mechanical ventilation and myoclonic movements from induction agents (e.g. etomidate). Normothermia should be maintained because shivering can also change the performance of demand pacemakers. Evidence of mechanical, as well as electrical, heart function is provided by looking at the pulsemeter that accompanies a pulse oximeter. Mechanical and electrical function should be checked after any patient movement and also at the start of mechanical ventilation. An external converter magnet should be available in the operating room. This should not be placed over the pacemaker routinely because it may adversely affect a programmable unit; however, it may prove invaluable if the unit has to be converted to an asynchronous mode because of interference from diathermy. Atropine and isoprenaline should also be readily available in the event of pacemaker failure. Ventricular fibrillation is managed conventionally in pacemaker patients, but the paddles must not be placed directly over the pulse generator. The stimulation threshold may alter following defibrillation, therefore equipment must be available for temporary pacing or for non-invasive transcutaneous pacing.

Interference from diathermy

Current pacemakers are well shielded and are less likely to be affected by electrodiathermy than older types. Monopolar diathermy involves the passage of radio-frequency alternating current between an active electrode and a return electrode (the ground pad). The electrical artefact from the diathermy may be sensed as an intrinsic myocardial potential resulting in inhibition of the pacemaker. In some units, if the electrical interference continues, the unit can revert to a fixed rate until the interference ceases. To ensure that interference is minimized, the ground pad of the diathermy unit should be positioned close to the site of surgery and as far away as possible from the pacemaker unit and leads. Diathermy must also be used in short bursts. Current flow between the two elements of the diathermy unit should not cross the pacemaker system. Bipolar diathermy should be considered if interference continues with monopolar diathermy.

Pacemakers and unusual environments

MRI is contraindicated in pacemaker patients. If an MRI scan is absolutely necessary the pacemaker can be removed before the scan and reimplanted afterwards.

Lithotripsy is a safe procedure in patients with permanent pacemakers. The pulses from the lithotripsy should be timed with the electrical activity of the heart. Care must be taken when the pacemaker has been placed in the upper abdomen, because direct impulses should not be sent through the unit.

Other methods of cardiac pacing

Non-invasive transcutaneous pacing is useful following cardiac arrest and can buy time before a transvenous system can be inserted. Electrode patches are placed on the anterior and posterior aspects of the chest. The anterior patch should be the cathode and be placed along the left costal margin. It is important to avoid placing the electrode patches over a muscle mass, because it will be stimulated by the applied current. The anode should be placed posteriorly, inferior to the left scapula. Pacing is done with the lowest effective power output; this is usually 80 mA.

Temporary transvenous pacing: through central venous access, a temporary pacing wire can be inserted and connected to an external pulse generator. These devices can operate in either asynchronous (fixed rate) or in synchronous (demand rate) mode.

Defibrillators are used to deliver electrical energy to the myocardium, which depolarizes a critical mass of the muscle to allow a stable heart rhythm to be restored. In the defibrillator, direct current (DC) is stored and released in a controlled fashion. DC is preferred to alternating current (AC) because it is more effective and causes less damage to the myocardium. DC is also less likely than AC to cause arrhythmias. The electrical charge is stored in a capacitor. The electrical energy delivered from the defibrillator depends on the charge and the potential. When charged, the electrical energy is discharged across the patient's chest as a current pulse. The pulse is applied via two paddles, which are placed on the sternum and the left mid-axillary line at the 5th to 6th rib space. In order to ensure that most of the applied charge depolarizes the myocardium, the transthoracic impedance of the patient should be low. The impedance can be reduced by applying firm pressure and by the use of conductive gel pads.

Defibrillators can also be used to correct atrial fibrillation. Less energy is applied and the charge is synchronized so that it is delivered during the R wave of the cardiac cycle. Internal defibrillators are also used when the chest is open during cardiac surgery. The electrodes are applied directly to the heart and less energy is used.

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Principles of Pressure Transducers, Resonance, Damping and Frequency Response

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The types of pressure of most clinical importance to anaesthetists are those within the blood vessels, such as the central veins, systemic arteries, intracardiac chambers, pulmonary arteries and the pulmonary capillary wedge pressure. Pressures of additional clinical significance are those generated within enclosed spaces such as the skull (intracranial pressure) or limb compartments and CSF pressure.

All body pressures are composed of a static and a dynamic component.

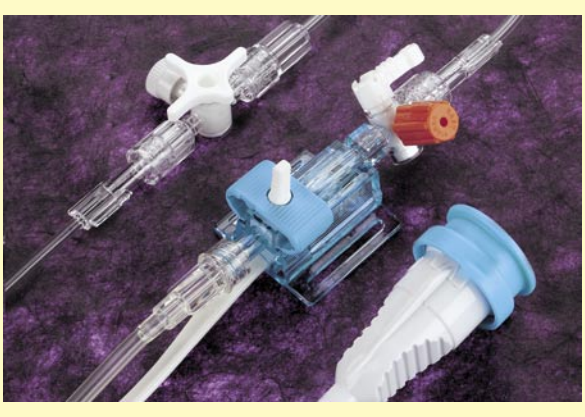
- The static component ('hydrostatic' pressure) is related to the weight of fluid supported above the reference point and to any externally applied or internally generated pressure. Internally generated pressure within the skull or limb compartments is most commonly caused by tissue swelling within the confines of an enclosed space.
- The dynamic component of pressure is related to kinetic energy generated by the interaction of contractile cardiac activity with the blood vessel walls, to which is added changes in flow resulting from fluctuations in intrathoracic pressure with respiration. These cause blood flow and rapidly travelling pressure waves within the circulatory tree. Pressure waves within blood vessels are progressive and mechanical, in that they carry energy associated with their oscillation through the bloodstream. The dynamic component of intracranial and intracompartmental pressure waves is also associated principally with the flow of blood through vessels and is transmitted throughout the enclosed space.

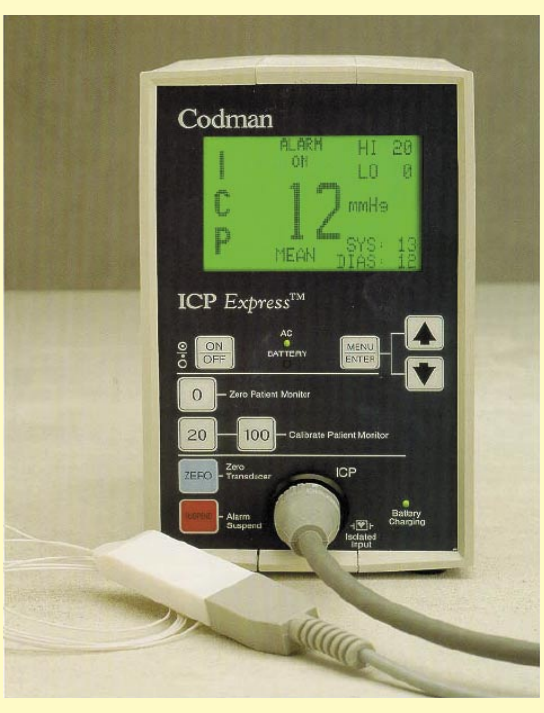
Methods of direct pressure measurement

Accurate recording of '*in vivo*' pressure waveforms involves the conversion of the biological pressure wave into an electrical signal by a transducer. The resultant electrical signal can then be amplified, processed and displayed electronically. Two alternative transducer arrangements are used clinically for measuring biological pressure waveforms (Figure 1).

- A miniaturized sensor on the tip of a catheter can be placed in the patient at the point of measurement.
- A fluid-filled pathway (manometer) can be used to link a catheter or cannula to a transducer placed some distance away from the site of measurement.

Although catheter tip sensor systems are the most accurate, their disadvantages are that they are more expensive because of their greater complexity, they are prone to fibrin deposition if used within the circulation, and they cannot be recalibrated once *in situ*. Therefore, manometric transducer systems are in more widespread clinical use.



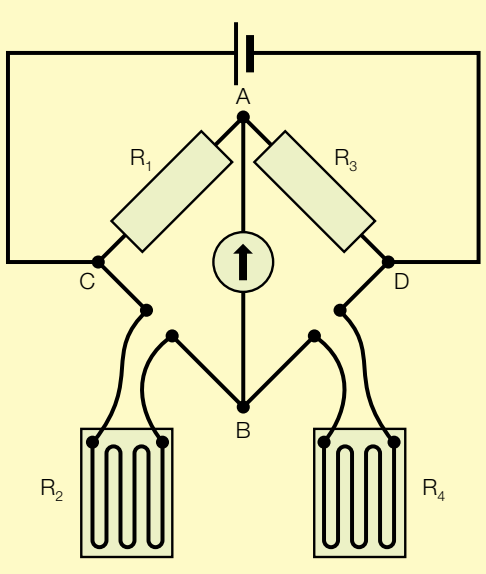


1
a Disposable manometric pressure monitoring set. *Photograph courtesy of BD UK Ltd*. **b** Intracranial pressure transducer connected to a monitor. A miniaturized strain gauge is situated at the tip of the fine white catheter. The natural frequency of the transducer is over 10 kHz. *Photograph courtesy of Codman/Johnson & Johnson*.

A variety of methods is used to convert pressure changes into an electrical signal, the most common of which is the strain gauge. A strain gauge consists of a fine metal wire bonded to a diaphragm. Pressure changes distort the diaphragm and stretch the wire, thus altering its electrical resistance. Piezo-resistive strain gauges measure the change in the electrical resistance of silicon when exposed to pressure. A Wheatstone bridge is used to detect the change in electrical resistance (Figure 2). Strain gauges have been miniaturized to allow their use on the tip of catheters to measure intracranial pressure. Other catheter tip transducer systems use pressure-induced changes in the intensity of light travelling along a fibreoptic pathway to measure intracranial pressure.

Strain gauge transducer and Wheatstone bridge

Resistors R_2 and R_4 are strain gauges incorporated into a Wheatstone bridge circuit with conventional resistors R_1 and R_3. A potential difference is applied between points C and D. The bridge is adjusted so that it is balanced when no strain is applied, and no potential difference is measured between points A and B. When strain is applied to gauge R_4, the bridge becomes unbalanced, and a potential difference proportional to the strain is measured between points A and B. Gauge R_2 may be placed close to R_4 without strain being applied to compensate for changes in resistance due to temperature. Alternatively, the two gauges may be sandwiched back to back so that applied strain causes an increase in resistance within one gauge, which is matched by a fall in resistance in its partner. This amplifies the magnitude of the potential difference between points A and B, and increases the sensitivity of the transducer.



2

Setting up a pressure transducer
Setting up a transducer system correctly is crucial to its accuracy. Manometric sets must be carefully primed with sterile flush solution at room temperature without pressurization of the solution bag, to avoid micro and macro air bubble formation within the fluid pathway. A manometric transducer should be positioned at mid-heart level. Each 10 cm height difference from this point equates to a hydrostatic error of 7.4 mm Hg from the true pressure reading.

All pressure transducers require zero balancing to atmospheric pressure before use, and at regular intervals thereafter, to compensate for drift. This may be impossible for catheter tip sensors once *in situ*. The electronic monitoring equipment, to which the transducer system is connected, must also be suitably calibrated.

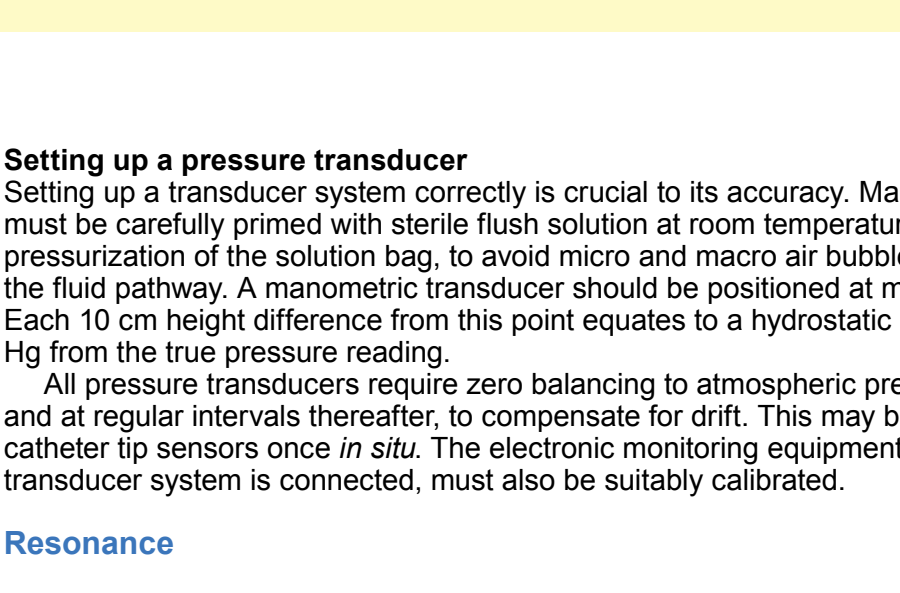
Resonance

Resonance occurs when the frequency of the *in vivo* driving oscillations matches the natural frequency of the driven transducer system, and oscillations of large amplitude are induced (Figure 3). This results in significant error by overshooting of the peaks and troughs in the actual pressure waveform, with an overestimation of the systolic pressure and underestimation of the diastolic pressure.

The natural or resonant frequency is the frequency at which the undamped transducer system oscillates freely with maximal amplitude. The natural frequency of a transducer system is proportional to the square root of the stiffness of the diaphragmand is inversely proportional to the square root of the mass of the oscillating fluid and diaphragm (Figure 3). The mass of oscillating fluid is proportional to the length and radius of the fluid pathway and density of fluid.

The resonant frequency of the system can therefore be raised by including a short, stiff, parallel-sided catheter joined to short, stiff, narrow-bore, interconnecting tubing, together with a transducer with a stiff diaphragm. Increasing tubing length from 30 to 150 cm can reduce resonant frequency by over 50% and from 15 to 150 cm may decrease resonant frequency from 30 to 7 Hz, leading to an overestimation of systolic blood pressure by up to 17%.

Resonance



As the frequency of driving oscillations increases, the amplitude of induced oscillations rises to a maximum at the natural or resonant frequency of the transducer system (f_0u). If the system is damped by absorbing some of the energy of the induced oscillations, the maximal amplitude attained is reduced. Damping also reduces the resonant frequency of the transducer system (from f_0u to f_0d), and extends the flat range of the system from XY to XZ. The resonant frequency of a manometric transducer system is calculated as:

$$\text{Resonant frequency} = \frac{1}{2\pi}\sqrt{\left(\frac{\text{stiffness of diaphragm}}{\text{mass of oscillating fluid and diaphragm}}\right)}$$

3

Damping

Damping is the process whereby some of the energy of the driven oscillations within the transducer system is absorbed, thus reducing their amplitude. Damping also reduces the resonant frequency of a transducer system (Figure 3), but this relationship is complex. Damping in the correctly functioning manometric system arises mainly from viscous drag in the fluid pathway, tubing connections and stopcocks. Damping increases by the third power of any decrease in the diameter of the tubing (33% narrower tubing increases damping by 135%); a far greater change than the rise in resonant frequency. As a consequence, the diameter of interconnecting tubing has the greatest effect on system performance.

Excessive damping, sufficient to obtund the shape of the pressure waveform, commonly results from compressible large air bubbles, a blood clot, soft compliant connector tubing, numerous connections and stopcocks, and catheter kinks within the system.

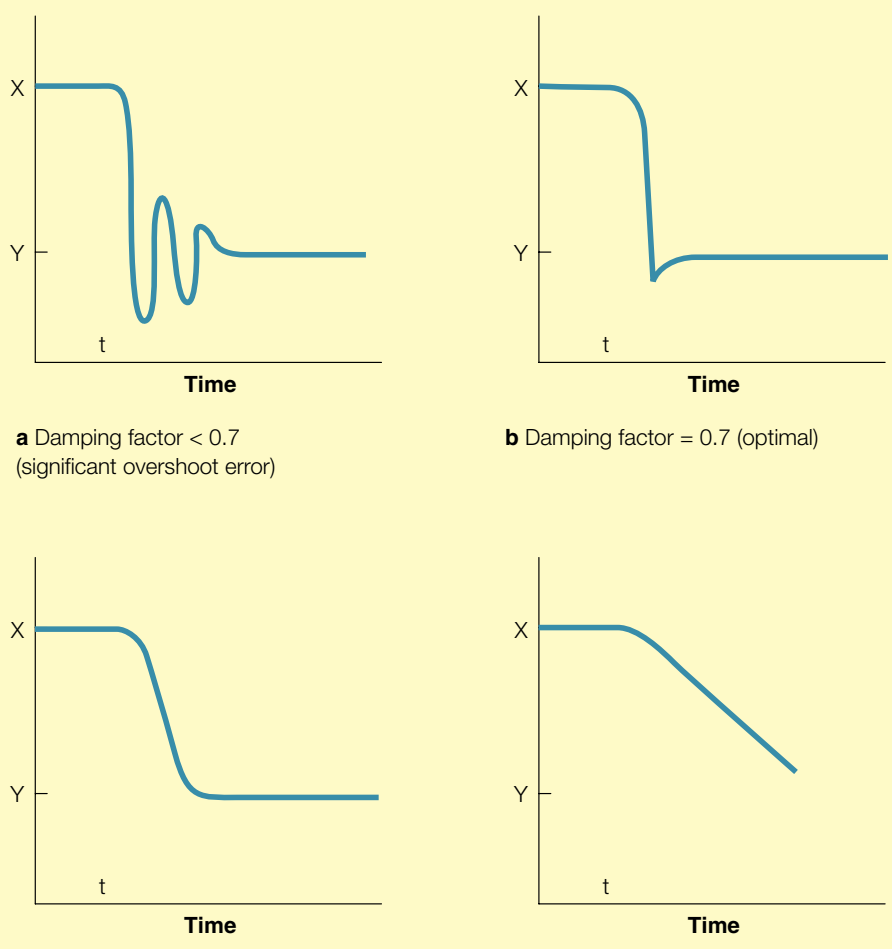
The damping factor is an index of the tendency of a transducer system to resist oscillation.

- Critical damping corresponds to a damping factor of 1, and represents the amount of damping required such that when a stepwise change in pressure is applied, the system returns to rest in the shortest possible time without overshooting the baseline (Figure 4).
- In contrast, optimal damping is the amount of damping necessary to maximize the frequency response or flat range of the system and corresponds to a damping factor of 0.7 (Figure 4). At this level, overshoot of the baseline is limited and the response of the pressure transducer accurately reflects the actual pressure change up to two-thirds of the natural frequency of the system in a close to linear fashion.
- Excessive damping with factors greater than 1 causes a significant delay between the input arriving at the transducer and an output being generated. This is called phase shift (Figure 4) and is measured in degrees. Distortion of the output by phase shift is minimal with a damping factor of 0.7.

Damping of a manometric transducer system

a In an underdamped transducer system, where the damping factor is < 0.7, significant overshoot and subsequent oscillation occurs when a stepwise pressure change from X to Y is imposed at time t. This results in a significant overestimation of the magnitude of the pressure change.
b In an optimally damped system, where the damping factor is 0.7, overshoot is limited to 6–7% of the initial pressure change and no oscillation occurs.
c In a critically damped system, where the damping factor is 1.0, the change in pressure is measured accurately with no overshoot.
d In an excessively damped system with a damping factor > 1.0, the full magnitude of the pressure change may not be registered.

With increasing degrees of damping, the system is progressively slower to respond to the applied change in pressure, and the increasing delay in the transducer output is termed phase shift

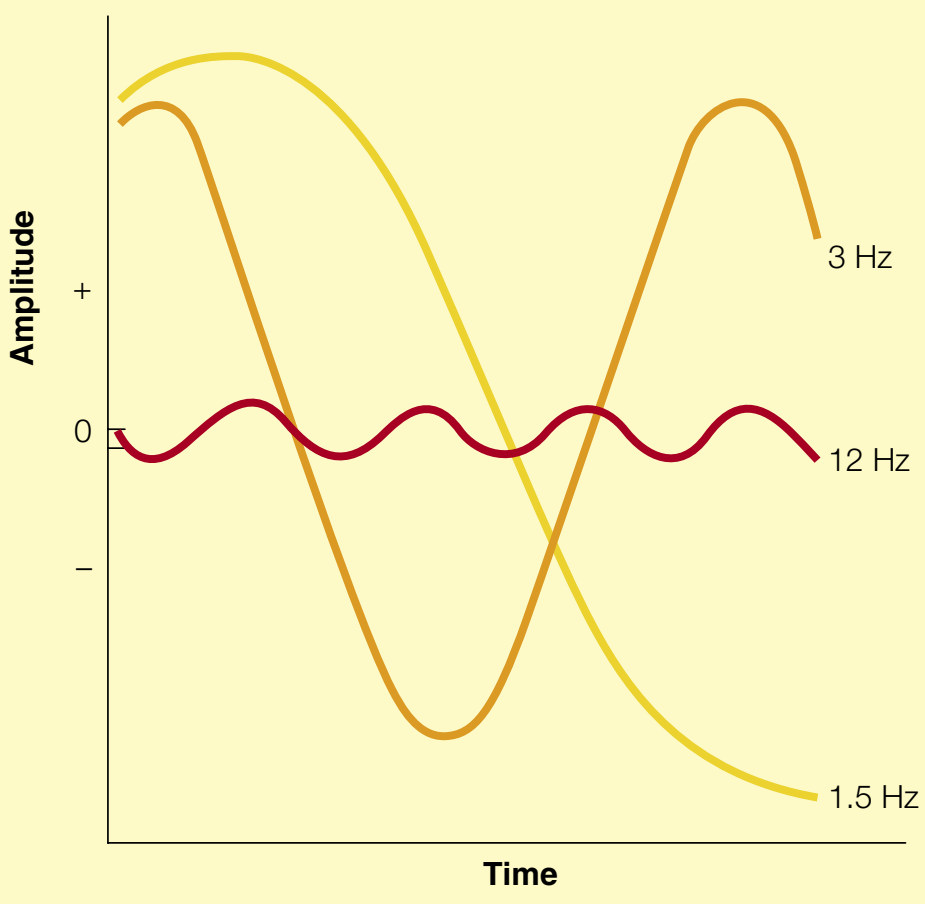


a Damping factor < 0.7 (significant overshoot error)
b Damping factor = 0.7 (optimal)
c Damping factor = 1.0 (critical)
d Damping factor > 1.0 (excessive with marked phase shift)

Waveforms

By means of Fourier analysis, it is possible to split complex waveforms mathematically into a summation of simple sine waves or ascending harmonics, each of which has an increasing frequency and decreasing amplitude (Figure 5). Summation of the first eight to ten harmonics of an arterial blood pressure waveform gives a reasonably accurate representation of its shape. This number of harmonics is required to track accurately the initial steep rate of rise in the pressure waveform corresponding to left ventricular ejection.

Fourier analysis of the arterial pressure waveform



The first or fundamental harmonic (1.5 Hz) together with the second (3 Hz) and eighth (12 Hz) harmonics of a single blood pressure beat waveform are shown, for a heart rate of 90 beats/minute. Progressively higher harmonics display decreasing amplitude. As a consequence, only the first 8–10 harmonics need to be summed to reproduce the shape of the arterial pressure waveform accurately

Minimum bandwidth
Minimum bandwidth is the minimum frequency range over which measurement by a transducer system is sufficiently accurate to reproduce the first eight harmonics of the *in vivo* pressure signal, resulting in an accurate electronic representation of the shape of the pressure waveform. For the measurement of arterial blood pressure, this is equal to eight times the fundamental frequency of the expected heart rate. At 90 beats/minute (fundamental frequency of 1.5 Hz), the minimum bandwidth would be 12 Hz, with the first eight harmonics comprising sine waves with frequencies of 1.5, 3, 4.5, 6, 7.5, 9, 10.5 and 12 Hz. At a heart rate of 120 beats/minute (2 Hz), minimum bandwidth would be 16 Hz. Progressively higher harmonics display rapidly decreasing amplitude, contribute less to the shape of the transduced waveform and are eventually lost within the 'noise' of the measuring system. Accurate reproduction of the amplitude of the pressure waveform, rather than its shape, requires accurate measurement of only the first five harmonics of the fundamental frequency.

Frequency response
The frequency response or flat range of a transducer system is the highest frequency to which the system can be exposed before it registers significant overshoot. Accurate measurement to a limit of 10% greater than the actual pressure is generally acceptable. The frequency response must be equal to, or greater than, the minimum bandwidth. The frequency response of the measuring system depends on its resonant frequency and the amount of damping.

The ideal measuring system has a resonant frequency much higher than the frequencies to be measured; frequencies up to 10–20% of the resonant frequency are accurately reproduced and no damping is required. This is because initial resonance occurs at a frequency much higher than the necessary bandwidth for accurate waveform reproduction. Catheter tip sensors are the closest available systems to this ideal. For the more commonly used manometric systems, the total measuring chain (consisting of catheter or cannula, tubing, stopcocks and transducer) has a much lower resonant frequency, and damping is therefore vital for increasing accuracy. Optimally damped systems can reproduce frequencies up to 67% of the resonant frequency accurately. Continuing the calculations introduced above, an optimally damped transducer system with a resonant frequency of 30 Hz or more will accurately reproduce the shape of the arterial pressure waveform.

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Co-morbidity

Anaesthesia
and intensive care medicine
on CD-ROM

Anaesthesia for the Obese Patient

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The incidence of obesity, with its attendant health risks, continues to rise. Consequently, increasing numbers of obese patients are presenting for surgery and their perioperative care presents a significant challenge to the anaesthetist. In 1997, in Britain, 13% of men and 16% of women were considered to be obese. Obesity is defined according to the body mass index (BMI) or with reference to the ideal body weight (IBW) (Figure 1).

- BMI = weight (kg)/[height (m)]^2
- IBW (kg) = height (cm) – 100 (men) or 105 (women).

Classification of obesity

	Body mass index	Percentage above ideal body weight
Overweight	> 26	30
Obese	> 30	40
Morbidly obese	> 40	100

1

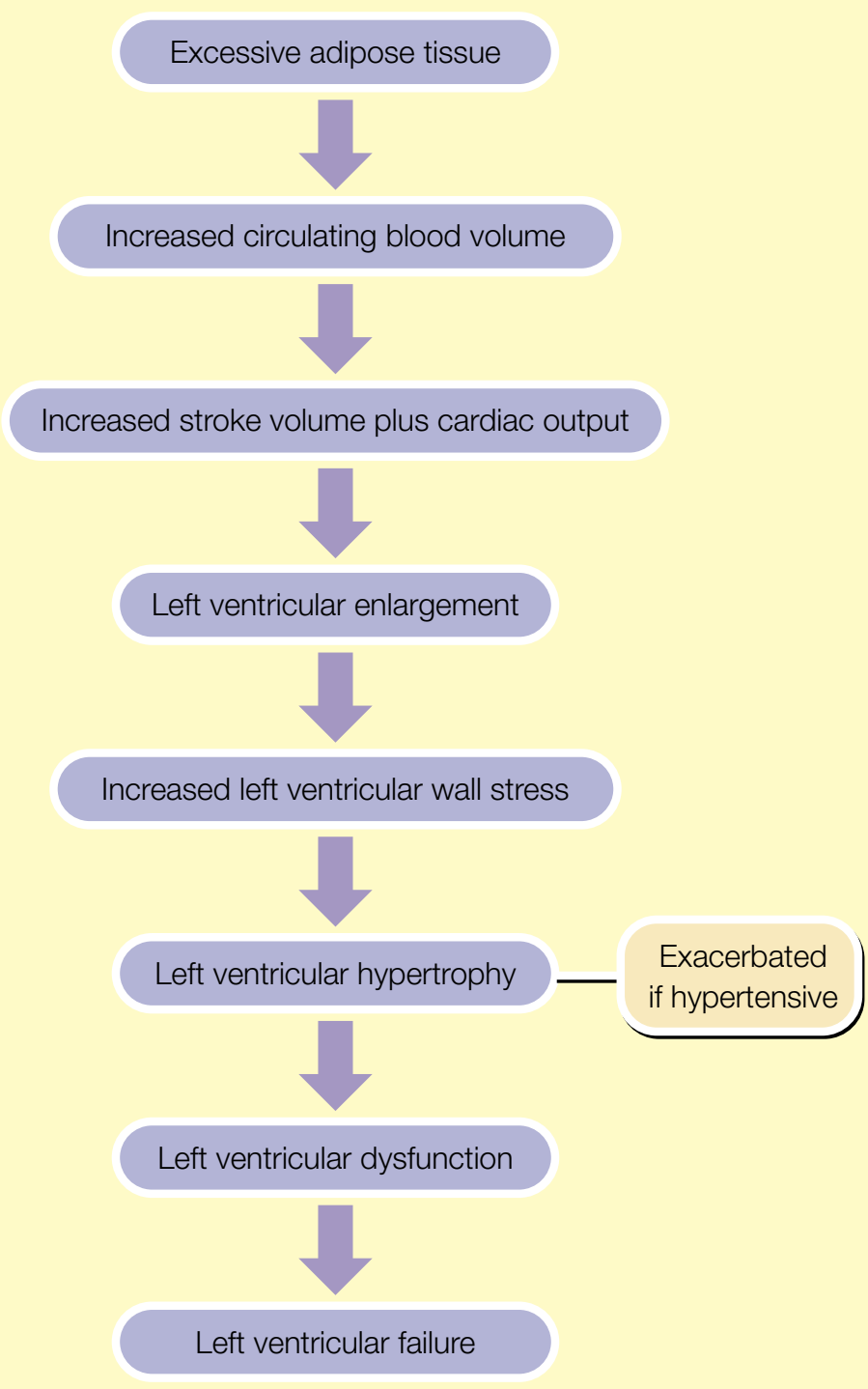
Pathophysiological effects of obesity

The pathophysiological effects of obesity are wide ranging and are greatest in the morbidly obese, though they occur in all obese individuals.

Cardiovascular system

Cardiac structure and function: cardiac output and blood volume are increased in obesity to meet the increased metabolic demands of a greater body mass. Chamber dilatation and ventricular hypertrophy occur to reduce wall stress and can progress to ventricular dysfunction and cardiac failure – a condition known as obesity cardiomyopathy (Figure 2). Cor pulmonate may also develop (Figure 3). These changes are related to the severity of obesity and are improved by weight loss.

Development of cardiomyopathy in obese patients



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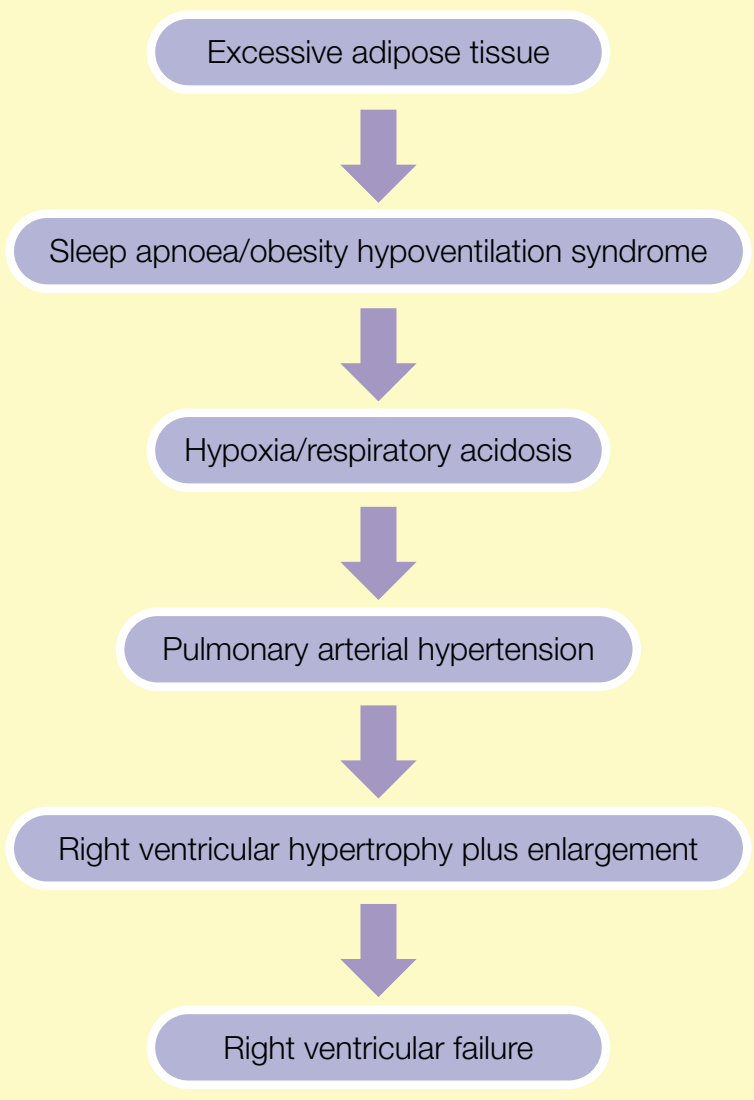
Development of cor pulmonale in obese patients



3

Hypertension is present in 60% of obese individuals and is severe in 10%. The aetiology remains unclear, but weight loss reduces blood pressure.

Coronary artery disease: the role of obesity as a risk factor for coronary disease is difficult to evaluate because of the association between obesity and hypertension, diabetes mellitus and hypercholesterolaemia, which are all coronary risk factors. There is an association between central obesity and an early age of onset of obesity, and the development of coronary artery disease.

Cardiac arrhythmias may occur secondary to chamber dilatation, ischaemic heart disease or fatty infiltration of the conducting system.

Respiratory system
The increased metabolic demands of obesity also require an increased minute ventilation to meet the increase in oxygen consumption and carbon dioxide production. The work of breathing is further increased because of the reduction in chest wall and lung compliance. Obese patients tend to take rapid shallow breaths, leading to greater mismatching of ventilation and perfusion. There is a reduction in functional residual capacity (FRC) because the increased adipose tissue in the chest wall and abdomen limits diaphragmatic excursion. If the FRC falls below closing volume, small airway closure occurs resulting in intrapulmonary shunting and hypoxaemia. This situation may occur in obese individuals under normal circumstances and is exacerbated by increasing age, the supine position and general anaesthesia (Figure 4). As a result of the above mechanisms, obese patients may become chronically hypoxic and develop secondary polycythaemia, pulmonary hypertension and ultimately right ventricular failure.

Relationship between functional residual capacity and closing volume

FRC, functional residual capacity; CV, closing volume

4

Obesity hypoventilation syndrome occurs in 4–10% of morbidly obese patients. It is characterized by chronic hypoxia and its sequelae, in association with a decreased responsiveness to carbon dioxide, and results in hypoventilation and hypercapnia.

Airway problems: excess adipose tissue in the soft tissues of the head and neck makes airway problems more likely, and intubation is difficult in 13% of this pateint population. Obesity also predisposes to the development of the sleep apnoea syndrome, which is characterized by upper airway obstruction and hypoxic episodes when the conscious level is reduced (e.g. during sleep). Classically, these patients have a history of heavy snoring, periods of apnoea during sleep and daytime somnolence because of disturbed sleep at night.

Gastrointestinal system
Hiatus hernia and gastro-oesophageal reflux are more common in obese individuals. Fasting, obese patients have higher residual gastric volumes of lower pH than the non-obese. Liver disease, mainly in the form of cholelithiasis, and fatty infiltration are more common in obese individuals, but hepatitis, fibrosis and cirrhosis can also occur. Obesity is a recognized risk factor for the development of hepatitis following volatile anaesthesia.

Endocrine system
Endocrine disturbances such as hypothyroidism and Cushing's syndrome may have a causal role in obesity. The most important consequence of obesity for the endocrine system is the development of diabetes mellitus.

Anaesthetic management

Preoperative assessment
Common to all patients, preoperative assessment comprises the history, physical examination and preoperative investigations, as well as discussing with the patient the proposed anaesthetic technique and perioperative care plan. The following aspects of the history and examination are of particular importance in obese patients.

- Evaluation of the severity of any cardiorespiratory compromise.
- Careful airway assessment to decide safe airway management.
- Assessment of acid aspiration risk (this also influences airway management).
- Confirmation of the presence of conditions associated with obesity (e.g. diabetes).
- Examination of potential sites for venous access, which may be problematic.
- Examination of the spine if epidural or spinal anaesthesia is contemplated.
- Establishment of a rapport and providing relevant information to the patient.

Preoperative investigations depend on the findings of the history and examination, and the intended surgery, but the following investigations may be helpful in obese patients:

- urinalysis to screen for diabetes
- full blood count to identify polycythaemia
- urea and electrolytes, which may be altered by antihypertensive or diuretic drug therapy
- ECG which may show ventricular hypertrophy, arrhythmias or ischaemic changes
- chest radiography, which is useful for determining heart size, signs of pulmonary oedema and as preoperative baseline
- pulmonary function tests to reveal any restrictive defects; any obstructive component should prompt a trial of bronchodilator therapy
- arterial blood gases to confirm hypoxia and hypercapnia; the response to oxygen therapy should be elicited if the patient is hypoxic on air
- echocardiography and exercise testing which may help to assess the severity of cardiac compromise
- specialist opinions for optimization of medical therapy before elective surgery.

Pharmacological considerations: the changes in blood volume, cardiac output, adipose tissue and total body water content that occur in obesity can alter drug pharmacokinetics.

Intravenous agents – propofol kinetics appear unaltered though recovery from thiopental (thiopentone) and benzo-diazepines may be prolonged.

Volatile anaesthetics – there is little evidence that recovery is prolonged in obesity despite the lipophilicity of these agents. Toxicity from metabolic products may be reduced by using relatively insoluble and minimally biotransformed anaesthetics (e.g. isoflurane, desflurane).

Muscle relaxants – pseudocholinesterase activity is increased, but doses of suxamethonium, less than 1 mg/kg, have been shown to provide adequate vocal cord paralysis. The dose and duration of action of atracurium is unaltered. Vecuronium has a prolonged duration of action and the dose should be calculated according to lean body weight.

Opioids – the doses of alfentanil and remifentanil should be calculated according to lean body weight. Although this restriction does not apply to other opioids, careful dose titration of all opioids is warranted because of their respiratory depressant effect.

Regional anaesthesia avoids the problems associated with general anaesthesia in obesity but is not without problems. Landmarks may be difficult to define and long needles may be required. For spinal or epidural anaesthesia the sitting position aids location of the midline and a nerve stimulator can aid needle placement for other blocks. Smaller volumes of local anaesthetic solutions should be used for spinal and epidural blocks, because spread is greater in obese patients. A final consideration, if a regional technique alone is planned, is the ability of the patient to tolerate the position required for surgery. Some obese patients are unable to lie flat because of respiratory compromise, which may be exacerbated by a regional block affecting thoracic segments. A combination of regional and general anaesthesia may be the optimal technique.

Pre-medication: H_2-antagonists or proton pump inhibitors combined with a prokinetic agent can be prescribed because of the risk of acid aspiration. An anxiolytic can be given, but heavily sedative or opioid premedication should be used with caution and perhaps avoided in the morbidly obese. The oral route is preferable to the intramuscular or subcutaneous routes because absorption from these sites is unpredictable.

Induction and airway management
Tracheal intubation and controlled ventilation are required for all but the shortest procedures in carefully selected patients. During the preoperative assessment, a decision should be made regarding the need for an awake fibre-optic intubation, but difficult intubation equipment and a range of face masks, laryngoscope blades, bougies and other airway adjuncts must always be available immediately. For difficult cases, two anaesthetists and an experienced assistant should be present. Careful positioning of the patient's head and shoulders will make airway management and intubation easier, and a rapid-sequence induction technique should be used because of the risk of acid aspiration. Adequate pre-oxygenation is essential because the combination of increased oxygen consumption and a reduced oxygen reservoir can cause a precipitous fall in oxygen saturation once apnoea occurs. Suxamethonium remains the muscle relaxant of choice because of its rapid onset and offset of action. The choice of induction agent depends on individual circumstances (e.g. cardiorespiratory disease) and obesity *per se* does not influence drug selection. All the commonly used anaesthetic agents have been used successfully in obese patients.

Maintenance and intraoperative care
A balanced anaesthetic technique with muscle relaxation and controlled ventilation, combined with regional anaesthesia is appropriate for many patients. As with induction agents, the choice of agent used to maintain anaesthesia depends on the patient's co-morbidities, the duration of surgery and whether elective ventilation is planned postoperatively. Some important aspects of intraoperative care in obese patients are described below.

Operating table – the table must be wide enough for the safe positioning of the patient and strong enough to take the patient's weight.

Staff – adequate numbers of staff must be present for patient transfer. The patient should be anaesthetized on the operating table so that only one transfer is required with the patient anaesthetized.

Monitoring the correct size of blood pressure cuff is required for the accurate measurement of blood pressure. Arterial cannulation is often desirable for serial blood gas analysis during and after surgery as well as for arterial pressure monitoring. Capnography must be available for induction to confirm correct tracheal tube placement. Central venous monitoring may be necessary for venous access and will aid fluid management, particularly in those with cardiac compromise. The use of an ultrasound probe is recommended to aid placement. Pulse oximetry is an essential tool for rapid detection of hypoxaemia during and after surgery.

Controlled ventilation is almost always required to ensure adequate gas exchange, often with a combination of high-inspired oxygen concentration and the application of positive end expiratory pressure. High inflation pressures may be unavoidable particularly if the lithotomy or Trendelenburg positions are used.

Blood loss is likely to be greater in the obese because surgery is technically more difficult. Adequate venous access must be secured and the threshold for cross-matching of blood may need to be reduced.

End of surgery – if extubation at the end of surgery is intended, it should not be attempted until residual neuro-muscular blockade has been reversed, the patient is awake, cooperative, has a good cough, and an acceptable respiratory pattern and oxygen saturation.

Postoperative complications
Postoperative complications are more common in obese patients, therefore transfer to a high dependency unit or ICU should be considered. Some patients undergoing minor surgery may be nursed safely on the general ward.

Respiratory complications: basal lung collapse during anaesthesia and resulting hypoxia is common, and is exacerbated by
the respiratory depressant effects of residual anaesthetic agent and/or opioid therapy in the postoperative period, as well as the effects of surgery. Collapsed lung segments also act as a focus of infection.

Hypoxia can also occur as a result of airway obstruction if the conscious level is reduced (e.g. in patients with obstructive sleep apnoea receiving opioids).

Respiratory complications may be minimized by:

- humidified oxygen therapy with pulse oximetry
- adequate 'balanced' analgesia
- aggressive physiotherapy and early mobilization
- using continuous positive airway pressure in patients at risk of airway obstruction during sleep or sedation
- nursing patients upright or in the lateral decubitus position is preferable to a recumbent position.

Thromboembolic complications are more common in obese patients. Adequate prophylaxis for deep venous thrombosis is mandatory and early mobilization should be encouraged.

Wound infections: longer incisions, greater wound retraction and the poor blood supply to adipose tissue make wound infections more common in the obese.

Postoperative analgesia
Adequate analgesia allows deep breathing and coughing, facilitates chest physiotherapy and aids early mobilization, which reduces the incidence of postoperative complications. In obese patients, various options for postoperative analgesia, either alone or in combination, are available.

Parenteral opioids are administered intravenously, most commonly using a patient-controlled analgesia device. Standard dosing regimens are adequate for obese patients. Careful monitoring of respiratory parameters and conscious level is necessary in obese patients and supplemental oxygen is essential.

Epidural analgesia using low-dose local anaesthetic solutions, alone or in combination with opioids, is the best method of providing analgesia following thoraco-abdominal surgery in obese pa♦ients, provided the epidural can be sited successfully. It may also be useful following pelvic or lower limb surgery.

Local anaesthetic techniques: local anaesthetic blocks performed for surgery will last for a variable length of time into the postoperative period. By using a catheter technique, useful analgesia can be extended.

Supplementary analgesics: though seldom sufficient alone, the use of regular paracetamol and non-steroidal anti-inflammatory drugs (if not contraindicated) has an additive effect with opioid or epidural analgesia. A balanced approach to analgesia may be particularly helpful in obese patients.

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Hepatitis and HIV Infections

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Blood-borne viral infections have implications for anaesthesia and intensive care because of their potential for transmission and as disease entities.

Hepatitis

Recently, there has been an explosion in the understanding and diagnostic subcategorization of viral hepatitis. The terminology has changed from either 'serum' or 'epidemic' hepatitis to a recognition of the many causative agents of hepatitis acquired either from faecal contamination (hepatitis A and E) or parenterally via body fluids (hepatitis B, C, D and G). Many hepatologists were aware that hepatotropic agents were responsible for the hepatitis seen in patients in whom neither hepatitis A or B could be identified and an increasing alphabet is now filling the gap formerly known as non-A, non-B hepatitis.

Hepatitis A virus (HAV)
HAV is a small RNA virus that causes acute hepatitis only. It is a common cause of both sporadic and epidemic hepatitis and is spread by the faeco-oral route. Symptoms appear about 2 weeks after infection, with an associated rise in transaminase levels and excretion of viral particles in the faeces. At the same time, anti-HAV and IgM anti-HAV antibodies appear; the former persist for life and the latter disappear within 3–12 months of infection. HAV antigen is present in the stools in the late prodrome and early symptomatic phase of the infection, and its presence in serum indicates viral shedding. The features of acute hepatitis and the presence of IgM anti-HAV and HAV antigenaemia are usually diagnostic. The disease is self-limiting and seldom leads to fulminant hepatic failure. It is possible to become infected with HAV after transfusion, if the donor was in the viraemic phase of the illness. This risk is estimated to occur with 1/1 million units of blood and its rarity is explained by the absence of a chronic carrier state with HAV.

Treatment: vaccines are available, but are not wholly effective in controlling outbreaks. They are not recommended for children under 2 years of age, but can be given to pregnant women because the virus is inactivated.

Hepatitis B virus (HBV)
HBV is a DNA virus and has the smallest genome of any DNA virus infecting humans. It has four gene regions: the S or envelope region (HBsAg), the C or nucleocapsid region (HBcAg and HBeAg), the P region (DNA polymerase), and a fourth region which is a transactivator of HBV replication (HBxAg). Genotypic variants exist with a geographical distribution similar to human ethnic distribution. In the UK, the prevalence is about 0.1%. As many as 10^{13} viral particles can be found in 1 ml of infected blood; this compares with 10^{1}–10^{4} particles in HIV-infected blood. HBV can survive in dry blood for up to 1 week. Trans-fusion-transmitted HBV has, however, been dramatically reduced since the introduction of third-generation screening tests in the mid-1970s.

Symptoms usually appear about 2 months after infection, with a concomitant rise in alanine aminotransferase (ALT) in the acute phase. HBsAg, HBeAg and HBV-DNA are all detectable in the blood slightly before the appearance of jaundice and other symptoms. Also, at this time, anti-HBc and IgM-anti HBc become evident, denoting acute infection. A month later, antibodies to HBe appear, resulting in clearance of HBeAg and a gradual reduction in HBV-DNA levels. Some months after this, HBsAg clears from the blood and anti-HBsAg antibodies become detectable. In 10–25% of patients, a chronic carrier state develops and there is persistence of HBV-DNA, indicating continuing viral replication, and HBsAg and HBeAg, which if found together indicate continuing viral replication with a high level of infectivity and active liver disease. The development of anti-HBe antibodies, which can occur at any time, implies disease resolution and quiescence of liver disease. However, in the face of increasing host immune activation, the virus can mutate to different forms that replicate, though they may not produce HbeAg. These forms are infective and can cause severe liver disease.

Treatment: vaccination is effective in eradicating HBV from the population. However, there are genetic variants of the HBsAg epitope cluster, which results in poor binding of some polyclonal and monoclonal antibodies. These variants are capable of transmission and of causing liver disease, and may be best dealt with by administering polyvalent (multiple antigen) vaccines.

In patients with chronic disease, 10–15% develop cirrhosis and 10% develop hepatocellular carcinoma. Interferon-α is effective in achieving sustained response rates in 30–40% of patients with chronic hepatitis B and for those who do not respond, nucleoside analogues may be promising adjuncts. In un-immunized individuals, percutaneous exposure leads to seroconversion in 12% (if infected blood is only HBsAg positive) rising to 30% if infected blood is also HBeAg positive. In such cases, the exposed individual should be given hepatitis B immunoglobulin and the recombinant DNA vaccine as soon as possible.

Seroconversion rates are high, therefore it is extremely important that healthcare workers are properly immunized, but vaccine failure can occur in as many as 12%. Achieving a protective titre of antibody will sometimes last up to 9 years, though boosters are recommended more regularly than this.

Hepatitis delta virus (HDV)
HDV is a small defective RNA virus, which has some similarity to satellite viruses that infect higher plants. It causes liver disease only in those already infected with HBV (superinfection) or where HBV is transmitted simultaneously (co-infection). In the acute phase, the disease has a high mortality and, in the chronic phase, there is a high risk of developing cirrhosis. HBV is the helper virus and provides surface antigen for the delta particle envelope, without which it is non-infectious.

Diagnosis depends on the circumstances. In cases of co-infection, anti-HDV may never become detectable or is detectable only in the convalescent serum sample, whereas in superinfection anti-HDV may rise to high titres. The level of IgM anti-HDV is also useful for diagnosis, but it tends to be present at low levels in some patients with chronic delta hepatitis. HDV-RNA can be detected in the serum of infected patients, but its disappearance does not mean the disease has been eradicated.

Treatment: interferon therapy has transient effects. The virus replicates by RNA control without the need for protein enzymic assistance and this ribozymic activity is attracting interest as a potential target for therapy.

Hepatitis C virus (HCV)
HCV was identified a decade ago and appeared to be responsible for most non-A, non-B post-transfusion viral hepatitis. It is an RNA virus that causes both acute, though seldom fulminant, hepatitis and chronic hepatitis. There is an 85% chance of the infection becoming chronic with the attendant risks of developing cirrhosis (20%) and hepatocellular carcinoma (1–5%). In addition, there is an increased chance of developing a variety of non-hepatic autoimmune conditions. Its prevalence worldwide is about 1%, though it is less in the UK.

Exclusion of blood donors with known risk factors for HIV, or with raised transaminases or antibodies to hepatitis B core antigen has reduced the incidence of transfusion-related non-A, non-B hepatitis. However, the real breakthrough came with the introduction of a test for antibodies to HCV. It is now estimated that the risk of developing HCV is about 1/103,000 transfusions. Although transfusion is an uncommon cause of HCV infection, once a patient is infected the likelihood of complications is high. For percutaneous exposure, the seroconversion rate is as high as 6–10%, which represents a risk 10–33 times greater than for HIV, but 10–20 times less than for HBV. This correlates very closely with the average measured viral loads encountered in these three diseases.

The variants of HCV seem to be distributed on geographical grounds and depend on the type of exposure that an individual has encountered. Type 3 occurs more commonly in intravenous drug users, whereas types 4, 5 and 6 seem to have some geographical concentration. HCV-RNA can be detected in the serum about 1 month after exposure to the virus and symptoms and transaminasaemia develop 1 or 2 weeks later. Symptoms are usually mild in the acute stage and may not include jaundice. It seldom progresses to a fulminating hepatitis. Anti-HCV is detected only after symptoms have appeared, generally 4–24 weeks later, and is of little use in establishing the diagnosis of acute HCV. The clinical disease may be related to different genotypes, for example hepatocellular carcinoma may be linked with subtype 1b, which is also more resistant to interferon therapy.

Treatment: response rates for chronic HCV infection treated with interferon are low (10–25%), especially in Europe and the USA, which may be explained by a higher prevalence of HCV-1b. Post-exposure immunoglobulin is not useful and there is no available vaccine against HCV. In the USA, the Food and Drug Administration has recently approved the combination of interferon and ribavirin, which several studies have shown leads to a sustained response in 40–50% of patients.

Hepatitis E virus (HEV)
HEV is similar to HAV in that it is contracted enterally in sporadic or epidemic outbreaks. It leads to an acute illness with no chronic carrier state, but mortality is increased in pregnant women in endemic regions. Diagnosis is usually made on the clinical and laboratory features of acute hepatitis, in the absence of serological markers for other forms of viral hepatitis, and a history of recent travel to endemic areas. Viral RNA can be detected with molecular amplification techniques and assays for antibody to the virus are available.

Hepatitis G virus (HGV, GBV-C)
Even with the discovery of HCV, it was appreciated that there remained a subgroup of transfusion-related hepatitis that was non-A to non-E related. Two separate centres discovered the viral sequence; one from a surgeon (initials GB) and one from a West African individual. Three related sequences are known as GBV-A, GBV-B and GBV-C, of which the first two are thought not to be pathogenic to humans whereas the immunoassay industry is holding out hopes for the latter. This somewhat confusing nomenclature rests under the canopy of HGV. It is doubtful whether HGV is especially hepatotropic or causes any particular disease. The prevalence of HGV viraemia, at least among donors in the USA, is about 1–2%, whereas in Africa it is at least 12%. Thus, the virus can be transmitted by blood transfusion and this raises some ethical considerations because molecular techniques have demonstrated the presence of a viral sequence that can be transmitted. For example, is it right knowingly to infect others and will the repeated transmission of this virus lead to pathogenicity? In 10% of individuals, seroconversion will follow percutaneous exposure to infected blood.

Other viruses
The potential for transmitting other viruses during transfusion also exists. Those capable of manifesting hepatitic features include cytomegalovirus, Epstein–Barr virus and herpes simplex virus – usually with other accompanying systemic symptomatology.

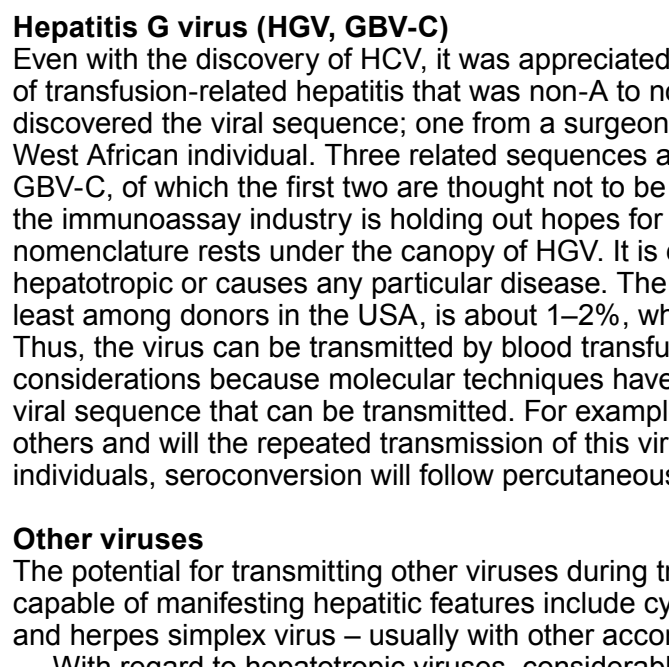
With regard to hepatotropic viruses, considerable efforts are being applied to characterize a new transfusion-transmitted virus (TTV) and time will tell whether this yields a new letter for the hepatitis alphabet.

Anaesthesia and intensive care
In the absence of chronic liver disease, with the associated alterations in drug handling, there are no extra implications for anaesthesia. Standard precautions should always be adopted. It is important to obtain evidence of the extent of hepatic synthetic dysfunction, generally by measuring the international normalized ratio. This may preclude neuraxial local anaesthetic techniques and suggest extra vulnerability to ischaemic hepatitis if the hepatic blood flow decreases. Managing acute and end-stage chronic liver failure is complex because multiple organ systems are involved and transplantation is often the only realistic option.

Human immunodeficiency virus (HIV)

HIV was first described in 1981, through the emergence of *Pneumocystis* pneumonia associated with candidiasis in otherwise healthy homosexual men. The retrovirus was identified as being a Lentiviridae. There are two main types, HIV-1 and HIV-2, but they also demonstrate significant genetic variation and there are subgroups of each virus. The viral genome has a propensity for change and evolution. As with other blood-borne viral infections, the patient develops viraemia following an initial inoculum, with a rapid increase in the viral load. The immune response then becomes established over a variable period of time and this has an impact on the viral load, which may stabilize or decrease (Figure 1).

Acute HIV infection



Transmission
It has been estimated that 56–92% of all infection is transmitted during the acute phase of infection when the viral load is high and the host is unaware of the infection. The virus is probably present in a range of body fluids, but those considered to be of high risk are blood, semen, vaginal secretions, peritoneal fluid, CSF and other cavity fluids. Less risk is associated with faeces, nasal secretions, saliva and urine, provided they are not contaminated with blood. There are several levels of screening for donated blood for transfusion, which start with donor selection. In the UK, blood is tested for HIV-1 and HIV-2 antibodies. In some countries it is also screened for HIV p24 antigen. A needlestick injury is associated with a 0.3% chance of seroconversion. Hollow needle injuries are more risky than solid needle injuries, because a larger inoculum is likely.

Presentation
Acute infection occurs after initial exposure, when there is a phase of viral replication and initiation of a host immune response. In this response phase, the patient may have a viral-type illness, which is non-specific and probably corresponds to seroconversion. This response varies between individuals but, in one study, 89% of patients experienced symptoms and signs including fever, fatigue, skin rash, myalgia, headache, pharyngitis, lymphadenopathy, arthralgia, oral ulcers, weight loss, nausea, vomiting and diarrhoea. Patients commonly present with opportunistic infections. These may be typical of an immunocompromised patient (e.g. *Pneumocystis* pneumonia, disseminated *Cryptococcus*, toxoplasmosis, widespread candidiasis) or may be more general (e.g. tuberculosis, pneumococcal pneumonia). Multi-resistant tuberculosis is a transmissible problem and precautions should be taken to minimize the risk of spread if the diagnosis is considered. Gastrointestinal disturbance is extremely common and may be infective, though a non-specific enteropathy is also seen (Figure 2). Neurological complications, often infective, are common. Non-infective presentation includes Kaposi's sarcoma.

Clinical syndromes associated with HIV[1]

Gastrointestinal
- Weight loss and malnutrition
- Diarrhoea – bacterial, viral, fungal
- Parasitic *(Cryptosporidium, Giardia, Entamoeba histolytica)*
- HIV enteropathy
- Hepatic – viral hepatitis B, C or D, tuberculosis, fungal *Cryptococcus, Candida*, histoplasmosis)
- Kaposi's sarcoma, lymphoma

Ocular
- Non-infective – conjunctivitis, keratitis, haemorrhage, cotton wool spots
- Infective – conjunctivitis, keratitis, retinitis, uveitis

Respiratory
- Any bacterial infection, *Pneumocystis carinii,* cytomegalovirus, cryptococcosis, coccidiomycosis, histoplasmosis
- Tuberculosis including *Mycoplasma avium type*
- Kaposi's sarcoma, non-Hodgkin's lymphoma

Bone marrow
- Peripheral blood cytopenias, anaemia, thrombocytopenia, granulocytopenia

Rheumatological
- Arthralgia, Reiter's syndrome, psoriatic arthritis, vasculitis

Cardiac
- Pericardial effusions, non-specific impairment of left ventricular function, myocarditis

Neurological
- Brain – HIV-related meningo-encephalitides, infections including herpes, varicella, cytomegalovirus
- Toxoplasmosis, *Cryptococcus, Nocardia*, tuberculosis, syphilis, Kaposi's sarcoma, lymphoma
- Spinal cord – vacuolar myelopathy, infection
- Peripheral neurology, polyneuropathy, demyelination, neuralgic amyotrophy

Psychological
- Any of the neurological causes above
- HIV encephalopathy

Renal
- HIV nephropathy (glomerular disease)

Oral problems
- Candidiasis, herpes simplex, varicella zoster
- Gingivitis, periodontitis
- Kaposi's sarcoma

[1] The list is not comprehensive, but indicates the range of problems.

Laboratory testing
Antibodies to HIV-1 can be demonstrated using enzyme-linked immunosorbent assay or Western blot techniques. In the acute phase, HIV-1 and HIV-2 antibodies are at best weakly positive or non-reactive and this will be misinterpreted as a negative result. HIV-1 RNA or viral p24 antigen should be tested; levels of 13 x 10^6 RNA particles/ml may be seen. A false-positive rate of 2–5% has been reported, therefore all tests should be repeated. This should be confirmed when seroconversion occurs later. During the acute phase, the CD4 count often falls and is followed by an expansion of the CD8 population, thereby altering the CD4:CD8 ratio at about day 16 of the acute illness. The expansion of the CD8 cytotoxic T cell subgroup is probably associated with antiviral activity.

Treatment
After the initial infection, the viraemia and the immune response 'equilibrate' at a 'set-point'. At this stage, there is a relationship between the viral load and prognosis. Those with a high persistent load do less well than those with a low load. Early aggressive treatment to reduce the load may lead to a better prognosis. It is hypothesized that, in the acute phase, when there is rapid proliferation of the virus, highly active antiretroviral therapy (HAART) may reduce the viral load and minimize damage to the CD4 T-helper lymphocytes. It may also reduce the emergence of resistance.

Nucleoside reverse transcriptase inhibitors (NRTI) (e.g. zidovudine, lamivudine) were used as monotherapy, with limited effect in suppressing HIV except materno-fetal transmission, but some patients have become resistant to them. Side-effects include gastrointestinal problems (e.g. diarrhoea, vomiting), pancreatitis and peripheral neuropathy.

Non-nucleoside reverse transcriptase inhibitors (NNRTI) (e.g. nevirapine, efavirenz) bind only to HIV-1 reverse transcriptase.

Protease inhibitors (e.g. saquinavir, ritonavir, indinavir, nelfinavir) are particularly effective when used in conjunction with NRTI. HIV-1 protease is an essential enzyme for viral replication and acts at the point at which virions become mature. Treatment results in the release of immature non-infectious viruses, which can be eliminated. Viral load is reduced, often to levels that are undetectable. It acts on maturing virus particles, therefore it does not have any impact on cells. CD4 that are already infected will be destroyed, but it does prevent spread of infection. The use of dual therapy seems to improve CD4 counts and to reduce viral load. Protease inhibitors have led to a dramatic alteration in the pattern and natural history of HIV, with decreased hospital admissions and fewer opportunistic infections. However, even with imperceptible viral load, an infective risk still exists. Protease inhibitors are metabolized by the P450 system and tend to either inhibit or induce cytochrome P450 isoenzymes. They therefore have the potential for drug interaction. They have a range of side-effects (Figure 3).

Side-effects of protease inhibitors

- Onset of diabetes mellitus and insulin resistance, type II diabetes
- Fatty deposition in neck – buffalo hump
- Peripheral lipodystrophy, hyperlipidaemia
- Gastrointestinal problems (nausea, vomiting, diarrhoea)
- Elevations of creatine phosphokinase, hepatic transaminases (occurs with saquinavir)
- Circumoral and peripheral paraesthesia (occurs with ritonavir)
- Hepatitis with elevations of transaminases and bilirubin (occurs with indinavir)
- 'Mitochondrial' toxicities (non-specific)

Anaesthesia
The problems that HIV poses for anaesthesia relate to the general problems of the disease and drug therapy. There are also non-specific considerations relating to dealing with a potentially infective condition. General problems include the chronic health status of the patient, who may be malnourished and wasted, and may have haematological, hepatic or renal problems. Local manifestations of the disease can cause technical difficulties. Chronic respiratory problems may alter oxygenation, in particular those who have had *Pneumocystis* pneumonia and are taking prophylaxis. Airway problems are common, from infection or from Kaposi's sarcoma. The implications of using an epidural should be discussed because of possible neurological involvement and the increasing number of HIV-positive women of child-bearing age. There is no evidence to suggest that complications following epidural are any higher in this population. This is important because caesarean section may reduce vertical transmission of HIV. There are inadequate data to make any statement about using blood patches if dural puncture occurs.

The side-effects of the drugs used to treat HIV may add to anaesthetic considerations.

Pain control in HIV patients is also a problem. This may be associated with the disease or the opportunistic infections, or be drug related.

Contaminating equipment is another problem when dealing with potentially infective patients. A sensible and hygienic approach to cleaning and sterilizing devices such as filters on anaesthetic circuits all help to reduce the risk of transmission; these measures should be universal.

Intensive care
The management of patients with HIV in the ICU should be the same as for other patients. Difficulties encountered include trying to maintain HAART, particularly if the gut is non-functional.

Presentation with HIV-related disease is also common. Primary presentation with *Pneumocystis carinii* is less common than it used to be. When it does present, it may be in undiagnosed patients. Neurological and gastroenterological presentation is also common. Rapid diagnosis is important. Prognosis is determined by the condition, the chronic health status of the patient and their immune system, and appropriate treatment. Prognosis appears to be worse in patients who fail to respond to appropriate treatment in the first few days. For example, *Pneumocystis carinii* pneumonia that is unresponsive after 4–5 days of aggressive treatment has a poor prognosis. The pattern of presentation is undoubtedly changing with the advent of HAART, but it is too early to anticipate the long-term effects on ICU admission.

Healthcare workers and HIV
The risk of contracting HIV infection at work is perceived to be low. Sensible precautions, such as wearing gloves, attention to hygiene and avoidance of 'sharps' injuries by careful practice are all advocated. Exposure to fluids or blood that might be infected constitute an exposure. Specialist advice should be sought immediately after exposure and it is likely that post-exposure prophylaxis would be implemented, within 1–2 hours. This should always be done with guidance from an HIV specialist. Currently it consists of a combination of two NRTI drugs (zidovudine and lamivudine) added to a protease inhibitor (e.g. indinavir). The side-effects of indinavir can be daunting and include gastrointestinal upset, headache, fatigue, paraesthesia or hypaesthesia, myalgia, nephrolithiasis, hyperbilirubinaemia and change in liver function (Figure 3).

The risk of an HIV-infected healthcare worker transmitting the disease to a patient is considered to be very low, provided the healthcare worker does not carry out 'exposure prone procedures'. These are procedures where the healthcare worker is at risk of injury with sharp instruments within an open body cavity and where the operator's hands may not be visible. If injured, the patient will be exposed to blood. A health worker infected with HIV should seek appropriate medical and occupational health advice.

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Pacemakers and Anaesthesia

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The first permanent transvenous pacemaker was implanted in 1962. It weighed about 250 g and was expected to last for less than 2 years. Since then, advances in microprocessor technology and the introduction of lithium power sources have resulted in the development of more complex and reliable pacing systems. As a result, the number of patients with pacemakers inserted to treat bradycardia and tachyarrhythmias has increased. Implantable cardioverter defibrillators (ICD) were first used in 1980; they provide a method of treatment for patients with ventricular arrhythmias that are not managed or amenable to anti-arrhythmic agents, ablative techniques or surgery.

Many patients present for surgery with a pacemaker or ICD implanted and anaesthetists need to understand the problems that can be encountered with all types of pacing device.

Pacemaker insertion

Indications: guidelines specifying the indications for insertion of a permanent pacemaker have been published but are likely to expand with increasing sophistication of the devices. Current indications for permanent pacing include symptomatic complete heart block, prolonged sinus arrest associated syncope, carotid sinus syndrome and malignant vasovagal syncope. Asymptomatic second degree and complete heart block remain controversial indications, as does pacing for cardiomyopathy and congestive cardiac failure.

In general, the pacemaker should aim to mimic normal physiological conditions. The ventricle should be paced if there is actual or potential atrioventricular (AV) block. The atrium should be sensed and paced unless there are contraindications such as chronic or repetitive atrial flutter or fibrillation. Rate-responsive pacemakers respond to the increased physiological demands of exercise in active patients, but may be unnecessary in inactive patients or in those with a normal chronotropic response.

Anaesthesia: pacemakers are often inserted under local anaesthesia but if general anaesthesia is required the technique and monitoring should be tailored to the individual. A temporary wire may be inserted and external defibrillator pads used.

Insertion of ICD: patients requiring insertion of an ICD are likely to have severe underlying cardiac dysfunction. Cardiac function should be optimized preoperatively. Invasive monitoring, external defibrillator pads and an emergency method of pacing are required.

Management of a patient with a pacemaker

Preoperative management

The general condition of the patient has the most important influence on the anaesthetic management. Co-morbid conditions should be addressed with further investigation and treatment as necessary. The original indication for pacemaker insertion should be sought and any recurrence or development of new cardiac symptoms noted and investigated.

Information about the type of pacemaker, its mode and rate of pacing, and the cardiologist and centre responsible for insertion are included on the pacemaker registration card, carried by the patient, and on the notes in the cardiology unit. A code on the card indicates the symptoms, ECG abnormalities and aetiology of the condition that precipitated pacemaker insertion. If the card is unavailable, the information can be obtained from the British Pacing and Electrophysiology Group National Database (website http://ccad3.biomed.gla.ac.uk/bpeg).

Pacemakers should be checked annually (including a battery check) or every 6 months for devices implanted more than 6 years previously. An up-to-date pacing check in a patient without new cardiological symptoms should ensure effective pacemaker function and an additional preoperative pacemaker check is not required.

A thorough examination of the cardiovascular system is required and the position of the pacing box must be confirmed. Usually, the box is in the pectoral region, though abdominal sites are used. Investigations should be performed as indicated by the patient's condition and the type of surgery. Electrolyte abnormalities, particularly of potassium, should be corrected. ECG can help determine the type of pacing by the position of the pacing spike. All patients should have a chest radiograph so that the position, number and integrity of the leads may be determined.

Intraoperative management

The patient should be monitored in a manner appropriate to the underlying condition and the type of surgery being performed. ECG monitoring is essential and mechanical methods of verifying pacing capture include pulse palpation, pulse oximetry and direct arterial pressure monitoring (if this is indicated by the patient's condition). Central venous cannulation may be appropriate, but should be performed with caution if the leads have been placed within the past month because they may be dislodged.

The presence of a pacemaker has little influence on the choice of anaesthetic drugs. However, there are reports of demand pacemakers being inhibited as a result of suxamethonium-induced fasciculations being interpreted as myocardial activity. Conditions likely to precipitate arrhythmias (e.g. hypercarbia, electrolyte disturbances) must be avoided.

The risk of developing bacterial endocarditis as a result of the implanted lead is small and prophylactic antibiotics are not recommended unless there is some other indication for their use.

Emergency drugs (e.g. atropine, isoprenaline) and alternative methods of pacing must be available in case of pacemaker failure. Transvenous wires with an external pulse generator or transcutaneous pacing, which uses electrodes attached to the skin, may be useful. Transoesophageal atrial pacing is also an effective and simple pacing method that can be used in anaesthetized patients, but requires an intact AV pathway; the system consists of a pacing oesophageal stethoscope, which paces the left atrium, the structure closest to the oesophagus.

Postoperative management

Reprogramming, particularly an increase in heart rate, should always be considered in patients with haemodynamic compromise or critical illness. Following exposure of the pacemaker to possible interference or damage, it is necessary to perform a pacing check.

Specific problems

Electromagnetic interference – advances in the design of protective circuits in the pacemakers have reduced, but not eliminated, the risk of damage from external electrical sources. The most common source of electromagnetic interference is surgical diathermy. Risks are reduced by the use of bipolar diathermy, application of diathermy in short bursts and, in monopolar systems, positioning of the ground plate as far away as possible from the pulse generator and leads. If difficulties are anticipated, it may prove necessary to reprogramme the pacemaker to a fixed rate mode preoperatively. Diathermy also interferes with ECG monitoring and alternative methods of monitoring the pulse should be used (e.g. direct palpation, pulse oximetry). At one time, magnets were used to convert the pacemaker to a fixed rate mode intra-operatively, but this is no longer recommended because the combination of diathermy and the magnet may induce a programme change (so called phantom reprogramming). The use of magnetic instrument pads during surgery can also cause phantom reprogramming.

Cardioversion or defibrillation may damage the circuitry inside the pulse generator. If the lead is damaged, the current can pass down the lead and may burn the myocardium, causing a threshold increase and loss of capture. If defibrillation is necessary, the current path should be perpendicular to the lead and as far away from the pulse generator as possible.

Mobile telephones – there have been reports of interference with certain types of mobile telephones. The ringing phase is the most vulnerable time especially if the phone is in a pocket near the pulse generator.

Transcutaneous electrical nerve stimulators (TENS) and peripheral nerve stimulators can cause a tachycardia or inhibit a DDD or rate-responsive pacemaker and it is recommended that these are reprogrammed to simpler modes.

MRI – a pacemaker is a relative contraindication to MRI. If MRI is essential, the pacemaker must be turned off or explanted before the examination (provided that the patient is not pacemaker-dependent). Scans can be performed with a pacemaker *in situ* but require multidisciplinary support and specialist expertise.

Ionizing radiation can damage the internal circuits in the pulse generator. Therefore a paced patient undergoing radiotherapy treatment should have the function of the pacemaker checked following treatment.

Lithotripsy treatment of renal calculi uses high-energy shock waves. In a patient with a pacemaker the shock wave must be carefully timed with the ECG and the focal point of the delivery probe must be kept at least 15 cm away from the pulse generator. If the pulse generator is positioned in the abdomen it is important to avoid passing a direct impulse through it. Rate-responsive and DDD pacemakers should be programmed to a simpler mode for the treatment and the function checked following treatment.

Management of a patient with an ICD

Patients presenting for surgery who have an ICD must have the anti-tachycardia and other functions disabled before surgery. Diathermy must not be used in the presence of an active ICD unit because of the risk of damage. External defibrillation facilities must be available and if defibrillation is required then the paddles or pads should be placed at a right angle to the plane of the defibrillating/pacing lead.

Passing the defibrillator current through the pulse generator will damage it permanently. The ground plate for the diathermy unit must be placed as far away from the surgical site and the ICD as possible, and this distance should be at least 15 cm. Central venous cannulation using the Seldinger technique can be arrhythmogenic and back-up defibrillation facilities must be available. Care must be taken with recently placed leads because of the risk of dislodgment. Following surgery, the device can be reactivated and the function checked.

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Repeat Anaesthesia: Hepatic Injury

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Hepatic injury following repeat anaesthesia is a rare complication that may be precipitated by many of the commonly used volatile anaesthetic agents. Halothane is the most common culprit, causing either a mild dysfunction or a more severe fulminant liver injury. Similar immune-mediated reactions may occur with enflurane, isoflurane and desflurane. There are no investigations that can accurately predict who will be affected, therefore those with a history of recent halothane anaesthesia or unexplained fever or jaundice after a previous anaesthetic should avoid repeat volatile anaesthesia. No cases of propofol-induced liver failure in adults have been published, therefore total intravenous anaesthesia may be suitable for these patients.

Postoperative hepatic injury has profound effects on the future conduct of anaesthesia. The injury ranges from asymptomatic derangement of liver enzymes to fatal liver failure. The major precipitants are non-anaesthetic such as sepsis, hypotension, hypoxaemia, transfusion-related viral infection (hepatitis B, hepatitis C, cytomegalovirus, herpes virus), transfusion reaction, surgical trauma to the liver or biliary tract, prolonged nutritional deficiency, or a combination of factors in patients with pre-existing liver dysfunction.

Aside from the usual measures to minimize physiological stress by careful attention to oxygenation, blood pressure and fluid status, there is little the anaesthetist can do to prevent recurrent hepatic injury during repeat anaesthesia.

Pre-operative assessment: comfort may be gained from the knowledge that a patient has survived a previous anaesthetic. If the patient's previous anaesthetic charts are available, valuable information may be gathered regarding difficulties with the airway or drug reactions. Vigilance must be maintained, even if the patient's last anaesthetic was uneventful, because new and significant pathology may have emerged since then. Also, postoperative complications may not have been recorded in the anaesthetic chart or in the medical case notes.

Halothane hepatitis

Halothane was introduced into clinical practice in 1956. Compared with other inhalational agents of the time, it was potent, non-irritant and non-flammable with minimal toxicity, and it rapidly gained widespread popularity. However, within2 years, reports describing cases of massive hepatic necrosis after halothane anaesthesia were published.

Incidence

In 1969, the National Halothane Study was published in the USA. In this retrospective study, the incidence of fatal hepatic necrosis was investigated in 856,000 patients undergoing general anaesthesia. Fatal hepatic necrosis occurred in 7/255,000 of the patients who received halothane. The study could not show a definite link between halothane and hepatic injury, but confirmed that fatal liver disease following halothane anaesthesia was uncommon. Subsequent studies have demonstrated an increased incidence of hepatitis of about 1/6000 halothane anaesthetics, and there is now a wealth of data describing the patterns of hepatic damage after halothane.

Characteristically, but not exclusively, halothane hepatitis develops in patients who have had repeat halothane anaesthesia over a short period of time. It may have been required for dressing changes, diagnostic radiology, or as part of multi-stage procedures for the treatment of trauma, burns or complications of previous surgery. The peak incidence occurs in those aged 50–60 years, and 70% of affected patients are over the age of 40 years. Children seldom develop halothane hepatitis (1/82,000). Obese patients appear more at risk, possibly because of increased halothane metabolism, or prolonged duration of exposure as halothane that has accumulated in adipose tissue is metabolized and excreted. Despite equal exposure to halothane, women are at greater risk than men (about 2:1). Drugs that induce cytochrome P450 (e.g. isoniazid, dexamethasone, phenobarbital (phenobarbitone)) increase the degree of hepatic injury.

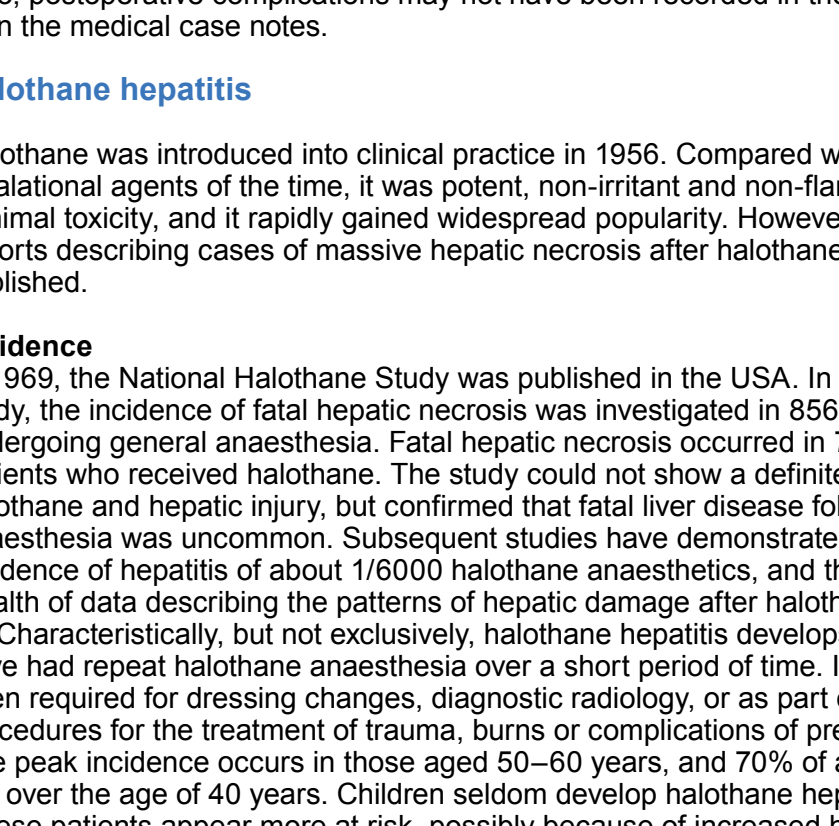
Pathology

Two forms of hepatic injury after halothane anaesthesia have been described:

- a common (20–30%), but mild, form in which there is a transient rise in liver enzymes
- a rare fulminant form with massive hepatic necrosis.

These are thought to be separate processes initiated by different metabolic pathways, and not varying severities of the same pathological mechanism. Halothane is metabolized in the liver by an oxidative pathway when the oxygen tension is high and by a reductive pathway when the oxygen tension is low (Figure 1); both may occur during uneventful anaesthesia.

Oxidative and reductive pathways of halothane metabolism



The main products of oxidative metabolism are HBr and trifluoroacetic acid (TFAA). The main products of reductive metabolism are bromine, fluorine, 2-chloro-1,1,1-trifluoroethane (CTF), 2-chloro-1,1-difluoroethylene (CDF).

Source: *Br J Anaesth* 1991; **67:** 88

1

Reductive halothane metabolism occurs when there is an imbalance between liver perfusion and oxygen demand, resulting in relative hepatocyte hypoxia. Under these conditions, the mixed function oxidase, P450, favours a reductive metabolic pathway with the formation of 2-chloro-1,1,1-trifluoroethane or 2-chloro-1,1-difluoroethylene. These byproducts have not been shown to be directly hepatotoxic. However, liver damage by free radical intermediates has been proposed. This type of hepatic injury is more common if halothane anaesthesia is associated with hypotension and hypoxia. The clinical features of this short, self-limiting illness are non-specific and include lethargy, fever, nausea and jaundice. Biochemical tests show an elevation of alanine and aspartate aminotransferase.

Oxidative halothane metabolism is more common than reduction metabolism and proceeds via a trifluoroacetyl (TFA) halide, which is not thought to be hepatotoxic. However, TFA halide may bind covalently to liver microsomal proteins. In susceptible patients, this TFA–protein complex acts as a hapten against which anti-TFA antibodies are formed.

On repeated exposure to halothane, a hypersensitivity response mediated by anti-TFA antibodies occurs and liver damage ensues. Typically, liver failure develops within 15 days of the last exposure to halothane. The clinical picture is similar to viral hepatitis or drug-induced hepatic damage, but as there are no pathognomonic features the diagnosis is often made by exclusion. Histologically, the pattern is predominantly centrilobular necrosis, but may range from multifocal necrosis to panlobular massive necrosis.

Treatment is essentially supportive, with transfer to a specialist unit when severe. Fulminant disease has a mortality of up to 50%.

Immunological effects: features supporting an immunological basis for the hepatic injury include the clinical picture of hepatitis with fever, rash, arthralgia and eosinophilia in pat*i*ents with a history of atopy, drug allergy or adverse reactions to halothane. In addition, there is a clear association with prior exposure to halothane and worsening response with subsequent halothane anaesthetics. In up to 70% of patients with halothane hepatitis, an enzyme-linked immunosorbent assay may be used to detect antibodies to TFA proteins. Proponents have suggested that free radicals from the reductive pathway may initiate the hepatic damage, which is then exacerbated by an immunological response.

Prevention

Halothane should be avoided in patients who have been exposed to halothane recently, or who have a history of halothane hepatitis. The Committee on Safety of Medicines (CSM) advises that halothane should be avoided if a patient has had an adverse reaction following a halothane anaesthetic, previous exposure within 3 months or a history of unexplained jaundice or pyrexia after exposure to halothane.
Hepatitis associated with other volatile agents

The use of halothane has declined with the introduction of newer volatile agents (enflurane, isoflurane, desflurane, sevoflurane). Isoflurane and desflurane are oxidatively metabolized producing an identical TFA hapten to that seen with halothane. The metabolite of enflurane is immunologically similar though not structurally identical. Consequently, enflurane, isoflurane and desflurane have the potential to produce hepatic injury by an immune response directed at TFA haptens or similar structures. The incidence of hepatotoxicity correlates with the degree of cytochrome P450-mediated metabolism, which is 20% for halothane, compared with 2%, 0.2% and 0.02% for enflurane, isoflurane and desflurane, respectively.

Enflurane hepatitis is uncommon with an incidence of 1/800,000. Isoflurane hepatitis is less common and a literature review revealed only one case report of desflurane-associated hepatitis. Isoflurane does not undergo reductive metabolism (nor does enflurane), free radicals are not produced and hepatic perfusion is maintained to a greater degree than with halothane, contributing to the low incidence of isoflurane-induced hepatotoxicty. With both enflurane and isoflurane hepatitis, the initial exposure has been reported to be to a different ♋gent than that believed to be precipitating the hepatic damage, indicating possible cross-reactivity. Consequently, the CSM guidelines regarding patients who sustain a hepatic injury after one halogenated agent indicate that it is probably best to avoid all others.

Sevoflurane is metabolized to a similar degree to enflurane but does not form trifluoroacetic acid. A mild elevation of liver enzymes after repeat sevoflurane anaesthesia has been shown, but there have been no cases of fulminant hepatic necrosis.

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Day case

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Assessment of Recovery in Day Surgery

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Surgical procedures of increasing complexity and duration can now be undertaken in day surgery units. For example, cholecystectomy and prostatectomy are now acceptable day case procedures. These procedures are appropriate for day surgery only if the clinician can ensure that the patient will return home safely, having recovered from the effects of anaesthesia and surgery. The assessment of recovery is therefore an important part of the patient's hospital stay. Recovery includes return of normal physiological and psychomotor function together with a minimal level of morbidity associated with anaesthesia and surgery.

Phases of patient recovery

Recovery is a continuous process, the beginning of which overlaps with the end of the surgical procedure. Patients are not fully recovered until they have returned to their preoperative physiological and psychomotor state. The process may last for days, but it can be divided into distinct phases.

Early recovery (first-stage recovery) – end of anaesthesia until the patient has recovered protective reflexes and motor function. This occurs in the recovery unit or post-anaesthesia care unit.

Intermediate recovery (second-stage recovery) – patients are fit enough to be transferred to the day surgery ward and then home. Patients are considered to have achieved 'street fitness'.

Late recovery (third-stage recovery) – full recovery and physiological recovery. The patient can return to work. Late recovery occurs in the patient's home.

Tests of recovery

Clinical

Day case anaesthetists may use their experience and knowledge to decide when a patient is fit for discharge. However, if clinicians are to delegate this decision, a well-designed scoring system is a useful tool for those assuming this responsibility. In some countries, time dictates how long patients remain in recovery areas. However, time-based recovery is inappropriate because of inter-patient variation and advances in surgery and anaesthesia that allow patients to move from one recovery phase to another more quickly than previously laid down or expected. Thus, criteria-based recovery has been introduced. In this system, the patient dictates the speed at which he or she progresses from one recovery stage to another.

Tests of early recovery involve recording the time at which specific events occur:

- eyes open
- date of birth recalled
- orientation
- able to obey commands
- stable vital signs
- recovered protective reflexes.

Scoring systems involve the evaluation of a number of patient factors. For first-stage recovery the Steward Score (Figure 1) and Modified Aldrete Scoring System (Figure 2) are used to determine when patients are ready for discharge from the recovery room; for second-stage recovery the Excitement Score or the Post-anaesthesia Discharge Scoring System (PADS; Figure 3) is used.

Scoring systems cannot be used to determine the patient's suitability for discharge home because they fail adequately to address pain, nausea, vomiting, surgical complications and patient ambulation. Discharge criteria have therefore been laid down to assist in the evaluation of a patient's street fitness following day surgery. Street fitness is an ill-defined term, which implies that the patient has recovered the ability to make everyday decisions under everyday circumstances. However, decision-making is not amenable to objective testing. Each day surgery unit has discharge criteria tailored to the population served by the hospital (Figure 4). One criterion that is often devalued is that the patient should feel confident about leaving hospital. In the author's hospital, this criterion is considered most important.

The patient must be discharged by the person who administered anaesthesia and the person who performed surgery, or by their designates. Written instructions for the postoperative period at home should be provided, including a contact telephone number. Owing to anxiety, extraneous noise and the amnesic effects of some drugs, patients may not assimilate verbal information, therefore written instructions are necessary. The patient must be accompanied by a responsible adult who will escort them home and ensure that they are not alone for at least the first 24 postoperative hours. Patients should avoid alcohol and refrain from driving for at least 48 hours.

Recently, the need to void urine and tolerate oral fluids before discharge has been questioned. In one study, the mandatory drinkers had a higher incidence of nausea and a longer discharge time. No patient in either group required admission. Eliminating the requirement to tolerate oral fluids may shorten the stay in the day surgery unit. Waiting for the patient to pass urine may also delay discharge. There is some evidence that patients who are not considered to be at high risk of developing urinary retention can be discharged safely without developing urinary problems at home. Risk factors for postoperative urinary retention are:

- history of postoperative urinary retention
- spinal/epidural anaesthesia
- pelvic surgery
- urological surgery
- perioperative catheterization.

Removing the requirement to tolerate oral fluids and void urine and separating the pain and nausea/vomiting scores has led to a modified version of PADS (Figure 3).

The use of guidelines together with common sense should prevent the premature discharge of patients who later experience postoperative complications requiring their readmission to hospital.

Steward Score[1]

Consciousness

• Awake	2
• Responding to stimuli	1
• Not responding	0

Airway

• Coughing on command or crying	2
• Maintaining a good airway	1
• Airway needs maintenance	0

Movement

• Moving limbs purposefully	2
• Non-purposeful movement	1
• Not moving	0

[1] Six points are required for discharge.

Modified Aldrete Scoring System[1]

Activity: able to move, voluntarily or on command

• Four extremities	2
• Two extremities	1
• No extremities	0

Respiration

• Able to breathe deeply and cough freely	2
• Dyspnoea, shallow or limited breathing	1
• Apnoea	0

Circulation

• Blood pressure within 20 mm Hg of preoperative level	2
• Blood pressure within 20–50 mm Hg of preoperative level	1
• Blood pressure ± 50 mm Hg of preoperative level	0

Consciousness

• Fully awake	2
• Arousable on calling	1
• Unresponsive	0

Oxygen saturation

• Saturation > 92%	2
• Needs oxygen to maintain saturation > 90%	1
• Saturation < 90% with oxygen	0

[1] Nine or more points are required for recovery to be confirmed.

Post-anaesthesia Discharge Scoring System for assessing home readiness[1]

Vital signs

Vital signs must be stable and consistent with age and preoperative baseline

• Blood pressure and pulse within 20% of baseline	2
• Blood pressure and pulse within 20–40% of baseline	1
• Blood pressure and pulse within 40% of baseline	0

Activity level

Patient must be able to ambulate at preoperative level

• Steady gait, no dizziness, or meets preoperative level	2
• Requires assistance	1
• Unable to ambulate	0

Nausea and vomiting

• Minimal: successfully treated with oral medication	2
• Moderate: successfully treated with intramuscular medication	1
• Severe: continues after repeated treatment	0

Pain

The patient should have minimal or no pain before discharge
The level of pain that the patient has should be acceptable to the patient
Pain should be controlled by oral analgesia
The location, type and intensity of pain should be consistent with the anticipated postoperative discomfort

Acceptable	2
Unacceptable	1

Surgical bleeding

Postoperative bleeding should be consistent with the expected blood loss for the procedure

• Minimal: does not require dressing change	2
• Moderate: up to two dressing changes required	1
• Severe: more than three dressing changes required	0

[1]Nine points are required for discharge.

Guidelines for safe discharge after day surgery

Vital signs must have been stable for at least 1 hour

The patient must be able to:
- orientate themselves in person, place and time
- keep oral fluids down
- void urine
- dress
- walk without assistance

The patient must not have
- more than minimal nausea and vomiting
- excessive pain
- bleeding

4

Psychomotor tests
Most psychomotor tests are complex and difficult to use routinely (Figure 5). To assess psychomotor function accurately requires tests to measure sensory, motor, physiological and central processing. This is difficult in the conventional setting. When testing any individual's psychomotor function the following precautions must be taken.
- Each individual acts as his/her own control.
- Time of day may affect performance.
- The hormonal effects of the menstrual cycle must be taken into account.
- Practice or learning effects must be reduced, either by allowing sufficient learning time before collecting results, or by having a control group not undergoing anaesthesia.

The ideal psychomotor test has the following qualities:
- quick and simple to perform
- no learning effect
- uses inexpensive equipment
- needs an unskilled operator
- is sensitive to the residual effects of all drugs used in anaesthesia
- has sufficiently reproducible results that firm conclusions may be drawn from individual measurements.

Despite the number of available tests, none has been validated by follow-up studies to provide adequate criteria to guide discharge in the day surgery environment. Lockwood has suggested that a psychomotor test suite comprising body sway, inspection time, critical flicker fusion, digital symbol substitution and a picture recall test should be used to study recovery from anaesthesia. It is unlikely that additional tests would reveal an effect not shown by this suite of tests.

Psychomotor testing therefore allows comparison between anaesthetic regimens. If one anaesthetic regimen leads to a swifter return to baseline psychomotor function then it would be valid to assume that the higher intellectual functions also return more quickly. At present, there is no place for these psychomotor tests in routine clinical practice.

Examples of psychomotor tests

Paper and pencil tests (measure the number of correct entries in a specific time)
- Trieger dot test
- Perceptual speed tests
- P deletion tests
- Digit symbol substitution test (most sensitive paper and pencil test)

Other tests
- Maddox wing test (measures imbalance of extraocular muscles)
- Reaction time tests
- Peg board tests
- Flicker fusion tests (tests central integrity)
- Tapping board tests
- Driving simulators
- Balance tests (measure postural sway)

5

Following regional anaesthesia
In the UK, the use of regional anaesthesia (spinal and epidural blocks) is uncommon. The perceived problems are concerns over post-dural puncture headache, urinary retention and the local anaesthetic agents available. However, if regional anaesthesia is used, it is important to ensure that the motor, sensory and autonomic blocks have receded before allowing patients to ambulate. Suitable criteria to judge if this has occurred are:
- normal perianal sensation
- plantar flexion of foot
- proprioception in big toe
- normal blood pressure on standing and sitting.

Ability to walk to the lavatory to pass water may be a suitable test of recovery from regional anaesthesia.

Patients, who have had a more peripheral nerve block (e.g. brachial plexus block) do not need to wait for the return of full sensation before discharge. They may be sent home with the anaesthetized area protected, with precise written and verbal instructions, and a 24-hour contact number.

Causes of prolonged recovery following regional and general anaesthesia are given in Figure 6.

Causes of prolonged recovery following regional and general anaesthesia

- Pain
- Nausea and vomiting
- Haemorrhage
- Cardiovascular or pulmonary dysfunction
- Wound drains
- Needing observation
- Lack of escort or inadequate home conditions

6

Safety and legal considerations

Following day case surgery, a patient may leave the clinician's care under the residual effects of anaesthetic drugs. It is an offence for a person to drive while under the influence of drugs. Operating machinery under the influence of these drugs may lead to an accident causing injury and/or damage to property. The effects of alcohol may be potentiated.

If not warned about these potential problems, the patient and anybody injured as a result of the patient's actions may hold the anaesthetist responsible. Patients must be warned of the danger and the fact documented.

Driving after anaesthesia
In 1972, Ogg found that 73% of car owners drove within 24 hours of outpatient anaesthesia. In 1996, the author found that no patients drove within 12 hours of surgery, but that 3.5% drove within 24 hours of general anaesthesia. The patients who drove within 24 hours had all been warned not to drive for at least 24 hours but were convinced that they were safe to drive. Safe driving requires an effective response to multiple secondary tasks. The primary task of control can be undertaken with impaired cerebral functioning, but the ability to react to the unexpected is crucial. A higher level of coordination is required to control a motorcycle or bicycle because the rider also has to balance. Previous research into the effects of anaesthesia on the ability to drive has involved single anaesthetic agents in volunteers not undergoing surgery.

A survey of motor insurers found that generally they would accept the medical advice given to the patient. However, one company commented that in the event of a claim, if the advice given was shown to be wrong, they might seek reparation from the hospital or individual concerned.

In the UK, 24 hours is the most common period of abstinence advised and is the time considered appropriate by the Medical Advisor to the Driver and Vehicle Licensing Agency. Recently, it has been suggested that the residual effects of anaesthesia and surgery extend into the second and third postoperative days. This may be a result of the residual effects of anaesthetic agents on higher cerebral centres or caused by the increased metabolic demands induced by the endocrine response to surgery. It is the author's practice to advise patients not to drive for 48 hours following general anaesthesia.

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Clinical Service and Audit: Working Clinical Systems

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Day surgery environment

In response to the Royal College of Surgeons' Working Party Report (1992) and the Audit Commission (1992) advice on day surgery, day surgery rates have increased and new facilities have been developed. Different day surgery services have evolved with different styles of management: premises vary from modifications of existing facilities, to free-standing units; operational policies vary from the proactive to the non-existent; and case mix is variable and not always 'true' day case. Where day surgery is not actively and continuously monitored and audited, good facilities can remain under-utilized or unpopular, or become inappropriately used. Some purpose-designed facilities still treat in-patients, thereby defeating much of the purpose of the original development and making audit more difficult. Many units still lack good information systems and have difficulty defining, auditing and controlling their activity, yet the success of their parent hospital in managing surgical beds is largely dependent on the good use of their day surgery facilities.

Information to enable audit to track the success of a day surgery clinical service closely parallels that required for management in this setting, and systems should be contemporaneous and accessible to busy clinicians, though they seldom are. The information generated should enable analysis of:

- the success and viability of the day surgery facility as a whole
- the quality of the day surgery practice within the facility.

If the clinical process fails and the patient is admitted, then not only has the patient's experience fallen short of what he/she and the clinicians expected, but also the savings have not been made. If operating lists are under-used, fewer patients are treated. If patients fare badly at home, clinicians are discouraged from undertaking day surgery or at least extending their practice. Information should be available to enable rapid identification of activity, and recognition and anticipation of both clinical and managerial problems on a daily basis. Such information can be used to drive true audit and continuous quality improvement.

Use of clinical systems

The need for clinical information systems that help patients and provide sound data to support clinical and managerial decisions is well recognized. The Audit Commission has stated that 'information is one of the most important resources that a hospital holds'. In order for a clinical service to evolve, data about individual patients must be grouped and abstracted, and then related to data about staffing facilities and other resources. It has been shown that clinical practice is seldom altered by evidence-based medicine. This must be due, at least in part, to the difficulties in obtaining relevant information.

Clinicians require different types of information, which is gained from diverse sources. In the context of daily practice, a high-quality clinical database can be used to provide accurate information for clinical practice, audit and administration. Clinicians perceive most health service information systems as offering no obvious benefits for patient care or themselves.

Service, audit and systems

Essential features of a computerized day surgery system

Patient information should be available for every stage of the process from pre-assessment and booking, through anaesthesia and surgery, to recovery, discharge and follow-up. Ideally, the patient record should be held on an on-line computerized management information and audit system, and should be instantly retrievable. It should be perceived as being easy to use and helpful by all staff, and be capable of being integrated with other systems to provide the comprehensive Electronic Patient Record (EPR) of the future. Alternatively, the ideal features of a day unit system should be embedded in a total EPR solution. The ability to cross-reference data easily, from a user-friendly and virtually instantaneous database, without the need to use complicated report packages, is particularly helpful in this environment. It should also be possible to identify omissions and inconsistencies in data entry readily. Clinical coding in hospitals is known to be fraught with difficulties. If surgical teams enter the diagnosis and procedures performed directly on to a system that already holds the relevant clinical codes, the coding can be automated. Sample parallel manual and automatic coding checks should be undertaken intermittently to validate coding and should demonstrate a high level of accuracy and completeness.

Any computerized system should also facilitate management processes in a fast throughput environment, and provide features such as:

- individualized surgical diaries
- direct booking on to operating lists in a manner that complies with the National Booked Admissions Project objectives
- a pre-assessment module to record clinical and booking details, decisions and alerts
- automatic generation of reminders for patients who have not confirmed their attendance
- automated communications with primary care workers
- automated generation of operating lists and, subsequently, the individual operating record
- automated coding
- extensive and flexible reporting.

As large numbers of patients pass through day surgery units, there is a potential wealth of clinical information waiting to be gathered; information relating to the unit as a whole, and to individual patients and clinicians.

The day surgery process – the need for information

The essential criteria for successful day surgery are well understood.

- Operations should be appropriate.
- Suitable patients should be identified.
- The work should be undertaken by experienced surgeons and anaesthetists.

Additional criteria for success include:

- well-informed patients
- good dedicated facilities
- first-rate organization
- good liaison with primary care workers
- follow-up and audit.

As more patients and procedures are perceived as treatable on a day-stay basis, successful application of these criteria becomes increasingly important. The ideal 'process' through which patients pass for their treatment should therefore incorporate:

- good identification of appropriate procedures by the referring surgeon (i.e. those without the expectation of excessive postoperative pain, bleeding or other complications)
- elimination of patients identified as unsuitable on medical or social grounds through a comprehensive pre-assessment process, now normally nurse-based and supported by anaesthetists
- efficient (and ideally integrated) booking and pre-assessment to minimize steps in the process, align urgency with the date of surgery and maximize use of operating time
- information for patients and carers about pre- and post-operative expectations.

Measures of all of these 'process functions' can be developed and easily audited. For example, numbers of patients who 'do not attend' on the expected day of surgery are likely to be higher when negotiated booking and pre-assessment are not performed. Poor pre-assessment, or none at all, results in a higher rate of cancellation on the day of surgery. Poor selection of either surgical procedure or inadequate pre-assessment results in higher unplanned admission rates. Poor discharge processes are likely to produce higher re-admission rates, callout of primary care services or difficulties at home. Poor booking processes can result in under-utilized operating time and wasted resources.

Standard management reports

Any day surgery facility should be capable of producing standard reports easily.

Simple, automated, daily reports showing cases performed, those who do not attend, cancellations and unplanned admissions can point to specific difficulties.

At a minimum, monthly reports should be generated (Figure 1). This data can be used to shape the service by determining:

- the correct number of lists for each specialty or surgeon
- the impact of pre-assessment
- the need for in-patient beds
- clinical complications.

Only when data of this quality are widely available will it be possible to compare general and specific practice in different units.

Suggested items for standard monthly reports

- Total activity of the unit
- Number of cases per specialty
- Pre-assessments performed and numbers accepted/rejected
- Numbers and procedures for each referring consultant
- Numbers and procedures for each operating surgeon
- Numbers, procedures and codes by specialty
- Cancellations on the day of surgery and reasons
- Non-attendance rates
- Unplanned admissions with reasons
- Sessions/lists used and utilization per session

1

Qualitative data

Information should not only ensure a successful, viable unit, but also help to promote safe clinical practice and a good experience for the patient. Data to promote safe clinical practice should be available through monthly reports as described above. Clinical complications and other important aspects of patient feedback require some direct information gathering. Clinical outcome measures and patient feedback are both desirable and increasingly sought by purchasers, and should include patient satisfaction as well as clinical outcome and complications. The increase in day surgery has been a cause of concern for all clinicians, including GPs, who are anxious about quality of care for their patients and a possible rise in night calls at a time when the availability of district nursing services is decreasing.

One system allowing access to qualitative data, which was first designed for use in the pioneering Norfolk and Norwich Day Surgery Unit (Daynamics® Calcius Systems Ltd), incorporates all the functions described above. The system is also used in the author's unit, in which an additional module was developed for audit. The responses to our structured postoperative telephone questionnaire, which patients receive the day after surgery, are entered directly on to the system, thereby linking the follow-up with the entire patient episode. This addition represents a significant advance in clinical audit by allowing rapid identification of clinical problems, and their relationship to procedures within the unit, answering many questions on a daily basis. Reasons for analysing patient responses through a postoperative telephone call are summarized in Figure 2. The format of the questionnaire is simple and contained on one screen. The enquiry is kept simple because telephone calls are time-consuming and complexity can impede decision making. The questions chosen (Figure 3) are directed at identifying;

- postoperative symptomatology
- recourse to primary care services
- patient expectation
- patient satisfaction
- readmission rates (i.e. readmitted after discharge).

Analyses of responses from telephone questionnaires carried out by other units have been published but, inevitably, if a manual collection process is used, a research worker is required to gather the data over a long period. It is preferable to be able to look at large numbers of variables in a short time, in order to 'trawl' for problem (or successful) areas of practice without having to set up complex reports each time (Figure 4). It should be possible for a clinician with minimal computer expertise to run reports such as these virtually instantaneously and the data should be easily importable into a standard data-handling package for further analysis if required (Figure 5).

Despite the efficiency of entering patient responses directly, the generation of hard copies of the patient feedback telephone calls makes daily review by a doctor or senior nurse easier. Patients' concerns can then be responded to, compliments passed on to the individual staff concerned (which appears to have a positive impact on staff attitudes and practice) and complications immediately identified.

Specific clinical issues that have been identified and followed up in the author's unit through this process include patients readmitted with retention or bleeding postoperatively, a low-risk patient suffering a pulmonary embolus the day after arthroscopic knee surgery (subsequently confirmed), and a non-epileptic child who had two possible convulsive episodes the day after surgery; the child was referred for further investigation and possible drug causes were investigated and reported. Patient complaints about waiting times have persuaded some surgeons to pilot an appointment system for operating lists. It is highly unlikely that these incidents would have been picked up without the follow-up.

Improvements in clinical practice have been made through education of clinicians, particularly in relation to performance of local anaesthetic techniques and postoperative analgesia. Clearly, a further, later follow-up for all patients would be desirable.

Rationale for the postoperative telephone call

- To provide a clinical service to patients
- To detect and remedy areas of practice that are unsuccessful
- To obtain patient 'feedback' for audit purposes
- To reassure hospital clinicians that their practice is safe and encourage more referrals
- To provide some outcome measures for clinicians, managers and purchasers
- To promote a good image for the day surgery facility

2

Example of a telephone follow-up questionnaire[1]

- In general, how did you feel?
  - very good
  - good
  - reasonable
  - not so good
  - bad

- Was this
  - better than expected
  - much as expected
  - worse than expected?

- Did you experience any
  - dizziness
  - drowsiness
  - feverishness
  - pain[2]
  - nausea[2]
  - vomiting[2]
  - bleeding?

- Have you had to contact anyone since discharge (unplanned)? Was it GP/ District Nurse/Practice Nurse/A & E Dept/Day Unit/SHO on-call?

- Is further help required?
- From whom?

- Overall were you
  - very satisfied
  - satisfied
  - dissatisfied?

- Did you like the unit?
- Did you like being a day case?
- Did you have trouble parking?
- General comments (entered free hand)

[1]Failure to contact the patient is also recorded.
[2]Quantified if present.

3

Examples of useful practical monitoring

- Complete breakdown of workload by specialty, surgeon, and age/sex of patient over any chosen period
- Individual clinician's personal records including their own patients' feedback
- Seniority of surgeons and anaesthetists working in the unit
- Procedures producing most postoperative difficulties
- Patients' experience of individual postoperative symptoms, by severity (graded), specialty, procedure, surgeon, anaesthetist, time of day, ASA grade and anaesthetic type
- Unplanned admissions by reason, surgeon, anaesthetist, and procedure
- Factors contributing to unplanned admissions, such as patient selection, pre-assessment, experience of surgeon, surgical technique, experience of anaesthetist, anaesthetic technique, timing of session (a.m./p.m.), and nursing factors
- Success rates in contacting patients postoperatively
- Patient satisfaction across all specialties, adults and children
- Primary care callouts
- Readmissions from home overnight
- Analysis of cancellations and rebooking workload for clerical staff

4

Examples of specific reports or audits

- Nausea and vomiting rates in children under 14 years undergoing squint surgery
- Patient satisfaction and unplanned admissions following the introduction of new lists or procedures to the unit
- Unplanned admission rates and reasons in gynaecological laparoscopy and inguinal hernia repair
- Comparison of individual anaesthetists' techniques in laparoscopic surgery
- Procedures producing 'severe' pain identified at patient feedback
- Success in contacting patients after discharge
- Satisfaction of carers with transfer of the service for special needs patients undergoing dental treatment in the new day surgery unit
- Use of laryngeal mask airways and endotracheal tubes
- Profile of unit work for identification of specialist registrar training requirements
- Analysis of patient comments/complaints
- Review of workload on some operating lists (leading to an increase in cases booked)
- Compliance with unit policy for senior operators and anaesthetists
- Identification of numbers of intraocular lenses following both extracapsular extraction and phaco-emulsification to obtain accurate costings for the lists
- Review of paediatric activity

5

Potential for future anaesthetic and surgical practice

Ideally, any patient's electronic record should include an anaesthetic record-keeping system to allow specific techniques, perioperative events, and drugs and their doses to be linked to postoperative follow-up.

Computer-aided drawing tools for surgical operating records could, potentially, allow data collection of the site and frequency of pathological lesions and their treatment.

The concept of being able to set up automatic reports to allow re-runs of previous audits is attractive and should be striven for.

Using the data to inform clinical practice

Clearly, the data collection described is not clinical research and, if these data are to become true audit information, audit criteria must be defined and performance measured against them. Nevertheless, important information can be gained and may provide pointers for more structured research projects. It becomes possible to gain a picture of what is really happening to patients. The patients have not been subject to double-blind, controlled trials; they have been treated in a real hospital by identifiable clinicians under real conditions. Such information is now essential to produce a realistic clinical governance agenda for day surgery.

Presenting results of surveys and audits at local surgical and anaesthetic audit meetings, to individuals and other groups (e.g. GPs) informs local practice. The information can be sensitive and requires diplomatic handling. It is wise to insist that clinicians who request data for audits gain prior permission from all colleagues whose work is involved, and that no clinical data are presented in identifiable form without the permission of the individual. Information should be provided to managers only with the permission of the clinician, though anonymized monthly activity reports are generally less contentious. Increasingly, however, clinicians will have to be accountable for their own information on outcomes and wide variations in practice will have to be justified.

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Design Requirements of Day Care Units

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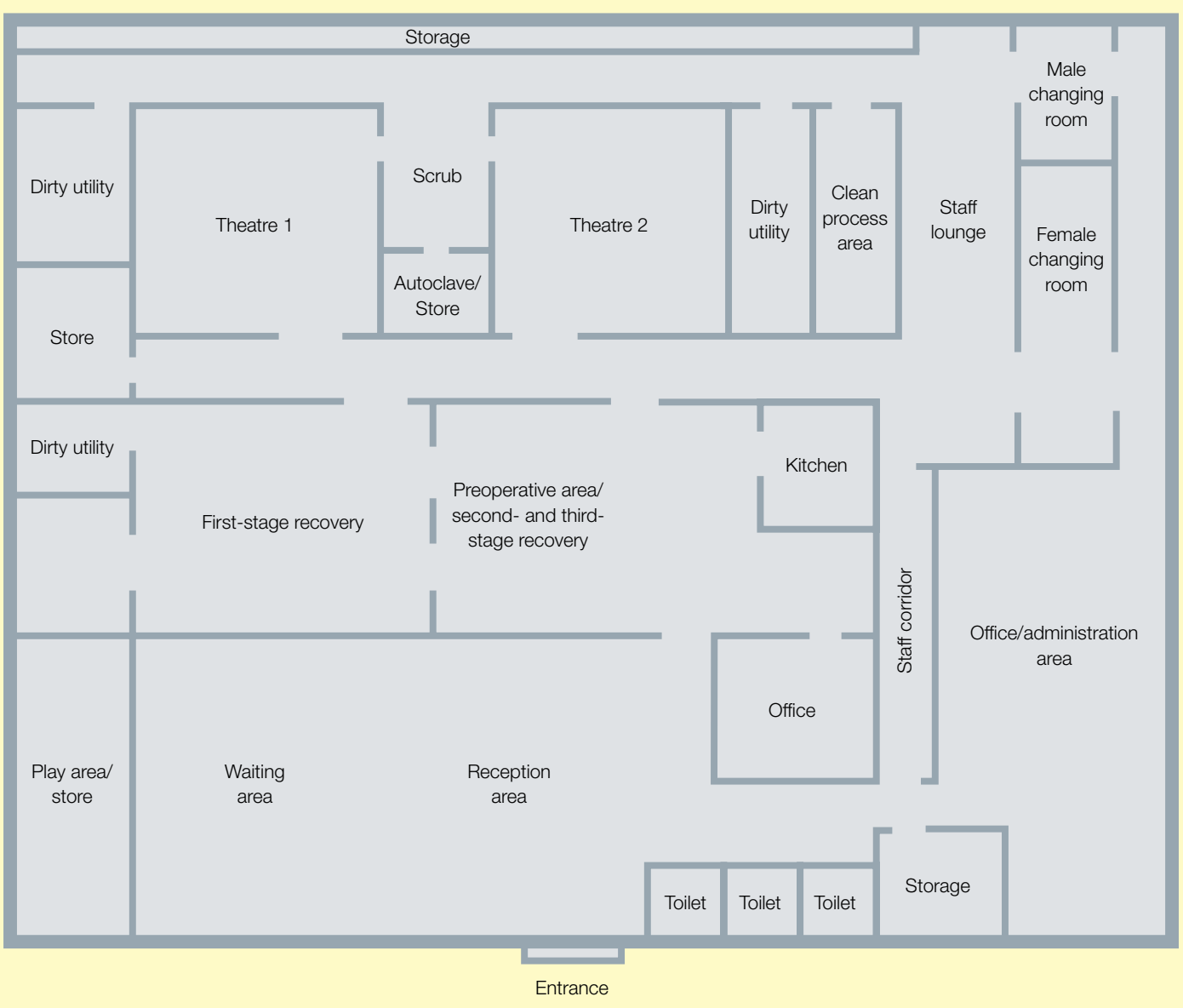
The efficient design of day care units is important to optimize costs and maintain quality of care and patient safety while processing large numbers of patients.

The rules that preclude the treatment of adults and children alongside each other significantly influence the provision of day surgery services for children. The design of the day care unit will reflect the level of need for paediatric care in the community by providing a dedicated children's unit, dedicated children's sessions within the adult unit, or accepting the fact that the use of the unit by children will be limited.

Basic design considerations

The day care unit must allow direct flow lines for patients and supplies, in order to avoid cross-infection and to maintain sterility. The layout must ensure that preoperative and postoperative patients do not meet. To maximize the efficient use of resources, the level of double handling of patients and supplies must be minimized, and careful consideration must be given to staff traffic patterns. The plan of a typical day care unit is shown in Figure 1.

Basic day unit design



1

Traffic patterns

In the USA, which has led the field in day surgery, there is a fixed prototype design for day care units. Each unit is divided into three zones. The front third is a non-sterile reception area for the public and houses the administration centre. The sterile area, containing the operating theatres, is situated in the back third of the building, and the middle section comprises patient preparation and recovery areas, storage facilities and staff lounges. The central section is accessible from both the sterile and non-sterile sides of the building along one or two corridors, one of which may be sterile.

Within the unit, the traffic pattern flows from front to back. Patients and staff enter through reception, staff move to the facilities in the central section, while patients complete the administrative procedures, and can remain with their escorts before moving into the central section for preoperative preparation. After surgery, patients are taken to the recovery area and monitored until they are safe to be discharged. They pass back through reception, where they can be collected by their escort.

Technology

An integrated management system, networked to the main hospital, provides an efficient method of processing patients on a daily basis, and produces statistical information, which can be used as an audit tool to ascertain patterns, manage productivity and resources. Such a system should improve legibility and accuracy of information and allow efficient management of supplies and a reduction in storage requirements in the unit.

General requirements

The decor should create a sense of relaxation and use finishes that are easy to clean and maintain. Floors should be on a single level, and should be non-slippery and hardwearing. Wherever possible, natural daylight should be used. Fire precautions should ensure that the building can be evacuated quickly and easily.

Specific requirements

Location/site selection and entrance

The main requirement is the need for easy access for patients, staff and services. Ideally, the unit should be freestanding, and of single-storey construction with dedicated car parking. Siting the unit on in-patient hospital sites allows direct access to support services without compromising independence. An easily identifiable main entrance is essential. There should be entrances for secondary supplies off the street. It should be possible for patients to be dropped off and collected by their escort at the entrance, which may be covered by a canopy to offer weather protection.

Reception area

The reception area is the non-sterile area of the unit where the administrative centre is located. It should contain a reception desk with information technology facilities and allow good visibility over the waiting area and any play facilities for children. The design of the desk should accommodate disabled patients.

The main waiting area should be informal, perhaps containing a fish tank and reading material, and should provide space for people using walking aids or wheelchairs. Sufficient lavatories should be provided including some with disabled access; one per ten users is recommended.

Patient preparation, second- and third-stage recovery area

The design of the patient preparation area and the second- and third-stage recovery area should incorporate administrative facilities.

Patients' trolleys may be separated by curtains hung from suspended tracks, and should allow adequate space for changing. A bedside cabinet should be provided for storage of valuables and a chair provided for the escort.

Male and female patients can be separated most easily by grouping those of the same gender together, according to the numbers of each on the operating list. This obviates the need to duplicate the facilities, and allows most efficient use of the ward area.

Trolleys are preferred to beds because they are more economical, occupy less space and avoid the need to transfer immobile patients from one platform to another. The use of thick mattresses makes them comfortable, while a 90° adjustable backrest promotes their use for first- and second-stage recovery. A mobile resuscitation trolley is needed.

The provision of hand basins (two per ten trolleys) and face mirrors allows patients to check their appearance before discharge. There should be a separate consulting/ examination room to provide privacy if required. This can also be used for pre-assessment or teaching.

Anaesthetic room and operating theatre(s)

Ideally, there should be a separate anaesthetic room that is large enough to allow free access around the patient's trolley to permit the use of local or general anaesthesia.

The room should contain a full suite of equipment to the level provided in a standard theatre suite. The alternative of anaesthetizing patients in theatre is less efficient because it requires the anaesthetist's time to prepare the patient, and causes delay while the theatre is cleaned. However, the cost involved in providing and equipping this second room may be prohibitive. Alternatively, a single anaesthetic room may serve two theatres, depending on list allocation.

The operating theatre should be large enough to accommodate the usual surgical equipment. It should also provide a good operating light, air-conditioning, piped services and scavenging facilities as well as scrub-up and lay-up facilities of a comparable standard to in-hospital theatres. Scrub facilities and sterile services may be designed to serve two theatres if interposed between them.

First-stage recovery area

The first-stage recovery area should have direct access to the theatres to allow access in the case of emergencies and to shorten transfer times. Piped services and the full range of monitoring and resuscitation equipment are mandatory. A minimum of two bed spaces per theatre should be accommodated to ensure rapid turnover times.

Ancillary services

Ancillary services must be provided in the most efficient manner.

- The delivery of sterile supplies and the removal of dirty utility needs to be effected directly through secondary entrances to prevent disruption to the flow of patients within the unit.
- It is important to situate the kitchen in the second-stage recovery area, where it can serve the needs of postoperative patients and offer their escorts light refreshments and beverages. Ideally, a well-stocked vending machine should be available within the waiting area.
- Sufficient accessible storage facilities must be incorporated in the design of the unit; the need for them is often under-estimated.
- The staff of the unit should have a private rest area incorporating kitchen facilities and pleasant changing rooms with personal lockers. Consideration has to be given to the ratio of female to male staff and this should be reflected in the area assigned to each changing room.

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General and Regional Anaesthesia for Day Case Surgery

Peter Davies

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Day case patients are discharged soon after surgery and thus need complication-free anaesthesia and surgery provided by senior staff. Although unexpected overnight admission (Figure 1) following day care surgery is often required for surgical reasons, it may also result from anaesthetic causes such as pain, postoperative nausea and vomiting (PONV) and delayed recovery. Attention to detail is therefore vital when selecting an appropriate anaesthetic technique for each patient.

Much day case surgery and anaesthesia is viewed as routine or simple, but it has to be performed to a high standard, therefore senior staff should perform day case anaesthesia. If complications arise when the patient has been discharged, they have to contact their GP or return to hospital. Following day surgery, 5–40% of patients contact their GP, usually for wound problems, but sometimes because of pain or PONV. With the increase in pressure on in-patient beds, many operations are now performed almost exclusively as day case procedures, therefore trainees in anaesthesia will have to gain supervised experience in the day surgery unit.

Reasons for unexpected overnight admission

Surgical reasons
- Longer operation than planned
- Bleeding
- Urinary retention
- Surgical complications

Social reasons
- Failure of escort
- Changed social circumstances

Anaesthetic reasons
- Pain
- Nausea and vomiting
- Drowsiness
- Anaesthetic complications

1

Premedication

Anxiolytic premedication
Anxiolytic premedication is seldom prescribed in day case patients because it is thought to delay discharge, though the few studies investigating it have demonstrated no increase in overnight admission or delayed discharge.

A patient who has had adequate preoperative counselling and preparation is less likely to be anxious. The simplest treatments for anxiety include reducing the waiting time for that particular patient by reorganizing the list and providing a relaxing environment with entertainment such as magazines or television.

If this is inadequate, temazepam, 20 mg p.o., is a suitable regimen. In children, midazolam, 0.5 mg/kg p.o., is an effective anxiolytic, if required. Most children also have local anaesthetic cream applied to prospective cannulation sites if intravenous induction is to be used.

Antacid therapy
There is an increase in volume and acidity of gastric contents in day case patients, and many advocate the routine use of an H_2-receptor blocker and metoclopramide. However, there is no evidence of an increased incidence of regurgitation and aspiration, therefore their routine use is unnecessary. For full effect, they must be taken the night before, and on the morning of, surgery.

In patients with a high risk of aspiration (e.g. those with gastro-oesophageal reflux or obesity), it may be necessary to prescribe the drugs and give detailed instruction at the pre-assessment clinic for them to be taken at home the night before surgery.

Perioperative analgesic drugs
Perioperative analgesic drugs can be given orally, rectally or intravenously. Oral absorption may be affected by anxiety and the rectal route may not be popular with the patient. It is important to obtain specific oral consent for rectal medications given under general anaesthesia or sedation.

- The mean time to peak plasma levels of diclofenac is 120 minutes orally (enteric-coated oral form) and 60 minutes rectally. Slow-release oral preparations are available, but they do not reach a steady state until several doses have been given. Intravenous drugs can be given but have their own problems. Diclofenac must be given by infusion over 20 minutes to avoid venous sequelae. The quickest-acting drug with the least complications is probably diclofenac, 1 mg/kg p.r. This can be self-administered by the patient preoperatively or given just after induction of anaesthesia.
- Parenteral ketorolac has few local effects, but its data sheet in the UK limits the initial dose to 10 mg. Most of the studies into the effect of this drug used doses of 30–90 mg.
- Tramadol is an opioid drug that is meant to be devoid of central side-effects, but it increases the incidence of PONV.

General anaesthesia

There has been an increase in the availability of short-acting agents for induction and maintenance of anaesthesia and although all of these drugs appear more expensive initially, there is increasing evidence of a reduced overall cost to health services and society. Few studies have examined the overall implications of different anaesthetic regimens, or surgical treatments, on total costs to the hospital, the patient or society. Early return to work, less use of expensive primary care resources, reduced overnight admission and less PONV could provide cogent arguments for the use of total intravenous anaesthesia with propofol, for all day case patients, despite the increase in total propofol costs to the hospital. This would help patients who are more worried about PONV than postoperative pain, as well as managers of day case units who are concerned about increased overnight admissions and surgeons who do not want in-patient beds filled with day case patients. Anaesthetists should provide high-quality symptom-free anaesthesia using multimodal postoperative analgesia.

Day case anaesthetic agents
Until recently, induction and maintenance of anaesthesia would have been discussed separately, but with the advent of total intravenous anaesthesia (TIVA), and volatile induction and maintenance anaesthesia (VIMA), the distinctions are blurred. Face masks and needles are still used with VIMA because it is safer to induce with a cannula *in situ*. Coughing and breathholding occur in 5–15% of inductions, though less often in more experienced hands.

The qualities of an ideal day case anaesthetic agent are listed in Figure 2.

Qualities of an ideal anaesthetic agent

- Fast predictable onset
- Fast predictable elimination
- Easily titratable depth of anaesthesia
- No active metabolites
- No accumulation
- Stable in solution in water/volatile liquid at room temperature
- No pain on injection/non-irritant on inhalation
- Good side-effect profile
- No PONV

2

Propofol is the most widely used induction agent in ambulatory surgery and, when used as part of TIVA, produces smooth induction with a rapid return to 'clear-headedness'. Propofol induction and maintenance anaesthesia, without nitrous oxide, using combination analgesic therapy is the treatment of choice for most patients undergoing day case anaesthesia. It has a low incidence of PONV. Its side-effect of pain on injection can be ameliorated by injection into larger forearm veins and the addition of 1% lidocaine (lignocaine), 2 ml.

The advent of target-controlled infusions (TCI) of propofol has made training in TIVA easier. Studies have shown TIVA- naïve anaesthetists find it easier to learn TCI compared with manually controlled infusions, but in experienced hands, the outcome of the two methods is similar. Figure 3 gives typical dose requirements for TCI and manually controlled propofol. The rate of infusion of propofol affects the speed of induction and the total dose required. With a rate of 600 ml/hour,induction takes up to 90 seconds requiring 1.96 mg/kg, whereas 1200 ml/hour takes about 60 seconds requiring 2.6 mg/kg, an increase of about 40 mg for a 70 kg patient.

Typical doses of propofol for manually controlled infusion and target-controlled infusion

	Manually controlled	Target controlled
Induction	1.5–2.5 mg/kg	4–8 μg/ml
Maintenance	12,10, 8 mg/kg/hour[1]	3–5 μg/ml

[1]The maintenance dose manually without nitrous oxide is 12 mg/kg/hour for 10 minutes, followed by 10 mg/kg/hour for 10 minutes with a maintenance thereafter of 8 mg/kg/hour.

3

Sevoflurane and desflurane have blood gas partition coefficients of 0.67 and 0.42, respectively, and are thus rapid acting with a short duration of action. Both drugs have demonstrated faster early recovery than older agents (e.g. isoflurane, propofol), but time to discharge is not reduced. The higher incidence of PONV with these volatile agents may account for this. Desflurane alone has demonstrated time to home readiness more than three times longer than propofol and, even when combined with ondansetron, desflurane does not lead to earlier discharge. Desflurane is unsuitable for gaseous induction of anaesthesia owing to its pungent odour and irritant airway effects. Sevoflurane produces rapid smooth induction of anaesthesia, and rapid offset with few side-effects except for PONV.

Isoflurane is widely used for maintenance of anaesthesia, despite higher incidences of PONV compared with propofol. Like desflurane, it is unsuitable for gaseous induction. The main reasons for continuing with isoflurane in the ambulatory setting are cost, familiarity with volatile anaesthesia and lack of equipment.

Opiates: despite the increased risk of PONV associated with the use of opiate drugs, they are used in most general anaesthetics as part of a balanced anaesthetic technique. The shorter-acting drugs (fentanyl, alfentanil, remifentanil) are in widespread use because they are cardiostable, non-allergenic and have a short duration of action. The older opiates (morphine, pethidine) provide good longer-lasting analgesia, but are associated with an increased incidence of PONV. These drugs are useful for treating severe postoperative pain when shorter-acting agents and other analgesic modalities have been tried.

Remifentanil is a relatively new esterase metabolized opiate, which has many of the requirements of the ideal ambulatory surgery anaesthetic agent. As more complex procedures are being performed in the ambulatory setting, the availability of a drug that can produce deep anaesthesia for a short period of time combined with haemodynamic stability and rapid recovery is of great benefit (e.g. for wisdom teeth extraction or anal surgery). In ventilated patients, it is given in doses of 1 μg/kg followed by infusion ranging from 0.1–0.75 μg/kg/minute (usually 0.25–0.5) when combined with expired isoflurane 0.8%, or propofol, 100 μg/kg/minute. A reduced induction dose of propofol, 1–1.5 mg/kg, is generally required. The time to wake-up is short owing to the context sensitive half-time of 3 minutes, but it is the quality of wakening which is impressive, with reduced coughing and breathholding. Fast recovery has been shown in studies demonstrating better psychomotor tests at 30, 60 and 90 minutes compared with alfentanil use.

In spontaneously breathing patients, it has been difficult to find a dose of remifentanil that produces anaesthesia but allows adequate respiration. Doses of remifentanil, 0.025–0.05 µg/kg/minute, with expired isoflurane 0.8–1.3% or propofol, 120–140 µg/kg/minute, provided maintenance of anaesthesia. In studies, the induction boluses of drugs have produced periods of apnoea, which makes dose selection difficult.

In some studies, remifentanil has been shown to produce a significant incidence of PONV but, owing to its rapid elimination, this effect is short lived. The short action of remifentanil means that any analgesic opiate effect wears off rapidly after termination of the drug, which may limit its usefulness in operations with significant postoperative pain

PONV

PONV is one of the main symptoms causing distress to day case patients and unexpected admission. The risk factors for PONV are listed in Figure 4.

Every day unit should have an action plan for patients at risk of PONV (Figure 5).

Airway maintenance

Risk factors for postoperative nausea and vomiting (PONV)

- Female gender
- Ambulatory surgery
- Opiates
- Starvation
- Gynaecological, ENT or ophthalmic surgery
- Early in menstrual cycle
- Previous PONV
- Motion sickness
- Nitrous oxide
- Non-smoker

4

Action plan for postoperative nausea and vomiting (PONV)

- All patients or high-risk patients
- Total intravenous anaesthesia, no nitrous oxide
- Triple analgesic therapy (non-steroidal anti-inflammatory drugs, opiates, local anaesthetics)
- Hydration
- Early treatment of postoperative pain
- Early treatment of PONV with 5-HT_3 antagonist

5

The advent of the laryngeal mask in 1988 revolutionized anaesthetic practice (Figure 6), particularly in ambulatory surgery. The laryngeal mask is less likely to cause sore throat compared with a tracheal tube and, in gynaecological laparoscopy, it decreases total operation time, which may allow more patients to be treated on an operating list, thus reducing overall costs.

In paediatric tonsillectomy, airway contamination is reduced when an armoured laryngeal mask airway is used compared with an uncuffed tracheal tube. Desaturations and surgical time are reduced in grommet insertion when compared with a face mask, and coughing and breathholding are reduced in cataract patients when compared with intubation. In short procedures, the laryngeal mask and spontaneous respiration avoid some of the problems of muscle relaxants. Though it has a short duration of action, suxamethonium causes muscle pains. None of the currently available non-depolarizing muscle relaxants can be given with certainty of easy intubation at 2 minutes and easy reversal after 10 minutes.

Much has been made of the dangers of unintubated spontan-eously breathing laparoscopy. With careful selection of patients, modern drugs and monitoring, this is a safe procedure. Complications arose in the past because of inadequate airways, unmonitored end tidal carbon dioxide concentrations and halothane anaesthesia, which all increase the likelihood of cardiac arrhythmias. Although in current use for ventilated gynaecological laparoscopy, ventilation through the laryngeal mask airway will occur against the increased intra-abdominal pressure which may overcome the laryngeal mask leak pressure of about 20 cm H_2O and cause increased intragastric air insufflation, perhaps resulting in an increased risk of regurgitation. Guidelines for laryngeal mask airway laparoscopy are given in Figure 7.

Uses of the laryngeal mask airway

- Gynaecological laparoscopy
- Tonsillectomy (adults and children)
- Dental extractions
- Intranasal surgery
- Head and neck procedures
- Shoulder operations
- Ocular surgery

6

Guidelines for laryngeal mask airway laparoscopy

- Elective gynaecological surgery only
- Body mass index < 31
- No symptoms of reflux
- Short procedures (< 30 minutes)
- Full monitoring
- Spontaneous breathing
- 2 litres of gas
- Trendelenburg tilt as needed
- Propofol infusion

7

Regional anaesthesia

Regional anaesthesia alone or combined with general anaesthesia or sedation should be standard practice for many ambulatory patients because it provides optimum operating conditions for the patient and the surgeon, with minimal side-effects. Regional anaesthesia alone is particularly suitable for less fit patients who would otherwise need overnight admission for general anaesthesia. Regional techniques provide good postoperative pain relief for patients and may allow the addition of more complex procedures to the routine mix of day case operations.

Regional anaesthesia for day case surgery has not been undertaken with great enthusiasm in the UK for various reasons, including the incidence of post-dural puncture headache in young people following early ambulation. Also nerve and plexus blocks take time and skill to set up and have a high failure rate. The advantages and disadvantages of regional anaesthesia compared with general anaesthesia are listed in Figure 8.

In the UK, much health authority funding has been used to increase the range and complexity of day case surgery, which requires long-lasting postoperative pain relief. The addition of drugs to local anaesthetics, and the manipulation of local anaesthetic drug concentrations and baricity have allowed a more predictable onset and offset of motor block, often providing prolonged analgesia, without delayed discharge. Many operations can be performed under local or regional anaesthesia. Plexus blocks and other regional techniques can also be performed with sedation or general anaesthesia to provide good postoperative analgesia. This reduces the benefit of avoiding sedative drugs in terms of PONV and recovery, but allows patients who would not otherwise tolerate regional anaesthesia the best of both worlds. Some advantages and disadvantages of local anaesthetic techniques in common day case surgical operations are given in Figure 9.

Comparison of regional and general anaesthesia

Advantages

Regional anaesthesia

- Prolonged analgesia
- Reduced postoperative nausea and vomiting
- Reduced confusion

General anaesthesia

- Fast
- No failures

Disadvantages

- Prolonged motor block
- Post-dural puncture headache
- Slow onset
- High failure rate
- Postoperative nausea and vomiting
- Confusion

8

Regional techniques for some common day case procedures

Surgical procedure	Regional technique	Advantages	Disadvantages
• Hernia repair	Field block	Good postoperative pain relief Speed Low failure rate	Needs supplementation
	Spinal	Speed Llittle supplementation	Post-dural puncture headache Urinary retention Delayed mobilization
• Cataract extraction	Peribulbar block	Reduces confusion and	Ocular complications discharge time
• Knee surgery	3-in-1 block	Good analgesia	Failed blocks
	Spinal	Speed Little supplementation	Post-dural puncture headache Urinary retention Delayed mobilization
• Foot surgery	Popliteal block, ankle blocks	Good analgesia	Failed blocks
• Hand surgery	Bier's block, brachial	Analgesia plexus blocks	Failed plexus blocks Minimal systemic disturbance

9

Spinal anaesthesia

The advent of 26–27 G pencil-point spinal needles has reduced the incidence of post-dural puncture headache from over 10% to about 1.5% for ambulatory patients. Few direct comparisons between spinal and general anaesthetic techniques have been conducted in the ambulatory setting, but time to fitness for discharge is longer after spinal anaesthesia compared with general anaesthesia, and is related to time to return of motor and bladder function.

Concerns regarding the neurotoxicity of high concentrations of lidocaine (lignocaine) have led to questions about its use in spinal anaesthesia. It has been widely used because of its fast onset and short duration of action, but it has been suggested that spinal bupivacaine should be used instead. Much research has been directed towards elucidating the optimum dose, concentration and baricity of bupivacaine to provide an adequate spinal block for surgery to proceed, but a short enough duration of action to allow timely discharge home. The optimum drug for knee arthroscopy is bupivacaine, 7.5 mg, which provides 100% success and street fitness after only about 3 hours (Figure 10). Clonidine, adrenaline (epinephrine) and fentanyl have been studied as additives to spinal local anaesthetics; the addition of fentanyl, 20 µg, can increase the length of postoperative analgesia, but not delay discharge.

Choice of spinal anaesthesia for knee arthroscopy

Drug	Dose (mg)	Time to discharge (minutes)	Successful block (%)
• 2% lidocaine (lignocaine)[1]	40	178	91
	60	216	91
	80	214	97
• Hyperbaric 0.5% bupivacaine diluted to 3 ml[2]	5	181	73
	7.5	202	100
	10	260	100

[1]Urmey *et al Anesthesiology* 1995; **83:** 528–34
[2]Ben David *et al Anesth Analg* 1996; **83:** 716–20

10

Major orthopaedic surgical techniques are being performed regularly as day case procedures. Arthroscopic shoulder surgery, and ligament reconstruction in the knee are operations with a high incidence of postoperative pain unless regional anaesthesia is used as part of the perioperative technique. Interscalene or suprascapular nerve block in the upper limb and 3-in-1 femoral block in lower limb procedures can produce long-lasting pain relief. Prolonged motor block is seen after these procedures and, in many UK orthopaedic centres, the discharge criteria after knee surgery include production of an adequate quadriceps contraction. Adequate physiotherapist-led instruction for the patient is needed regarding ambulation and protection of the blocked limb (Figure 11).

Postoperative instructions following local anaesthetic block

Local anaesthetic block	Postoperative instructions
• Spinal	Needs full ambulation and ability to pass urine
• Bier's block	No discharge for 30 minutes after release of tourniquet
• Brachial plexus block	Sling for limb, protection of numb, weak limb Return if no full return of power and sensation in 18 hours Take analgesics as soon as the first pain is felt
• Lower limb nerve block	Teach ambulation with crutches, protection of numb, weak limb Return if no full return of power and sensation in 18 hours Take analgesics as soon as the first pain is felt
• Inguinal field block	Discharge early so patient reaches home before block wears off Take analgesics as soon as the first pain is felt

11

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Web site of the Society of Ambulatory Anesthesia (SAMBA)www.sambahq.org. (search for 'core curriculum').

Postoperative Analgesia for Day Case Surgery

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A significant proportion of surgical procedures are performed as day cases and, owing to economic pressures, this is continuing to increase. However, inadequate postoperative analgesia is a major problem resulting in patient dissatisfaction, delays in discharge and in the resumption of normal activities.

Analgesia needs to be maintained throughout the recovery period and to allow comfortable mobilization. Many studies suggest that, despite good analgesia at discharge, patients suffer pain once they are home; this has recently been highlighted as a major problem in children. The provision of good postoperative analgesia needs careful planning, which should begin in the preoperative period.

Preoperative management

Explanation is of paramount importance, because allaying anxieties can decrease the severity of postoperative pain. A verbal description of the analgesia to be provided should be reinforced with concise written information. If local anaesthesia is planned, it is necessary to explain how this will feel on wakening, the duration of its action and any side-effects. Consent for suppository administration and neural blockade should be obtained.

Patients need to be educated about how to express any postoperative pain they may feel and how it may be treated. Regular, pre-emptive analgesia is a particularly important concept, which must be explained to the patient. In paediatric day case surgery, it is important to communicate appropriately with both the parent and child.

Preoperative analgesics, usually oral or rectal non-steroidal anti-inflammatory drugs (NSAIDs), may be given though the usefulness of preoperative pre-emptive analgesia is debatable.

Peroperative management

Analgesic strategies should be aimed at enabling the patient to be pain free on regaining consciousness. This can be achieved using a balanced approach with a combination of NSAIDs, local anaesthesia and, if necessary, small amounts of short-acting opiates.

NSAIDs (Figure 1): paracetamol acts synergistically with other NSAIDs, so both should be given. In children, paracetamol, 30–40 mg/kg p.r. or 20 mg/kg p.o., is the accepted loading dose, followed by regular dosing of up to 90 mg/kg/day. Diclofenac is also available as topical eye drops, which are effective as analgesia following strabismus surgery.

Side-effects – concerns have been raised over the side-effects of NSAIDs. They inhibit platelet function and should not be used in patients with pre-existing coagulation defects or those undergoing extensive tissue dissection. NSAIDs are commonly given for adenotonsillectomy, but should be withheld if there is excess blood loss or if there is any evidence of a coagulopathy.

No increase in gastrointestinal side-effects is seen with short-term use (up to 3 days) of NSAIDs, provided that the patient has no history of gastrointestinal irritation.

NSAIDs should be avoided if there are any signs of renal impairment or if other nephrotoxic drugs are being administered. The renal tubules are protected from the effects of dehydration by mechanisms utilizing prostaglandins, so it is important to keep patients well hydrated.

Of adults with asthma, 5–10% are sensitive to NSAIDs, therefore it is worth checking specifically if such individuals have taken NSAIDs previously without problems; if in doubt, NSAIDs should not be given. In children with asthma, NSAIDs seldom cause respiratory complications, but they should be avoided if nasal polyps are present or if the child has had recent repeated hospital admissions, especially if they have required intensive care.

NSAIDs commonly administered peroperatively

Drug	Route of administration	Dose (mg/kg)
Diclofenac	Oral or rectal	1
Ibuprofen	Oral	5
Ketorolac	Intravenous	0.5

1

Local anaesthesia can be used in a number of ways to provide excellent analgesia with few side-effects and often obviates the need for opiates (Figure 2). However, care must be taken not to delay early ambulation and patients must be advised about any possible interference with motor function. If sensation is impaired at discharge, warnings should be given especially about touching or drinking hot liquids, which may cause inadvertent scalds.

In laparoscopic cholecystectomy, 20 ml of 0.5% bupivacaine may be administered into the hepatodiaphragmatic space. Bupivacaine is generally preferred to lidocaine (lignocaine), because of its longer duration of action, which can be prolonged by the addition of 1:200,000 adrenaline (epinephrine). Ropivacaine has recently been introduced and has a similar duration of action, but causes less motor blockade.

Spinal and epidural anaesthesia are seldom used in the UK, but are commonly used in day case procedures in other countries.

Opioids: if possible, opioids should be avoided because of the increased incidence of nausea and vomiting but, if their use is necessary, the shorter-acting opioids are preferred.

- Remifentanil and alfentanil are so short-acting that they provide little postoperative analgesia.
- Fentanyl, 1–2 μg/kg provides 30–60 minutes of analgesia allowing time for NSAIDs to become effective. Fentanyl is the drug of choice in treating significant postoperative pain in the early stages of recovery and should be given in small boluses of 0.2–0.4 μg/kg.
- Morphine causes increased nausea and vomiting especially if administered intravenously. However, doses of 0.1 mg/kg are used intramuscularly, for example, in day case adenotonsillectomy.
- Codeine phosphate may be given by the intramuscular, rectal or oral routes, and it may be useful for more painful procedures.
- Tramadol combines an opioid action with a central adrenergic effect, but has a significant incidence of postoperative nausea and vomiting.

Examples of the use of local anaesthesia

Technique	Type of local anaesthetic	Surgical procedures	Comments
Topical	*Emla* 4% lidocaine (lignocaine) gel	Myringotomy Circumcision	Emla for myringotomies 4% lidocaine (lignocaine) gel for circumcision which can be continued on discharge
		Laparoscopic sterilization	4% lidocaine (lignocaine) gel can be applied to clips
Infiltration	0.25% bupivacaine 1–2% lidocaine (lignocaine)	All surface wounds	Pre-incisional wound infiltration probably offers no benefit
		Laparoscopic sterilization	Mesosalpingeal infiltration
Intra-articular	0.5% bupivacaine	Arthroscopy and arthroscopic surgery	Usually 25–30 ml are used for knee arthroscopy
Nerve blocks	0.25–0.5% bupivacaine 1–2% lidocaine (lignocaine)	Upper limb surgery	No adrenaline (epinephrine) for digital nerve blocks
		Lower limb surgery Hernia repair Orchidopexy	Inadvertent femoral nerve block may result in leg weakness
		Circumcision	No adrenaline (epinephrine) for dorsal nerve blocks
		Otoplasty	Great auricular nerve block decreases vomiting
		Eye surgery	
Plexus blocks	0.25–0.5% bupivacaine 1–2% lidocaine (lignocaine)	Upper limb surgery Lower limb surgery	
Caudal epidural block	0.125% bupivacaine 0.75% ropivacaine	Surgery below the umbilicus	Ketamine (preservative-free), 0.5 mg/kg, or clonidine,1–2 μg/kg, prolongs the block
Intravenous regional	0.5% prilocaine	Upper limb surgery	Limited postoperative analgesia

2

Postoperative management

In the immediate postoperative period, it is important to establish good analgesia before discharge. Small amounts of intravenous fentanyl may be given until analgesia is achieved. Most patients can tolerate oral medication shortly after surgery. A large variety of soluble oral analgesics are available, enabling rapid absorption and action.

Most day case units have a drug discharge policy with combinations of paracetamol, NSAIDs and codeine preparations as regular oral analgesics continued for at least 3 days postoperatively (Figure 3). If paracetamol and codeine (or its derivatives) are used as a combined preparation, the patient should be warned not to take other medications containing paracetamol. Also, higher doses of codeine may cause constipation. The discharge drugs should be given to the patient with both verbal and written instructions emphasizing the importance of regular pre-emptive analgesia. Controlled or slow-release preparations may be beneficial, especially at maintaining analgesia overnight.

Patients need to know who to contact in the event of any problems. Postoperative follow-up, either by a community nurse or by telephone, increases patient satisfaction and can help improve postoperative analgesia. The adequacy of the analgesia provided should be regularly assessed and audited.

Non-pharmacological techniques of improving patient comfort may help. Psychological strategies such as relaxation and distraction therapy and physical strategies such as the application of heat or cold, massage, exercise or rest have been used in combination with pharmacological methods. Acupuncture and transcutaneous electric nerve stimulation and other similar techniques have also been studied but their clinical efficacy is yet to be proven.

Postoperative oral analgesia

Expected severity of pain	Analgesic regimen
Mild	Paracetamol, 15 mg/kg (up to a maximum of 1 g) 6 hourly
Moderate	Paracetamol, 15 mg/kg (up to a maximum of 1 g) 6 hourly plus NSAID (e.g. ibuprofen, 5–10 mg/kg 8 hourly, or diclofenac, 1 mg/kg 8 hourly)
More severe	Paracetamol and codeine combination (e.g. Co-codamol, 2 tablets 6 hourly[1], Co-dydramol, 2 tablets 6 hourly[2], Co-proxamol, 2 tablets 6 hourly[3] plus NSAID (e.g. ibuprofen, 5–10 mg/kg 8 hourly, or diclofenac, 1 mg/kg 8 hourly)

[1]Co-codamol tablet is paracetamol, 500 mg, with codeine, 8 or 30 mg.
[2]Co-dydramol tablet is paracetamol, 500 mg, with dihydrocodeine, 10 mg.
[3]Co-proxamol tablet is paracetamol, 500 mg, with dextropropoxaphene, 32.5 mg.

3

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Web site of the Society of Ambulatory Anaesthesia (SAMBA) www.sambahq.org. Search for 'core curriculum'.

Selection Criteria and Preoperative Evaluation for Day Surgery

Stuart Collins

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Day surgery has expanded rapidly in recent years and it is estimated that soon 60–70% of all elective surgery will be performed as day cases. Correct patient selection and preoperative evaluation are important to minimize morbidity and unplanned overnight stays, and to maintain patient satisfaction.

Preoperative assessment

Assessment should identify patients who are suitable for day surgery, prepare them for their operation and enable any preoperative testing to be performed. Questionnaires or structured telephone calls can be used, but many units now use a nurse-led clinic under clinical guidance with a standardized questionnaire and predetermined selection criteria (Figure 1). It is important to establish that the patient is in the optimum condition for the planned procedure.

Pre-assessment questionnaire

Suitable for day surgery? Yes No If no inform: GP Consultant Patient

Name: Date of assessment: Proposed date of operation:
Consultant: Proposed operation:
Unit no.: Patient Tel. no. Home: Work:
Date of birth:
Next of kin: Telephone no.: Relationship:

Have you had any serious illness in the past?

Previous admissions to hospital (date, problem, type of operation, type of anaesthetic)

Have you or any of your relatives ever had a problem with a general anaesthetic?
Yes / No Action taken

Medications currently being taken. include all prescriptions, aspirin and 'the pill'

BMI Blood pressure Weight Height Pulse

Investigations ordered

- Do you have haemophilia, anaemia or another blood disorder? Yes / No
- Do you have diabetes? Yes / No
- Do you have kidney disease or kidney failure? Yes / No
- Have you ever had liver disease, hepatitis or been jaundiced? Yes / No
- Have you had a heart attack? Yes / No
- Do you get angina or chest pain at rest or with minimal exercise? Yes / No
- Do you have a pacemaker? Yes / No
- Have you had heart disease, rheumatic fever or high blood pressure? Yes / No
- Do you get breathless walking, climbing one flight of stairs or lying flat? Yes / No
- Do you have asthma, bronchitis, or chest disease? Yes / No
- Have you ever had a convulsion, fit, blackout, or do you have epilepsy? Yes / No
- Do you get swollen ankles? Yes / No
- Do you have a hiatus hernia? Yes / No
- Do you get indigestion or heartburn? Yes / No
- Have you ever had a stroke? Yes / No
- Do you have arthritis or muscle disease? Yes / No
- Have you had any corticosteroid drugs in the past? If so when? Yes / No
- If female, are you or could you be pregnant? Yes / No
- Do you smoke or have you smoked in the last 6 months? Yes / No
  If you smoke, how many a day? Yes / No
- Do you drink alcohol? If yes, how many units per week? Yes / No
- Urinalysis Yes / No

Check list

Starve	Yes / N/A	Suture and wound care	Yes / N/A
Shave	Yes / N/A	Drains and dressings	Yes / N/A
24-hour postop information	Yes / N/A	Pain control	Yes / N/A
Stairs after discharge?	Yes / N/A	Information leaflet received/given	Yes / N/A
		Transport home discussed?	Yes / N/A

Name of person collecting: Tel. no.
Name of 24-hour carer: Tel. no.
I have understood the information given to me at my pre-anaesthetic assessment and I have also received information about my operation.
Signature of patient: Date:
All the above information is correct to the best of my knowledge and understood by the patient:
Assessment nurse signature: Date:

Anaesthetist's comments:

1

Selection criteria

The boundaries in day surgery are continually being pushed back and recent studies suggest that significant associated morbidity is low, even in patients with controlled systemic disease. Selection criteria help to establish consistency and agreement among medical staff. The appropriateness of the selection criteria should be reviewed regularly by auditing cancellation rates, patient morbidity and patient satisfaction. Determining suitability solely on the American Society of Anesthesiologists (ASA) classification is unhelpful.

Social factors – the patient must be prepared to have the procedure performed as a day case, live close to the hospital, and have a responsible, able, adult carer at home with them for 24 hours postoperatively.

Surgical factors – the proposed surgery must have a low incidence of postoperative complications and any pain should be controllable by local anaesthetic techniques and analgesics administered orally or rectally. The duration of surgery does not affect the likelihood of same-day discharge, provided longer cases are listed early in the day. A stand-alone unit is different from an integrated unit with facilities for overnight stay, and the patients and surgical procedures should be selected accordingly.

Medical factors – it is difficult to agree on absolute medical contraindications to day surgery because significant postoperative morbidity is uncommon. However, certain medical conditions are associated with an increased risk and render the patient unsuitable for general anaesthesia (Figure 2). With invasive procedures, it is essential that the patient's physical condition is matched to the planned procedure. It is important to consider whether treating the patient as an in-patient would lessen the risks or change the anaesthetic approach.

Medical contraindications for day case anaesthesia

Morbid obesity
- Body mass index > 35 kg/m^2 or weight > 125 kg

Cardiovascular disease
- Poorly controlled angina, arrhythmia or cardiac failure
- Hypertension > 180/100 mm Hg
- Significant valvular or congenital heart disease
- Myocardial infarction or stroke within 6 months

Respiratory disease/airway
- Poorly controlled asthma or chronic obstructive pulmonary disease (patients taking oral corticosteroids, with poor exercise tolerance or with a peak expiratory flow rate < 200 litres/minute are unlikely to be suitable)[1]
- Severe restrictive lung disease (e.g. kyphoscoliosis)
- Previous failed intubation
- Significant obstructive sleep apnoea

Metabolic/endocrine/haematological
- Poorly controlled diabetes or insulin dependent[1]
- Active liver disease
- Anaemia (haemoglobin < 10 g/dl)[1]
- Haemophilia/anticoagulation[1]
- Cholinesterase deficiency[1]
- Hypo- or hyperkalaemia (acceptable range 3–6 mmol/litre)

Renal disease
- Patients requiring renal support[1]

Neuromuscular disease
- Myasthenia gravis
- Significant multiple sclerosis
- Malignant hyperpyrexia susceptibility
- Poorly controlled epilepsy
- Parkinson's disease interfering with daily activity
- Significant motor neuron disease

Acute substance abuse

[1] Patients might be suitable – discuss with lead clinician.

2

Cardiovascular disease
Patients with well-controlled cardiovascular disease should not be denied the opportunity to have their surgery in the ambulatory setting. However, patients with poorly controlled angina, congestive cardiac failure, symptomatic valvular disease, uncontrolled arrhythmias or recent myocardial infarction or stroke (within 6 months) are unsuitable for elective surgery. Minor surgical procedures are categorized as being of low risk for significant cardiac events. Hypertension is associated with an increased risk of developing perioperative cardiac events and should be treated before surgery. A reasonable upper limit for blood pressure is 180/100 mm Hg. It is important to explain to the patient, and their GP, the reasons for controlling hypertension perioperatively so that treatment is initiated. In general, cardiac medication should be taken as usual on the day of surgery.

Respiratory disease
Asthma, chronic obstructive pulmonary disease and smoking all predict adverse perioperative events, but patients with well-controlled disease are likely to be suitable for day surgery. A regional anaesthetic technique can be considered for the more seriously affected. Patients with poorly controlled disease, marked exercise limitation or a recent exacerbation of their condition should have their surgery postponed. Smokers should be encouraged to stop smoking.

Diabetes
Diabetes may be associated with cardiovascular and renal disease or autonomic dysfunction. Diabetes is a predictor of adverse intraoperative and postoperative events, but patients with good diabetic control and a good understanding of their disease should be allowed day surgery. Patients with Type 2 diabetes are, in general, more suitable for day surgery than those with Type 1 diabetes; however, well-motivated patients taking insulin can be considered if their procedure is of short duration and carried out early in the morning. Many Type 1 diabetics understand their insulin requirements better than their anaesthetist does. Hypoglycaemic agents are best avoided until the procedure is completed and the patient has resumed eating and drinking.

Obesity
Obesity is often associated with cardiac disease, diminished respiratory reserve and gastro-oesophageal reflux. A body mass index greater than 35 kg/m^2 is associated with perioperative anaesthetic and surgical problems, and is often used as a cut-off point for patient suitability. Obese patients can be anaesthetized in a day case setting, but they should be encouraged to lose weight before agreeing to any elective procedure in any setting. The patient trolleys and operating tables in the day unit have a maximum safe weight limit. Antacid prophylaxis can be prescribed for symptomatic reflux.

Renal and hepatic disease
Patients on renal support or those with active liver disease are usually unsuitable for day surgery.

Neuromuscular disease
Patients with myasthenia gravis, motor neuron disease, hereditary dystrophies or a susceptibility to malignant hyperpyrexia are generally unsuitable for general anaesthesia in the day unit. Patients with poorly controlled epilepsy are unsuitable, but well-controlled epileptics can have day surgery, provided appropriate drugs are chosen. Although not strictly a neuromuscular disease, pseudocholinesterase deficiency is a relative contraindication to day surgery.

Musculoskeletal disease
Patients with severe degenerative neck disease, predicted difficult airway, or previous failed intubation are probably best anaesthetized in the main hospital, depending on the facilities of the day unit. Patients with significant obstructive sleep apnoea should be observed overnight in hospital.

Haematological disease
Patients with bleeding diatheses may be suitable for day surgery if the deficient factors are corrected preoperatively and the surgery is not too invasive. The opinion of a haematologist should be sought.

Medication
Corticosteroids: patients taking corticosteroid supplements are usually able to undergo day surgery because the stress response to minor surgery has not been found to cause problems. Oral supplementation can also be prescribed. However, patients taking higher doses of corticosteroids require individual medical review.

Oral contraception and hormone replacement therapy are associated with a slightly increased risk of thromboembolic events, but patients are not advised to stop their medication before surgery because the risk of unwanted pregnancy is felt to be greater. Their continued use in patients undergoing lower limb surgery or requiring tourniquet use is more contentious and, if they are continued, the use of subcutaneous heparin would seem prudent.

Warfarin: if the patient needs to stop taking warfarin before surgery, but has a significant risk of thromboembolic events, admission and anticoagulation therapy with heparin are required.

Monoamine oxidase inhibitor use does not preclude day surgery, but suitable anaesthetic drugs should be selected carefully.

Age
Old age should not be a barrier to day surgery. The patient's physiological age is more important than their chronological age; however, they must be assessed carefully for social and physiological factors. The lower age limit for day surgery depends on many factors and should be set locally.

Investigations

In general, patients are over-investigated for day surgery, and the cost:benefit ratio is not always apparent. Preoperative testing should be performed only if indicated by the medical history or by physical examination and if an abnormal test would affect patient management.
Blood tests: full blood counts are usually performed to detect anaemia and therefore should be reserved for patients with a history of heavy bleeding, dyspnoea, renal disease or if they appear unduly pale. Urea and electrolyte assays are usually performed to detect abnormalities in potassium or to detect abnormalities in renal function, and should be reserved for hypertensive and diabetic patients, patients taking diuretics and those with a history of renal disease. A blood sugar level should be performed if indicated by urinalysis. Clotting studies may be indicated if there is a history of excessive bleeding or hepatic disease.

Radiographs: chest radiographs are seldom required. A radiograph of the cervical spine may be indicated in patients with rheumatoid disease or Down's syndrome.

ECG: the usefulness of a preoperative ECG in day surgery is controversial. Up to 30% of ECGs are abnormal in patients over 60 years old, but in only 20% of patients does this lead to a change in management. Patients over the age of 60 or with a history of chest pain, dyspnoea, diabetes or hypertension, should be considered for an ECG. A preoperative ECG can provide a useful baseline.

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Dental/maxillofacial

Anaesthesia
and intensive care medicine
on CD-ROM

Anaesthesia and Dental Trauma

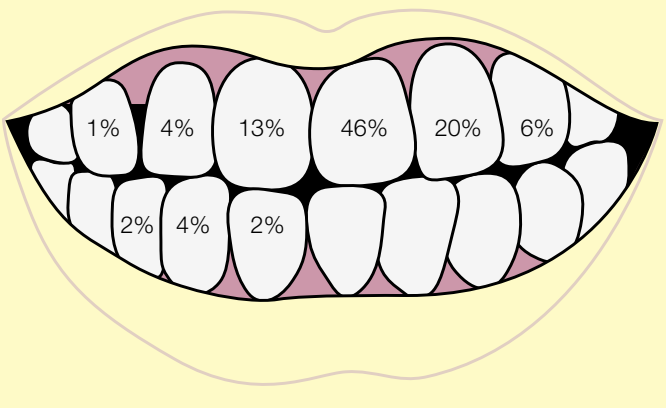
Harry Owen

Harry Owen is Associate Professor in Anaesthesia and Intensive Care at Flinders University of South Australia and Honorary Consultant at Flinders Medical Centre. He graduated from Bristol University and trained in anaesthesia in Bristol, Melbourne and Glasgow. His research focuses on use of new technologies, including simulation, to improve undergraduate education and postgraduate training.

Dental trauma is unpleasant for the patient and the anaesthetist. Dental trauma caused by the straight Magill blade was well known and Macintosh claimed an advantage of his curved blade was a reduced risk of trauma to teeth. The incidence of dental trauma in anaesthesia is 0.01–0.7%. In malpractice claims, anaesthetic-related dental trauma is the most common injury accounting for up to 33% of claims filed in the UK, the USA and Australia. In Australia, the average cost of settling a claim for dental damage is A$2,400 (range A$100–12,800) but the total costs incurred in managing these claims are far higher.

The most common technique of tracheal intubation involves using a laryngoscope to lift the base of the tongue and epiglottis. The pattern of dental trauma, shown in Figure 1, confirms reports that a common mistake is to use the laryngoscope blade as a lever with the upper teeth as the fulcrum. The left upper central incisor is the tooth most at risk.

Pattern of dental trauma in patients examined by a dentist after anaesthesia



1

In the early 1960s, Dr William Haddon launched a movement to base injury-prevention programmes on sounder scientific concepts. Haddon developed a generic approach to the analysis, control and management of injury, which can be applied to all types of hazards associated with energy transfer. Haddon divided accidents into three phases, pre-event (factors that determine whether an accident occurs), the event itself and post-event (everything that determines the consequences of the injuries received). Combining the phases and factors (humans involved, equipment and environment) yields a matrix, that can be used to determine where best to apply strategies to prevent or control injury (see Figure 2). Applying this to the problem of dental trauma in anaesthesia reveals three broad strategies:

- risk avoidance – don't let the event happen
- damage control – if damage occurs, minimize its consequences
- insurance – have someone else pay for the damage.

Haddon's Matrix applied to dental trauma during anaesthesia

Phases	Factors		
	Human	**Equipment**	**Patient factors**
Pre-event	• Good intubation technique • Aware of risk factors for dental damage • Dental history and examination undertaken and understood • Know when and how to use different intubation techniques	• Appropriate range of intubation equipment readily available in hospital • Dental protection devices readily available	• Good dental hygiene • Normal oral anatomy • No drug therapy or diseases contributing to dental problems • Knows what dental treatment has been undertaken • Elective procedure
Event	• Careful and appropriate use of equipment • Good assistance	• Use devices to protect teeth • Use laryngoscope blades designed to reduce contact with teeth • Use warning devices on laryngoscope blades • Intubating without a laryngoscope	• No loose teeth • No malaligned or prominent teeth • No isolated teeth • No heavily restored teeth • No dental prostheses • Normal airway anatomy and no risk factors for difficult intubation • No urgency
Post-event	• Know how to manage situation • Dental help readily available	• Materials to splint teeth safely readily available	• Able and willing to cooperate with treatment

2

Preventing dental trauma is the ideal approach, but the perceived costs of managing occasional dental trauma have to be balanced by the inevitable increased costs to reduce the incidence of dental trauma. A logical approach to reduce dental trauma is to consider intubation strategies for each patient, based on the history, examination and planned procedure.

The primary objective of intubation is patient safety and oxygenation must always be prioritized above dental protection. However, if two alternatives are equally suitable, the most 'tooth-friendly' technique should be preferred. It is important to warn patients of the risk of dental damage associated with intubation. If risk factors for dental damage are present an alternative to direct laryngoscopy should be considered.

Patient factors

The preoperative assessment must include a dental history and an oral examination and the findings should be noted.

Condition of teeth

Major restorations and caries reduce the strength of teeth and make them more likely to break even when small forces are applied to them. Periodontal disease affects the supporting structures of the tooth and increases the risk of dislodgement. Malaligned teeth are more likely to be exposed to unusual forces. An isolated tooth does not have the support of its neighbours and may also have the same condition that led them to be lost so is more likely to be dislodged.

Patient's age

The neonate may not have teeth on view, but delicate tooth structures are just under the gum and can easily be damaged. Infants and young children may have loose deciduous teeth that are easily dislodged. Force applied to a deciduous tooth can also damage the underlying developing permanent tooth. Occasionally, severe caries is seen in adolescents and young adults though this age group generally has healthy teeth. In older patients, dental prostheses are more common.

Dental prostheses

Bridges, particularly to replace upper incisors, are most at risk of damage. They are designed to sustain the forces associated with mastication and do not tolerate forces applied in other directions. Crowns can be weaker than normal teeth. While the porcelain 'jacket' is strong, the supporting post may give way under pressure. Veneers may sheer off if lateral forces are applied. Composite resins are being used increasingly to restore teeth and may be used to repair chipped teeth or as a veneer. Resin restorations can be difficult to detect but forces applied through the laryngoscope can fracture this material. Devitalized teeth as a result of trauma or root canal treatment become more brittle than healthy teeth and are more likely to break when loaded.

Difficulty with intubation

Difficulty with intubation is an important risk factor because it may lead to additional or unusual forces being applied to oral structures including teeth. Earlier use of a bougie or flexible-tip laryngoscope or an alternative method of intubation should always be considered when risk factors for difficult intubation are observed.

Emergency surgery

Urgent cases have an increased risk of dental damage possibly because of the necessary haste and because a laryngoscope is usually used. It is probably prudent to explain this to the patient.

Drug therapy and co-morbidities

Many conditions and drug treatments have dental implications, which is why taking an accurate history is important. Any drug or disease that results in a dry mouth (xerostomia) increases the risk of dental pathology. For example a patient taking methadone as part of a drug rehabilitation programme has an increased risk of dental disease. All opioids reduce salivary flow and promote dental disease. While a patient is abusing narcotic drugs it is likely that dental hygiene is not attended to, making dental pathology even more likely. Methadone is presented in a sugary syrup and this also promotes caries. Also, if the patient has acquired HIV or AIDS, problems may arise from HIV periodontitis and xerostomia from the disease and/or drug treatment.
Intubation alternatives

There are several alternative intubation techniques that may reduce the risk of dental trauma.

Flangeless or reduced-flange laryngoscope blades: the most extreme example of this is the Bizzarri-Guiffrida blade which has no flange at all, but this makes it more difficult to use. The Bellscope blade is shaped to reduce the risk of contact between teeth and flange.

Warning devices: a number of prototype systems that warn when pressure is being applied to teeth have been described.

Lightwand intubation: the malleable wand of the *Trachlight*® and the need for very little mouth opening should reduce the incidence of dental trauma from intubation.

The intubating laryngeal mask airway (LMA): the *Fastrach*® could reduce the risk of teeth being broken, but loose teeth could still be subluxed during insertion and manipulation of the LMA.

Fibre-optic intubation is used routinely in some centres but the cost limits its routine use in most hospitals.

Don't intubate: the growing range of airway management systems (e.g. the LMA Proseal®) may provide an acceptable alternative to intubation in some patients. However, objects put in the mouth to protect the device (e.g. a Guedel airway) may increase the risk of dental damage. A real 'bite block' sits between the molars which are designed to tolerate high forces. Anything put between the incisors increases the risk of subluxation of the upper incisors.

Mouthguards: there is no good evidence that using a generic mouthguard protects teeth from damage during laryngoscopy. In one study, when the mouthguards were removed they sometimes had teeth embedded in them. Custom mouthguards may be useful, especially if there are anterior bridges, but they need to be fabricated in advance of the procedure and may make intubation more difficult. ◆

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Anaesthesia for Facial Trauma

Joy E Curran

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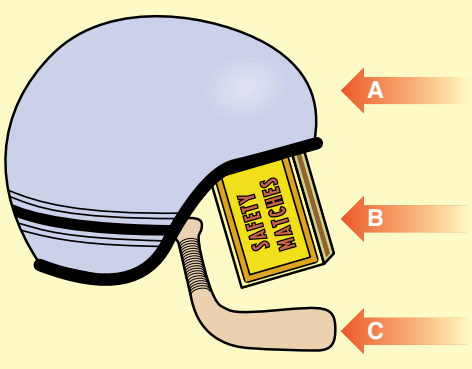
Facial trauma has particular importance for anaesthetists because it directly involves the upper airway. Trauma to the face can also affect the vital structures involved in four of the five senses, the underlying brain, the soft tissues (with implications for the cosmetic result) and the bony skeleton.

The main cause of facial injury in developed countries was road traffic accidents (RTAs) until the later half of the 20th century when assault became the most common cause. Sports injuries and falls (especially in those under 5 years of age) are the second most common cause. Industrial accidents have decreased as safety regulations have become more stringent, but like gunshot and missile injuries they can cause complex fractures with gross comminution and soft tissue loss.

Many patients with facial trauma following RTAs and assaults have ingested alcohol and/or social drugs. Young men account for 75% of facial trauma patients.

Types of injury
Figure 1 shows the relative strength of the bones of the skull and face. Facial fractures follow the lines of weakness of the facial bones. Guerin in 1866 and Le Fort in 1901 described these in their classic papers. Facial fractures are still known by the Le Fort classification (Figure 2). A patient may have multiple levels of fracture.

Strength of the skull and face bones



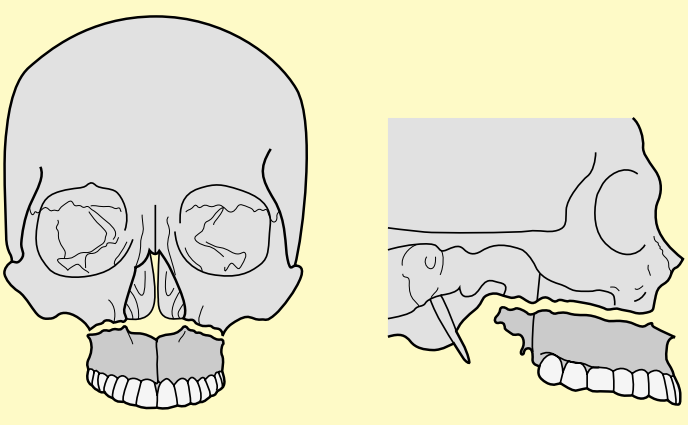
The 'matchbox' structure of the mid-facial skeleton provides a 'crumple zone' which cushions the effect of impact force B on the brain. Impact force A is transmitted directly to the brain producing the most severe injury. Impact force C is transmitted indirectly to the cranial base via the rigid structure of the mandible (represented here as a bent baseball bat)

Source: Banks P, Brown A. *Fractures of the Facial Skeleton*. Oxford: Butterworth-Heinemann.

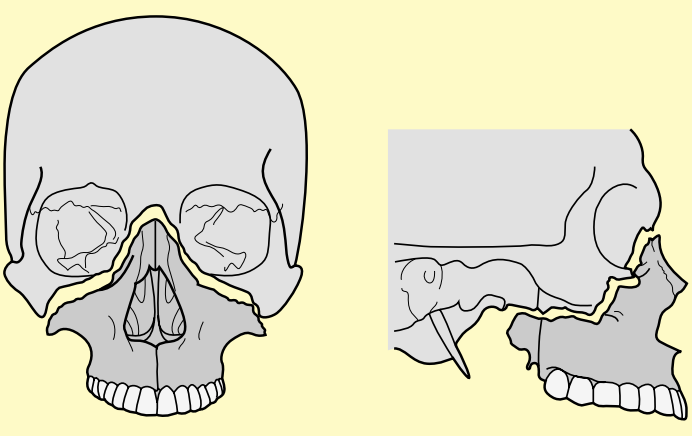
1

Le Fort fracture lines

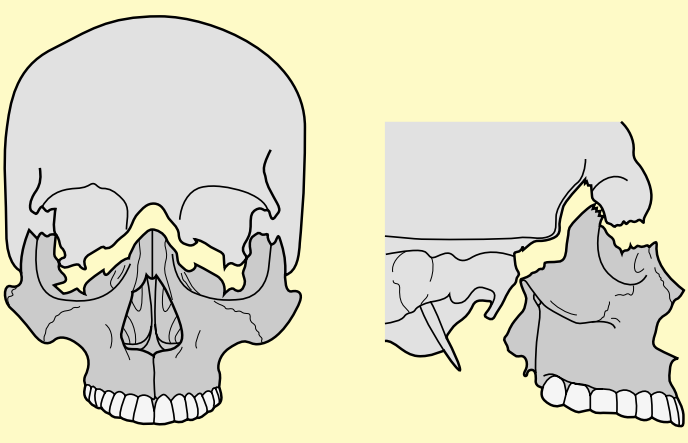
a Le Fort I fracture



b Le Fort II fracture



c Le Fort III fracture



a The Le Fort I fracture line passes through the inferior wall of the antrum and allows the tooth-bearing segments of the upper jaw to move in relation to the nose. **b** In a Le Fort II fracture the maxilla and nose can move as a block in relation to the frontal bone and zygoma. **c** In a Le Fort III fracture the facial bones are able to move separately from the base of the skull. Le Fort II and III fractures may be associated with a dural tear resulting from fracture of the cribriform plate of the ethmoid bones

2

Initial management

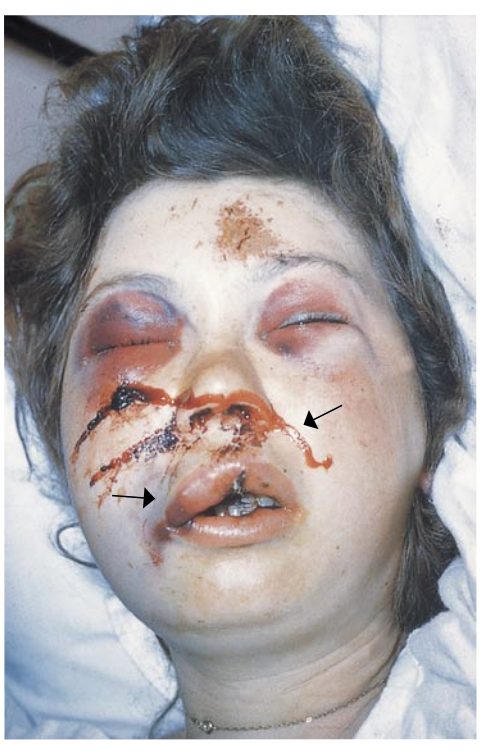
Other injuries
About 15% of severely traumatized patients also have maxillofacial injuries. 5–10% of patients with blunt trauma to the head and face have an associated cervical spine injury; cervical spine immobilization is essential until this is excluded. A survey of patients with Le Fort fractures in the late 1980s found that 26.5% presented with either airway obstruction or decreased respiration requiring immediate airway and ventilatory control. The head injury that often accompanies facial injury affects the need for airway control.

Early management
The immediate and early management of all trauma patients must follow the ABC of resuscitation. Of the facial injuries, the eye should be treated first, then the soft tissues (within the first 12 hours) and finally reconstruction of the facial skeleton (this can wait for a semi-elective theatre slot).

Airway problems
Minor airway problems become major ones in the presence of decreased consciousness, examples are:
- blood, which can be considerable
- vomit, teeth, dentures, bony fragments
- the anterior insertion of the tongue can be disrupted in bilateral mandibular fractures allowing the tongue to fall back.

All of these can be compensated for in the awake patient but can cause rapid loss of the airway once consciousness is lost or diminished. Conscious patients tend to place themselves in the best position for their airway.

Problems with the airway that need immediate control occur with extensive disruption as a result of missile or industrial injuries; they are uncommon following RTAs or assaults. Infrequently, a bleed from a mandibular fracture into the floor of the mouth and base of the tongue can obstruct the oropharynx. Haemorrhage may be closed within the maxilla causing significant swelling over a few hours (resulting in typically tense shiny cheeks; Figure 3), or open, in which case there can be a large blood loss from the pterygonal venous plexus or maxillary artery.



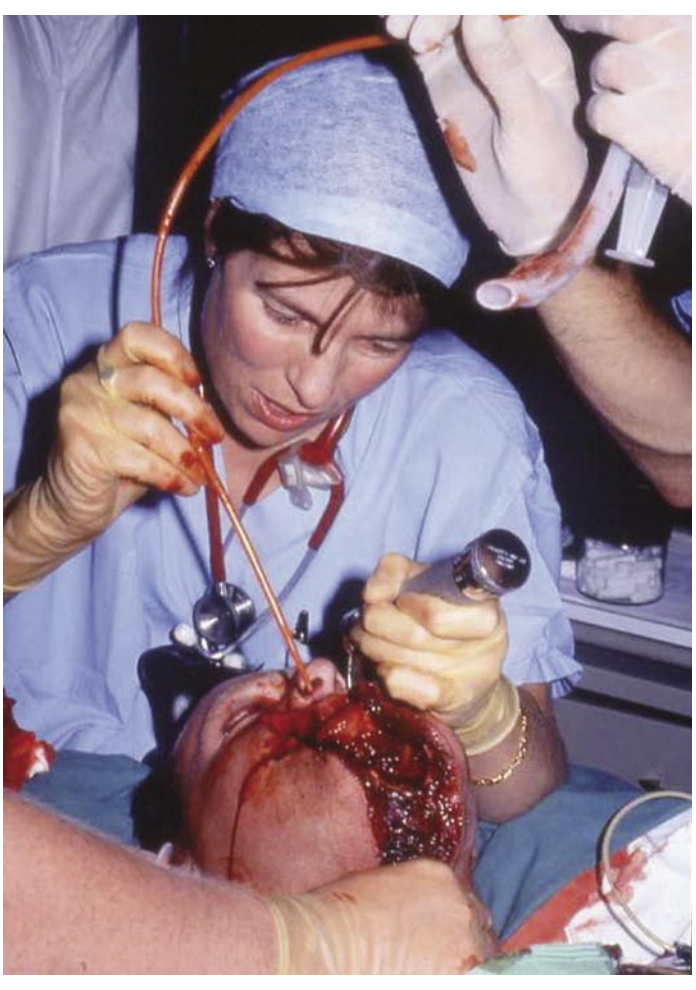
3 The classic 'moon-face' appearance of a patient with multiple fractures of the mid-facial skeleton. 'Tramlines' can be seen caused by CSF leak (arrows).

Airway control
In the emergency situation, a straightforward route to securing the airway is required. This should be via an oral tracheal tube or a surgical airway (tracheostomy or cricothyroidotomy under local anaesthesia). Retrograde passage of a guide (e.g. an epidural catheter) via the cricothyroid membrane in severe disruption is potentially useful. The main problems are:
- blood and debris preventing a good view (ensure effective suctioning with a wide bore, blunt ended sucker; induction in the lateral or prone position will allow blood to drain)
- distorted anatomy
- cervical spine immobilization (removing the hard collar and using manual in-line stabilization allows better oral access; a gum-elastic bougie is useful and must be to hand)
- full stomach needing cricoid pressure (if this makes the view impossible, release it)
- associated head injury may make the patient uncooperative (protect the brain from further damage by avoiding hypoxia, hypotension and hypercapnia).

Good assistance is crucial and fibre-optics not very useful. The classic rapid sequence induction is the best choice, but if lying on their back being pre-oxygenated for 3 minutes will cause the patient to drown in their own blood then think again (Figure 4). Local anaesthesia works poorly on surfaces covered with blood or clot therefore awake intubation is difficult. A surgical airway under local anaesthesia might be possible, if the patient is cooperative and able to lie on his back. Cricothyroidotomy is quicker and requires less expertise than a formal tracheostomy. Each case should be considered on its merits, bearing in mind one's own expertise. Always have a backup plan should the first plan fail.

Haemorrhage control
Bleeding from the soft tissues of the face can be packed and explored later. A maxillofacial surgeon is the best person to carry this out and to suture facial lacerations under local anaesthesia. A steady flow of blood from the nose and mouth with profound cheek swelling is probably the result of a closed injury to the middle third. Bleeding from a base of skull fracture should be excluded by palpating the pharyngeal wall for tears and fractures. The anterior and posterior nasal spaces can then be packed (Figure 5).

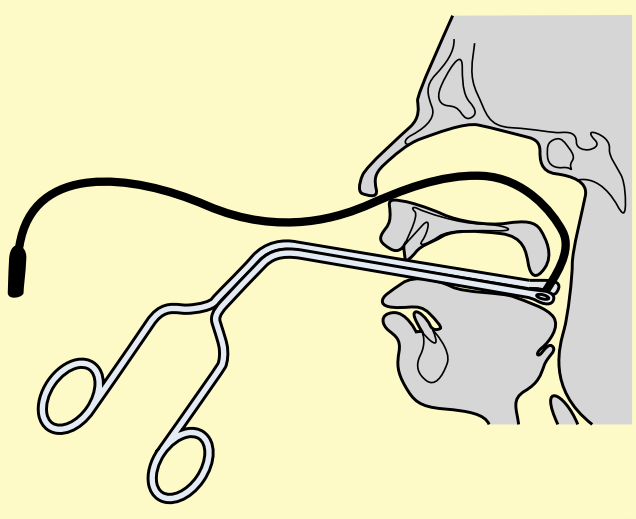
Occasionally a tear of the terminal branches of the maxillary artery can result in life-threatening haemorrhage. This requires a good nasal pack. Careful application is essential because this is not well tolerated by an awake patient and when incorrectly placed can cause partial obstruction of the airway.



4 Intubation with a bougie.

Method of inserting a postnasal pack

a



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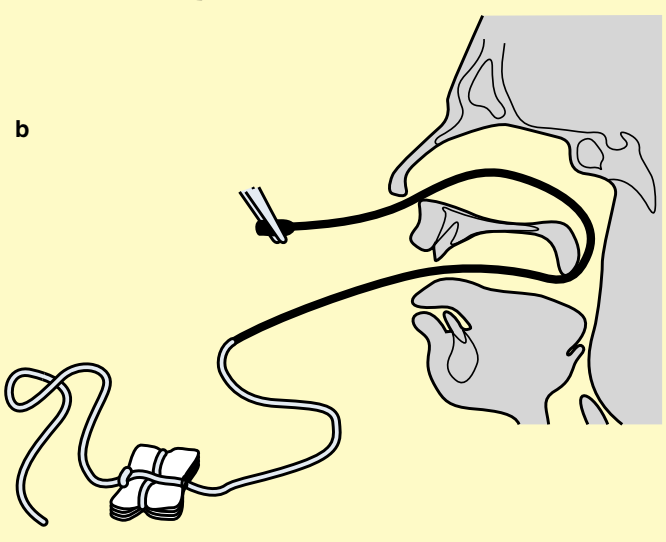

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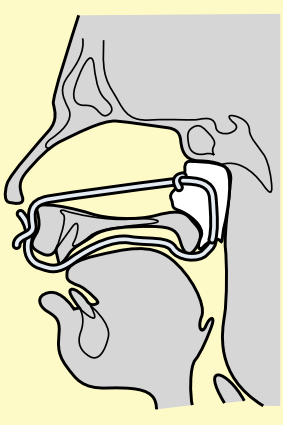

Source: Banks P, Brown A. *Fractures of the Facial Skeleton.* Oxford: Butterworth-Heinemann.

5

A fracture of the body of the mandible occasionally causes complete rupture of the inferior alveolar artery. Normally, the artery goes into spasm, but if it fails to do so, copious haemorrhage can occur. This is an emergency, which requires immediate reduction of the fracture followed by the bone segments being held in rough alignment by wires around the adjacent teeth. A laceration to the tongue can cause profuse haemorrhage that is hard to control. Bleeding from the ear can be caused by a fracture of the base of the skull or a fracture of the condylar head, which has been forced backwards and torn the external auditory meatus.

After securing the airway, follow the BCDE priorities of basic life support (Figure 6). Ensure good ventilation, check the chest and obtain a radiograph of the chest and the cervical spine and pelvis if appropriate. It is rare to get circulatory shock from maxillofacial injuries, therefore if it is present look elsewhere for the loss. Monitor the neurological deficit, initially by using the AVPU scale (Figure 7) together with pupillary reactions. Then the Glasgow Coma Score (see *Anaesthesia and Intensive Care Medicine* **3:4:** 132) should be measured at frequent intervals.

Priorities for basic life support

- A Airway with spine control
- B Breathing and ventilation
- C Circulation and control of haemorrhage
- D Assessment of disability and neurological deficit
- E Exposure and environmental control

6

Monitoring neurological deficit using AVPU scale

- A responds appropriately and is aware
- V responds to verbal stimuli
- P responds to painful stimuli
- U does not respond – unconscious

7

Soft tissue injuries
Soft tissue swelling can occur rapidly or insidiously. It is at its maximum 10–12 hours after injury. Therefore, patients who have suffered more than a single isolated fracture should be kept under close observation for this time.

Lacerations to the soft tissue should be thoroughly cleaned and sutured under local anaesthesia within 24 hours. Fractures to the facial skeleton can be treated later if the patient's underlying condition is poor or an experienced surgeon is unavailable. This may involve reopening wounds, but most facial fractures are reduced and plated via the oral mucosa; only upper facial injuries require skin incisions.

Pain control
In general, even extensive trauma to the face does not cause a large amount of pain. One exception is a mobile fracture of the body of the mandible, which can give a lot of discomfort and be a cause of restlessness. Minor analgesics such as paracetamol and a non-steroidal anti-inflammatory drug (NSAID) usually suffice. In general, avoid excessive sedation in case there is occult head injury.

Preventing infection
There is widespread use of prophylactic broad-spectrum antibiotics; usually amoxicillin (amoxycillin) with metronidazole or augmentin. Although they do not penetrate the CSF well, neurosurgical opinion is that if there is a breach in the CSF then antibiotics that are in the oral and pharyngeal tissues will penetrate sufficiently. However, retrospective studies indicate that prophylactic antibiotics do not significantly affect the incidence of meningitis in patients with a CSF leak.

Dural tears
A dural tear is possible with all Le Fort II and III mid-face fractures. Normally the CSF leak stops after a few days. Its detection is possible clinically from the observation of tramlines on the face or the halo effect on bedding; this can be seen in the patient in Figure 3. These are caused by CSF not coagulating and blood that does. Testing glucose and protein levels is of little clinical help. Definitive diagnosis is by high resolution CT or MRI.

There is a small risk (about 1%) of meningitis, at the time of injury and also years later, if the cribriform plate is involved. If the posterior wall of the frontal sinus has been fractured, a late presentation of a mucocele may occur, which requires neurosurgical input. Most cases of CSF rhinorrhoea stop spontaneously and virtually all stop after the fractures have been reduced.

Late management
Delaying definitive treatment for facial fractures allows resolution of head injury, treatment of other more life-threatening conditions, soft tissue swelling to diminish and an experienced surgeon to be present.

Preoperative assessment
Particular areas for preoperative anaesthetic assessment are the mechanism of trauma; any possibility of head, cervical spine or other injury, and any history of drug or alcohol abuse.

Airway assessment
In mandibular fractures, trismus caused by pain is likely to limit mouth opening. This usually disappears on induction. Fragments of bone in the temporomandibular joint can prevent mouth opening even after induction. The mobility of early fractures tends to make laryngoscopy easier than normal. Check for teeth that have been loosened or broken in the impact of the trauma and be aware that missing teeth could have been inhaled.

Intubation
Before commencing induction it is essential to discuss the operative plan with the surgeon. In most patients with mid-facial fractures intraoperative dental occlusion is required and an oral tracheal tube prevents this. For surgery to the zygoma and orbital floor an oral south-facing tracheal tube is probably best. Panfacial fractures involve the structural bones and the smaller bones of the nasal complex, which means that access to the nose as well as occlusion is required.

There is debate regarding the nasal route of tracheal intubation in the presence of a base of skull fracture or the Le Fort II and III fractures. Two cases of intracranial placement of a nasal tracheal tube have been reported in the literature. Only two, retrospective, studies have looked at outcome for this group of patients, but they did not show any increase in the incidence of meningitis when the nasal route was used for intubation.

If surgery cannot be carried out with an oral tube, the three main options are: formal tracheostomy; nasal intubation (using fibre-optic guidance); and submental intubation. Submental intubation involves passing the tracheal tube through the floor of the mouth. Figure 8 lists the advantages and disadvantages of each approach. Unless postoperative ventilation for more than 24–48 hours is likely to be required the author favours using the nasal route.

In complex cases the position of the tracheal tube may need to be changed intraoperatively. The author usually starts with an oral tube and then the surgeon places a nasal tube through to the pharynx after fixation of the small bones in the mid-zone, the author then re-intubates with the nasal tube.

Maintenance
For maintenance of anaesthesia, a total intravenous technique using propofol and a short-acting opiate (alfentanil or remifentanil) has a number of advantages. It allows rapid awakening, with early return of glottic reflexes, immediate assessment of conscious level in the patient with head injuries, and cooperation with eye testing after zygomatic and orbital floor work. It is also less emetogenic than the volatile agents. Deliberate hypotension is of limited benefit in most cases and may harm the patient with a head injury.

The general principles of a head-up tilt, carbon dioxide control and rehydration should be borne in mind. Most of these injuries cause little pain and so large doses of opiates are unnecessary. The surgeon will often use local anaesthetic with adrenaline (epinephrine), which is helpful. A rectal or intravenous NSAID is useful and intravenous or intramuscular tramadol is a good analgesic because it causes less respiratory depression and sedation.

Comparison of tracheostomy, nasal intubation and submental intubation

Advantages	Disadvantages
Tracheostomy	
• Avoids controversial nasal route • Allows dental occlusion intra- and postoperatively • Better for long-term ventilation	• Most invasive of the techniques • Extra procedure • Risks of haemorrhage, tracheal damage – stenosis, tracheomalacia and infection
Nasal intubation	
• Allows dental occlusion intraoperatively • Avoids an extra surgical procedure • Avoids a surgical scar •	• A fibre-optic scope is preferable • Poor for prolonged postoperative ventilation and weaning • The nose must be patent Risks of nasal haemorrhage, sinusitis and unproven possibility of an increase in the infective complication of meningitis
Submental intubation	
• Technically easy • Allows dental occlusion intra- and postoperatively • Low complication rate • Cosmetically acceptable scar	• Many surgeons are unfamiliar with the technique • Not good in prolonged ventilation and weaning • If an armoured tube is used re-intubation may be necessary, because the connector does not detach from the tube

Most patients can be extubated at the end of surgery. This should be awake if the stomach is full or if re-intubation would be difficult. A deep extubation is less likely to lead to laryngospasm and coughing. Airway problems at extubation are as common as at intubation. If a nasal tube has been used, it can be left in the nose and pharynx until the patient is fully awake to maintain a clear airway and splint any nasal haemorrhage until the airway is safe.

Postoperative care

Good recovery facilities are important. Patients must be observed for further soft tissue swelling, eye signs may need checking and the Glasgow Coma Score should be monitored if there was any suggestion of head injury. For moderate and severe facial injuries, high dependency facilities are required for 10–12 hours postoperatively. ◆

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Anaesthesia for Maxillofacial Surgery

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Maxillofacial surgery encompasses a range of hospital-based procedures of the head, neck and mouth that overlap with ENT, plastic, general surgical and neurosurgical operations. In the UK, most maxillofacial surgeons are qualified as dental and medical practitioners. Because of the wide range of maxillofacial procedures, the patients encountered range from the very young to the elderly.

Dental procedures include exodontia and removal or biopsy of orocutaneous lesions. The most common maxillofacial surgical operation is dental extraction. In the UK, most dental extractions are carried out under local anaesthesia in 'high street' dental clinics, only the more complicated cases are referred for hospital care.

Facial injuries or trauma involve skin, soft tissues and/or bony fractures. Most trauma patients can be operated on in a planned manner though some require urgent intervention, for example if the airway is compromised or if scalp lacerations threaten to cause large blood losses.

Corrective (orthognathic) procedures for facial bone deformities are sometimes carried out for aesthetic reasons but more commonly for orthodontic ones. Most patients are young children and adults.

Excision of benign or malignant tumours necessitates long, extensive operations, sometimes involving pedicle or free-flap techniques.

Tracheostomies are often carried out by maxillofacial surgeons.

General procedures such as thyroidectomy, parathyroidectomy and excision of parotid glands occasionally come under the maxillofacial remit.

General considerations

The presence of an experienced anaesthetist is essential because the incidence of a difficult airway and/or intubation is high.

Routine monitoring for general anaesthesia should include inspired oxygen concentration, oxygen saturation, ECG, capnography, agent monitoring, non-invasive blood pressure and temperature. For extensive procedures, invasive monitoring should be considered, such as invasive blood pressure, central venous pressure and urinary catheterization.

Intravenous access is mandatory, even for minor non-invasive procedures.

Generally, nasal intubation is preferred for intra-oral procedures. However, simple extractions can be carried out safely with an orotracheal tube or a laryngeal mask airway (LMA).

The surgical field interferes with the airway therefore LMAs, tracheal tubes and tracheostomy tubes should be well secured and observed for position and patency.

A mouth or throat pack is often placed to prevent blood and debris falling down the trachea and oesophagus; however, great care must be taken to document this and fail-safe mechanisms should be developed to ensure their removal before extubation. Orogastric or nasogastric tubes are required for extensive operations.

Head and neck operations often require a head-up tilt position and normotension; occasionally, the surgeon requires controlled induced hypotension. Discussion with the surgeon regarding the extent of the procedure and airway maintenance is necessary before starting any anaesthetic.

Postoperative admission to a high dependency unit or ICU should be considered for patients undergoing extensive prolonged operations.

Concomitant head injury, cervical spine instability and a full stomach should be considered to be present in trauma patients until proved otherwise.

Inhalational or intravenous induction of anaesthesia is suitable for most patients. Inhalational induction is preferred for children and also whenever a difficult airway and/or intubation are anticipated. Some patients require awake fibre-optic intubation. Inhalational agents or intravenous propofol are suitable for maintenance of anaesthesia. Remifentanil, either with propofol or with an inhalational agent, is sometimes an extremely favourable option. Spontaneous ventilation may be a suitable technique, but controlled ventilation with or without muscle relaxation is preferred for longer procedures. Dexamethasone is commonly administered to reduce surgical oedema. Paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs; e.g. diclofenac, ibuprofen) and opioids (e.g. fentanyl, alfentanil, remifentanil, morphine, codeine) may be used for intraoperative analgesia. Local anaesthetic infiltration may also be used for procedures carried out under general anaesthesia as an adjunct to other analgesics.

Extubation may be carried out in the lateral position under deep anaesthesia, or when the patient is awake (especially after difficult intubation). Consideration should be given to extubating 'difficult' airways over a tube exchange catheter with the facility to insufflate oxygen if necessary. Recovery in the post-tonsillectomy position is preferred.

Postoperatively, patients are generally nursed with some head-up tilt once they have regained consciousness, which helps to control bleeding, reduce swelling and minimize venous engorgement in free flaps.

Postoperative analgesia is best provided as a combination of residual local anaesthesia, together with simple analgesics and the addition of opioids when necessary, either by patient-controlled or nurse-controlled analgesia. Care should be given to patients who have had a free-flap procedure to treat opioid-induced constipation, which can lead to venous engorgement and possible flap failure.

Anaesthesia for dental procedures

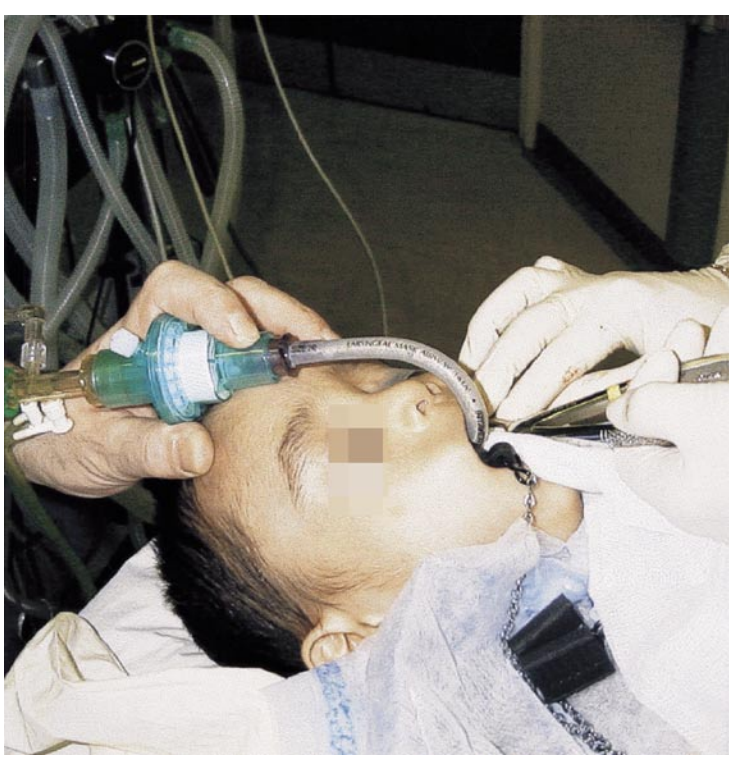
In the UK, general dental practitioners working in dental clinics are not permitted to perform dental procedures under general anaesthesia or sedation in children. Therefore, all children requiring such treatment must be treated in hospital. Since 1 January 2002, general anaesthesia for adults requiring dental extraction can be performed only in hospital. Before a patient is offered a general anaesthetic for dental extraction a thorough and clear explanation of the risks involved and the alternative methods of pain control available must be given to them (see page 239). However, certain groups of patient require general anaesthesia:

- children, commonly those less than 10 years of age, who will not tolerate the dental chair and local injections
- patients with special needs
- adults who cannot tolerate local anaesthesia (e.g. needle-phobia, multiple impacted wisdom teeth, failed local anaesthesia, previous allergy to local anaesthesia).

Dental extraction in children

Extraction of decidual teeth is usually easy and quick and can be performed as an outpatient procedure. The child should be prepared and fasted as for any general anaesthetic. The anaesthetic technique should allow rapid recovery and discharge from hospital. Premedicant analgesia (e.g. oral paracetamol) before induction is helpful. Local anaesthetic cream (*Emla* or *Ametop*) can be applied for older children who may agree to intravenous cannulation and induction. Occasionally, sedation with oral midazolam may be used as premedication. However, most children choose inhalational induction. Each child needs to be assessed as to which monitors will be tolerated before induction; most will accept a pulse oximeter. Sevoflurane is particularly suitable for both induction and maintenance of anaesthesia. Once anaesthesia is deep enough, intravenous access is secured and the remaining monitors attached. For intravenous induction, propofol is useful for its rapid recovery and anti-emetic properties, though pain associated with the injection is possibly more evident with children.

Airway management depends on the extent of the procedure. A nasal mask for extraction of incisor teeth alone or easily accessible molars, can be used with or without a nasal airway. Usually the surgeon uses a mouth pack, and a mouth 'prop' on the opposite side of the mouth to the proposed extractions. Jaw thrust may be needed to maintain airway patency but a fastidious surgeon ensures that the lower jaw is always supported. The reinforced LMA (RLMA) is preferred for multiple extractions or if surgical difficulty is anticipated. The RLMA can easily be moved from one side of the mouth to the other as the operator moves and usually provides an unobstructed airway. Additionally, the inflated cuff probably prevents airway and stomach soiling by blood better than a tracheal tube (Figure 1). Some anaesthetists prefer tracheal intubation.



1 This child is having multiple extractions under general anaesthesia.
Note the reinforced laryngeal mask airway (RLMA) and gauze pack. The anaesthetist's hand can steady the head and the surgeon holds up the lower jaw. The LMA is removed while inflated and the child still deeply anaesthetized.

Intraoperatively, NSAIDs or paracetamol administered as a suppository provide some postoperative analgesia. Additionally, local anaesthetics can be infiltrated, especially if large back molars are being extracted. It is rare to require opioids, but rectal codeine phosphate may be the most suitable.

When the procedure is finished, the child is placed on his side. The LMA is removed with the cuff inflated, or extubation is performed, preferably under deep anaesthesia. Recovery is initially best in the post-tonsillectomy position, but once the child is awake he or she should be sat up. Further postoperative analgesia (e.g. paracetamol and/or ibuprofen) may be prescribed to take home.

Children who are unsuitable to be treated as outpatients for medical reasons, should be assessed for treatment as a day case or in-patient.

Dental extraction in adults

Dental extraction in adults is usually performed as a day case procedure either under general anaesthesia or sedation. Patient preparation and monitoring for sedation, is the same as for general anaesthesia. Midazolam in small incremental doses is most commonly used together with local anaesthetic infiltration, though propofol in subanaesthetic doses is an alternative in experienced hands. Supplemental oxygen via nasal cannulas is given, and jaw support may be needed to maintain the airway. An alternative is inhalational sedation using up to 70% nitrous oxide in oxygen or sevoflurane in oxygen followed by local anaesthetic infiltration. Many patients are willing to try sedation rather than general anaesthesia once the technique has been explained carefully.

Some adults may request or require general anaesthesia. Intra-venous induction is most commonly performed although many of these patients are needle phobic. The airway can be maintained on LMA or by tracheal intubation, the choice depends on the anticipated ease of extraction and whether or not the surgeon is familiar with working around an LMA. If nasal intubation is to be performed, nasal bleeding can be reduced by using a nasal vasoconstrictor preparation (*Otrivine*) or by warming the tracheal tube. Local anaesthetic infiltration intraoperatively by the dentist is recommended. Intravenous NSAIDs (e.g. diclofenac) with suitable opioids are also used for analgesia. Dexamethasone is optional, but may have an anti-emetic effect. The LMA or tracheal tube is removed with the patient in the lateral position under deep anaesthesia or awake if preferred, bearing in mind that blood pressure surges associated with awake extubation with a nasal tracheal tube in place can lead to bleeding. NSAIDs, paracetamol or occasionally opioids are given for postoperative analgesia. Tramadol may be useful if the extractions are difficult and painful and the patient wishes to go home.

Anaesthesia for orthognathic surgery

Patients requiring orthognathic surgery are either children with congenital or familial facial bone and soft tissue deformities, or adults who have sustained previous facial trauma or infection, or have unresolved childhood deformities.

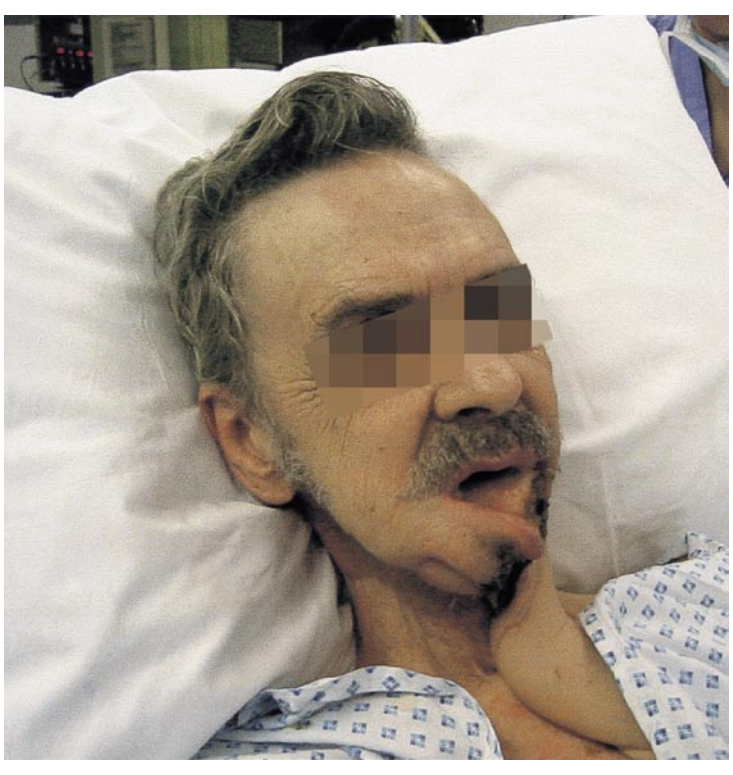
Cleft lip and palate
Cleft lip and palate are the most common congenital maxillo-facial deformities. They can occur in isolation or as part of a syndrome (e.g. Pierre Robin syndrome, Treacher Collins syndrome, Stickler syndrome). Other bony deformities such as maxillary dysostosis can also be isolated, or part of a syndrome (e.g. Goldenhar's syndrome). Cleft lip is usually corrected in infancy. A specialized paediatric anaesthetist should be involved and difficult intubation should be anticipated. Inhalational induction, oral tracheal intubation with spontaneous or controlled ventilation, is a standard technique. Paracetamol, NSAIDs and local anaesthesia are used intraoperatively for analgesia. Opioids may be added if required. Extubation is best achieved after full awakening and paracetamol supplied for postoperative analgesia, with codeine if necessary.

In adults, bone deformities are usually corrected in specialized centres with surgery often involving osteotomies based on the Le Fort classification. Invasive monitoring and intravenous fluid and blood transfusion may be required. Inhalational or intravenous induction, followed by nasal tracheal intubation and inhalational maintenance is common practice. Fibre-optic intubation may be needed, particularly if fixed trismus follows disturbance of the mandibular condyles after childhood infection or trauma. Analgesia is achieved intraoperatively with opioids, local anaesthesia and NSAIDs. A nasogastric tube is useful to empty the stomach of blood, and can be removed at the end of the case. Bi-maxillary osteotomies may be extensive and lead to considerable blood loss. Extubation can be awake or ‘deep’ depending on the surgical procedure and the pre-existing deformity. Postoperatively, patient- controlled analgesia may be needed in conjunction with simple analgesics.

Anaesthesia for maxillofacial tumours

Benign or malignant tumours, cysts and abscesses can develop in most oral and facial zones. Tumours and cysts are usually scheduled for elective operations, but abscesses and biopsies may require more urgent intervention. Patients requiring biopsies can usually be fasted adequately before induction of anaesthesia. A difficult airway should be anticipated and a plan for intubation prepared.

Patients with oral cancers can be elderly, with a high incidence of excessive alcohol or cigarette consumption. Operations for such malignant tumours may be extensive, requiring prosthetic implants, bone grafts (from the iliac crest, ribs, radius or scapula) or flaps (local or free transfer) and can be prolonged (some procedures last more than 12 hours; Figure 2). Before induction of anaesthesia, the airway should be assessed to plan for possible intubation difficulties, paying particular attention to the position of the tumour in relation to the airway. Other investigation results such as nasendoscopy (performed by the surgeons) or CT scans should be sought if appropriate.



2 This patient has had several intra-oral tumour resections and a scapular flap forms the base of the mouth. A pedicle flap is also present. Intubation was achieved on three separate occasions using an awake fibre-optic technique.

The mode of induction of anaesthesia depends on the degree of anticipated difficulty. Intravenous or inhalational induction, asleep or awake fibre-optic intubation are all suitable. Usually a nasal tracheal tube is required. If tracheal intubation is deemed impossible, then tracheostomy should be performed in the awake patient with local anaesthetic infiltration, or in the asleep patient by inhalational anaesthesia with a facemask or LMA. A nasogastric tube is required for postoperative feeding following extensive resections. Ventilation for long operations has to be controlled and muscle relaxants may be used as needed unless contraindicated (e.g. dissection for motor nerves with the use of nerve stimulator). For maintenance of anaesthesia, inhalational or intravenous agents are suitable. Opioid analgesia is required in most patients.
A tracheostomy may be performed at the beginning or at the end of the operation particularly if resections have been extensive and swallowing dysfunction is anticipated postoperatively. Invasive monitoring is required. The surgeon may request controlled hypotension, dexamethasone, antibiotics and anticoagulation. Postoperative sedation and possibly ventilation in the ICU should be planned for extensive long procedures or if free-flap vasculature is dependent on patient position, when a ‘still’ head is advantageous. In cases where a tracheostomy is not performed and the patient is not going to ICU postoperatively, extubation should be performed as appropriate with provision for dealing with any subsequent difficulties should they arise. Postoperative analgesia is usually achieved with NSAIDs and opioids.

Patients with oral tumours may require repeated anaesthetics, testing the anaesthetist’s skill with airway management. Even the technique of awake fibre-optic intubation may progressively prove to be difficult in these patients. ◆

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Blind Nasal Intubation

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Magill and Rowbotham pioneered blind nasal intubation in the 1920s as an alternative to oral intubation at the Queen's Hospital, Sidcup, to facilitate surgical access for head and neck surgery performed by Gilles. With practice many anaesthetists became proficient at the technique, which involved careful positioning of the head to facilitate the passage of a tube through the nose and into the trachea without the need for laryngoscopy, forceps to guide the tip of the tracheal tube, or deep anaesthesia. The introduction of muscle relaxants in the 1940s, allowing oral intubation without deep planes of anaesthesia, led to the blind nasal approach to intubation waning in popularity. Recently, agents such as sevoflurane and propofol that allow laryngeal depression and intubation with rapid recovery and equipment such as the intubating fibre-optic laryngoscope, have resulted in the blind nasal intubation technique becoming rarely used in current practice.

However, with concerns about prion transfer from lymphoid tissue leading to the introduction of disposable equipment for tonsillectomy, there may now be a case for re-evaluating blind nasal intubation. It is an easily learnt and safe technique, which provides a secure airway using disposable equipment and without the need for inserting a re-usable laryngoscope blade or forceps next to the tonsillar lymphoid tissue in the oropharynx. Indications and complications of the technique are given in Figure 1.

Blind nasal intubation

Indications when its use can be considered
- Poor mouth opening (e.g. trismus)
- Surgery on the jaw, teeth or maxilla
- Trauma to the jaw, teeth or maxilla
- Swelling of the tongue, or soft tissues of the oral cavity
- Lack of equipment (e.g. laryngoscope, in an emergency)

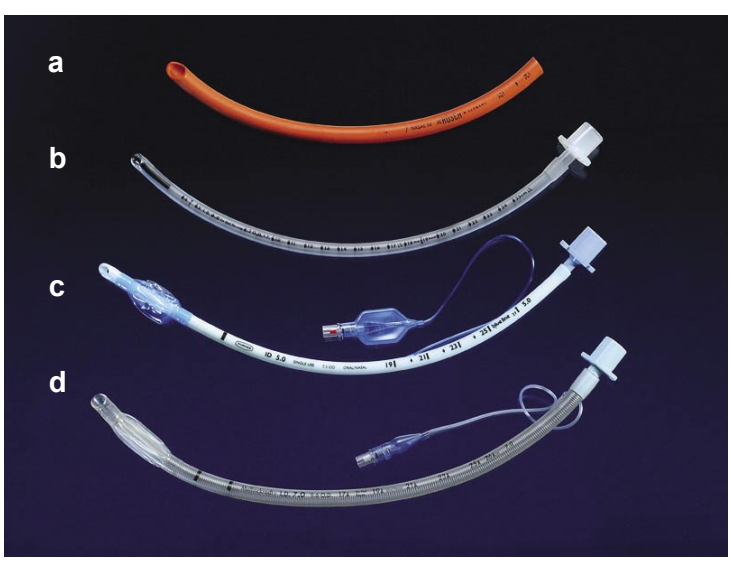
Complications
- Trauma to the structures in the nasopharynx
- Trauma to the larynx and vocal cords
- Perforation of the pharynx or trachea
- Misplacement of the tracheal tube
- Oesophageal ventilation causing air to fill the stomach
- Anaesthesia (local or general) may obstruct an already compromised airway
- Haemorrhage, causing airway obstruction
- Coughing

Contraindications
- Inadequate depth of anaesthesia
- Bilateral blocked nostrils
- Partial airway obstruction from tumour, abscess or trauma
- Recent surgery to the airway
- Coagulopathy
- Fractured base of skull
- Unprepared patient (e.g. full stomach)

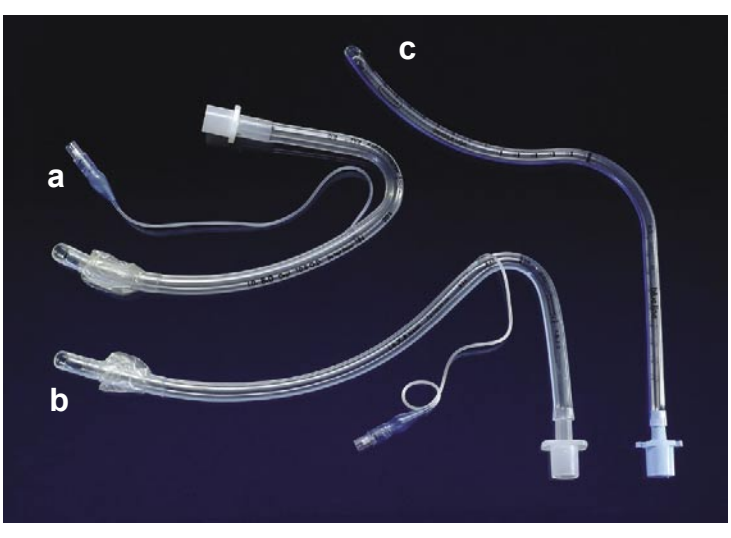
1

Equipment
The first nasotracheal tubes used by Magill were cut from red rubber hose purchased from a hardware store, trimmed to size and smoothed with emery paper. Advances in plastic and latex technology now allow the manufacture of preformed, soft, shaped tubes with cuffs to ensure an airtight seal (Figure 2). Universal connectors allow attachment to standard anaesthetic circuits.

To be suitable for blind nasal intubation, the nasotracheal tube must be soft enough not to cause trauma to the nasopharynx, but stiff enough to be pushed past the turbinates and through the vocal cords without becoming deformed. It requires a curve to allow it to sit directed dorsally as it passes through the nostril, but caudally as it enters the trachea through the larynx and this can be achieved with both preformed (Figure 3) and flexible tracheal tubes (Figure 2). Attachment to a standard anaesthetic circuit can be achieved at the nostril, but this may lead to local pressure damage because of the weight of the connectors or kinking of the tracheal tube. An alternative method is to use a preformed 'north-facing' tracheal tube of suitable length with the connector situated over the forehead (Figure 3). The connector can then be padded to prevent pressure damage to the underlying tissue.



2 Four nasotracheal tubes: **a** uncuffed red rubber tube; **b** uncuffed plastic tube; **c** blue line (Portex, Hythe, UK) ivory tube; **d** Mallinckrodt (St Louis, Missouri) flexo-metallic tube.



3 Three RAE® Mallinckrodt (St Louis, Missouri) preformed plastic tracheal tubes. **a** south-facing cuffed oral; **b** north-facing cuffed nasal; **c** north-facing uncuffed oral. Note the different angles of the north-facing oral and nasal tubes.

The diameter of the tracheal tube is important. A balance has to be achieved between a tracheal tube that is large enough to allow air to enter and leave the lungs and one that is small enough not to damage the tissues of the nasopharynx and larynx. A suitable compromise is to use one with a diameter of 6.0–7.5 mm.

Anaesthesia
Blind nasal intubation can be performed under general or local anaesthesia and in a patient who is either breathing spontaneously or who has received a muscle relaxant.

The use of antisialogogue premedication and topical vasoconstrictor nasal drops may enhance the conditions for intubation.

Local anaesthesia can be achieved using nebulized lidocaine (lignocaine), but much of the drug may be lost. Alternatively the airway can be anaesthetized using topical applications of local anaesthetic in the nose (cocaine or lidocaine (lignocaine) applied with pledgets, sprays or gels); the oropharynx and glottis (lidocaine (lignocaine) spray, gargle or through bilateral superior laryngeal nerve blocks); and the trachea (lidocaine (lignocaine) sprayed through a needle following cricothyroid puncture).

Spontaneous ventilation techniques allow breath sounds to be heard through the tracheal tube as it is guided through the airway. They also confer the advantages of a widely opened larynx during inhalation, increasing the aperture through which the tracheal tube needs to pass to enter the trachea, and allowing confirmation of correct placement of the tracheal tube in the trachea.

Position
Magill described the following position for blind nasal intubation; 'the optimum position of the patient's head for blind nasal intubation is simply that of a man sniffing the morning air. The head is in normal relation to the cervical vertebrae except for slight extension at the occiput-atlas junction. In this position the course of the airway from nose to glottis is maximally open and a catheter mounted on a stylet or a suitably curved rubber tube will follow that course naturally and enter the glottis in many cases. Of course, in the recumbent position a pillow under the occiput is usually necessary for this purpose.'

Individual anaesthetists may develop their own variations on this position through trial and error, but the 'sniffing the morning air' description remains firmly entrenched in anaesthetic teaching.

Technique
The patient is prepared for theatre, monitoring is attached and a suitable anaesthetic technique performed. The patient is then positioned, either supine or sitting, in the 'sniffing the morning air' position with the anaesthetist either above the patient's head or to the side. A suitable, lubricated tracheal tube is advanced through a nostril initially in a dorsal direction and advanced gently past the turbinates. The tracheal tube is then rotated so its curve lies in the sagittal plane with the distal end directed caudally before being advanced with gentle pressure through the pharynx. From here it will often pass into the trachea, but the tip of the tracheal tube may also advance into the oesophagus, or press against tissues anterior to the larynx, in the valecula or in the pyriform fossa. These can often be seen as bulges in the soft tissue of the neck. If the trachea is not entered, then the tracheal tube should be withdrawn into the pharynx, the patient's head repositioned appropriately and the tube re-advanced. Various modifications of the technique have been described, which may increase the chances of success, including inflation of the tracheal tube cuff when it is in the pharynx to position the tip of the tube in the midline, and palpation of the larynx while lifting the chin during tracheal tube advancement.

A disadvantage of the blind nasal technique is that direct visualization of the tube passing through the vocal cords is not performed. Confirmation of tracheal tube position is required using other methods, such as auscultation of the chest and abdomen, capnography and the oesophageal detector device, before surgery continues. ◆

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Difficult Airways

Ian Calder

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Classification of difficult airways can be based on technique (Figure 1) or aetiology, though neither is entirely satisfactory. The aetiological approach (Figure 2) is helpful for the examination candidate trying to remember the causes of airway difficulty.

Technical classification and prevalence of difficulty

Face mask	1:500
Laryngeal mask	Rare
Direct laryngoscopy	1:100
Fibre-optic laryngoscopy	Operator dependent
Intubation	1:2000 (failure, general surgery), 1:300 (failure, obstetrics)
Tracheostomy	?

1

Aetiological classification

Reflexes
Includes coughing, breath holding, laryngospasm, salivation and regurgitation

Stiffness
Includes the arthritides affecting neck, jaws and glottis, fixation devices, scleroderma

Deformity
Often allied with stiffness. Includes cervical deformities (Klippel-Feil), radiotherapy and burn contractures, dwarfism, Pierre Robin, Treacher Collins, and major facial deformity caused by trauma or chronic infections

Swelling
Includes infections, tumours, trauma, acute burns, anaphylaxis, haematoma and acromegaly

'High tariff' patients
Patients in whom additional problems may contribute to a decline in the operator's performance because of constraints in technique (e.g. patient with full stomach) or added stress (VIPs, obstetric patients, children, uncooperative patients)

2

Attempts at standardization have been made, such as that of direct laryngoscopy by Cormack and Lehane (Grades 1–4: all glottis; only arytenoids; only epiglottis; no glottic structure). Mask ventilation and intubation are more difficult to grade. Benumof has suggested that the term 'difficult mask ventilation' should apply when two operators are needed (one holding the mask, the other squeezing the bag) and oral or nasal airways are required. The American Society of Anesthesiologists (ASA) defines difficult intubation as one taking more than three attempts or longer than 10 minutes. However, Benumof notes that this misses cases in which difficulty is immediately obvious and suggests that difficulty be recorded after failure of 'an optimal best attempt'

Prediction
Difficult airways are generally symptomless and routine airway examination does not identify them. A logical approach is to try to identify patients unable to extend at the cranio-cervical junction and/or with diminished jaw protrusion, which are the main factors involved in both standard airway control and direct laryngoscopy.

Failure to predict airway difficulty seldom causes an airway disaster. The ASA's analysis of closed legal claims (Figure 3) shows that disasters usually follow repeated attempts to intubate, which result in loss of the airway due to glottic swelling, laryngospasm, or both, or perforation leading to mediastinitis or cervical abscess. These complications should be avoidable, whether difficulty has been predicted or not.

Main causes of anaesthetic airway mortality

- Oesophageal intubation
- Repeated attempts at intubation – loss of airway
- Perforation of pharynx or trachea – infection

3

Expression of risk
Various methods of predicting airway difficulty have been studied. The results express the performance of the tests in terms of sensitivity, specificity and positive predictive value. These concepts are easily misunderstood and confused (Figure 4). The likelihood ratio makes it easier to understand the significance of the sensitivity and specificity data as applied to an individual patient. The likelihood ratio is calculated by dividing the sensitivity by 1 – specificity. The result is the number of times more likely it is that a patient with a positive test result will be in the difficult group. The likelihood ratio is interpreted against the prevalence of the problem.

Terms used in prediction

Sensitivity
Positivity in disease. Makes no comment on positivity in health. High sensitivity tends to be associated with low likelihood of true result (e.g. Is the patient human? – supremely sensitive – and useless)

Specificity
Negativity in health. High specificity means few false-positive results but tends to lead to true-positive results being missed (e.g. Are the teeth wired together? – many other causes of difficulty)

Positive predictive value
The proportion of times a positive test is right; often confused with sensitivity

Likelihood ratio
Sensitivity/1 – specificity
The number of times more likely a positive test result makes a diagnosis

4

The best-known, and most studied test, the three grades (not four) of pharyngeal visibility described by Mallampati (see *Anaesthesia and Intensive Care Medicine* **1:1:** 31) has a sensitivity of about 50% and a positive predictive value of about 10% when applied to standard surgical populations. In other words, the test misses half the true positives and the prediction is wrong nine times in ten. This is not to belittle the test, which remains a logical approach to the problem, but demonstrates the difficulty of accurately diagnosing a relatively rare condition, with many causes. Other tests such as the sternomental or sternothyroid distance are even worse, and have been memorably described by Farmery as having 'an accuracy approaching worthlessness'. The positive predictive value is increased if two or more tests are positive, but it should be kept in mind that a few more true positives will be missed (decreased sensitivity) if the threshold for a positive prediction is raised.

Available tests
Most tests have been studied in relation to difficult laryngoscopy (Figure 5). A recent study of difficult mask ventilation identified five independent risk factors: age over 55 years; no teeth; beard; BMI over 26; history of snoring. Unfortunately, the likelihood ratio of difficult mask ventilation if two factors are present is only 2.6.

Airway difficulty prediction tests

Interdental distance
Lower limit of normal said to be 3.6 cm

Mallampati
Three grades, worst for observer error, probably measures mouth opening and cranio-cervical extension. No evidence that large base of tongue is a factor, though often quoted. In a general surgical population the likelihood ratio of the Mallampati is about 2, which for difficult laryngoscopy with a prevalence of about 1%, means that a positive result does not increase the risk of difficulty much

Thyromental, thyrosternal distance
Said to have 'accuracy approaching worthlessness'. Likelihood ratio about 1.8

Jaw protrusion – A, B, C
B has poor positive predictive value, while C is a reliable but rare predictor

Wilson risk sum
Scoring system based on multiple tests. No real improvement on Mallampati alone

5

Effect of increased prevalence of difficulty: the accuracy of the tests has been shown to increase when they are applied to a population with an increased prevalence. For instance, when applied to patients with cervical spine disease where the prevalence of Grade 3 laryngoscopy was 20%, the Mallampati achieved a positive predictive value of 78% and a likelihood ratio of 14. The tests are fairly reliable predictors of easiness, because the prevalence is very high.

When to attempt prediction of difficulty: in the event of a disaster, there may be criticism of aspects of the case that have little relevance to the outcome. Although the available tests are inaccurate in predicting difficulty in a general surgical population it is prudent to make the attempt. In populations with higher prevalence of difficulty, such as cervical disease, temporomandibular joint disease or acromegaly, where a positive prediction is more likely to be accurate, it is foolish not to record an attempt.

Communication
Patients found to have a difficult airway, should be told. Medic-Alert registration should be considered. Failure to communicate might be regarded later as legally actionable.

Airway plans
It is sensible to consider the consequences of failure to secure an airway. The causes of airway-related mortality mentioned above should be kept in mind. General Von Moltke's dictum 'Few plans withstand contact with the enemy' emphasizes the need for forethought and flexibility. ◆

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General Anaesthesia for Dentistry

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Although general anaesthesia is used to reduce the pain and anxiety associated with dental treatment, most dental procedures can be managed with good local anaesthesia, with or without conscious sedation. Since the 1960s, there has been a fall in the use of general anaesthesia for dentistry and in the mortality associated with it. However, eight people died as a result of dental anaesthesia between 1996 and 1999; five of these were children. Investigations and inquiries into these deaths were critical of the standard of care provided in areas such as preoperative assessment, peroperative monitoring, resuscitation and transfer to a critical care facility. In response to these concerns the General Dental Council (GDC), the Royal College of Anaesthetists (RCA) and the Department of Health (DOH) have issued closely linked guidelines for standards of care in dental general anaesthesia.

Who may administer general anaesthesia for dentistry?

Dental anaesthesia developed in free-standing dental surgeries and the administration of a dental anaesthetic was considered a traditional right of a medical or dental practitioner. Since 1998, the administration of dental general anaesthesia has been restricted to the following categories of staff.

- An individual on the Specialist Register of the General Medical Council as an anaesthetist, who should meet the RCA's continuing education and professional development requirements (CEPD).
- A trainee working under supervision as part of an RCA- approved training programme.
- A non-consultant career grade anaesthetist (NCCG) with a National Health Service (NHS) appointment, working under the responsibility of a named consultant anaesthetist who must be a member of the NHS department where the NCCG is employed. The NCCG should also meet the RCA's CEPD requirements.

Each anaesthetist must have had appropriate experience of, and training in, dental anaesthesia.

The RCA recommends that all children should be anaesthetized by a consultant or NCCG who has regular relevant paediatric experience, or a trainee supervised by someone in the preceding categories.

Who should receive general anaesthesia for dentistry?

There is wide variation in the use of general anaesthesia for dental treatment. In 1995, a DOH report concluded that a significant number of general anaesthetics were being given on demand, rather than to meet a defined clinical need. It was also noted that some practitioners failed to recognize that general anaesthesia is always accompanied by some risk. Most dental procedures can be performed under local anaesthesia and it is recommended that general anaesthesia is limited to the following groups.

- Patients who are unable to cooperate because of immaturity or physical or mental disability.
- Patients in whom local anaesthesia has repeatedly proved unsuccessful or is unlikely to be completely effective because of the extent of surgery or the presence of infection.
- Patients with a history suggestive of hypersensitivity or allergy to the contents of the local anaesthetic ampoule.
- Patients who suffer from extreme nervousness and who refuse to undergo any form of dental treatment while conscious. However, many nervous adults and children can undergo treatment successfully under local anaesthesia and conscious sedation and facilities for conscious sedation of a high standard should be more widely available.

Assessment of the patient

The GDC expects a dentist who refers a patient for general anaesthesia to discuss the risks involved and alternative methods of pain and anxiety control with the patient. Clear justification for the use of general anaesthesia should be contained in the referral letter together with details of the patient's relevant medical and dental history. Referral letters are inadequate in up to 50% of cases. Members of the paediatric, oral surgery and other dental departments who refer patients for general anaesthesia must also comply with the GDC guidance.

Dental, medical or nursing staff may be responsible for patient assessment and most staff are capable of selecting patients with the aid of written guidelines specifying medical, surgical and social criteria for ambulatory or in-patient general anaesthesia. Ambulatory dental anaesthesia is usually limited to patients assessed as American Society of Anesthesiologists (ASA) physical status class I and II unless the service is located within the main hospital block.

For those with health issues, an appointment should be made for assessment by an anaesthetist. In some centres the first opportunity to meet the anaesthetist occurs on the day of surgery. However, a separate preoperative assessment allows more time for the patient (or parent/legal guardian) and anaesthetist to decide together whether general anaesthesia has an acceptable risk/benefit ratio and decreases the likelihood of the treatment being cancelled on the day of surgery.

The anaesthetist and operating dentist should explain all the procedures that will be performed including the method of pain relief. Treatment should be specifically aimed at avoiding the need for repeated general anaesthesia. The current guidelines of the regulatory bodies regarding informed consent should be followed.

Where should general anaesthesia for dentistry take place?

The traditional sites for dental anaesthesia have included dental surgeries, community dental practices, dental hospitals, day care units, specialized outpatient clinics and the main in-patient operating theatre of a general hospital. However, since 1 January 2002, general anaesthesia for dentistry has been confined to a hospital setting with critical care facilities.

The DOH has defined a hospital setting as an NHS hospital and its associated clinics or day care facilities: 'where trained personnel are immediately available to assist the anaesthetist with the resuscitation of a collapsed patient so that the patient's airway, breathing and circulation are supported fully without delay and where facilities and staff are able to support and maintain a collapsed patient pending recovery or supervised transfer to a high dependency unit (HDU) or an intensive care unit (ICU) which may be on a separate hospital site'.

In the context of dental anaesthesia a critical care facility refers to: 'an area or room which has the space, equipment and appropriately trained personnel to enable critical care and resuscitation to be efficiently and effectively undertaken … and … should there be a sudden or serious collapse of the patient … to provide expert medical care and treatment with appropriate drugs and equipment immediately and to have additional skilled support from personnel trained specifically as a team which can manage life-threatening situations.

All personnel involved in the administration of general anaesthesia must have up to date advanced life support skills'.

Paediatric anaesthesia

Children requiring general anaesthesia should be treated within a hospital setting which has a 'child-friendly environment'. As far as possible, children should be treated separately from adults, with provision for parents to accompany children during anaesthetic induction and recovery. 'Teams providing dental general anaesthesia for children must be able to provide appropriate emergency care, including being fully conversant with suitable equipment and drug dose regimens and have additional skilled resuscitation support available'.

Giving a general anaesthetic for dental treatment

The same standards must apply to dental anaesthesia in terms of personnel, equipment and drugs as for other forms of general anaesthesia.

Personnel

The status of the dental anaesthetist has been specified above. The operating dentist must be appropriately trained and sufficiently experienced to undertake the planned surgery. The anaesthetist and dentist must each have appropriately trained and competent dedicated assistants (i.e. the presence of four people is required in the room wherever a general anaesthetic is administered). Patients recovering from anaesthesia must be continuously monitored and cared for by the anaesthetist or an individual who is directly responsible to the anaesthetist and is appropriately trained in adequate recovery facilities. Staffing levels should allow at least one recovery nurse for each unconscious patient. Staff must be appropriately trained where dental anaesthetic services are provided for both adults and children.

Equipment

Equipment must be suitable for the age of the patient being treated. The dental chair, trolley or operating table must be able to tilt head down and suction must be available with a selection of pharyngeal and endobronchial catheters. A continuous flow anaesthetic machine must be used. The machine must have an oxygen/nitrous oxide interlinkage to prevent delivery of a hypoxic mixture, an oxygen failure alarm, an emergency nitrous oxide shut-off system and an in-line oxygen concentration monitor.

Maintenance should be in accordance with the manufacturer's guidelines and the documentation of each service episode should be retained. Facilities for the supply, storage and scavenging of medical gases must meet relevant regulations.

The anaesthetist must check all equipment before use including the patient breathing systems. Local guidelines must be followed with regard to all equipment designed for single use only. A full selection of oral and nasopharyngeal airways, laryngeal masks, laryngoscopes, nasal and oral tracheal tubes and breathing circuits should be available in addition to appropriate dental equipment.

In the operating theatre, the Association of Anaesthetists of Great Britain and Ireland (AAGBI) considers the use of a pulse oximeter, non-invasive blood pressure monitor, electrocardiograph and a capnograph to be the minimum monitoring devices that should be available. Paediatric pulse oximeter finger probes should be used in children because adult probes may give misleading values.

The technique of anaesthesia may require vapour analysis and measurement of expired volumes and airway pressure. In addition a nerve stimulator and a means to measure the patient's temperature should be available. In recovery, pulse oximetry and non-invasive blood pressure monitoring is recommended. There should be immediate access to spare anaesthetic and monitoring apparatus in the event of failure.

Drugs

A full range of local and general anaesthetic, neuromuscular blocking, analgesic, sedative and anti-emetic drugs must be available in addition to the drugs likely to be needed in anaesthetic and medical emergencies.

Anaesthetic technique

Most patients undergoing dental anaesthesia are treated on an ambulatory basis and appropriate drugs and techniques should be used. The duration of surgery may be minutes or may extend to 1 hour or more.

In general, the age of the patient and the extent of surgery determine the choice of induction and maintenance of anaesthesia, control of the airway and management of pain relief. However brief the procedure, non-invasive monitoring should be used though it may not be practicable to apply the sensors before induction in a small child. Inhalational induction with sevoflurane is widely used in young children and it is difficult to justify the use of halothane in view of its high arrhythmogenic potential in this area of practice. An argument can be made that intravenous access for administration of anaesthetic or emergency drugs is essential in all patients regardless of the length of the procedure. It is helpful if other members of the team as well as the anaesthetist are trained to insert intravenous cannulas.

Pre-emptive analgesia with paracetamol or non-steroidal anti-inflammatory drugs by oral or other routes is effective and should be considered for every patient. The administration of a local anaesthetic by infiltration or nerve block provides analgesia and prevents surgically induced cardiac arrhythmias. For third molar extraction the addition of dexamethasone has been shown significantly to diminish postoperative swelling and decrease demand for analgesia.

Control of the airway may be by nasal mask, laryngeal mask or tracheal tube. The nasal mask, always accompanied by a mouth pack, is suitable for brief dental extractions. For more extensive surgery or in the presence of nasal obstruction a reinforced laryngeal mask (RLM) should be used. The RLM decreases the incidence of hypoxaemia when compared with the nasal mask. An RLM does not give the degree of airway protection provided by a tracheal tube, but the RLM has proved to be satisfactory in third molar extraction lasting up to 20 minutes. A mouth pack should always be used.

For more prolonged surgery a preformed nasal tracheal tube is generally used, though an oral tube is satisfactory for unilateral extractions in adults and preferable in small children in view of the risk of haemorrhage from adenoidal tissue. A throat pack is required and care must be taken to remove it at the end of the procedure.

A high incidence of hypoxaemia has been found in patients recovering from dental anaesthesia. Pulse oximetry should always be applied and supplemental oxygen given until the return of consciousness.

Management of the emergency

In addition to the risks associated with general anaesthesia, dental anaesthesia is always accompanied by the potential for obstruction and contamination of the airway, and the induction of cardiac arrhythmias associated with dental surgery.

The DOH requires that all personnel involved with the administration of general anaesthesia must have up-to-date advanced life support skills. All staff involved in the provision of dental anaesthesia or the supervision of patients during recovery should practise simulated emergency scenarios as a team. It is unacceptable for reliance to be placed on the general 'crash call' team for the immediate provision of advanced life support.

A range of appropriately sized equipment for tracheal intubation and administration of positive pressure ventilation with 100% oxygen concentrations must be available, in addition to equipment for administration of parenteral fluids and drugs. In addition, a defibrillator that is suitable for all age ranges treated must be available. Most automated external defibrillators are unsuitable for children below the age of 8 years (25 kg). Emergency drugs should include pre-loaded syringes of agents specified in current Resuscitation Council (UK) algorithms and other drugs necessary to deal with anaesthetic and medical emergencies. Up-to-date adult and child advanced life support protocols should be clearly displayed in addition to written guidelines on the management of anaphylaxis and malignant hyperthermia. ◆

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Ludwig’s Angina

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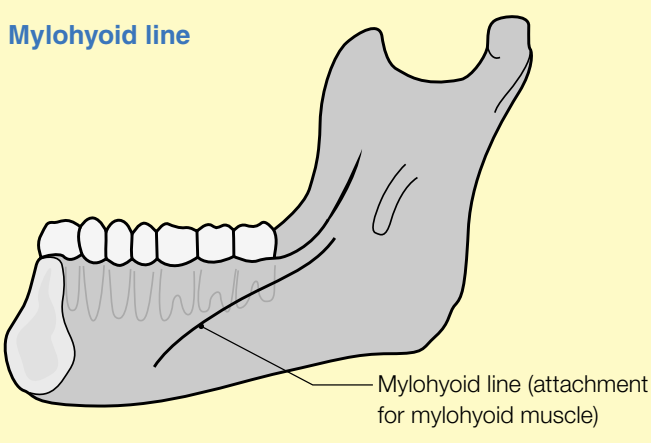
Ludwig’s angina is a rapidly spreading bilateral submandibular cellulitis, usually, though not always, from infection arising from the lower second or third molar teeth, and often without abscess formation. It was first described in 1836 by Wilhelm von Ludwig who noted that the tongue was pressed upwards and backwards with pressure on the larynx causing difficulty in swallowing and breathing (angina means a suffocating sensation) leading to death from respiratory arrest.

The submandibular space is a potential space lying above the hyoid bone and is made up of the sublingual space above the mylohyoid muscle and the submaxillary (or submylohyoid) space below. The sublingual space communicates anteriorly with the submental space and posteriorly with the lateral pharyngeal spaces. The submaxillary space is divided into central submental and lateral submaxillary spaces by the anterior belly of the digastric muscle. However, because of free communication around the posterior border of the mylohyoid, the sublingual and submaxillary spaces can be considered as a single unit: the submandibular space. Also, loose connective tissue, rather than true fascia, separates the two sides of the mouth allowing infection to spread bilaterally.

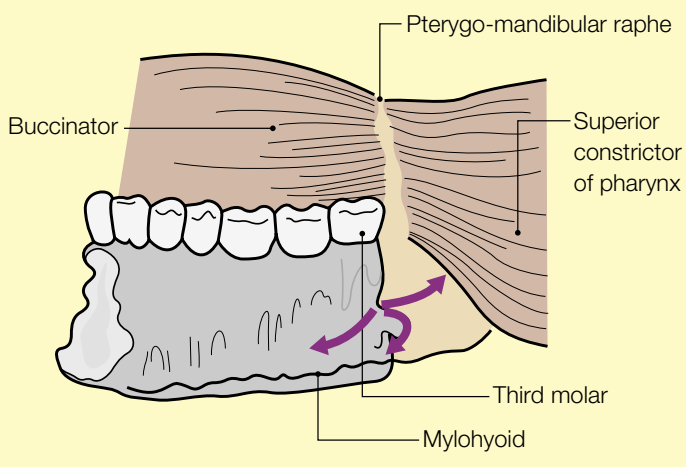
The mylohyoid forms the floor of the mouth and attaches to the lingual surface of the mandible in an obliquely downward line from posterior to anterior (Figure 1 and 2). The root apices of the bicuspid and first molar teeth are usually superior to the line of this muscle and therefore infections from these teeth tend primarily to affect the sublingual space.

Mylohyoid line



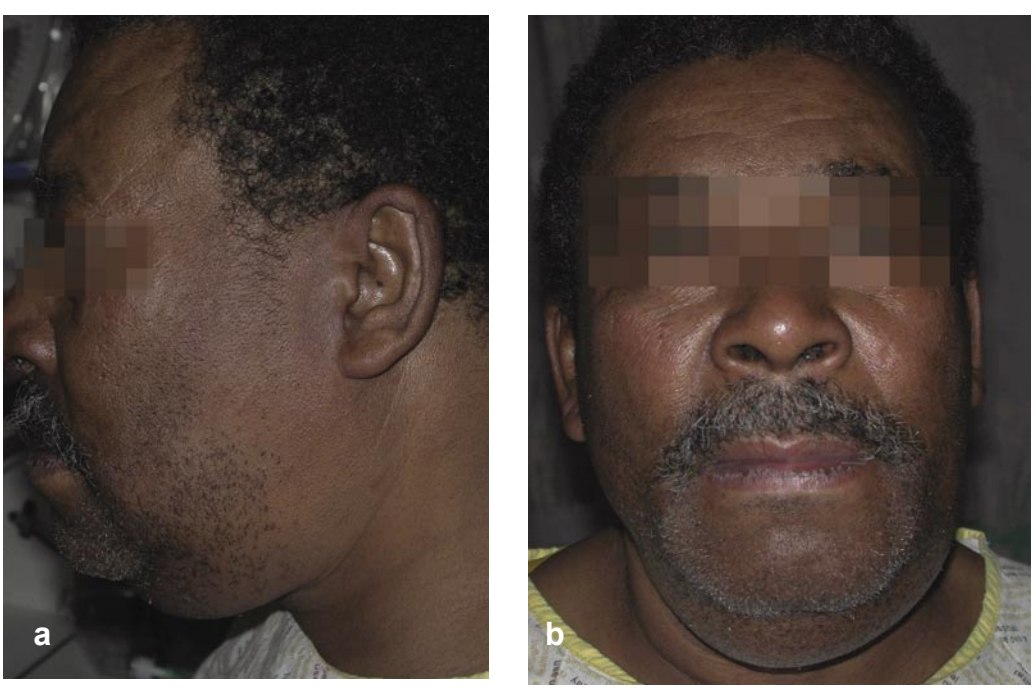
1

Paths of infection from the third molar causing Ludwig’s angina



2

Root apices of the second and particularly the third molar teeth lie inferior to the mylohyoid line of muscle attachment. Infections from these teeth primarily affect the submaxillary space producing a large indurated swelling at the angle of the mandible as well as swelling towards the hyoid bone. The mandible, hyoid and superficial layer of the deep cervical fascia limit tissue expansion anteriorly and therefore impaction and swelling spread through the whole submandibular unit producing brawny oedema with posterior and superior displacement of the tongue and airway compromise (Figure 3).



a and b Ludwig's angina. There is cellulitis and gross oedema of the left submandibular space extending to the right side and into the neck.

The authors thank Dr Mahesh Kumar for permission to use these photographs.

Clinical course

Ludwig’s angina is primarily a disease of dental origin with over 90% of cases related to dental infection (usually of third molars). Other causes include gland sialadenitis, compound mandibular fractures, lacerations and wounds of the floor of the mouth, and secondary infection of oral malignancies. The disease has also been reported in a neonate.

Improved dental hygiene and antibiotic therapy have reduced the incidence of Ludwig’s angina and most physicians and dentists seldom see the disease. Streptococci or mixed oral flora are the most commonly reported pathogens but staphylococci, *Escherichia coli, Pseudomonas* and anaerobes such as *Bacteroides* and *Peptostreptococcus* have also been isolated. There is likely to be synergism in mixed infections because the production of metabolic products by anaerobes enhances the virulence of the aerobes, which in turn provides a favourable environment for anaerobes through oxygen removal.

If antibiotic treatment is not instituted early, or is unsuccessful, the disease progresses rapidly leading to elevation and displacement of the tongue. There is firm, hard induration of the floor of the mouth with perioral oedema. The patient presents with pain, fever, trismus and dysphagia. The patient may experience anxiety about their inability to swallow or maintain an airway. Unchecked, the disease may spread posteriorly to involve secondary fascial spaces known collectively as the masticator space causing severe trismus. Occasionally there may be spread to deep cervical spaces and even to the mediastinum with serious life-threatening sequelae.

Ludwig’s angina can produce systemic sepsis with fever (or hypothermia), tachycardia, respiratory distress and leucocytosis.

Management

Patients who present to hospital with Ludwig’s angina are seriously unwell with an infection that may produce upper airway obstruction with alarming speed. Successful management involves the cooperation of the medical staff including the dentist, maxillofacial surgeon, anaesthetist, intensivist and microbiologist. Airway control is the priority.

Airway control

Asphyxia is the most common cause of death and control of the airway is essential. The swollen, elevated tongue pushed up against the palate with associated glottic oedema in an already anxious and septic patient ensures that any technique is extremely challenging. There are three options for managing the airway.

Observation may be appropriate in a high dependency environment allowing early aggressive medical therapy an opportunity to work. However, signs of impending respiratory obstruction (dyspnoea, stridor and cyanosis) may appear rapidly and late, heralding a medical emergency. Because medical staff now have little exposure to this disease a judgement to manage the patient conservatively with observation must be considered carefully by senior staff. Generally, observation is appropriate for patients who present in the early stages and who have no signs of airway obstruction.

Surgical airway – a tracheostomy performed under local anaesthesia is associated with immediate and long-term morbidity. Surgery also risks spreading the infection to deep cervical or mediastinal structures.

An anaesthetic airway can be established by a gaseous induction and direct placement of a tracheal tube or use of the fibre-optic intubating laryngoscope. The technique chosen depends on the skills of the staff involved. Although many authorities recommend the fibre-optic endoscope as the ‘gold standard’ the literature contains many case reports and series where gas induction has been used successfully to secure the airway in these patients. With either technique an armoured tracheal tube should be used as the submandibular swelling has been reported to compress an ordinary PVC tube, rendering ventilation impossible.

Choice of airway: a review of the literature found that only 35% of patients required oral or nasal tracheal intubation or tracheostomy for airway control. Since the 1980s, the use of tracheostomy under local anaesthesia has become less common. All patients with Ludwig’s angina have submandibular oedema with an elevated tongue and trismus, therefore these signs are poor differentiators of the need for definitive airway control versus observation. Radiological investigations, particularly CT scan and ultrasound, may help define the extent of tissue oedema or presence of loculated infection and therefore help in any decision about airway control.

Antibiotics

The advent of surgical decompression of the submandibular space reduced mortality from 100% in 1850 to 40–60%. The introduction of antibiotics reduced that figure to under 5%. Traditionally, high-dose penicillin was used. A broader spectrum of therapy is now recommended to cover penicillin-resistant Gram-positive cocci and anaerobes. A combination of clindamycin, penicillin (or ciprofloxacin) and metronidazole is usually recommended before definitive microbiological results are received.

Surgery

Surgical drainage was once universally required but some authorities now recommend reserving it for cases in which antibiotic therapy fails. Isolated removal of the infected tooth and limited intra-oral drainage is unsuccessful. CT-guided needle aspiration of the submandibular space has also been tried but as the disease is essentially a fascial cellulitis often without localization of pus this technique is unhelpful.

Surgery usually involves bilateral incisions parallel and inferior to the mandible with deep dissection into the submandibular triangle, through the mylohyoid muscle and into the sublingual region. The primary goal is decompression of all fascial spaces and the secondary goal evacuation of pus and obtaining tissue for microbiology. Any infected teeth are also removed. The classical ‘cut throat’ incision between the chin and the hyoid bone is no longer deemed necessary. Clinical experience has demonstrated that even if there is no pus, serious cellulitis resolves more rapidly if incised. Submandibular incisions also allow the swelling to extend inferiorly releasing the pressure that forces the tongue onto the palate and posterior pharynx.

Corticosteroids

The use of glucocorticoids in septic patients is controversial, but some authorities recommend their use to reduce the submandibular swelling. One regimen includes an initial dose of dexamethasone, 10–20 mg followed by 4–6 mg every 6 hours for 48 hours. The role of corticosteroids in outcome has not been evaluated.

Medical support of the patient
The patient must be nursed in a high dependency environment with maintenance of fluid balance/hydration and regular cardiovascular and respiratory monitoring.

Dental care
Continuing primary oral health care following the acute infection is important. ◆

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Sedation for Dental Procedures

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Most patients regard dental treatment as uncomfortable and potentially painful: their reactions range from normal apprehension, through various degrees of anxiety to irrational fear or even phobia. The adverse physiological effects of these psychological responses can increase the risks of treatment and should be controlled. This may be of even greater importance in patients with medical conditions (Figure 1).

Medical conditions and sedation

Conditions for which sedation is beneficial
- Angina
- Controlled hypertension
- Asthma
- Epilepsy
- Movement disorders

Conditions that may require modification of techniques
- Controlled heart failure
- Chronic anaemia (diagnosed and managed)
- Chronic airways disease
- Well-controlled diabetes

Conditions in which caution is required
- Severe cardiorespiratory disease
- Hepatic disease
- Severe psychological illness
- Drug abuse
- Alcohol abuse

1

The General Dental Council (GDC) defines conscious sedation as: 'A technique in which the use of a drug or drugs produces a state of depression of the central nervous system enabling treatment to be carried out, but during which verbal contact is maintained throughout the period of sedation. The drugs and techniques used to provide conscious sedation should carry a margin of safety wide enough to render loss of consciousness unlikely. The level of consciousness must be such that the patient remains conscious, retains protective reflexes and is able to understand and respond to verbal commands.'

The GDC also requires that all clinicians using dental sedation have clinical experience of the technique and that they are assisted by a second person who is able to monitor the patient and assist in the event of an emergency.

The purpose of sedation is to:
- enable treatment to be provided and/or accepted
- reduce stress associated with traumatic or prolonged procedures
- control gagging
- stabilize blood pressure in patients with cardiovascular or cerebrovascular disease.

Patient assessment
A satisfactory first visit is crucial to the success of subsequent treatment under sedation. Ideally, this meeting should take place away from the surgery environment. Patients should be given instructions for sedation at this visit (Figure 2). Dental treatment must be appropriate and realistic. The management options are listed in Figure 3. The simplest technique is generally considered to be best.

Instructions for patients receiving dental sedation

For your safety, please read and follow these instructions carefully

Before sedation: on the day of treatment
- Take your routine medicines at the usual times
- Have only light meals and non-alcoholic drinks on the day of your appointment
- Bring a responsible adult with you who is able to escort you home and then care for you for the rest of the day

After sedation: until the following day
- Do not travel alone – travel home with your escort, by car if possible
- Do not drive or ride a bicycle
- Do not operate machinery
- Do not drink alcohol
- Do not return to work or sign legal documents

2

Management options for dental treatment

Local anaesthesia
- Alone
- With nitrous oxide/oxygen mix
- With intravenous sedation (e.g. midazolam)
- With oral sedation

General anaesthesia

3

Inhalational sedation

The use of nitrous oxide and oxygen in subanaesthetic concentrations as a method of sedation became popular in the late 1940s. Nitrous oxide has excellent anxiolytic, sedative and analgesic properties, with little depression of myocardial function or ventilation (Figure 4). Induction and recovery are rapid. Administration by titration reduces the risk of over-sedation.

Inhalational sedation

Advantages
- No needles
- Level of sedation easily altered
- Minimal impairment of reflexes
- Rapid induction and recovery
- Some analgesia

Disadvantages
- Sedation depends on good psychological support
- Mask may limit access
- Postoperative amnesia variable
- Nitrous oxide pollution

Contraindications
- Nasal obstruction
- Poor cooperation
- First trimester of pregnancy
- Fear of masks

4

Equipment
Inhalational sedation (Relative Analgesia) machines are similar to traditional Boyle's anaesthetic machines, but modified to make them safe for use by an operator-sedationist. Typical Relative Analgesia machines have independent controls for regulating total gas flow and the mixture of oxygen and nitrous oxide. Modern machines are incapable of delivering a gas mixture containing less than 30% oxygen and have breathing systems with scavenging for the removal of waste gases.

Clinical procedure
The nasal mask is attached and the machine adjusted to administer 100% oxygen at an appropriate flow rate. Verbal encouragement is important at this stage. 10% nitrous oxide is introduced and the patient informed that they may feel light-headed, have changes in visual or auditory sensations or tingling of hands and feet and a feeling of suffusing warmth. This concentration is maintained for 1 minute, during which verbal reassurance continues. The concentration of nitrous oxide is then increased by 10% for a further 1 minute and then in increments of 5% until the patient appears and feels sufficiently relaxed. Local analgesia is then administered. When correctly titrated, patients are aware of operative procedures and are cooperative without being fearful. Restlessness is often an indication that the concentration of nitrous oxide is too high. At the end of treatment, 100% oxygen is administered.

Monitoring
The sedationist and the dental nurse must observe the patient's respiration, the level of sedation and skin colour. Electromechanical devices (e.g. pulse oximeter, ECG) are not routinely used unless the patient has serious medical problems.

Nitrous pollution and scavenging
Long-term exposure to nitrous oxide is potentially harmful. The Health and Safety Executive specifies a time-weighted maximum level of 100 ppm of nitrous oxide in the working environment. This is normally achievable only using active scavenging.

Intravenous sedation

Midazolam is well suited to sedation for dentistry (Figure 5). It is impossible to determine the correct dose of midazolam on the basis of the patient's body weight or age therefore a titration technique is essential.

Sedation with midazolam

Advantages
- Rapid onset (5 minutes or less)
- Good patient cooperation
- Good amnesia

Disadvantages
- No clinically useful analgesia
- Respiratory depression
- Occasional disinhibition effects
- Occurrence of sexual fantasies (rare)
- Postoperative supervision for a minimum of 8 hours is required
- Not reliable for sedating children
- Elderly patients are easily over-sedated

Absolute contraindication
- Allergy to any benzodiazepine

Caution required
- Pregnancy and breastfeeding
- Severe psychiatric disease
- Alcohol or drug abuse
- Impairment of hepatic function
- Needle phobia
- Doubts about the ability to provide a suitable escort

5

Intravenous midazolam produces a period of acute detachment for 20–30 minutes followed by a state of relaxation for a further 1 hour or so. Most patients have little or no recollection of the operative procedure. Some respiratory depression occurs in patients undergoing midazolam sedation. Overdosage and/or excessively rapid 'bolus' injections may cause profound respiratory depression. This is unpredictable, and so pulse oximetry must always be used.

Clinical procedure
It is important to ensure that the patient is prepared for the procedure and that the dental team is prepared for the patient. Written consent is required for both the dental procedure and sedation. Induction should be carried out with the patient lying supine. Pulse oximetry is mandatory for all patients and must be in place before induction. Continuous blood pressure and/or ECG monitoring may be advisable for unfit patients. Supplementary oxygen must be available.

The following regimen is appropriate for most fit patients aged 16–65 years, though variation in the response to sedation is common. Midazolam, 2 mg, is administered slowly, followed by a pause of 90 seconds. Additional 1 mg increments are given every 30 seconds until a satisfactory level of sedation is achieved. Slurring of speech and/or a slowed response to commands and a relaxed demeanour confirm that the sedation end-point has been reached. Ptosis is an unreliable sign. Local analgesia is then administered.

Elderly patients often require small doses of midazolam. A suggested administration regimen for these patients is 1 mg injected slowly followed by a wait of at least 4 minutes, then additional 0.5 mg increments given every 2 minutes until sedation is adequate. At the end of the procedure, the patient must remain under the supervision of the sedationist or a suitably trained nurse. Patients must be discharged into the care of an escort, who must be given written and verbal care instructions.

Reversal of midazolam sedation
Flumazenil reverses the sedative, cardiovascular and respiratory depressant effects but not intraoperative amnesia. Elective reversal with flumazenil may occasionally be indicated. Flumazenil has a shorter half-life than midazolam. However, clinically significant re-sedation does not occur when midazolam is used for short clinical procedures.

Oral and intranasal sedation

Oral sedation is useful for patients who are unable to accept venepuncture. The sedation produced may be adequate for the dental procedure to be carried out or it may then be possible to administer intravenous sedation. The most commonly used drugs are temazepam and midazolam. Midazolam may also be administered intranasally. Oral and transmucosal techniques are less predictable and should be used by experienced sedationists only. ◆

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Special Needs Patients and Dental Procedures

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Terms such as special needs, disability and handicap have different interpretations. Definitions have been proposed by the World Health Organization in the International Classification of Impairment, Disabilities and Handicap, and special educational needs are defined in the 1993 Education Act. In practical terms, the special needs patient is one who has learning and/or physical disabilities. Down's syndrome, cerebral palsy and autism account for most cases, but rare syndromes are also encountered. Some rare diseases have profound anaesthetic implications, such as airway and cardiac problems in patients with Goldenhar's syndrome. An anaesthetist was recently convicted of manslaughter after a child with Goldenhar's syndrome died during dental treatment.

Special needs patients often allow only limited dental examination and treatment, so that dental care may have to be carried out under general anaesthesia. The use of local anaesthetic alone, or with sedation, has a limited place in moderately or severely affected patients.

The clinical setting: in contrast to efforts aimed at supporting special needs patients in their community, general anaesthesia is being increasingly confined to the hospital environment. Day surgery units allow patients to be treated and discharged home within 6 hours, minimizing the disruption to their lives. It is ideal to have a regular team of staff and considerate scheduling of lists within the day surgery unit.

Preoperative assessment: the patient's cooperation may be limited, making examination difficult. The patient's medical history should be sought from other sources (e.g. hospital or GP records). The anaesthetic value of any investigations should be determined. Preoperative assessment is best carried out by the same senior clinicians carrying out the procedure. Good communication between members of the dental, anaesthetic and theatre teams is important. The decision to ask patients to attend hospital for a separate pre-anaesthetic assessment must be balanced against the inconvenience caused to the patient and the risk of unexpected admissions to hospital if they do not attend. Prolonged preoperative starvation should be avoided.

Consent: in England, Wales and Northern Ireland, no one can give consent to treatment on behalf of another adult. However, doctors can treat incompetent adult patients without consent if they need treatment, and if it is in the patient's best interest. This decision is made after consulting the patient's carer, but they have no legal status in the decision-making process.

Premedication: special needs patients often require repeated general anaesthetics and any measure that improves the experience for them should be embraced. Many patients do not need sedative premedication if parents or carers are involved and simple distraction techniques are used. However, premedication is necessary for some. The choice of drug is best tailored to the individual patient, bearing in mind that some will not swallow pills or tolerate the use of topical anaesthetic cream. Intramuscular ketamine, 4 mg/kg, given 10 minutes before induction is used. However, ketamine is now a controlled drug. Therefore, injectable midazolam, 0.5 mg/kg up to a maximum of 15 mg, added to paracetamol elixir, 20 mg/kg, to mask its bitter taste and given orally 30–40 minutes before its desired effect, is a useful alternative.

Peroperative anaesthetic technique: the choice is influenced by:
- the difficulties of communicating with patients, their limited cooperation and the presence of a carer
- an understanding of the dental treatment plan, which may involve all four quadrants of the mouth and last over 1 hour.

Induction of anaesthesia can be challenging and carers often express the patient's anxiety. Practices used in paediatric anaesthesia are useful for children and adults. These include involving the carer to reassure and distract the patient, omitting formal monitoring before induction if it increases distress and a flexible approach to the choice of intravenous or inhalation induction (with sevoflurane followed by intravenous cannulation when the patient is asleep).

A nasotracheal tube is the airway of choice (unless contra-indicated) together with a throat pack, allowing good access for the dentist. Neuromuscular paralysis with a nondepolarizing neuromuscular blocker and mechanical ventilation are often used, given the high incidence of co-existing medical disease and the duration of treatment.

Simple analgesics combined with local anaesthesia are usually satisfactory. Diclofenac, 1 mg/kg, given as a suppository in children or in an infusion in adolescents and adults is helpful unless contraindicated. Opioids are seldom used.

Recovery: patients generally make a good recovery to their pre-operative status, but conventional discharge criteria must be modified for each patient, and are usually best agreed with the patient's carer. The carer will also know whether tablets or elixirs are preferred when prescribing medicines to take home. ◆

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Endocrinology

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Anaesthetic Management of the Diabetic Patient

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Diabetes mellitus is the most common endocrine condition encountered in surgical patients. 50% of diabetic patients require surgical intervention, usually for ophthalmic, vascular or infective complications. They have increased perioperative mortality and morbidity compared with the general population. The main aims in the anaesthetic management of these patients are:

- to reduce the period of starvation with early recourse to oral intake and a normal glycaemic regimen
- to optimize blood glucose levels throughout the perioperative period in order to minimize metabolic disturbance and end-organ damage.

Diagnosis

Diabetes mellitus includes a number of disorders in which the universal finding is hyperglycaemia. Recently, the World Health Organization (WHO) and the American Diabetes Association (ADA) have jointly published new diagnostic criteria. This has led to an increase in the number of people recognized as having diabetes mellitus. The diagnosis may be confirmed by a random plasma glucose concentration greater than 11.1 mmol/litre or a fasting plasma glucose concentration greater than 7.0 mmol/litre (previously 7.8 mmol/litre), providing this result can be replicated. Impaired glucose tolerance, now renamed impaired fasting glycaemia, is confirmed by a fasting plasma glucose concentration of 6.1–7.0 mmol/litre.

Classification

The WHO and ADA have also developed a new classification system identifying four types of diabetes mellitus.

Type I is caused by autoimmune or viral destruction of susceptible β cells in the islets of Langerhans in the pancreas, which are responsible for the production of insulin. Their destruction results in no endogenous insulin being produced. Type I usually presents in patients under 30 years of age. Its inheritance is multifactorial. There is a strong genetic association with increased expression of human leucocyte antigens (HLA) DR3 and DR4 found on chromosome 6. The worldwide incidence of type I diabetes mellitus is 0.4%, but it is more common in developed countries.

Hyperglycaemia occurs as a result of reduced peripheral uptake of glucose, which is usually insulin mediated. There is also increased proteolysis, lipolysis and subsequent gluconeogenesis. This leads to massive protein loss and depletion of fat stores, further increasing the plasma glucose concentration. Glucose cannot be used for energy in these circumstances, therefore the liver produces ketoacids as an alternative energy source. This results in acidaemia. Exogenous insulin is vital to maintain glucose and acid–base
homeostasis.

Type II patients have reduced secretion of the active form of the insulin molecule. They have increased amounts of inactive insulin precursors, combined with increased peripheral insulin resistance as a result of impaired glucose transport mechanisms. This also reduces muscle glycogen synthesis. The worldwide incidence is 6.6%. The diagnosis is more common in patients over 40 years of age and in populations that have changed from a traditional to a Western diet and lifestyle. Type II diabetes has a strong familial link, with over 90% concordance between monozygotic twins.

Patients are usually overweight (unlike type I patients who are often thin) and do not have the propensity for acidotic states because they usually have enough insulin to prevent ketoacidosis. They may occasionally present with hyperosmolar non-ketotic coma (HONK). Glycaemic control can be maintained with oral hypoglycaemic agents but exogenous insulin may be used in extreme situations. These diabetic patients are the most susceptible to end-organ disease, therefore good blood sugar control is mandatory.

Type III patients suffer from hyperglycaemia precipitated by drugs (e.g. thiazide diuretics, corticosteroids, β-blockers) or concurrent disease. Associated diseases may include genetic disorders (e.g. Huntingdon's chorea, Down's syndrome, dystrophia myotonica), pancreatic disease (e.g. pancreatitis, haemochromatosis) or endocrine diseases (thyrotoxicosis, acromegaly, Cushing's syndrome). Successful treatment or removal of the cause usually results in normoglycaemia.

Type IV is also known as gestational diabetes. It usually presents during the third trimester of pregnancy and affects about 4% of pregnancies. Detection and treatment are vital to prevent fetal macrosomia. Oral hypoglycaemic agents are teratogenic and subcutaneous insulin is usually needed. Insulin requirements drop suddenly post-partum and normal glucose homeostasis is quickly restored. The mother has an increased risk of developing type II diabetes later in life (30–50% incidence within 10 years).

Long-term complications

Poor blood glucose control can result in acute metabolic disturbance and, if sustained, can cause chronic end-organ damage. The treatment of acute diabetic emergencies is outside the scope of this article.

There are two theories explaining how chronic hyperglycaemia may cause damage at the molecular level.

- Protein glycosylation in which irreversible covalent bonds form between excess glucose and protein compounds, altering their function and interaction with other compounds.
- Polyol pathway in which glucose is metabolized to fructose via sorbitol. Saturation of this pathway produces excess sorbitol, which activates aldose reductase, an enzyme that further enhances sorbitol production. A positive feedback loop is produced. The increased level of sorbitol causes tissue damage. Animal studies using aldose reductase inhibitors have shown promising results in the reduction of end-organ damage but they may be toxic to humans.

The pathological findings associated with chronic hyper-glycaemic end-organ damage are primarily those of micro-vascular disease, particularly affecting the cerebral and coronary vessels. The cardiovascular, neurological, renal and ophthalmic systems are those most commonly affected. Microvascular organ damage may be the main indication for surgery and it also complicates perioperative anaesthetic management.

Cardiovascular: patients with diabetes mellitus have accelerated formation of atheromatous plaques as well as generalized microvascular disease. Perioperative myocardial ischaemia and infarction are more common than in the general population. The risk of life-threatening arrhythmias is greater because the threshold for the initiation of ventricular fibrillation is reduced. Hypertension is common, caused by the loss of vessel elasticity secondary to protein glycosylation. Good blood pressure control can reduce mortality, though β-blockers, thiazide diuretics and calcium antagonists can worsen glycaemic control. Other cardiovascular complications include peripheral vascular disease and cardiac failure.

Neurological: peripheral and autonomic neuropathies are the most common neurological complications of diabetes mellitus. Peripheral neuropathies typically have a symmetrical 'glove and stocking' distribution. The extent of the neuropathy should be documented accurately to prevent medico-legal problems. Up to 40% of type I patients and 17% of type II patients have autonomic neuropathy. A careful history may elicit symptoms but the condition is often asymptomatic and detectable only by screening. Autonomic neuropathy should be suspected if the patient complains of abnormal sweating, bladder dysfunction, diarrhoea or dizziness. Other features may include cardiovascular instability and gastroparesis (potentially causing regurgitation and/or aspiration). Autonomic neuropathy can be confirmed by:

- a drop in postural blood pressure on standing, or absence of increase in diastolic blood pressure after 5 minutes of hand grip
- absence of sinus arrhythmia on ECG or by palpation
- absence of cardiac response to the Valsalva manoeuvre.

Renal: patients with type I diabetes mellitus have the highest incidence of end-stage renal disease and progress most rapidly from microalbuminuria to proteinuria, nephrotic syndrome and eventually chronic renal failure. Strict glycaemic control can delay the onset of microalbuminuria, which signals the inevitable progression to end-stage renal disease. The extent of renal disease can be assessed by preoperative creatinine, urea and electrolyte measurements.

Ophthalmic: blindness may be caused by cataracts or exudative or proliferative retinopathy. Perioperative hypertension can cause vitreous haemorrhage.

Respiratory: problems include a reduction in lung volumes and a decrease in diffusing capacity. Chest infections are common. Obese diabetic patients may demonstrate signs and symptoms of obstructive sleep apnoea (see *Anaesthesia and Intensive Care Medicine* **3:6:** 196).

Stiff joint syndrome: the high incidence of difficult intubations in patients with type I diabetes may be caused by protein glycosylation. Airway assessment may be normal but the inability to perform 'prayer's sign' (approximation of the palmar proximal interphalangeal joints) as well as limited atlantoaxial extension can indicate a potentially difficult intubation.

Infection: hyperglycaemia may result in leucocyte dysfunction. This increases the incidence of wound infection and delayed healing, particularly if the blood glucose is above 14 mmol/litre. Peripheral vascular disease exacerbates poor wound healing. Insulin requirements increase in the presence of infection.

Treatment

Treatment iscovered elsewhere.

Anaesthetic management

The aim of perioperative management is to maintain good blood sugar control. Hypoglycaemia can occur preoperatively following excessive starvation or late cessation of long-acting hypoglycaemic agents. Hyperglycaemia is exacerbated by the metabolic response to surgery. Controlling hyperglycaemia prevents immediate metabolic disturbance and electrolyte abnormalities and reduces the incidence of long-term end-organ damage.

Metabolic response to surgery: metabolic disruption occurs in all patients undergoing surgery, the extent depending on the operation as well as the severity of the underlying disease. The stress response involves the release of catecholamines, cortisol, growth hormone, thyroid hormones and other catabolic hormones. The production and peripheral action of insulin, an anabolic hormone, is decreased, causing an overall rise in blood glucose levels. Metabolic disruption is exaggerated in diabetic patients and may continue postoperatively because peripheral insulin resistance remains high.

Preoperative preparation: patients must be evaluated to assess their current and long-term glycaemic control and the efficacy of their present treatment regimens (Figure 1). Simple bedside tests and glycosylated haemoglobin (HbA_{1C}) levels can assess recent control of blood sugar. An HbA_{1C} level less than 10%, indicates good control over the previous 6–8 weeks. Acute hyperglycaemia is a contraindication to surgery and anaesthesia because it may cause postoperative metabolic disturbance, increased infection, microvascular damage and delay wound healing. Patients must be metabolically stable and assessment may require blood gas analysis if recent diabetic ketoacidosis has been a problem.

Preoperative investigations

- Full blood count – haemoglobin; raised white cell count indicates infection
- Urea and electrolytes – renal function
- Glucose – current glycaemic control
- HbA_{1C} – long-term glycaemic control
- ECG – arrhythmias, ischaemia, previous cardiac events
- Urinalysis – glucose ± ketones

1

Associated complications (cardiovascular, renal, neuropathic) must be actively sought and investigated appropriately. It is particularly important that cardiac disease is excluded and an ECG is mandatory. Autonomic neuropathy must be identified because it may have major anaesthetic implications. Pre-existing renal impairment may affect drug choices. Airway assessment is important to anticipate unexpectedly difficult intubation. Diabetic patients should have operative priority to reduce the starvation period.

Perioperative blood sugar management: the aim is to maintain blood sugar levels at 6–10 mmol/litre. This may be achieved in several ways. Management should include measurement of blood glucose every 2 hours and of electrolytes every 6 hours. The regimen used depends on the type of diabetes mellitus and the extent of surgery.

Type II – for minor surgery in patients with good blood sugar control, short-acting oral hypoglycaemic agents should be omitted on the morning of surgery. Longer-acting medication must be stopped 24 hours before surgery. Blood glucose levels should be monitored closely throughout the perioperative period. Once oral intake has resumed, oral hypoglycaemic medication should be restarted immediately. If the patient is controlled by diet, monitoring blood glucose levels is usually the only requirement. Insulin should be considered in patients with poor glycaemic control. For major surgery, patients should be converted to an insulin regimen and treated as if they had type I diabetes mellitus.

Type I – for minor surgery, patients may follow a 'no insulin, no glucose' regimen provided both carbohydrate and insulin are administered early postoperatively. Postoperative nausea and vomiting must be minimized and blood glucose monitoring is imperative. Alternatively, an infusion of 5% dextrose may be commenced and 50–75% of the patient's normal morning insulin dose given subcutaneously. Both regimens have drawbacks including an increased risk of ketoacidosis and an enhanced stress response. Absorption of insulin from subcutaneous tissues is inconsistent during surgery because skin and muscle perfusion may be altered by other physiological variables. For anything other than minor surgery, insulin and dextrose infusions remain the management of choice. Long-acting insulin should be omitted 24 hours preoperatively, but short-acting preparations may be continued until the morning of surgery. The insulin/dextrose infusion should be commenced concurrently with starvation and continued until oral intake is resumed postoperatively. There are two main insulin/dextrose regimens. In the Alberti regime (Figure 2) insulin is added to a 500 ml infusion bag containing 10% dextrose and potassium. It is a safe regimen because simultaneous infusion of both insulin and dextrose is guaranteed. The disadvantage is that if blood glucose levels are outside an acceptable range a new infusion must be prepared with a different amount of insulin. Insulin is also adsorbed by plastic and glass surfaces. This may be a problem with the Alberti regimen, which has a high volume solution with a low insulin concentration. The alternative approach is to use separate infusions of insulin and 5% dextrose containing potassium (Figure 3). This is much more flexible because the two infusions can be controlled independently. If a single cannula is used for both infusions a one-way valve must be incorporated to prevent insulin entering the dextrose administration set. Ideally, separate cannulas should be used but hypo- or hyperglycaemia may occur if either of the cannulas occludes.

Alberti regimen (Alberti and Thomas, 1979)

500 ml 10% dextrose solution + 10 U insulin + 10 mmol KCl
Run at 100 ml/hour, check blood glucose every 2 hours

- If blood glucose < 5 mmol/litre, use 5 U insulin per bag
- If blood glucose 5–9.9, use 10 U insulin per bag
- If blood glucose 10–14.9, use 15 U insulin per bag
- If blood glucose ≥ 15, use 20 U insulin per bag

2

Insulin sliding scale

5% dextrose + 10 mmol/litre KCl – run at 125 ml/hour
0.9% NaCl + insulin at 1 U/ml

- If blood glucose ≤ 4.9, give 0.5 U insulin/hour i.v.
- If blood glucose 5–14.9, give 2 U insulin/hour i.v.
- If blood glucose 15–19.9, give 4 U insulin/hour i.v.
- If blood glucose ≥ 20, review

3

Postoperative management: the insulin/dextrose infusion regimen should be continued until the patient is able to resume and maintain oral intake. Intravenous administration can be converted into subcutaneous boluses before each meal, with regular blood glucose monitoring. During recovery, insulin requirements reduce and it is recommended that once subcutaneous requirements are less than 20 U/day a normal preoperative regimen may be restarted. Early patient mobilization hastens a return to metabolic homeostasis. This requires attention to adequate analgesia. Treatment of postoperative nausea and vomiting allows an earlier return to a normal diet.

Choice of anaesthetic: the aim is to minimize metabolic disturbance.

Regional anaesthesia has many advantages. A conscious patient permits early detection of hypoglycaemic episodes and reduces the risk of aspiration. Postoperative nausea and vomiting is minimized allowing the patient to return to a normal diet sooner. Regional techniques for pelvic and limb surgery reduce the stress response to surgery, and thus reduce a rise in blood glucose. Hypotensive episodes related to the regional technique may be exaggerated in the presence of autonomic neuropathy and may cause further deterioration of end-organ function. Strict asepsis is vital to avoid infection, especially epidural abscess formation. Regional anaesthesia in patients with peripheral neuropathy is not recommended for medico-legal reasons.

General anaesthesia can mask the signs of hypoglycaemia and therefore requires regular blood glucose measurement. A rapid sequence induction may be required in patients with evidence of autonomic neuropathy to prevent aspiration; difficult intubation should always be anticipated. Hypoxia and hypercarbia may exacerbate the stress response, hypotension may worsen end-organ damage and hypertension increases the risk of vitreous haemorrhage. The stress response may be lessened by the use of high doses of opiates. The resulting respiratory depression and delayed return to consciousness may be confused with hypoglycaemia. Sympathomimetics and diuretics antagonize insulin, while clonidine, monoamine oxidase inhibitors and β-blockers potentiate its action. It is advisable not to use fluids containing lactate (e.g. Hartmann's solution) because metabolic acidosis may be exacerbated; lactate is converted to glucose by gluconeogenesis, further disrupting glycaemic control. Transfusion of packed cells may disrupt glucose homeostasis because citrate promotes gluconeogenesis. Stiff joints require great care with preoperative positioning. Diabetic patients are also at risk from skin trauma, ulceration and nerve injury. ◆

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Recognition and Management of Phaeochromocytoma

Andrew K McIndoe

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Phaeochromocytomas are tumours of chromaffin cells. The name derives from the observation that catecholamine storage granules in these cells turn brown when stained with chromic acid. Although phaeochromocytomas are thought of primarily as tumours of the adrenal medulla, they occur wherever chromaffin cells are found. 95% occur in the abdomen, of which 85% are in the adrenal gland. The remainder tend to be near the kidney or in the organ of Zuckerkandl. Outside the abdomen they occur in the sympathetic chain, the heart and the posterior mediastinum.

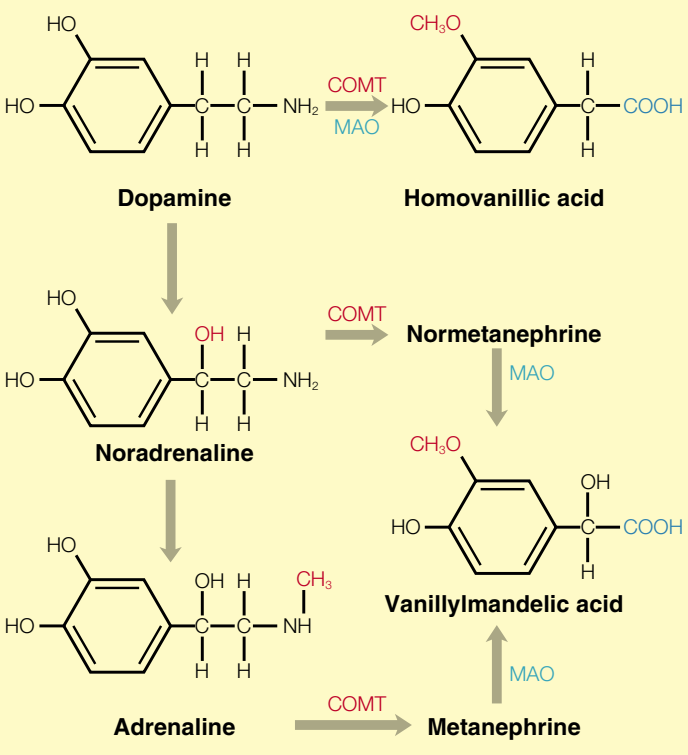
The sympathetic nervous system

The sympathetic nervous system comprises the sympathetic chain (T1–L2), a number of peripheral plexuses and the adrenal medulla. All are supplied by preganglionic cholinergic neurons connecting the CNS to sympathetic effectors derived from chromaffin cells. Chromaffin cells produce noradrenaline, adrenaline and dopamine. The sympathetic chain lies posterior to the aorta on either side of the thoracic column and is made up from the cell bodies and ganglia of most of the chromaffin cells. Postganglionic neurons derived from the sympathetic chain are noradrenergic and innervate vascular smooth muscle, mediating vasoconstriction. More peripheral chromaffin cells are located in the cervical ganglia, carotid bodies, and a number of abdominal plexuses, but most significantly in the adrenal medulla. Typically the normal adrenal medulla contains four to five times as much adrenaline as noradrenaline. Catecholamine secretion is achieved by exocytosis into the blood stream, in response to pain, stress, hypoglycaemia and hypoxia. Chromaffin cells are also present in the remains of the organ of Zuckerkandl located near the inferior mesenteric artery, which is a significant source of catecholamines during fetal development.

Catecholamine biochemistry

The principal catecholamines are adrenaline, noradrenaline and dopamine (Figure 1). All are derived from dietary tyrosine or synthesized from the amino acid precursor phenylalanine. Within the chromaffin cells, tyrosine is hydroxylated to dopa (dihydroxyphenylalanine), which is transported to the nerve terminals. Dopa is decarboxylated to dopamine and accumulates in storage vesicles or granules in the nerve terminal. The membranes of these vesicles contain dopamine β-hydroxylase, which catalyses the conversion of dopamine to noradrenaline. There is no further conversion in the peripheral sympathetic nerve terminals, but in the adrenal medulla noradrenaline is N-methylated to adrenaline in a reaction controlled by phenylethanolamine-N-methyltransferase (PNMT) and facilitated by glucocorticoids. The adrenal medullary catecholamines are stored in granules with ATP. Mg^{2+}-dependent ATPase controls uptake into these granules and inhibits subsequent release.

Catecholamine biochemistry



COMT, catechol-O-methyl transferase
MAO, monoamine oxidase

1

Once released, the amines are rapidly eliminated. Up to 90% of the noradrenaline released at the synapse is taken up again by the presynaptic nerve ending (uptake 1). The process is highly energy dependent and is saturable. It is blocked by cocaine, metaraminol, tricyclic antidepressants and phenothiazines (Figure 2). Noradrenaline is recycled into storage granules or deaminated by mitochondrial monoamine oxidase (MAO). Although circulating catecholamines can also be destroyed by this route, 70% of adrenaline is methoxylated by catechol-O-methyl transferase (COMT) in the liver and kidney (uptake 2) a process that is also saturable. Most of the circulating adrenaline and noradrenaline is destroyed by COMT, therefore measurement of urinary O-methylated derivatives (metanephrines) has traditionally been viewed as a good index of secretion (Figure 1). A small proportion of catecholamines are conjugated with sulphate or glucuronide in the liver, gut and red blood cells.

Catecholamine synthesis and elimination

Facilitation	Inhibition
Synthesis	
Tyrosine hydroxylase	Metyrosine Dopamine Noradrenaline
Storage	
Dopamine β-hydroxylase	Reserpine Guanethidine
Release	
Angiotensin	α_2-receptor stimulation
Ephedrine	Magnesium
Amphetamine	Guanethidine Bretylium
Reuptake	
Noradrenaline	Cocaine Metaraminol Tricyclic antidepressants Phenothiazines
Monoamine oxidase (MAO) breakdown	
Progesterone	Monoamine oxidase inhibitors (MAOIs) Oestrogen
COMT breakdown	Corticosteroids Phenoxybenzamine

2

The overall cardiovascular response to adrenoreceptor stimulation is moderated by the baroreceptors and other reflex mechanisms (Figure 3). Thus, a sudden rise in aortic pressure in response to an α_1-agonist (e.g. phenylephrine) may result in reflex bradycardia and subsequent redistribution of plasma volume. Specific agonists and antagonists at the four adrenoreceptor subtypes are listed in Figure 4.

Adrenoreceptor effects

Receptor	Principal effects
α_1	Vasoconstriction, uterine contraction, increased sweating, decreased insulin release, decreased glucagon release
α_2	Inhibition of further noradrenaline release (presynaptic adenylate cyclase inhibition)
β_1	Chronotropy, inotropy, arrhythmogenicity, renin secretion
β_2	Smooth muscle relaxation in the bronchi, vascular wall, uterus, adipose tissue, lipolysis, insulin and glucagon secretion

3

Adrenoreceptor agonists and antagonists

Agonists	Antagonists
α_1-receptor	
• Phenylephrine • Methoxamine • Adrenaline • Noradrenaline • Isoprenaline (weak)	• Doxazosin • Phentolamine • Phenoxybenzamine • Magnesium
α_2-receptor	
• Clonidine • Adrenaline • Noradrenaline • Isoprenaline (weak)	• Phentolamine • Phenoxybenzamine
β_1-receptor	**β_1- and β_2-receptor antagonists**
• Isoprenaline • Adrenaline • Noradrenaline	• Propranolol • Esmolol • Labetalol • Atenolol
β_2-receptor	• Bisoprolol • Celiprolol (β_1 selective)
• Isoprenaline • Adrenaline • Noradrenaline (weak)	

4

Predisposition

Most phaeochromocytomas (90%) occur sporadically and are benign. However, familial predisposition occurs in multiple endocrine neoplasia type 2 (MEN 2A, 2B and 2C), von Hippel–Lindau disease, neurofibromatosis type 1 (von Recklinghausen disease), and familial carotid body tumours. MEN 2A (Sipple's syndrome) displays autosomal dominant inheritance and is characterized by the association of medullary thyroid carcinoma, phaeochromocytoma and parathyroid hyperplasia. The underlying genetic link seems to be a mutation of the *RET* gene resulting in an oncogene that drives cellular proliferation in the target endocrine organs that make up the MEN 2 triad. These patients often have bilateral adrenal phaeochromocytomas and are more likely to have adrenaline-secreting tumours than sporadic phaeochromocytomas. In von Hippel–Lindau syndrome the mutation is slightly different, resulting in the inactivation of a tumour suppressor gene. Patients can develop bilateral kidney tumours and cysts, phaeochromocytomas, retinal angiomas, pancreatic cysts and tumours, cerebellar or spinal haemangioblastomas, epididymal cystadenomas, and tumours of the inner ear.

Diagnosis

History and physical examination: symptoms are variable. Hypertension is the most common clinical sign. It may be sustained or paroxysmal. Patients also describe episodes of anxiety, excessive sweating, palpitations (both fast and slow) and headache. The presentation depends on the nature of the tumour. Those secreting mainly noradrenaline present with hypertension, headaches and slow, thudding palpitations, whereas those secreting adrenaline present with tachycardias and anxiety attacks. Nausea and vomiting may be a result of excessive dopamine release. Intense vasoconstriction can also give rise to pallor and goose pimples. The symptoms are not specific, only 0.5% of those tested on clinical suspicion with hypertension prove to have a phaeochromocytoma.

Differential diagnosis: it is difficult to distinguish the normally functioning sympathetic nervous system from the episodic overactivity of a phaeochromocytoma because catecholamines tend to be reabsorbed or metabolized quickly following their release. Attempts at measurement of plasma catecholamines give only a brief snapshot of the pharmacological state of the sympathetic system and may give rise to false-negative results. Sensitivity may be improved by detecting the plasma metabolites normetanephrine and metanephrine (Figure 1). The abnormal threshold for normetanephrine is 2.5 pmol/ml and that for metanephrine is 1.4 pmol/ml. Alternatively the 24-hour excretion of urinary catecholamines and metabolites can be measured. The abnormal threshold is over 140 nmol/litre for adrenaline and over 800 nmol/litre for noradrenaline.

Phaeochromocytomas are rare and biochemical screening tests give many false-positive results despite repeat testing. Specificity can be enhanced by follow-up of borderline abnormal patients with a clonidine suppression test. Clonidine is an α_2-agonist and usually causes a decrease in physiological release of noradrenaline from sympathetic nerve terminals. Lack of suppression is suggestive of a phaeochromocytoma in the absence of reuptake inhibitors (tricyclic antidepressants, cocaine, metaraminol, phenothiazines). Alternatively a glucagon stimulation test can be used which, in the presence of a phaeochromocytoma, results in a greater than threefold increase in plasma noradrenaline within 2 minutes of intravenous glucagon administration.

Localization: CT localizes adrenal phaeochromocytomas with a sensitivity of 93–100%. Sensitivity is 90% for extra-adrenal tumours but is slightly higher using MRI. Both techniques have poor specificity, but if there is doubt, nuclear imaging using ^{123}I-metaiodobenzylguanidine scintigraphy enhances the ability to identify and localize the catecholamine source. Extra-adrenal tumours can also be located by selective vena caval sampling for plasma catecholamines and metanephrines or by positron emission tomography for selectively bound radionuclide markers.

Preoperative preparation

Surgical excision can be undertaken safely only when stability has been imposed pharmacologically on the sympathetic system. The main clinical objectives are to achieve stable blood pressure, heart rate and rhythm and to allow time for blood volume to be restored to normal. The over-production of catecholamines can be interrupted, blocked or antagonized at the point of synthesis, release or receptor action (Figures 2–4). Control of blood pressure by β-adrenoreceptor blockade alone may cause hypertension secondary to β_2-blockade or may cause cardiac failure because of the fall in contractility in the face of high afterload. The traditional approach is to institute α-adrenoreceptor blockade and then to add β-adrenoreceptor blockade if necessary.

Oral phenoxybenzamine has been used for many years. It covalently binds to α_1- and α_2-adrenoreceptors. It blocks catecholamine-induced vasoconstriction and catecholamine reuptake (Figures 3 and 4) resulting in β-adrenoreceptor stimulation that manifests as a tachycardia. Therefore, use of phenoxybenzamine usually necessitates the use of adjuvant β-blockade. Preoperative control is good, but postoperatively, patients remain sleepy and may require large amounts of intravenous fluid to maintain blood pressure until the blockade has worn off, despite stopping phenoxybenzamine 24–48 hours before surgery.

Doxazosin is a competitive selective α_1-adrenoreceptor antagonist that can be given as a single daily oral dose of up to 16 mg. Because doxazosin does not block presynaptic α_2-adrenoreceptors, it does not cause a tachycardia and β-blockade is necessary only if the tumour secretes adrenaline. Doxazosin has a longer duration of action than other competitive antagonists (e.g. prazosin) so administering the drug up to and including the eve of surgery allows adequate perioperative cover without the complication of significant postoperative hypotension.

Selective β_1-adrenoreceptor blockade is indicated for patients who have an adrenaline-secreting phaeochromocytoma. It is also likely to be required for those established on phenoxybenzamine preoperatively with a tachycardia induced by α_2-adrenoreceptor mediated reuptake inhibition. Suitable options include atenolol, 100 mg/day, or bisoprolol, 10–20 mg/day.

Having achieved preoperative cardiovascular stability, the main determinant of perioperative risk is the baseline myocardial state of the patient. Chronic exposure to high circulating catecholamine concentrations can result in cardiomyopathy therefore a screening echocardiogram is advisable in addition to an ECG (Figure 5).

General principles of elective phaeochromocytoma surgery

Preoperatively

- Determine where the tumour is and what it secretes
- Investigate myocardial function with ECG and echocardiogram
- Establish α_1-adrenergic blockade to control hypertension (e.g. doxazosin)
- Consider adding β_1-adrenergic blockade to control heart rate or rhythm (e.g. atenolol or bisoprolol)

Peroperatively

- Sedative premedication
- Invasive blood pressure monitoring pre-induction
- Obtund pressor response to intubation at induction
- Central venous pressure (CVP) monitoring (antecubital long line or internal jugular line)
- Maintain anaesthesia with a moderate degree of vasodilatation (e.g. isoflurane)
- Establish adequate surgical analgesia by T9–L1 epidural or opioid infusion
- Control blood pressure surges in response to surgical manipulation with: α-receptor antagonists (e.g. phentolamine, 1–2 mg) magnesium sulphate infusion (therapeutic range 2–4 mmol/litre)
- Control tachydysrhythmias with β-blockade (e.g. labetalol, 5 mg)
- Wind down epidural infusion before final cross-clamp of drainage veins of tumour
- Keep up with fall in CVP with intravenous fluids when pressor effects diminish

Postoperatively

- HDU/ITU care with invasive blood pressure/CVP monitoring until normalized
- Wake up early to minimize hypotension secondary to residual α_1-blockade
- Use posture and intravenous fluids to maintain blood pressure; vasopressors tend to be ineffective

Peroperative management

Adrenalectomy can be performed using an open lateral retroperitoneal approach or by laparoscopic transperitoneal surgery. Open surgery is quicker and less likely to result in surges in catecholamine release, but is more painful postoperatively. Recovery time from a laparoscopic procedure is shorter and patients mobilize within 24 hours and can be discharged within 48 hours. However, they spend longer on the operating table and more marked peaks in catecholamine release are observed during surgical manipulation. Control of these cardiovascular perturbations is the main challenge facing the anaesthetist because they occur regardless of depth of anaesthesia, analgesia and efficacy of central neural blockade. Preoperative preparation with adrenoreceptor antagonists blunts the magnitude and rate of cardiovascular change but does not eliminate the effects of physical manipulation of the tumour. Reliable invasive monitoring of arterial and central venous pressure is essential. Use of epidural analgesia (T9–L1) or opioid infusion (e.g. remifentanil, alfentanil) helps by eliminating noxious stimuli from provoking catecholamine release but more direct antagonists are also required. A general anaesthetic using one of the volatile agents has the advantage of providing some vasodilatation, but in practice this will need to be supplemented by other agents (Figures 2–4).

Magnesium sulphate has several potentially beneficial actions. It is anti-arrhythmic as a result of myocardial calcium channel blockade, regulation of intracellular potassium and ATP activation. It acts as a vasodilator by blocking the adrenoreceptor response to noradrenaline and angiotensin II. It also inhibits catecholamine release from the adrenal medulla and peripheral adrenergic nerve terminals. It is normally presented as a 50% solution in a 10 ml ampoule (500 mg/ml = 2 mmol/ml). The effective therapeutic plasma concentration is 2–4 mmol/litre. This can usually be achieved with an initial loading dose of 40–60 mg/kg intravenously followed by an infusion of 2 g/hour. Side-effects include a prolongation of neuromuscular blockade and inhibition of platelet activity.

Phentolamine is a competitive α_1- and α_2-adrenoreceptor antagonist that can be given intravenously by infusion or in 1–2 mg increments. It acts within one circulation time and can be administered in direct response to observed changes in systemic blood pressure. It is generally presented as a 10 mg/ml preparation in a 1 ml ampoule which should be diluted to a 1:10 solution for clinical use. Side-effects include a tachycardia secondary to presynaptic α_2-blockade.

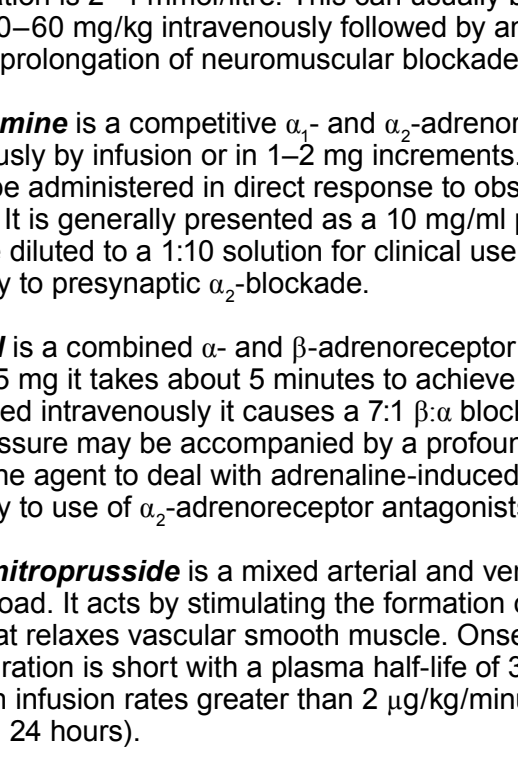
Labetalol is a combined α- and β-adrenoreceptor blocker. Given in incremental doses of 5 mg it takes about 5 minutes to achieve an effect that can last for several hours. Used intravenously it causes a 7:1 β:α blockade. Therefore an observed fall in blood pressure may be accompanied by a profound fall in heart rate. It makes a useful second-line agent to deal with adrenaline-induced tachydysrhythmias and tachycardias secondary to use of α_2-adrenoreceptor antagonists.

Sodium nitroprusside is a mixed arterial and venous dilator that reduces preload and afterload. It acts by stimulating the formation of cyclic guanosine monophosphate (GMP) that relaxes vascular smooth muscle. Onset time is rapid over a few seconds and its duration is short with a plasma half-life of 3–4 minutes. Cyanide poisoning can occur with infusion rates greater than 2 μg/kg/minute but are unlikely in the short term (less than 24 hours).

Towards the end of the operation one needs to anticipate the sudden exponential drop in blood pressure that usually accompanies application of the final clamp to vessels draining the phaeochromocytoma (Figure 6). Even with the presence of central venous monitoring it can be difficult to predict the final volume status of the patient, because the intermittently high levels of circulating catecholamines during the procedure tend to cause marked changes in central venous filling pressure. This is a time to reduce the hypotensive effect of other agents including the epidural.

Clamping of adrenal vein accompanied by fall in blood pressure during elective laparoscopic adrenalectomy[1]

Drug	Unit								
Phentolamine	mg	1	2	1	1 2				
Labetalol	mg								
Air	l/min	2	2	2	2	2	2	2	
Oxygen	l/min	1	1	1	1	2	2	1	
Isoflurane	In	1.5	1.5	1.5	1.6	1.0	1.0	1.2	
Isoflurane	Ex	1.2	1.2	1.2	1.3	1.0	1.0	1.1	
	Time	4.00	4.15	4.30	4.45	5.00	5.15	5.30	



CVP	7	14	7	9	6	8	11	
FiO2	.45	.45	.45	.45	.45	.6	.5	
SaO2	100	100	100	100	100	100	100	
Temperature	37	37	37	37	37	37	37	
ETCO2	44	43	43	43	43	34	40	
IV fluid					500	500		

[1]This fall may be profound in the under-filled, heavily α- and β-blocked patient.

Postoperative management

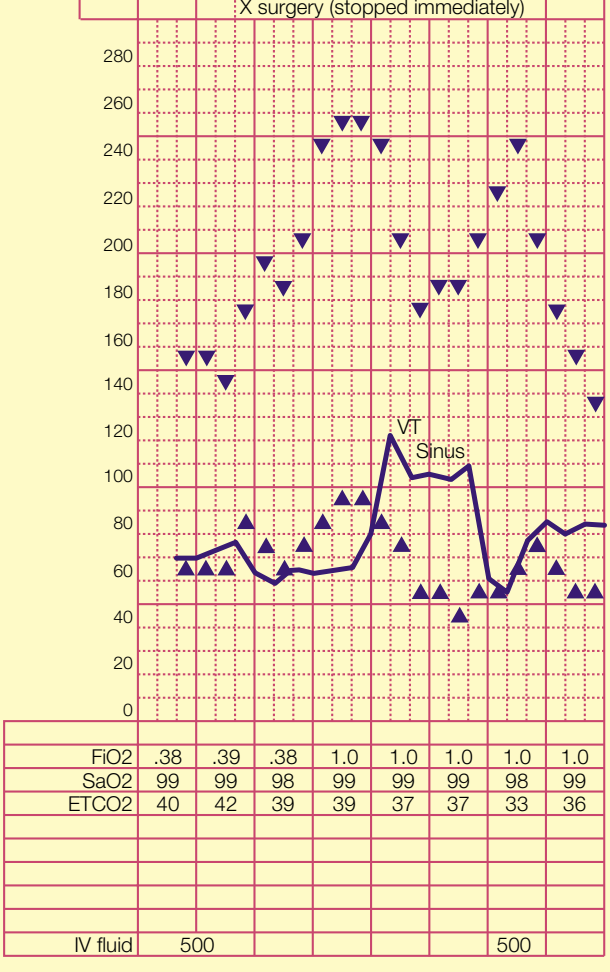
Postoperative care should be based in a high dependency care area with facilities to monitor and react to continuous invasive blood pressure and central venous pressure changes. Postoperative hypotension is the most commonly encountered problem (Figure 6), because the source of catecholamines has been removed but the effects of adrenergic blockade remain. It can be difficult to treat because pressor agents in standard doses are ineffective. Attention to fluid balance and posture are the most effective interventions. Early extubation should be attempted. An awake reticular activating system helps to maintain blood pressure by stimulating release of noradrenaline from sympathetic nerve endings. Normal secretion of catecholamines from the contralateral adrenal gland will have been suppressed by the phaeochromocytoma, and adrenoreceptors will be blocked and down-regulated for some time. Analgesic requirements depend largely on whether surgery has been open or laparoscopic. Those who have had open surgery probably require continued epidural analgesia, while those who have had laparoscopic surgery tend to require oral analgesia only. Blood glucose should be monitored because hypoglycaemia may occur. Steroid replacement therapy is not usually required unless bilateral adrenalectomies have been performed

Emergency presentation

Phaeochromocytomas may present unexpectedly during coincidental surgery because of their non-specific symptoms and episodic nature (Figure 7). An awareness of the known associations should alert the anaesthetist to the possibility of an underlying phaeochromocytoma when faced with a sudden unexplained severe hypertensive episode, but because most cases are sporadic one needs to keep an open mind. If the diagnosis is suspected on the table, all stimulation should be stopped immediately. If the tumour secretes predominantly noradrenaline, systemic hypertension may be accompanied by a baroreceptor-mediated reflex bradycardia. Peripheries will be cold and pale as a result of vasoconstriction and the patient may have ‘goose bumps’.

Emergency presentation of a noradrenaline secreting phaeochromocytoma during thyroidectomy[1]

Drug	Unit								
Fentanyl	mg		200		50				
Propofol	mg		100						
Vecuronium	mg		8						
Hydralazine	mg				5 5				
Phentolamine	mg				2 2		1	1 2 2	- 10 -	- 10 -
Labetalol	mg							5		
Magnesium	g								4	
Nitrous oxide	l/min	0	0.7	0.7	0	0	0	0	0	0
Oxygen	l/min	8	0.6	0.6	8	5	5	5	5	5
Isoflurane	In	2	1.5	2.0	5.0	3.0	2.0	2.0	1.5
Isoflurane	Ex	1.0	0.8	1.2	3.2	2.6	1.4	1.4	1.2
	Time	0	15	30	45	60	75	90	



FiO2	.38	.39	.38	1.0	1.0	1.0	1.0	1.0
SaO2	99	99	98	99	99	99	98	99
ETCO2	40	42	39	39	37	37	33	36
IV fluid	500						500	

[1]Note how ineffective vasodilators (hydralazine and isoflurane) alone were in managing the hypertension. Use of phentolamine provided transient control of blood pressure but also caused a tachycardia that responded to β-blockade. Cardiovascular control was finally achieved with a combination of α-blockade (phentolamine) and magnesium.

7

Myocardial ischaemia may be evident on the ECG and may be complicated by tachydysrhythmias, especially if the tumour secretes adrenaline. Severe hypertension may be accompanied by pulmonary oedema. There is no justification for proceeding with surgical excision in these circumstances, because mortality is unacceptably high without preoperative adrenoreceptor blockade. Control should be attempted with the agents described above (Figure 4) and the operation should be terminated with the minimum of surgical stimulation as quickly as possible. Postoperative intensive care should include cardiac troponin assay and 24-hour urinary catecholamine excretion. The patient can then be re-booked at a later date, having planned and implemented a multidisciplinary approach to the problem. ◆

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Airway Trauma in ENT

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Airway trauma in ear, nose and throat (ENT) surgery can be broadly categorized as:
- external laryngeal injury caused by blunt trauma or penetrating injuries to the neck
- iatrogenic injury related to intubation trauma, prolonged intubation or tracheostomy.

External laryngeal injury

Patients requiring airway management can be divided into those presenting with obvious respiratory distress requiring immediate intervention to establish a patent airway and effective ventilation and those presenting with no obvious respiratory distress who require careful evaluation and observation. Up to 25% of these patients subsequently require airway intervention.

Immediate intervention for airway control may involve tracheostomy under local anaesthetic for massive cervical and laryngeal trauma, orotracheal intubation or intubation through a large open wound in the airway. Orotracheal intubation should be performed by experienced personnel without the use of cricoid pressure, which may result in cricotracheal separation and loss of airway patency. In this situation, the risk of aspiration is less significant than the potential loss of the airway. Fibre-optic intubation is difficult under these circumstances owing to airway distortion, bleeding and the difficulties of passing a fibrescope past areas of airway damage. It is not recommended.

Orotracheal intubation should be attempted with a selection of small tubes, with straight and curved laryngoscopy blades available. If elevation of the vallecula with a curved blade fails to pull a dislocated epiglottis forward, a straight laryngoscope blade may be required to elevate the epiglottis directly. Oral intubation may cause further laryngeal trauma by forcing debris lower down the airway and worsening laryngotracheal disruption.

No obvious respiratory distress – patients presenting with no obvious respiratory distress require a high degree of suspicion for airway trauma. Preventable deaths occur in up to 10% of patients with airway trauma. Symptoms suggestive of laryngeal trauma include dyspnoea, pain, dysphagia and hoarseness. Examination may reveal abrasions over the anterior neck, upper airway noises resulting from oedema or foreign bodies, stridor, haemoptysis with frothy blood, subcutaneous emphysema, loss of palpable landmarks in the thyroid or cricoid cartilage, and pneumothorax. Careful, gentle assessment should be undertaken to avoid accidental dislodgement of unstable cartilage fragments, which may cause airway compromise. Flexible fibre-optic laryngoscopy identifies oedema, haematomas and vocal fold paralysis caused by recurrent laryngeal nerve injury while CT scans identify laryngeal cartilaginous damage.

Small mucosal lacerations, small haematomas and single non-displaced fractures of the thyroid cartilage can be managed conservatively with close observation. Treatment includes voice rest, head elevation, humidified air to prevent crusting, antibiotics and early steroid use to reduce oedema. Intervention by oral intubation or tracheostomy may be required if airway deterioration occurs.

Iatrogenic airway trauma

Laryngeal trauma from tracheal intubation still occurs despite the change to high volume, low pressure cuffs in patients of all ages. Although most changes are superficial and heal quickly, a few patients develop glottic or subglottic stenosis and present with airway compromise many weeks or months after a period of prolonged intubation. Some patients sustain severe airway damage after relatively short periods of intubation. Early, nonspecific changes in the airway include oedema and superficial ulceration resulting in granulation tissue, which may form firm scar tissue.

Patients who complain of a sore throat and weak voice after intubation may have arytenoid subluxation. Attempts to induce this lesion in cadavers have failed and it has been suggested that the condition is better termed 'post-intubation crico-arytenoid dysfunction'. An understanding and awareness of the factors that predispose to iatrogenic laryngeal trauma is important in reducing morbidity associated with these injuries (Figure 1). ◆

Factors predisposing to intubation trauma

Tube placement
- Emergency intubation by unskilled individuals
- Repeated attempts at intubation
- Improper use of introducers
- Abnormal larynx

Tube characteristics
- External diameter, shape, stiffness and material
- Cuff volume and pressure

Duration of intubation
- No universal agreement on safe period
- Decision for tracheostomy at 5–14 days dependent on general condition
- Longer duration with infants than with adults

General conditions
- Gastro-oesophageal reflux with spillover
- Impaired mucociliary clearance
- Acute or chronic disease states with poor tissue perfusion and hypoxia
- Infection

Anaesthesia for Endoscopic Surgery

Anil Patel

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Anaesthesia for endoscopic procedures of the supraglottis, glottis and subglottis requires close cooperation between anaesthetist and surgeon, an understanding of each other's problems and knowledge of specialist equipment. Shared airway procedures are unique in that both anaesthetist and surgeon are working in the same anatomical field. The anaesthetist is concerned with adequate oxygenation, removal of carbon dioxide, maintenance of an adequate airway and the prevention of soiling of the tracheobronchial tree, while the surgeon requires an adequate view of a clear motionless operating field.

Patients vary from young, otherwise fit and well individuals, presenting with voice changes secondary to benign vocal cord pathology (e.g. small nodules, polyps), to elderly, heavy smokers with chronic obstructive pulmonary disease presenting with voice changes, dysphagia and stridor caused by glottic carcinoma. Different anaesthetic techniques are suitable for different patients.

Preoperative assessment

Standard airway assessments to predict the ease of ventilation, visualization of the laryngeal inlet and tracheal intubation should be performed. An assessment of airway pathology and its impact on airway management should be made.

A history of previous endoscopic procedures and outcome should be noted. Dysphagia, best breathing position, breathing pattern during sleep, voice changes and stridor give an indication of the severity of disease. Patients may have no obvious stridor on initial examination but it may become apparent as the patient lies down, changes from their best breathing position or on minimal exertion. Inspiratory stridor is usually associated with lesions above the glottis whereas expiratory stridor is usually seen with lesions below the glottis.

The severity and size of lesions at the glottic level are assessed by direct or indirect laryngoscopy, undertaken by surgeons in an outpatient setting; a photograph of the findings is often recorded in the notes. Information about subglottic and tracheal lesions is provided by chest radiography, CT and MRI.

The size, mobility and location of lesions should be identified before anaesthetizing the patient.

Size of the lesion gives an indication of potential airflow obstruction. Stridor indicates a significantly narrowed airway. In the adult, stridor implies an airway diameter of less than
4.5 mm, but the absence of stridor does not exclude a significantly narrowed airway.

Mobility – very mobile lesions (e.g. multiple large vocal cord polyps or papillomas) can cause airway obstruction following induction of anaesthesia because their mobility and the loss of supporting tone in the larynx can allow them to 'fall' into the airway.

Location – supraglottic lesions, if mobile, can obstruct the airway or make visualization of the laryngeal inlet difficult. Subglottic lesions may allow a good view of the laryngeal inlet but cause difficulty during the passage of a tracheal tube or during jet ventilation.

Foreign body aspiration is most common in children aged 1–4 years and most foreign bodies enter the right main bronchus. The symptoms and signs are relative to the size of the object, its mobility and location. Partial obstruction of the larynx or trachea presents as stridor, dyspnoea, coughing and drooling. Bronchial foreign bodies mainly cause coughing, wheezing, dyspnoea and reduced ventilation on the affected side.

Vocal cord pathology

Nodules are benign lesions of the vocal fold that are usually bilateral and caused by vocal abuse.

Polyps are benign lesions of the vocal fold, common in adults. They are usually unilateral and can be sessile or pediculated, oedematous or angiomatous. The aetiology is multifactorial and includes vocal abuse and trauma. They often require surgery with careful dissection or laser phonosurgery.

Cysts are benign lesions commonly seen in adults. They are caused by obstruction of a glandular duct resulting in a mucous retention cyst. They are often seen in young women, particularly professional voice users, and are treated with careful dissection.

Granulomas are benign lesions induced by healing granulo-matous tissue, which develops after microtrauma. They are usually found on the posterior third of the vocal process following trauma during intubation or extubation. Resection is required if they are large and disturbing breathing.

Papillomas are benign lesions caused by human papilloma virus infection and can undergo malignant transformation. In adults, hoarseness is usually the main symptom while in children airway obstruction can occur. Following laser resection, papillomas can recur and some patients require repeated laser phonosurgery at 3–12-monthly intervals.

Malignant tumours are usually unilateral and occur mainly on the middle third of the vocal fold. 80% are found in men aged 40–65 years. Over 97% of patients are smokers with a high alcohol intake. Treatment depends on tumour staging and involves local resection, radiotherapy or transoral laser resection.

Other lesions are caused by haemangiomas, submucous haemorrhage, Reinkes oedema and chronic laryngitis.

Anaesthetic techniques for endoscopy

Ideal technique: there is no ideal anaesthetic technique for all endoscopy procedures. The technique depends on the patient's general condition, the size, mobility and location of the lesion, the use of a laser and surgical requirements.

The ideal technique would:

- be simple to use
- provide complete control of the airway with no risk of aspiration
- control ventilation with adequate oxygenation and carbon dioxide removal
- provide smooth induction and maintenance of anaesthesia
- provide a clear motionless surgical field, free of secretions
- not impose time restrictions on the surgeon
- not be associated with the risk of airway fire or cardiovascular instability
- allow safe emergence with no coughing, bucking, breath holding or laryngospasm
- produce a pain-free, comfortable, alert patient with minimum hangover effects.

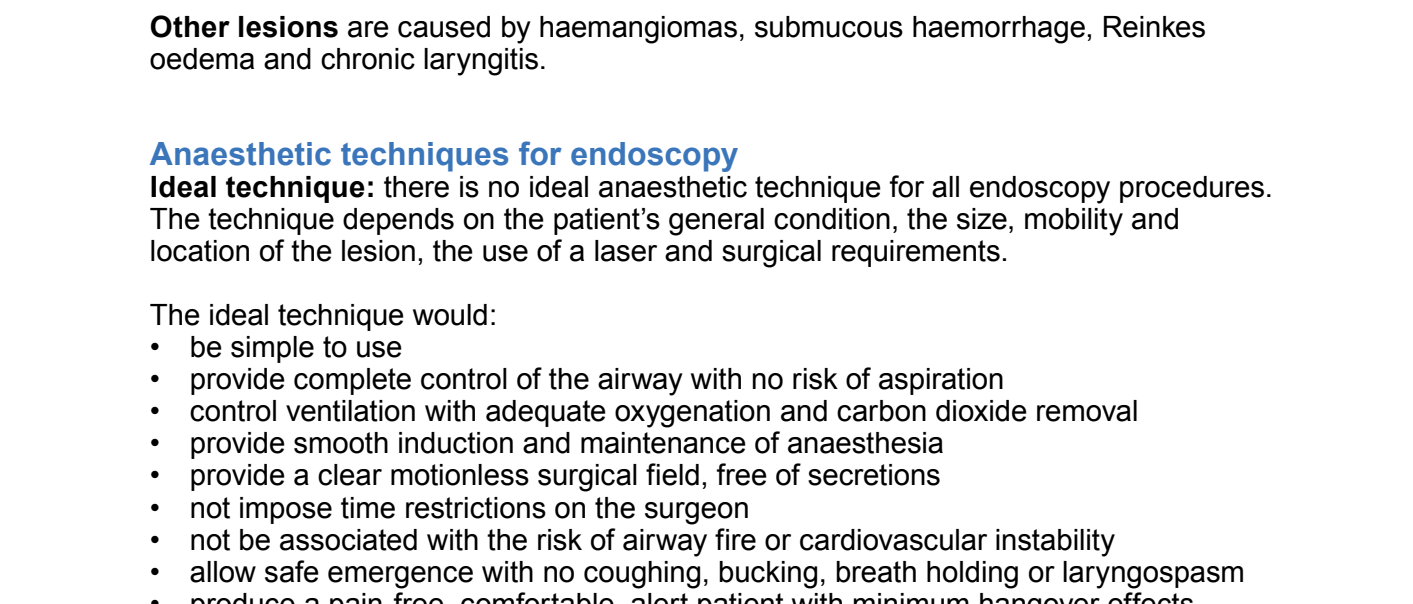
Some of these ideals conflict. The presence of a cuffed tracheal tube provides control of the airway and prevents aspiration but may obscure a glottic lesion and is not laser safe (Figure 1b). A cuffed laser tube provides some protection against laser-induced airway fires but has a greater external diameter to internal diameter ratio and may obscure laryngeal lesions. Jet ventilation techniques require specialist equipment and knowledge and an understanding of their limitations.

Basic technique: following intravenous induction of anaesthesia, mask-bag ventilation is manually confirmed before administration of muscle relaxants appropriate to the length of surgery. Laryngoscopy is undertaken to visualize the lesion, establish laryngoscopy grade and administer topical local anaesthetic (lidocaine (lignocaine)). Confirmation of pathology is important because the disease may have progressed since the last outpatient visit and the anaesthetic plan may have to be changed. Topical local anaesthetic is essential for the supraglottis, glottis and subglottis for cardiovascular stability, reduction of airway reflexes and smooth recovery.

Intubation techniques

Microlaryngoscopy tubes

Microlaryngoscopy tubes have a small internal and external diameter and have been designed specifically for endoscopy procedures because the small external diameter allows the surgeon a good view of the glottis (Figure 1c). Advantages of microlaryngoscopy tubes include control of the airway, the presence of a cuff, which protects against aspiration, and a motionless field for the surgeon. Disadvantages include the inability to use a laser because of the risk of an airway fire, obscuring the posterior commissure area where pathology may be missed, and increased airway resistance allowing spontaneous ventilation for short periods only.



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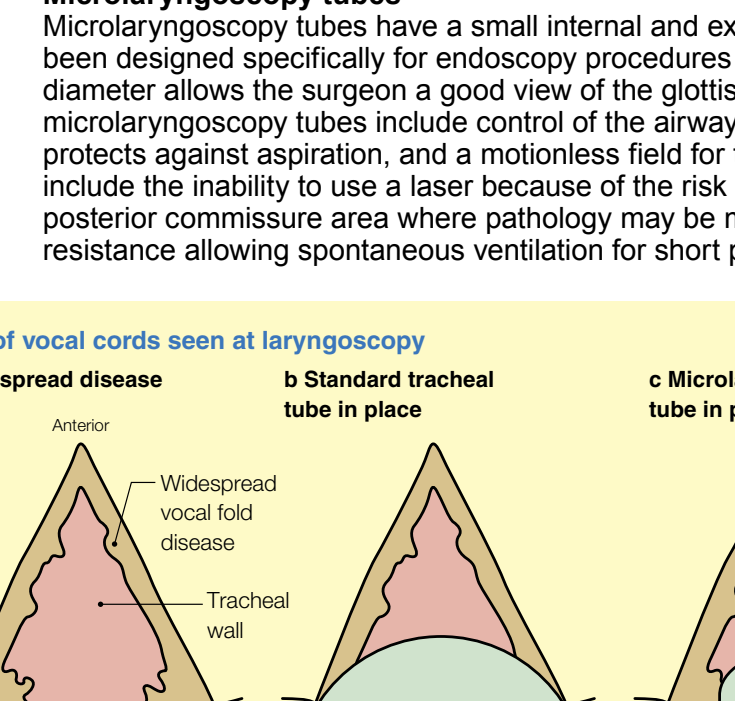
Laser tubes

Laser microsurgery of the airway allows precise surgical cutting, coagulation and sealing with little postoperative oedema. Lasers are used for the resection of papillomas, vascular lesions of the vocal cords, granulomas and laryngeal carcinomas. Carbon dioxide lasers are the most commonly used in airway surgery and are targeted towards the glottis by aiming mirrors integral to operating surgical microscopes. The two main hazards from the use of a laser are the risk to operating theatre staff from diverted laser radiation and the risk to the patient from a laser-induced airway fire.

An airway fire occurs only if the three components of the fire triangle are present (Figure 2). To minimize these risks the inspired oxygen concentration should be the lowest that maintains adequate oxygen saturations, and air should be used in preference to nitrous oxide. The potential fuel source should have laser-resistant properties (laser tubes) or be removed (supraglottic jet ventilation technique). The only non-flammable laser tube is the Norton (Figure 3) which is constructed of steel. Most laser tubes have laser-resistant properties, but ignite with sustained laser energy strikes. Laser tubes have greater external diameter to internal diameter ratios owing to their laser-resistant protective coverings and may obscure airway lesions.



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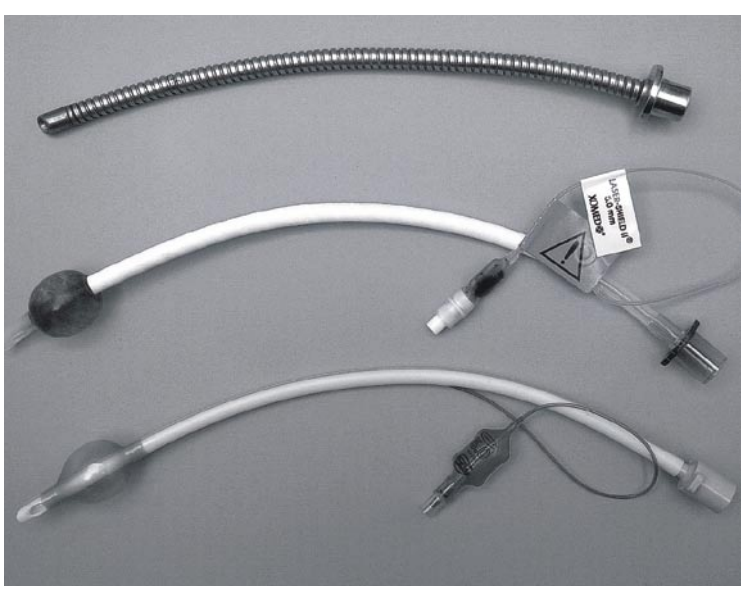
Anaesthetists involved in cases using lasers for airway surgery should be familiar with the causes of a laser airway fire, the limitations of laser-resistant tubes and an airway fire drill (Figure 4).

Non-intubation techniques

Spontaneous ventilation technique

Spontaneous ventilation techniques are used in the management of foreign body aspiration and for the dynamic assessment of the airway in patients with, for example, tracheomalacia. The technique allows a clear view of an unobstructed glottis. Anaesthetic management of patients with foreign body aspir-ation should aim to provide adequate oxygenation, a smooth induction, prevention of fragmentation or distal movement of the foreign body, sufficient depth of anaesthesia to prevent coughing, bronchospasm and laryngospasm, and smooth recovery.



3a Metal Norton tube with no cuff. **b** 5.0 mm internal diameter Xomed Laser Shield II. **c** 5.0 mm internal diameter Portex microlaryngoscopy tube.

Airway fire drill

Immediate action simultaneously
- Put out fire – flood field with saline (which must be immediately available)
- Remove energy source – stop laser
- Remove oxidant source – disconnect circuit, stop ventilation, stop gases
- Remove fuel source – extubate and remove burning fragments

Urgent action
- Review airway – ensure no burning fragments
- Oxygenate – 100% oxygen by bag and mask
- Review damage – flexible or rigid bronchoscopy
- Establish airway – re-intubate, laryngeal mask airway or jet ventilate

Assessment
- No airway damage – may proceed with surgery
- Severe airway damage – tracheostomy or oral intubation, ICU admission and controlled ventilation

4

Following inhalation induction with sevoflurane or halothane in 100% oxygen, intravenous access is established at an appropriate depth of anaesthesia, if not already present. When a suitable depth of anaesthesia is reached, laryngoscopy is undertaken and topical local anaesthetic (lidocaine (lignocaine)) administered above, below and at the level of the vocal cords. 100% oxygen is administered by face mask with spontaneous ventilation and anaesthesia continued with inhalational or intravenous (propofol) agents. At a suitable depth of anaesthesia the surgeon undertakes rigid laryngoscopy and bronchoscopy.

Insufflation technique
The insufflation technique requires a spontaneously breathing patient. Insufflation of anaesthetic gases and agents can be via a number of routes, including:
- a small catheter introduced into the nasopharynx and placed immediately above the laryngeal opening
- a tracheal tube cut short and placed through the nasopharynx emerging just beyond the soft palate
- a nasopharyngeal airway
- the side-arm or channel of a laryngoscope.

Insufflation techniques are useful in the removal of foreign bodies, evaluation of airway dynamics (tracheomalacia) and relatively fixed lesions (glottic, subglottic stenosis). Movements of the vocal cords are minimal or absent despite a spontaneously breathing technique provided an adequate level of anaesthesia is maintained. Limitations of insufflation techniques include:
- no control over ventilation
- loss of protective airway reflexes and the potential for the airway soiling
- theatre pollution with volatile agents requiring the presence of high-intensity suction catheters near the mouth.

Insufflation techniques may not be suitable for soft floppy lesions, particularly in the supraglottis or glottis, which may obstruct the airway following the onset of general anaesthesia.

For satisfactory insufflation techniques an adequate depth of anaesthesia is vital. If the depth of anaesthesia is too light, movement may occur, the patient may cough or laryngospasm occur. If the depth of anaesthesia is too great the patient may become apnoeic with cardiovascular instability. Careful observation throughout the procedure, noting movements, respiratory rate and depth, cardiovascular stability and constant observation for unobstructed breathing are vital, with the concentration of volatile anaesthetic adjusted accordingly.

Intermittent apnoea techniques
Intermittent apnoea techniques have been described for the laser resection of juvenile laryngeal papillomatosis, where the presence of a tracheal tube obstructs surgery. Following induction of general anaesthesia and confirmation of ventilation by face mask, muscle relaxants are administered followed by tracheal intubation. The patient is hyperventilated with a volatile anaesthetic agent in 100% oxygen. The tracheal tube is then removed, leaving the surgeon a clear unobstructed immobile surgical field. After an apnoeic period of typically 2–3 minutes, surgery is stopped, the tracheal tube is reinserted and the patient hyperventilated once more. The advantages of the technique are the immobile unobstructed surgical field and the inherent safety in the use of a laser with the potential fuel source (tracheal tube) removed. Disadvantages of the technique include:
- risk of aspiration of blood and debris with the tracheal tube removed
- variable levels of anaesthesia
- interruption to surgery for reintubation
- potential trauma through multiple reintubation.

Jet ventilation techniques
In 1967, Sanders first described a jet ventilation technique using a 16-gauge jet placed down the side-arm of a rigid bronchoscope and relying on air entrainment to continue ventilation with an open bronchoscope. Sanders used intermittent jets of oxygen (rate 8/minute, 3.5 bar driving pressure) to entrain air and showed the technique maintained supranormal oxygen pressure with no rise in the carbon dioxide pressure

Since 1967, modifications to Sanders' original jet ventilation technique have been made for endoscopic airway surgery. Supraglottic jet ventilation describes a technique in which the jet of gas emerges in the supraglottis by attachment of a jetting needle to the rigid suspension laryngoscope (Figure 5). Subglottic jet ventilation involves placing a small (2–3 mm) catheter or specifically designed tube (Benjet, Hunsaker) through the glottis and into the trachea. Transtracheal jet ventilation involves the placement of specifically designed percutaneous transtracheal catheters through the cricothyroid membrane or trachea.

5 Rigid suspension laryngoscope with jetting needle.

As well as modifications to the site at which the jet of gas emerges, changes to the frequency of jet ventilation have been described. High frequency (greater than 1 Hz, 60 breaths/minute) is used with ventilatory rates typically about 100–150/minute. High frequency jet ventilation allows:
- a continuous expiratory flow of air, enhancing the removal of fragments of blood and debris from the airway
- reduced peak and mean airway pressures with improved cardiovascular stability
- enhanced diffusion and interregional mixing within the lungs resulting in more efficient ventilation.

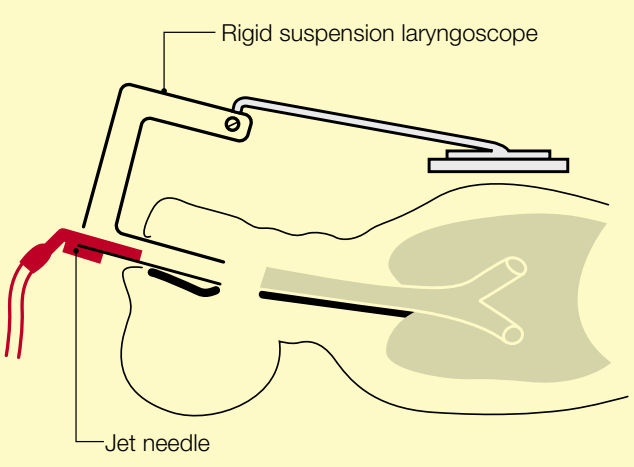
These advantages are of particular importance in patients with significant lung disease and obesity.

A typical jet ventilation technique includes preoxygenation followed by intravenous induction and maintenance with a target-controlled infusion of propofol, supplemented by bolus administration or infusion of alfentanil or remifentanil. At a suitable depth of anaesthesia, manual confirmation of mask ventilation is made before administration of muscle relaxants. Laryngoscopy is undertaken and topical lidocaine (lignocaine) administered. Face mask ventilation is continued with 100% oxygen until the surgeon is ready to site the rigid (suspension) laryngoscope on to which a jetting needle has been attached in preparation for supraglottic jet ventilation. Alternatively, a laryngeal mask airway can be inserted after induction and used to ventilate the patient with 100% oxygen until the surgeon is ready to site the laryngoscope. At the end of surgery, the laryngeal mask airway is reinserted before antagonism of residual muscle relaxation and cessation of intravenous anaesthesia, to facilitate smooth emergence.

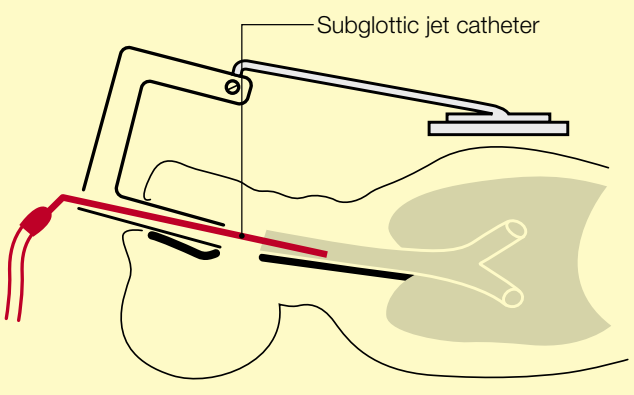
Supraglottic jet ventilation (Figure 6a) is commonly used in endoscopy procedures because it allows a clear unobstructed view for the surgeon with no risk of laser-induced airway fires. In common with all jet ventilation techniques, there is a risk of barotrauma with possible pneumomediastinum, pneumothorax, subcutaneous emphysema and pneumopericardiun. Other problems include:
- gastric distension with entrained air
- malalignment of the rigid suspension laryngoscope or jetting needle resulting in poor ventilation
- blood, debris or fragments being blown into the distal trachea
- vibration and movement of the vocal cords
- inability to monitor end-tidal carbon dioxide concentration.

Jet ventilation

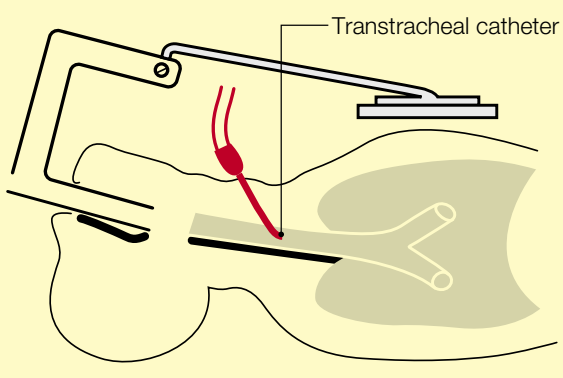
a Supraglottic jet ventilation



b Subglottic jet ventilation



c Transtracheal jet ventilation



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Subglottic jet ventilation (Figure 6b) allows delivery of a jet of gas directly into the trachea. The technique is more efficient than supraglottic jet ventilation and results in reduced peak airway pressures, no vocal cord motion, a good surgical field and no time constraints for the surgeon in the placement of the rigid laryngoscope. The main disadvantages are the potential for a laser-induced airway fire due to the presence of a potential fuel source within the airway, and a greater risk of barotrauma than in supraglottic jet techniques.

Ventilators incorporating alarms and automatic interruption of jet flow when preset pause pressure limits have been reached (i.e. blockage of entrainment and exhalation have occurred) should be used.

Transtracheal jet techniques (Figure 6c): elective transtracheal catheter placement under local anaesthesia in individuals with significant airway pathology or under general anaesthesia for elective laryngeal surgery has been described. Transtracheal jet techniques carry the greatest risks of barotrauma of all jet ventilation techniques. Other potential problems include blockage, kinking, infection, bleeding and failure to site the catheter. The use of transtracheal jet ventilation for endoscopic surgery of the larynx requires careful evaluation of the potential risks and benefits.

Recovery from anaesthesia

Smooth emergence and recovery from anaesthesia are essential. Some studies show a 10–20 fold increase in reintubation following laryngoscopy or panendoscopy when compared with general surgical re-intubation rates. The recovery profile with a laryngeal mask airway provides smooth emergence from anaesthesia and some groups advocate the exchange of microlaryngoscopy tubes, tracheal and laser tubes for a laryngeal mask airway for recovery. ◆

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ENT Emergencies

Richard Semenov

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Ear, nose and throat (ENT) emergencies can cause acute life-threatening situations; they require a calm approach and good leadership skills. Good communication between anaesthetist and surgeon is vital in the management of these patients. This article concentrates on three emergency situations.

Acute epiglottitis

Acute epiglottitis is caused by *Haemophilus influenzae* type B. Epiglottic swelling can cause upper airway obstruction. It is most common in children aged 2–5 years and can progress rapidly from a simple upper respiratory tract infection to acute airway embarrassment. The typical clinical picture is a drooling child, who wants to sit up, with tachypnoea, suprasternal recession and stridor. The absence of a cough helps to distinguish it from laryngotracheobronchitis (croup). Complete airway obstruction may be provoked by pharyngeal examination, intravenous cannulation and excessive excitement. In severe cases, the diagnosis is made on clinical assessment.

The child and parents should be kept calm while experienced anaesthetic, paediatric and ENT help is sought. Anaesthesia should be induced using sevoflurane in 100% oxygen with the patient in the sitting position until tracheal intubation is possible. Induction is usually slow and the apparatus for difficult intubation and the facilities for urgent tracheostomy must be available. Atropine may be given once the intravenous cannula is sited. An oral tracheal tube one size smaller than normal should be used and this can be changed to a nasal tube for increased comfort if intubation is straightforward.

Halothane has been the agent of choice for inhalational induction when a patient's upper airway is partially obstructed. Recently, reports of the use of sevoflurane in the difficult airway have been published. If the airway obstructs completely after reaching a deep plane of anaesthesia, the redistribution of the inhalational agent from the brain to the other body compartments is the primary determinant of time to awakening. Halothane has a higher blood gas solubility, therefore it should redistribute to other compartments more quickly than sevoflurane and the brain concentrations of halothane should fall more rapidly and the patient should regain consciousness faster than with sevoflurane. However, induction with halothane takes longer than with sevoflurane because of its higher blood:gas solubility coefficient, which allows more time for halothane to distribute round the body. The concentration gradient from blood, brain and alveoli to other compartments is therefore lower than with sevoflurane. The blood: tissue solubility coefficient is similar for the two agents. As a consequence, when the airway obstructs, it takes longer to return to consciousness with halothane.

Acute epiglottitis is becoming rare in children, probably because of effective vaccination against *H. influenzae*. The Hib vaccine was introduced in the UK in October 1992. Hib-vaccinated children who develop epiglottitis grow penicillin-sensitive streptococci, making penicillin the first choice treatment, rather than the cephalosporins or chloramphenicol required for *H. influenzae*.

The incidence of acute epiglottitis in adults has increased because of the frequent use of antibiotic agents in childhood with an associated failure to develop immunity against *H. influenzae*. Greater awareness and recognition of the disease may also have played a role. Cases of epiglottitis caused by unusual pathogens are being reported among immunocompromised patients, such as drug abusers.

Obstructed airway in head and neck surgery

If asked about the management of an obstructed airway, many anaesthetic trainees suggest an awake fibre-optic intubation. However, serious complications may be associated with its use. There are three main sites of obstruction:

- supraglottic and glottic lesions causing obstruction
- mid-tracheal obstruction, often secondary to retrosternal goitres and thyroid carcinomas
- lower tracheal and bronchial obstruction, usually from large mediastinal masses (e.g. lymphomas, thymomas, carcinomas).

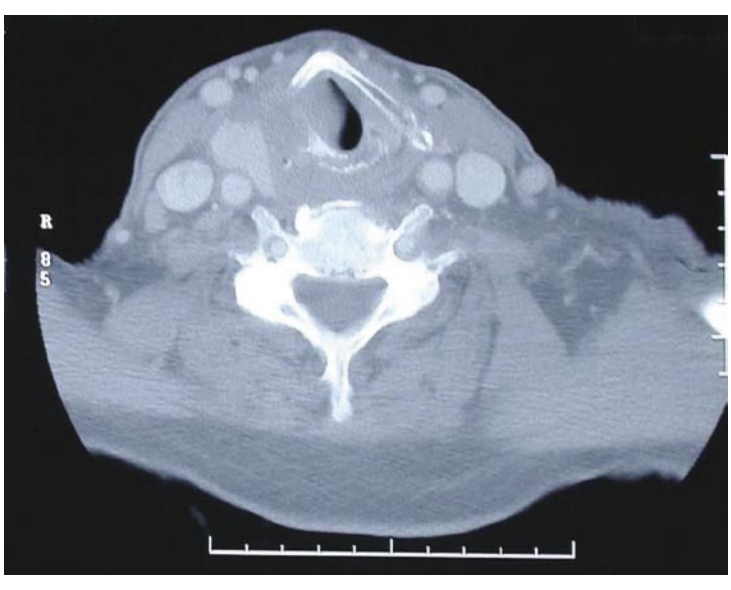
Supraglottic and glottic lesions

Careful preoperative assessment is essential for the management of upper airway obstruction. The implication of stridor is that there is a reduction of airway diameter of at least 50%. Patients often present late owing to the slow-growing nature of the tumours. With severe obstruction there may be difficulty in breathing that wakes the patient at night in a panic. The presence of nocturnal symptoms suggests advanced obstruction. A fibre-optic nasendoscopy will usually have been performed by the ENT surgeon in the outpatient clinic. It does not involve spraying the larynx with local anaesthetic or making contact with the vocal cords, both of which are hazardous and can precipitate complete airway obstruction. A CT scan of the neck is helpful to assess the subglottis and the lower extent of the tumour.

Senior ENT and anaesthetic staff should discuss the case before the patient's arrival in the anaesthetic room. If it is decided to undertake a general anaesthetic a secondary plan should be prepared, in case problems arise, and it should be discussed with the patient. Patients with moderate stridor, in whom intubation is considered possible, should be managed with an inhalational induction in theatre with the ENT surgeon gowned and ready (plan A). A tracheostomy tray and rigid ventilating bronchoscope should be available. Safety lies in the maintenance of spontaneous ventilation, induction takes time and should not be hurried. Difficulty often arises when the patient first loses consciousness. The skill lies in avoiding coughing and subsequent laryngeal spasm. A nasal airway can be helpful.

When anaesthesia is deep enough, laryngoscopy should be attempted and a rapid decision made as to whether a tube can be passed. If a decision is made to intubate, a maximum of two attempts should be made because persistent attempts may result in total obstruction. Correct position should be confirmed with capnography. If it proves impossible to intubate, the surgeon should perform a tracheostomy while the patient maintains spontaneous respiration (plan B). A laryngeal mask airway can be useful to maintain the airway but may prove difficult to insert with a supraglottic tumour.

Patients with severe stridor resulting from a supraglottic or glottic lesion (Figure 1) often come to hospital for the first time as an emergency or have deteriorated following radiotherapy. They should have no sedation and be given a helium:oxygen mixture to improve symptoms. They should have a preliminary surgical airway performed under local anaesthetic. This can be a tracheostomy or an emergency cricothyroidotomy cannula can be placed through the tracheal rings below the level of the tumour to allow subglottic jet ventilation. A formal tracheostomy may be difficult because these patients are often hypoxic, hypercarbic and confused, therefore a short procedure to secure adequate ventilation is often advisable.



1 Glottic stenosis causing stridor.

Mid-tracheal obstruction

With mid-tracheal obstruction the fibre-optic bronchoscope may be useful. The exact site and extent of the obstruction should be defined before embarking on an anaesthetic. A CT scan is essential for lesions of the trachea and bronchi. As in the case of upper airway tumours, the formulation of plan A and plan B is critical. The scan provides a guide to whether a 7 mm tube will pass through the narrowest site of the compression. If this is the case, a conventional induction of anaesthesia can be performed. If there is any doubt, evidence of malignant invasion into the trachea or marked tracheal deviation, an awake fibre-optic intubation is the method of choice, which requires an experienced operator.

Lower tracheal and bronchial obstruction

Patients with symptomless lower tracheal and bronchial obstruction from mediastinal masses can develop unexpected respiratory obstruction during anaesthesia. During spontaneous respiration there is a subatmospheric intrapleural pressure and widening of the airways during inspiration. Administration of a muscle relaxant may alter the support of the bronchial tree and collapse of the airway can occur with positive-pressure ventilation. Tissue biopsy should be performed whenever possible under local anaesthetic and if superior vena caval obstruction is present urgent radiotherapy and chemotherapy may be necessary, even in the absence of a histological diagnosis. A rigid bronchoscope may relieve obstruction. Cardiopulmonary bypass may have to be considered.

The bleeding tonsil

The problems of the bleeding tonsil include:

- stomach full of blood and risk of aspiration
- potential difficult airway, oedematous and obscured by blood
- hypovolaemia
- not yet recovered from a recent anaesthetic.

Anaesthetists should be alert to the possibility of an unsuspected bleeding disorder. A recent episode of tonsillitis makes the procedure technically more difficult and increases the risk of postoperative haemorrhage. There is conflicting opinion as to whether non-steroidal anti-inflammatory drugs used for postoperative pain increase the incidence of bleeding.

Post-tonsillectomy haemorrhage is seldom a catastrophic acute arterial bleed. It is usually a venous or capillary ooze and therefore resuscitation rather than immediate operation is the first management step. The child may have swallowed a lot of blood and hypovolaemia can be severe before the diagnosis is made.

After effective resuscitation, the patient presents further problems in theatre. There is a risk of aspiration of gastric contents (mostly altered blood), and significant amounts of the anaesthetic agents used previously may still be present. Experienced anaesthetic assistance is required. There are two methods of intubation.

- An inhalational induction in the left lateral position, with suction available, the trachea is intubated during spontaneous ventilation. Induction may be prolonged and hindered by continued bleeding. Few have much experience of intubating in this position.
- A rapid-sequence induction and intubation has the advantages of familiarity and rapidity. It should be attempted only if intubation was easy at the initial procedure. Visualization of the larynx may be difficult if there is torrential haemorrhage, two separate suction units should be ready for use.

Nasogastic aspiration should be performed before extubation. Extubation should be performed when the patient is awake and laryngeal reflexes have returned, to minimize the risk of aspiration of gastric contents. ◆

Gas, Tubes and Flows

Kwong Fah Koh

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Understanding fluid flows through tubes and airways requires a knowledge of fluid mechanics. Oxygen, air and nitrous oxide are gaseous fluids and largely obey the laws of fluid dynamics.

Gas laws
Gases are described in terms of pressure, volume and temperature. The three are related according to the ideal gas law:

$$PV = nRT$$

where: P is the pressure (kPa), V the volume (ml), T the temperature (Kelvin), n is Avogadro's number (number of moles of a gas in a fixed volume) and R the gas constant (8.3143 J/gm mol/K). A mole of gas contains 6.023×10^{23} molecules and occupies 22.4 litres at standard temperature and pressure (i.e. 0°C and 760 mm Hg).

The ideal gas law incorporates Boyle's and Charles' laws. At a constant temperature, the volume of a given mass of gas varies inversely with its absolute pressure (Boyle's law). At a constant pressure, the volume of a given mass of gas varies directly with its absolute temperature (Charles' law). However, there are no ideal gases because there are significant intermolecular attractions (van der Waal's forces) between gas molecules, therefore constants are added to both the pressure and volume relationship in the ideal gas laws:

$$(P+a/V^2).(V-b) = nRT$$

where a corrects for attraction between molecules and b corrects for the volume occupied by molecules.

In clinical practice, mixtures of gases are used and their behaviour is described by Dalton's law of partial pressures. This states that in a mixture of gases, the pressure exerted by each gas is the same as that it would exert if it alone occupied the container, so the total pressure in a system is a sum of all the partial pressures of the different gases.

Movement of gases
Fluids flow when there is a pressure difference. Hagen–Poiseuille's law states that flow through a horizontal straight tube of uniform diameter is proportional to the pressure gradient and the fourth power of the radius, and is inversely related to the viscosity of the gas and the length of the tube.

$$F = \frac{\Delta P \pi r^4}{8 \mu l}$$

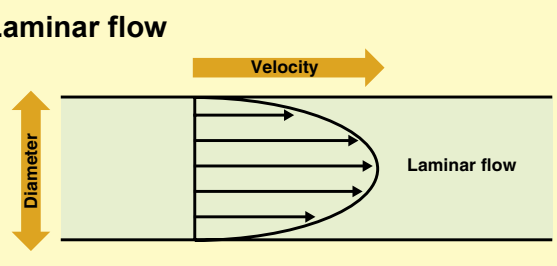
where: F is the flow rate through the tube (cm^3/s), ΔP the pressure gradient, π is 3.14, r the radius of the tube (cm), μ the fluid viscosity (g/cm/s), and l the length of the tube (cm).

The law assumes that flow is laminar. When flow exceeds a critical velocity, the flow velocity profile loses its parabolic profile and becomes turbulent. This occurs when the Reynold's number becomes larger than 4000. Reynold's number is affected directly by flow rate through the tube and density of the gas and is inversely related to viscosity of the gas and the radius of the tube. The higher the number, the more turbulent the flow. Flow is laminar at Reynold's numbers less than 2000.

Flow becomes turbulent when the velocity is high, when there are sharp angles, changes in diameter or multiple branching (Figure 1). This can be seen in the upper airway. During normal respiration, flow in the trachea is usually a mixture of turbulent and laminar flow. If there is an obstruction (e.g. glottic stenosis), the radius of the airway decreases and the flow velocity increases. This accentuates turbulence and gas flow decreases. Such patients often assume an extended neck position to minimize the angles present and increase the upper airway diameter in an attempt to decrease the turbulence and improve gas flow.

Laminar and turbulent flow characteristics

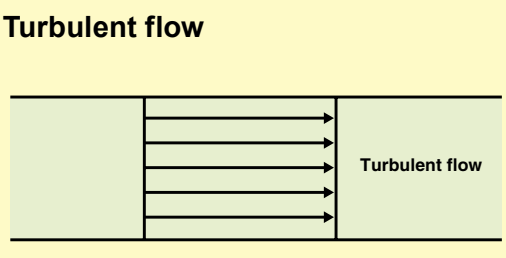
Laminar flow



- Viscosity
- Radius^4
- ΔP^4

Reynold's number < 2000

Turbulent flow



- Density
- Radius^2

$\Delta P^{½}$
Reynold's number > 4000

1

Flow, viscosity and density
The viscosities of common anaesthetic gases are fairly similar but their densities differ greatly (Figure 2). When the airway is narrowed, flow becomes turbulent and the density of a gas assumes greater significance. The density of oxygen is quite close to that of air, but the density of 70% nitrous oxide in oxygen is 60% higher. The density of 80% helium in oxygen is only 30% that of air. During an airway obstruction, using heliox (80% helium, 20% oxygen) can improve gas flow by reducing turbulence. This improved flow can be 1.73 times greater than air or 100% oxygen. Nitrous oxide should be avoided during induction if there is significant airway obstruction.

Density and viscosity of gases at 20°C, 101.3 kPa

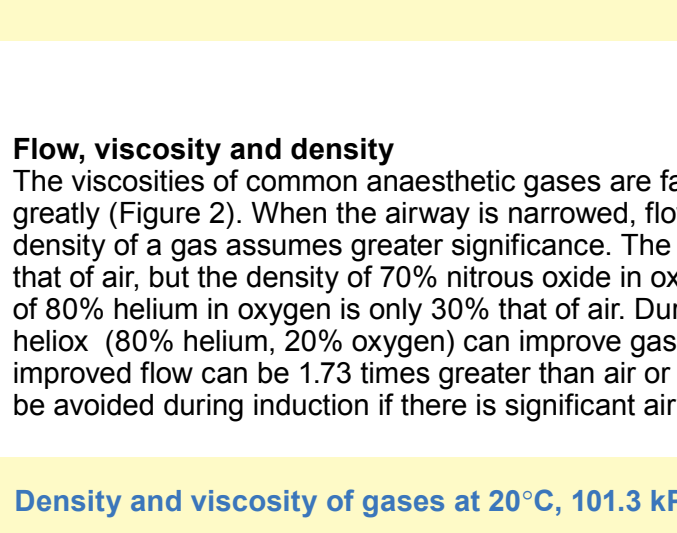
	Viscosity	Density
Air	18.2	1.196
Nitrogen	17.6	1.165
Oxygen	20.4	1.331
Nitrous oxide	14.6	1.831
Helium	19.6	0.166

Air contains 0.04% carbon dioxide with 50% relative humidity

2

Flow through tracheal tubes
The largest possible tracheal tube used to be regarded as the 'correct' size (8 or 9 mm internal diameter). However, larger tracheal tubes cause more trauma to the pharynx, larynx and tracheal wall. Smaller tubes are easier to insert and cause less trauma. Studies have shown that smaller tracheal tubes (6 or 7 mm internal diameter) do not significantly increase airway resistance (Figure 3). Airway pressure is usually measured at the proximal end of the tracheal tube. Because of this, the airway pressure measured is higher when a small tube is used than when a larger diameter tube is used. However, when the intratracheal pressures are measured, they are not significantly higher during the inspiration and expiration phases. Tube sizes of 6 and 7 mm internal diameter are acceptable for positive-pressure ventilation during routine anaesthesia.

Flow rate compared with pressure drop for a range of tracheal tubes



The red line is the suggested upper limit of acceptable resistance for an adult.

Reproduced with permission from: Nunn J F *Applied Respiratory Physiology*. 3rd ed, Butterworths.

3

In intubated patients, mechanical ventilators can overcome impedance to inspiratory flow, but not the impedance to passive expiration. In weak patients, resistance to exhalation through long narrow tubes, compounded by turbulence, can delay weaning. Such patients benefit from a larger tracheal tube or a tracheostomy. The reduced resistance (from using a short, large- bore tube) during expiration minimizes the work of breathing during expiration and thus aids weaning.

Flowmeters
A flowmeter consists of a bobbin in a tapered glass tube. As the bobbin moves upwards, the gap around it increases so that a higher flow is required to support the bobbin. At low flows, the gap between the bobbin and the tube is small so the flowmeter resembles a tube. The flow is laminar and thus is dependent on the viscosity of the gas. At higher flow, the gap is wider and the flowmeter resembles an orifice that has a turbulent character. Gas flow is thus dependent on density rather than viscosity. If oxygen and helium are passed through identical flowmeters, the measurements of flow will be accurate at low flows, because their viscosities are quite close. However, at high flows, the helium will relatively under-read as flow is increased because of its lower density.

Flow through constrictions
The Bernoulli effect describes the fall in pressure at points of constriction, where flow velocity is higher. This effect is seen in devices using the Venturi principle, such as gas nebulizers, some flowmeters and face masks (Ventimask). Jet ventilators force gas through a narrow orifice. The resultant jet creates a low pressure area that causes gas entrainment. When a jet ventilator is used, it is important that the airway is unobstructed during inspiration (to allow entrainment) and expiration (to prevent breath stacking).

Some effects of high gas pressures
Gas density increases in direct proportion to pressure. Air at 10 atmospheres has ten times the density of air at sea level. Thus, the work of breathing at higher atmospheric pressure (e.g. during diving) is greater. The maximum breathing capacity is decreased because density is increased due to increased pressure. To circumvent this problem, helium, with a density one-seventh that of nitrogen is used with oxygen (heliox) at high pressure.

Flowmeters are affected by pressures, because flow is affected by density at higher rates of flow. A flowmeter would read lower at high pressures. ◆

FURTHER READING

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Obstructive Sleep Apnoea

John Ruddock

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Adults who are said to have obstructive sleep apnoea (an apnoea-hypopnoea index (AHI) of more than 15 episodes per hour of sleep) have a variety of upper airway conditions. In this article, the term obstructive sleep apnoea (OSA) is used for the occurrence of repeated obstructive episodes over several respiratory cycles. 'Sleep-disordered breathing' is a better general term.

The nature of sleep
The principal function of sleep is to restore the function of the prefrontal cortex, thereby restoring higher centre cognitive activity. This is brought about by the delta (slow) wave activity generated by the cerebral cortex under the influence of centres in the thalamus. This is the EEG activity that characterizes the Rechtschaffen and Kales sleep stages 3 and 4. The delta activity per 30-second sleep epoch in these sleep stages is 20–50% in stage 3 and over 50% in stage 4. Normally 25–40% (2–3 hours) of sleep should occur in these stages. They occur mainly in the first two or three 90-minute sleep cycles. Even small amounts of sleep deprivation result in measurable changes in certain cognitive function tests. Making appropriate responses to unexpected events is particularly impaired and while alertness can be restored by stimulants such as caffeine, these higher centre cognitive functions cannot be restored by stimulants.

To achieve sleep stages 3 and 4 the individual needs to progress through stages 1 and 2 and it is in these lighter sleep stages that airway inadequacy may express itself in sleep-disordered breathing. The progression to deep sleep coincides with the establishment of regular respiration and anything that impairs this regularity, impairs the progression to deep sleep.

Airway maintenance during sleep
The upper airway is maintained by tone in the skeletal musculature of nose, nasopharynx, oropharynx, tongue and larynx. Efferent discharges to these muscle fibres have tonic and phasic components. The phasic components are in synchrony with inspiration. The effect is to brace the airway against a tendency to collapse. (The flaring of the nostrils with intense inspiratory effort is part of this phasic activity.) During sleep, the tonic efferent discharge falls in parallel with the reduction in tone throughout all the skeletal musculature and is at a minimum during rapid eye movement (REM) sleep. The upper airway becomes increasingly susceptible to forces provoking airway narrowing, such as pressure from fat around the pharynx or the collapsing effect of inspiration, which is accentuated when there are pathological conditions, such as nasal obstruction, affecting the upper airway. The airway may become unable to support adequate respiration during sleep. How the brain senses this inadequacy is not known, but the result is the inability to progress to deep sleep.

Compensations for airway impairment during sleep
Airway impairment during sleep is compensated for by posture, respiratory drive, pharyngeal reflexes and sleep disruption.

Posture – normally individuals automatically adjust their sleeping posture to compensate for airway narrowing. They may turn their head to the side, elevate their head to the 'sniffing the morning air' position, turn on their side or lie prone. The afferent loop for this response is unknown. The airway remains patent or is occluded for only a few respiratory cycles until the compensating adjustment in posture has been made. During REM sleep, when the individual is sleeping on their back, the generalized paralysis prevents compensatory changes in posture and OSA events may persist throughout the REM period.

Pharyngeal reflexes – when people with airway narrowing are given a sedative, such as midazolam, 3–5 mg, and propofol, 50–100 mg, their airway may become obstructed if they are lying on their back. Just as in REM sleep, they are unable to move to make appropriate compensatory postural changes. The obstruction persists, but is intermittently relieved, probably because the respiratory drive increases as the carbon dioxide level rises. Local pharyngeal reflexes respond to a negative pressure within the lumen to increase the tone of the airway musculature and these would be stimulated when the force of inspiration increased against the airway obstruction. The afferents for these reflexes may also be within the thorax because airway obstruction leads to negative intrathoracic pressure. In addition, the increased respiratory drive augments the phasic tone of the airway musculature.

Failure to progress in sleep – when progressive airway narrowing during sleep has produced maximal levels of respiratory drive and phasic tone the final measure to preserve adequate respiration during sleep is sleep disruption. Arousal is linked by neural mechanisms within the brain to a certain critical level of respiratory stimulation. The arousal causes the tone in the airway to return and so relieve the airway obstruction. This is the situation in OSA.

Categories of sleep-disordered breathing

Upper airway resistance
Upper airway resistance is an arbitrary term for two typical responses.

- Postural changes, such as head extension, may be inadequate to compensate for airway impairment. An increase in respiratory drive may be required to overcome the resistance and augment the phasic component of tone in the airway musculature. There are no apnoeas, but airflow may wax and wane (hypopnoea) owing to increasing obstruction. There may be paradoxical respiration. The respiratory drive increases until the arousal threshold is exceeded. The arousal causes the tone in the airway to return. The airflow is increased and the snoring is reduced.
- Others have a different response, which may be induced by a lower metabolic rate and cardiac output. In these individuals, the waning airflow seems to be the result of a reduced respiratory drive and any snoring occurs when the airflow increases during the arousal phase. The inference is that airway reduction impairs respiration and leads to a rise in the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) until this has a stimulatory effect on the respiratory centre, which incurs a delay. At a particular level of respiratory stimulation there will be an arousal, hyperventilation and overcompensation. The $PaCO_2$ falls below the respiratory threshold and there is a hypopnoea or central apnoea and the cycle is repeated.

OSA
Effective compensatory reflexes safeguard the airway during sleep and prevent persistent obstruction. Significant OSA occurs when the ability of these reflexes is exceeded. There is a limit to which postural change can aid the situation, the respiratory drive can be at a maximum and the protective pharyngeal reflexes may be impaired.

Mild OSA – in REM sleep, postural changes are obtunded but there are other compensations in response to OSA. There may be a microarousal (momentarily coming out of REM sleep) or REM sleep may be reduced. Commonly, OSA occurs in REM sleep only when the individual is lying on their back; when they lie on their side, they have REM sleep without apnoeas and without desaturations. These individuals desaturate when on their back during each of their three or four REM episodes each night, probably to 70%. Mild OSA does not have an impact on daytime somnolence. In the presence of coronary vascular disease there are probable implications in the postoperative management of people with mild OSA (see rebound REM below). Many people desaturate during REM sleep without having OSA because a reduction in respiratory effort occurs as part of the normal reduction in skeletal muscle tone that occurs during REM sleep.

Moderate OSA – obstructive apnoeas occur in sleep stages 1 and 2 if individuals sleep on their back. There is probably an impairment in the local pharyngeal reflexes. The theory is that pharyngeal mucosal oedema from the repeated trauma of airflow turbulence and actual damage to nerve endings has resulted in the impairment or loss of these protective pharyngeal reflexes. The result is that the airway is obstructed, the carbon dioxide level rises, the oxygen level falls and the respiratory drive increases until the individuals arouse. They suffer repeat arousals, of which they are not usually aware, but sleep is disrupted and progression to deep sleep is impaired. Individuals with moderate OSA who lie on their side may not have obstruction and sleep can progress, though they may show features of 'upper airway resistance'. They may not have severe daytime somnolence.

Severe OSA – patients either obstruct in all sleep positions or remain on their backs throughout the night despite repeated obstructive events. They do not have any sustained delta sleep and REM sleep is usually severely disrupted. These patients are somnolent with severe impairment to their quality of life. Treatment is with nasal continuous positive airway pressure (CPAP). Patients will still obstruct if they do not use CPAP, unless during their treatment period they have lost a great deal of weight. However, treatment eliminates somnolence and their cardiovascular system is not subjected to the strain of repeated episodes of hypertension and tachycardia.

Cardiovascular system – negative intrathoracic pressure during apnoea leads to a fall in systemic blood pressure and heart rate. It also causes increased venous return and stimulation of the baroceptors of the aortic arch and therefore at the end of the apnoea when the arousal results in relief of the airway obstruction, there is a rise in blood pressure and heart rate. This is usually coincident with the nadir in peripheral oxygen levels. The result is severe cardiovascular instability. Cardiac dysrhythmias (supraventricular and ventricular ectopics, atrial fibrillation and periods of complete heart block) often occur in these patients. There is an increase in daytime blood pressure. Essential hypertension in these patients may be refractory to medical treatment until the OSA is treated with nasal CPAP, similarly in patients with upper airway resistance.

Central apnoea
The 'central' event is caused by a reduction in respiratory drive. The most common cause is when an individual enters an episode of periodic respiration as a result of a change in sleep stage or position and there are alternations of hypo- and hyperventilation. They may be a normal event during sleep onset, after an arousal or during REM sleep. Their association with 'upper airways resistance' has been discussed. In addition, central apnoeas may occur when there is respiratory failure – the hypoxic drive during sleep results in hypocapnia and respiratory cycling. Altitude causes similar events. Respiratory drive and airway musculature are affected in patients with brain lesions (e.g. after a stroke). In addition, there is the long-period respiratory cycling of Cheyne–Stokes breathing in which the low cardiac output of heart failure results in a prolongation of feedback.

Mixed apnoea
Some patients have mixed apnoea (obstructive plus central apnoea). They have a central apnoea with an initial patent airway, however, the absence of phasic drive and the presence of surface tension effects from the mucous lining of the airway result in airway closure. Also, pharyngeal reflexes do not operate when there is no respiration. When respiration restarts, the opening of the airway produces a characteristic snore.

OSA

Aetiology: a number of head and neck and neuromuscular pathologies provoke sleep-disordered breathing and may render the individual unable to compensate effectively. The most common aetiology is a history of nasal obstruction that originates in developmental or traumatic abnormality of the nasal airway. Over time the increased respiratory effort required for adequate breathing results in pharyngeal wall collapse, thickening and folding of the mucosa, elongation of the uvula, submucosal oedema and a tendency to breath through the mouth, that restricts the post-lingual airway. In middle age, particularly in men, fat is deposited in the neck and this further compresses the airway. These occurrences are insidious as are their effects on sleep. An individual and resilient sleep pattern is established.

Investigation: a simple sleep study is all that is required, provided it is interpreted with an understanding of what may be happening to the sleep staging. A polysomnogram is unnecessary and impractical for investigating most people. The important parameters of the sleep study are gender, body mass index, Epworth Sleepiness Score, sleep position, snoring events, oxygen saturation, heart rate, abdominal and chest respiratory efforts and airflow. Monitoring leg movements is also useful. In the Epworth Sleepiness Score the patient is asked to score their likelihood of falling asleep on a scale of 0–3 for eight different activities or periods of the day. The maximum score for extreme sleepiness is 24; normal scores are less than 10.

Implications for anaesthesia: few patients have perioperative sequelae due to OSA. Often those at risk are in or approaching the morbidly obese range and appropriate anaesthetic safeguards (e.g. short-acting agents, awake fibre-optic intubation) are used for that reason. However, there are reports of cases in which the anaesthetist has not been prepared for OSA and anecdotal reports of patients, not necessarily obese, who have died during the perioperative period in whom OSA has been implicated.

The confounding factors related to obesity are difficult venous access, difficult airway maintenance, difficult intubation, hypoxia, thromboembolic phenomena and gastro-oesophageal reflux. Apart from these, the focus of concern for adults with OSA is the recovery period. The airway is maintained in these patients by the respiratory drive and the capacity for arousal; the factors that are obtunded by general anaesthetics. The anaesthetic technique must ensure that when the patient is required to maintain their own airway, they will be awake with a good respiratory drive. Appropriate anaesthetic agents to achieve this aim are desflurane and remifentanil.

Preoperative assessment: patients who are likely to have OSA have a history of snoring, sleep apnoea and daytime somnolence. Men are more likely to have the condition than women because of the different distribution of fat tissue in the neck. Obese patients with severe OSA have a reduced functional residual capacity and desaturate profoundly, regularly to 60% throughout the night. A person with OSA who is not obese will not desaturate to this degree. The diagnosis is made from an overnight oximeter recording on an obese patient who is sleeping; conversely the anaesthetist can be reassured by a negative trace. Objective evidence that the patient has been to sleep can be obtained from the heart rate record. If severe OSA is suspected, elective surgery must be deferred. A patient with severe OSA needs to be stabilized on nasal CPAP.

Upper airway resistance and moderate OSA are often present in patients with a history of snoring and sleep apnoea, in those with a thick neck, large tongue or retracted mandible. The recovery position and Guedel airway are likely to be needed until the patient is awake. The need for effective postoperative analgesia in these patients may warrant the use of an oximeter or care in the high dependency unit.

Low body mass index (BMI) and severe OSA – most patients with significant sleep apnoea have a BMI of 30 or more. However, severe OSA can occur in patients with a normal BMI as a result of maldevelopment of maxilla or mandible. If the condition is associated with neurological deficit or motor weakness, hazards for the patient following general anaesthesia include laryngeal incompetence, which could lead to aspiration or respiratory failure.

Mild OSA and 'rebound REM' – all patients have impaired sleep during the immediate postoperative period. For patients with sleep-disordered breathing, this means that the number of hypoxic events will be reduced. In particular, there is inhibition of REM sleep, partly due to the effect of analgesic drugs such as morphine. A person who desaturates during REM sleep may not therefore desaturate during the first few nights after surgery. A few nights later, there may be increased amounts of REM sleep to compensate for the period of deprivation. As a result, the patient may desaturate for long periods in the postoperative period when they will not usually be receiving supplementary oxygen. For most patients, desaturation during REM is probably not hazardous, but where there is coronary insufficiency, it should be avoided by the use of nasal CPAP. The combination of mild OSA and coronary insufficiency may be responsible for postoperative myocardial infarction.

Anaesthesia in severe OSA: a patient with severe OSA who is having surgery to remove nasal polyps to assist nasal CPAP therapy can probably have their airway managed with a flexible laryngeal mask (LMA) in the hands of an experienced anaesthetist. After securing intravenous access and giving an anticholinergic agent, glycopyrrolate, 200 μg, anaesthesia is induced with oxygen and sevoflurane, with or without propofol, 10 mg increments. A Guedel or nasopharyngeal airway may be needed. If airway compromise occurs, suxamethonium, 100–150 mg, may be needed, alternatively if hand ventilation is achieved without suxamethonium, a small amount of atracurium, 25 mg. Remifentanil, 10 μg increments, are given and the flexible laryngeal mask (size 5 males; size 4 females) inserted. Anaesthesia is maintained by ventilating with oxygen, desflurane with or without air or nitrous oxide and by using a remifentanil infusion. If normal levels of $ETCO_2$ (end-tidal carbon dioxide level) are not achieved for a maximum inspiratory pressure of 20 cm H_2O, the use of a tracheal tube needs to be considered.

At the end of the operation the muscle relaxant is reversed and the patient recovered, sitting up, with the flexible LMA and bite guard in place until they are well awake. The LMA is removed, provided adequate levels of oxygen saturation and $ETCO_2$ have been achieved. Patients with nasal packs require nursing in the high dependency unit. Postoperative CPAP intervention requires a full-face mask.

If a tracheal tube has been used for anaesthesia for surgery, then awake extubation with the patient sitting upright is the preferred option with the use of a nasopharyngeal airway or rigid LMA where appropriate. Postoperative analgesia with opiates may need to be withheld and the patient warned about this. Non-opiate analgesia is preferred. Regional anaesthetic techniques are not necessarily indicated because they impact on the strength of respiration. ◆

FURTHER READING

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Percutaneous Tracheostoma

Robert Broomhead

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Prolonged ventilatory support of intensive care patients using nasal or oral tubes, is associated with a number of problems. Tracheal tubes are uncomfortable and require the patient to be sedated. These tubes are more liable to occlusion (kinking, biting, secretions) and their length and contours make it difficult to pass catheters for effective tracheobronchial suctioning of secretions. Oral tubes can be difficult to secure and constant movement increases the chance of tracheal damage. They also prevent adequate oral hygiene procedures. Nasal tubes are associated with infection in the paranasal sinuses.

Placement of a tracheostomy reduces or removes these problems. It also reduces the dead space and the resistance to, and work of, breathing. The benefits of tracheostomy are outlined in Figure 1 and the complications listed in Figure 2. The decision to perform a tracheostomy is based on an appraisal of the risks and benefits for each patient (Figure 3). Tracheostomy was advocated after 1 week of continued ventilation to avoid subglottic ulceration. Recently, the trend has been towards early placement in patients predicted to have prolonged requirements for ventilatory support, or airway protection.

Advantages of percutaneous tracheostomy

- May be performed in the ICU (removing the hazards of transferring critically ill patients)
- Performed by intensivist/anaesthetist (does not require referral to a surgeon and organization of theatre time)
- Often quicker than open surgical technique
- Fewer postoperative infections
- May be reduced incidence of tracheal stenosis
- Aids weaning from ventilator
- May reduce patient's length of stay in ICU

1

Complications of tracheostomy

Immediate
- Submucosal placement of guidewire and/or dilation
- Cricoid damage
- Trauma to the posterior wall of trachea
- Marked fall in oxygen pressure
- Cardiac dysrhythmia
- Haemorrhage
- Surgical emphysema
- Pneumothorax
- Misplacement of tracheostomy tube into pretracheal tissues
- Occlusion of tracheostomy tube tip against tracheal wall or due to cuff herniation
- Perioperative death

Delayed
- Infection of stoma
- Tracheostomy tube blockage with secretions
- Ulceration of trachea at site of the cuff
- Erosion at stoma site leading to catastrophic bleeding (innominate artery) or tracheo-oesophageal fistula
- Pneumonia

Late
- Granuloma formation in the trachea
- Tracheomalacia
- Tracheal stenosis
- Failure of stoma to close once decannulated

2

Contraindications for percutaneous tracheostomy

- Infection/inflammation at the proposed tracheostomy site
- As a means of emergency airway access
- Uncorrected bleeding diathesis
- Enlarged thyroid gland
- In children
- Burns/trauma to anterior neck
- Difficult anatomy (e.g. obesity, deformity)
- Marked cardiovascular or respiratory instability

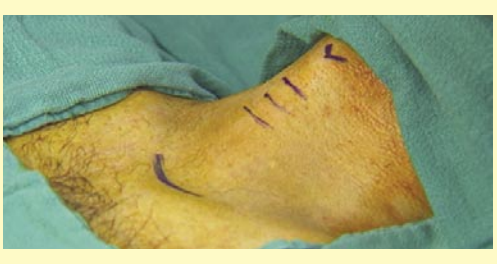
3

Consent – percutaneous tracheostomy is usually undertaken on patients who are already sedated and intubated in the ICU and from whom formal consent cannot be obtained. If the patient is sufficiently awake the procedure should be explained to allay anxiety. An explanation should also be given to the relatives.

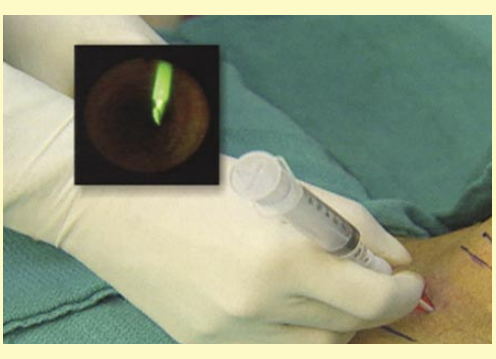
Technique
All the apparatus required is checked and prepared before the procedure (Figure 4). A tracheostomy tube is selected and checked to ensure that the cuff inflates correctly, and that it fits over a suitable dilator/introducer. A tracheostomy tube of 8.0 mm internal diameter is adequate for most adults and usually fits satisfactorily over a 24 FG dilator.

Percutaneous tracheostomy

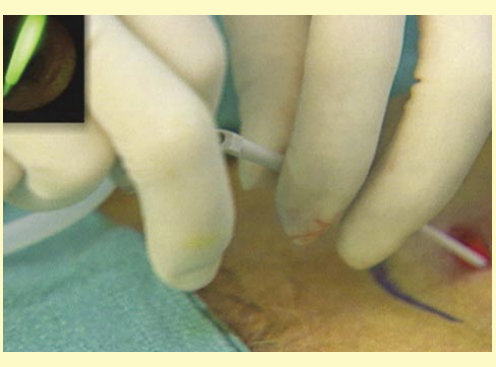
These illustrations show insertion at a lower than normal site



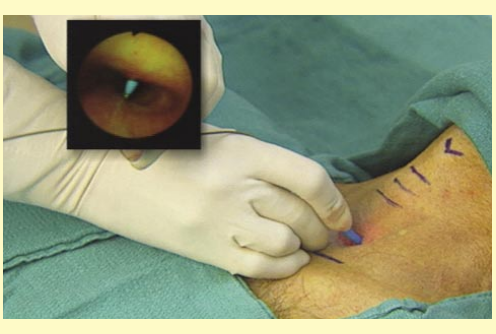
a Surface anatomy.



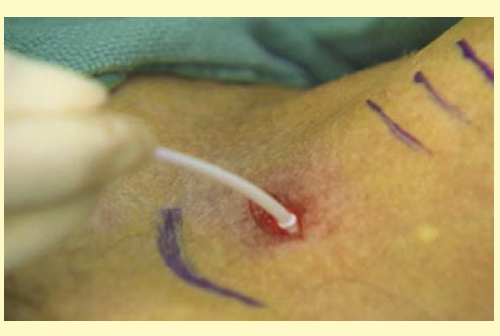
b Identification of the tracheal lumen with cannula.



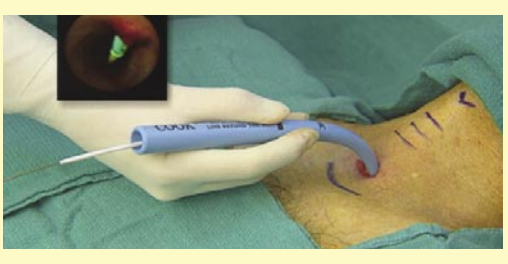
c Insertion of guidewire through cannula.



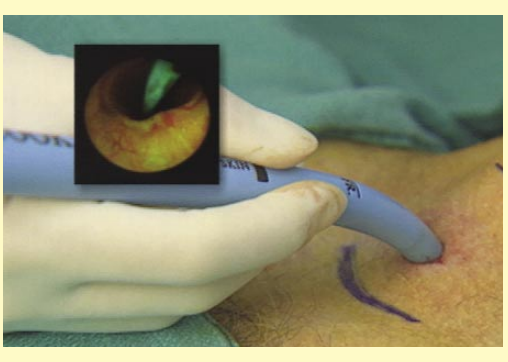
d Preliminary dilation of stoma.



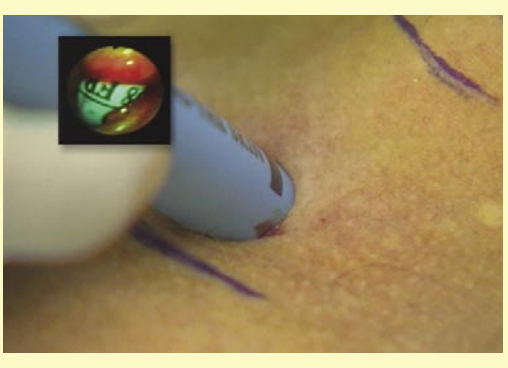
e Dilator guide passed over guidewire.



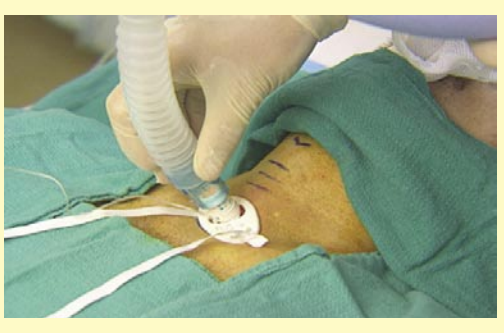
f *Blue Rhino®* dilator passed over guidewire.



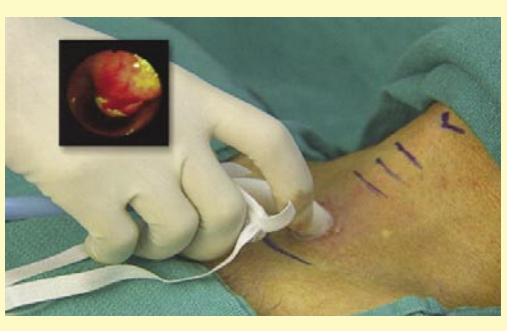
g Gentle dilation, no excessive force required.



h Dilation of stoma. Marks on dilator indicate depth of insertion.



i Introduction of tracheostomy tube.



j Connection to ventilator.

Inset: laryngoscopic appearance.
Figures reproduced with the permission of Cook® Critical Care Products.

4

An anaesthetist undertakes responsibility for the anaesthetic, and the management of the airway, partially withdrawing the tracheal tube at the appropriate time. Most units use a fibre-optic laryngoscope or bronchoscope via the tracheal tube during the procedure. This allows visualization of the tracheal puncture site, and the correct position and orientation of the guidewire placed by the operator.

Blood pressure, ECG and oxygen saturation are monitored throughout the procedure. Monitoring end-tidal carbon dioxide is also strongly recommended. The patient is anaesthetized, paralysed and ventilated with 100% oxygen. A positive end-expiratory pressure (PEEP) of 5–10 cm H_2O is generally recommended. Pressure-controlled ventilation may be useful to maintain tidal volumes during withdrawal of the tracheal tube.

The patient is positioned supine with head and neck extended sufficiently to allow identification of the landmarks. This is facilitated by the placement of a pillow or rolled towel under the shoulders. Problems may occur with the final position of the tracheostomy tube as a result of the head and neck being extended too far. The trachea and skin each move to a different extent during extension.

Full surgical aseptic technique is used; the operator should scrub and wear surgical cap, mask, gown and gloves. All personnel should wear eye protection and a mask because the patient's blood and secretions may be blown into the air around the operative site.

The anterior neck and upper chest is cleaned and prepared using an alcoholic chlorhexidine skin preparation solution and the operative area is draped. The cricoid cartilage is identified below the thyroid notch. The position of the second tracheal cartilage is estimated below this. These points may be marked. The area of skin at the intended tracheostomy site is infiltrated with 1% lidocaine (lignocaine) containing 1: 100,000 adrenaline (epinephrine). This provides local analgesia, causes blanching of the area and reduces oozing from skin vessels.

A short horizontal skin incision (about 1.5 cm) is made over the trachea. Some operators advocate blunt dissection in the midline down to the trachea using curved artery forceps. The aim is to identify the space between the first and second (or second and third) tracheal rings, which are the recommended sites of tracheostomy stoma.

At this point, the anaesthetist pulls back the tube to avoid it being transfixed by the needle. Withdrawal requires deflation of the cuff, therefore the ventilator settings will have to be adjusted to maintain adequate ventilation. Withdrawal of the tube is best performed under direct laryngoscopy, until the top of the deflated cuff is visible in the glottic aperture. The palpating finger of the operator can also feel as the tip of the tube passes above the site of intended puncture. Once the tube is withdrawn sufficiently it is secured in this position for the remainder of the procedure.

The Ciaglia Percutaneous Tracheostomy Introducer Set (Cook® Critical Care Products) provides a cannula over a needle, which can be attached to a 5 ml syringe. The anterior wall of the trachea is punctured; confirmation of which is provided by the ability to aspirate air. The syringe may be partially filled with saline, if desired; aspirated air can then be seen to bubble through the saline. The cannula is then advanced off the needle in a caudal direction and a J-tipped guidewire passed through the cannula and down the trachea. The fibre-optic laryngoscope is invaluable in confirming the correct position and orientation of the guidewire. With the guidewire in position, the cannula is removed and the initial puncture site is preliminarily dilated to accept a guiding catheter, over which, either serial dilators, or the *Blue Rhino*® tapering dilator is passed, to enlarge the stoma progressively. Marks on the dilators indicate the limit to which the dilator should be introduced into the trachea. Unnecessary force or incorrect alignment of the dilator during its insertion may result in failure to follow the contour of the guidewire. This can cause kinking of the guidewire increasing the risk of introducing the dilator into the pre-tracheal tissue and causing damage to anatomically related structures.

Once a suitably sized stoma has been created, a previously checked flexible tracheostomy tube is loaded onto a dilator and guided through the stoma into the trachea. The dilator is removed, the cuff inflated and the patient ventilated through the new tracheostomy. Only when ventilation is assured and satisfactory via the tracheostomy should the tracheal tube be removed.

The tracheostomy tube is secured with tape round the patient’s neck with the patient's head and neck flexed to a normal position. Some operators suture the flange of the tracheostomy tube to the skin but this is not essential, may lead to a false sense of security and often results in skin infection at the suture site.

Alternative methods of maintaining the airway

In surgical tracheostomy the surgeon dissects the anatomy and is in control of the airway directly, before the tracheal tube is withdrawn and the stoma is created. In percutaneous tracheostomy, the tracheal tube is withdrawn early in the procedure and maintained in a precarious position until the stoma is created and the tracheostomy tube inserted. Techniques to improve the traditional partially withdrawn tracheal tube method include:

- oxygen insufflation via a catheter at the level of the carina
- use of a microlaryngeal tube inserted to a level beyond the intended stoma site and not withdrawn during tracheal puncture
- laryngeal mask airway
- tracheal tube through a laryngeal mask airway.

Aftercare

A newly created tracheostomy stoma is a surgical wound and should be treated accordingly. High standards of aseptic technique should be maintained during wound dressing. The stoma does not ‘mature’ for 7–10 days. Every effort should be made to ensure that the tracheostomy tube is secured in its correct position and is not being pulled into unsatisfactory angles by the weight of ventilator tubing.

If displacement of the tracheostomy tube occurs within the first few days of creating the stoma, replacing it may be impossible and the attempt may create a false passage. It is much safer to re-intubate the patient and re-establish the tracheostomy under controlled conditions. ◆

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www.cookcriticalcare.com (Provides an illustrated tutorial).

Straight Laryngoscopy: Function, Technique and Design

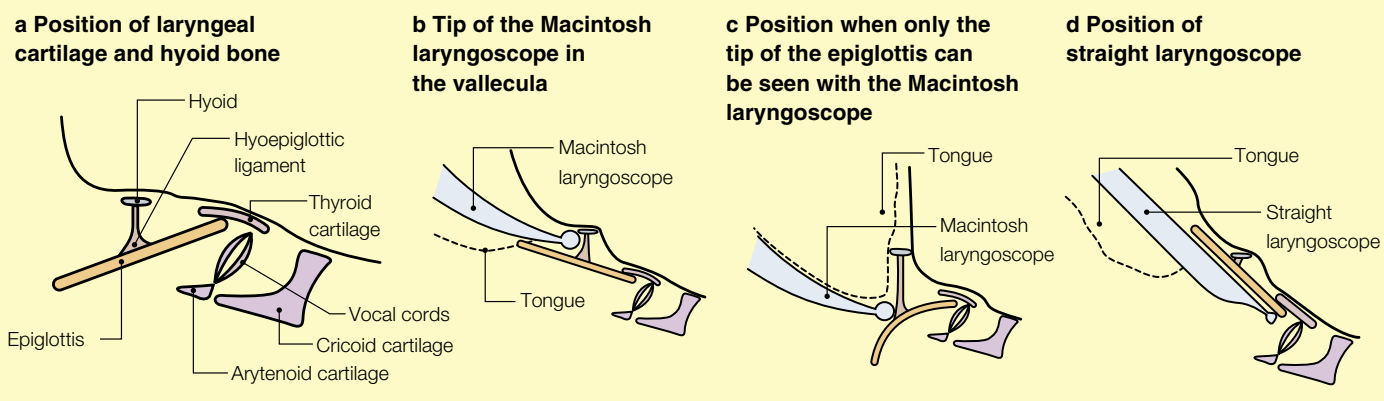
John Henderson

John Henderson is Consultant Anaesthetist at the Western Infirmary, Glasgow, UK. He trained at Glasgow Royal Infirmary, was a fellow in New York and staff anesthesiologist in Boston. He has used awake fibre-optic intubation since 1977. He is Guidelines Project Officer of the Difficult Airway Society.

Tracheal intubation under vision was originally performed with the straight laryngoscope. Curved laryngoscopy with the Macintosh laryngoscope (introduced in 1943) became the standard technique because it was perceived to be less demanding than straight laryngoscopy. There is increasing evidence that tracheal intubation can be achieved under vision with the straight laryngoscope in most patients in whom this is impossible with the Macintosh. Many of the complications of difficult intubation with the Macintosh laryngoscope might be avoided if anaesthetists were skilled in straight laryngoscopy.

Straight laryngoscopy has a good theoretical basis. All laryngoscopes are used to move the tongue to the left and to elevate the epiglottis so that the vocal cords are revealed. The normal relationship of the laryngeal cartilages and the hyoid bone is shown in Figure 1a. Figure 1b shows the tip of the Macintosh laryngoscope in the vallecula, close to the hyoepiglottic ligament. Elevation of the hyoid tensions the hyoepiglottic ligament and thus elevates the epiglottis indirectly. Figure 1c shows the situation where no more than the tip of the epiglottis is seen with the Macintosh laryngoscope. Some of the bulk of the tongue remains trapped between the tip of the laryngoscope and the hyoid bone, and the tip of the laryngoscope cannot enter the vallecula. The epiglottis cannot be elevated and is displaced posteriorly so that it obstructs the potential line of sight of the larynx. Figure 1d shows the position of the straight laryngoscope, introduced from the side of the mouth, in such a patient. The tip of the laryngoscope is posterior to the epiglottis, which is elevated directly. Theoretically, the straight laryngoscope performs better than the Macintosh because of its ability to elevate the epiglottis directly in difficult patients, and to improve the line of sight.

Straight laryngoscopy



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The technique of straight laryngoscopy is different from the Macintosh, and initial use often proves difficult.

- The laryngoscope is inserted and kept lateral to the incisors. The tip may pass initially into the right pyriform fossa, so that medial movement of the tip is necessary.
- Maximum mouth opening requires more deliberate attention.
- The tip of the laryngoscope is passed posterior to the epiglottis, which is elevated directly.
- Optimum depth of insertion (tip close to vocal cords) requires attention.
- Vector of force applied to the laryngoscope handle is different.

Further information about the technique is available from the Further reading or, in more detail, from the author.

The most widely used straight laryngoscope is the Miller. Passage of the tracheal tube with the Miller laryngoscope can be difficult. The Belscope is angulated to reduce the risk of dental damage. The Henderson laryngoscope shares with the Belscope an atraumatic tip and a light that cannot be dimmed by secretions or soft tissues. The cross-section of the Henderson laryngoscope is designed to facilitate passage of the tracheal tube so that tracheal intubation is integrated with direct laryngoscopy in a single rapid process. Optimal (paraglossal) technique with any of these laryngoscopes has much to offer. Moderate expertise requires 50 or more initial intubations, followed by continuing regular use. ◆

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Transtracheal Jet Ventilation

Ali Diba

Ali Diba is Consultant Anaesthetist at the Regional Burns/Plastics and Maxillofacial Hospital in East Grinstead, West Sussex, UK. He qualified from Southampton University. He is an expert in the management of the difficult airway. His interests include critical care of burns patients and infusional anaesthesia.

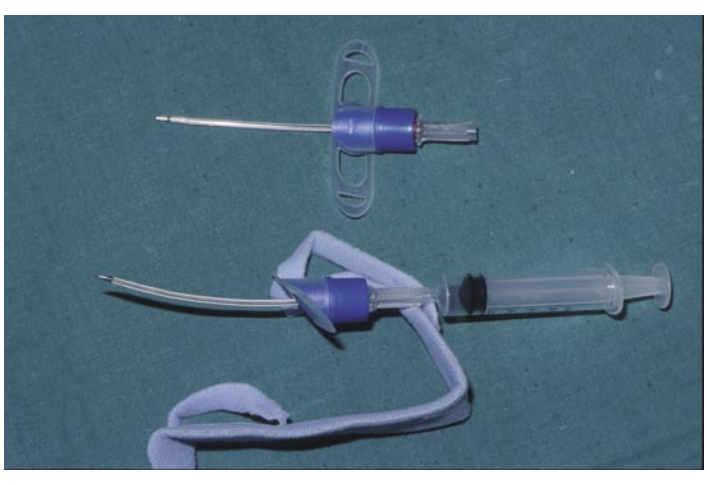
Transtracheal jet ventilation (TTJV), also called needle cricothyroidotomy, is a simple, safe and effective technique for ventilating apnoeic lungs electively or in an emergency. No patient should suffer hypoxic injury as a result of failure to ventilate the lungs without a competent attempt at TTJV having been made. Failure to ventilate still causes death under anaesthesia. An incidence of about 1/10,000 is quoted for failure to intubate associated with failed mask ventilation at anaesthesia.

Using dedicated equipment minimizes the chances of apparatus-related failure. Little experience is necessary, however, familiarity encourages earlier use in an emergency and allows a more confident approach to the difficult airway as a whole, especially if the technique is available as a backup in case of failure of the first strategy for management of the patient's airway. A number of centres worldwide use TTJV electively for peroperative ventilation.

History
In 1967, Sanders demonstrated ventilation of the lungs of anaesthetized patients using high-pressure oxygen at bronchoscopy. Transtracheal ventilation was described in 1971 by Spoerel in India. In 1983, Layman reported TTJV, without complication, in 60 patients with gross pathology requiring oral surgery, using an intravenous catheter inserted through the cricothyroid membrane. In 1985, Ravussin designed a dedicated transtracheal catheter, which remains the device of choice.

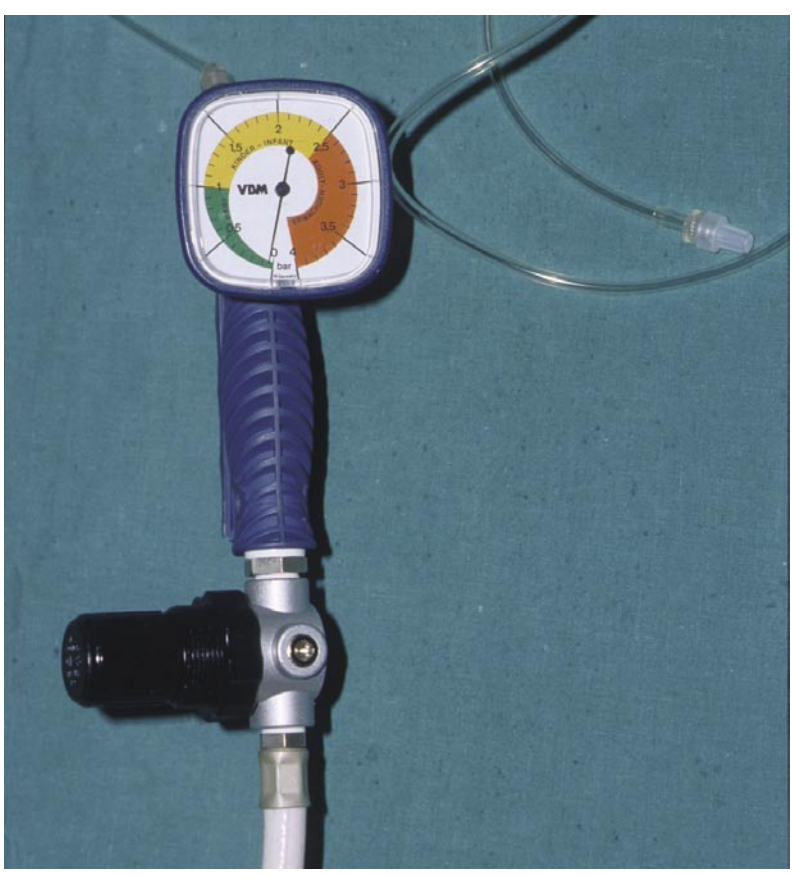
Apparatus
Safety in TTJV depends on intratracheal placement of the catheter. The ability to freely aspirate 'air' from the catheter following insertion is paramount. Conventional plastic intravenous cannulas tend to kink at the skin or within the trachea because of the acute angle between skin entry and tracheal axis which may preclude this safety check and decrease the efficiency of ventilation.

The Ravussin Jet Ventilation Catheter (VBM Medizintechnik GmbH, D-7247 Sulz a.N. Germany) is available in 13 G for adults (Figure 1) and proportionately shorter 14 G and 18 G versions for children and babies. It is made of Teflon, which is stiffer than plastic and is gently curved with an angled connector, which when sitting flush on the skin allows the catheter to point axially down the trachea without kinking. A Velcro strap passed around the neck keeps the whole assembly firmly in place. A 15 mm diameter ISO male connector around the Luer-Lock allows temporary low-pressure oxygen insufflation from a conventional anaesthetic system.



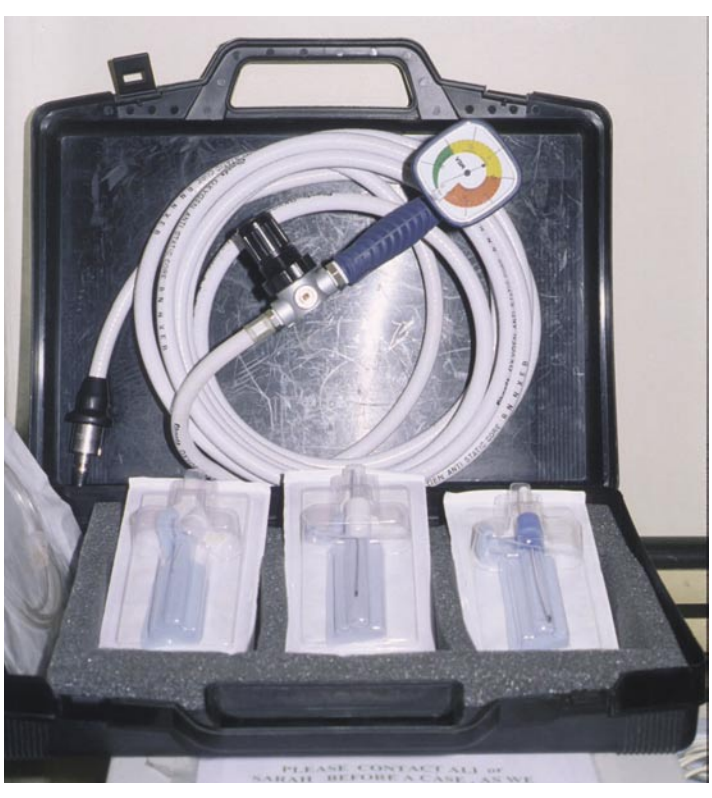
1 Ravussin Jet Ventilation Catheter for adults (13 G).

The TTJV catheter is connected to a high pressure (4 bar) oxygen source through a Sanders injector. A variable outlet pressure version (Figure 2) is used for added safety if the system might be used in children.



2 Variable pressure injector.

A complete TTJV system should be available in all areas where anaesthesia is administered or where unconscious patients may be admitted (Figure 3). It is not feasible to assemble the equipment from disparate items when the need for TTJV is identified in an emergency situation.



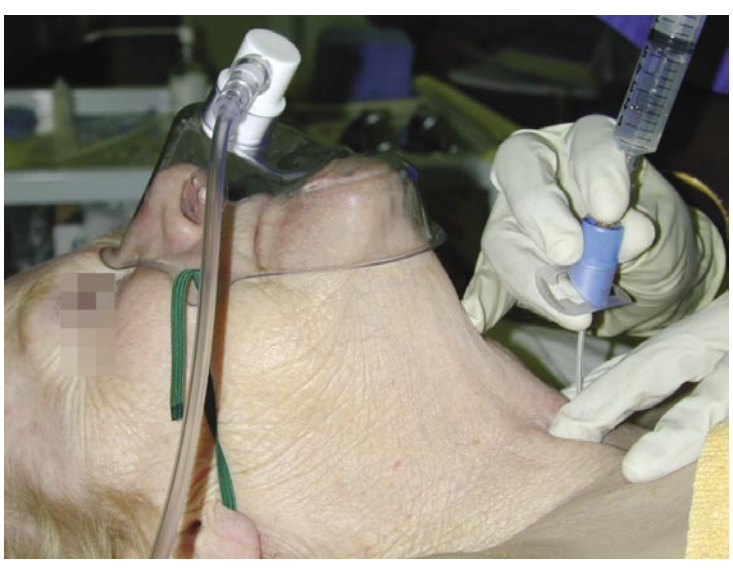
3 Difficult intubation trolley.

Low pressure gas, as delivered from the common gas outlet of an anaesthetic machine (limited by the machine safety pressure relief valve or anaesthetic bag compliance to 320 or 80 cm H_2O) and delivered through a narrow-bore transtracheal catheter will, at best, provide temporary apnoeic oxygenation by providing gas flows of only 200 to 80 ml/s for a 14 G cannula. TTJV requires a high-pressure gas source and implies that adequate gas exchange can be maintained.

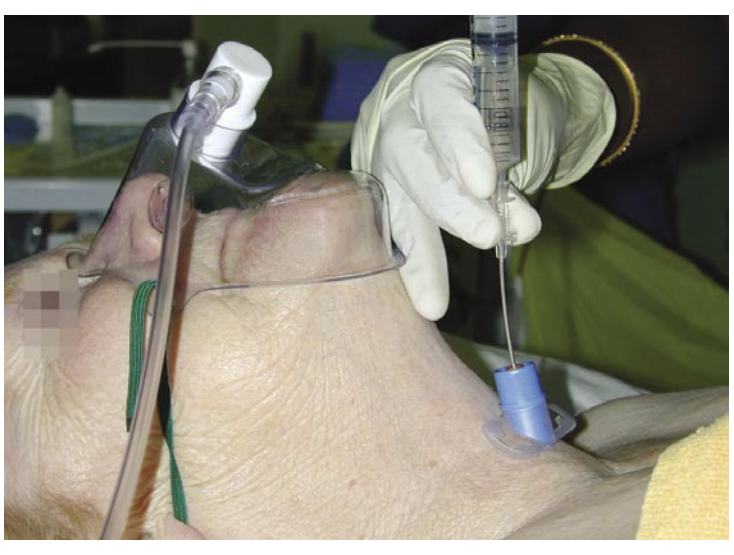
For protracted ventilation, high frequency jet ventilators are available that allow the driving pressure, breath rate and I:E ratio to be controlled individually. They can measure end-expiratory intratracheal pressure through the ventilating cannula, thus stopping subsequent breaths if gas egress from the lungs is obstructed.

Technique
The patient's head is positioned as if for a tracheostomy with head and neck extension. The trachea is most easily approached percutaneously through the cricothyroid membrane, though lower cartilaginous interspaces are also practicable. The membrane is best identified with the fingertip and nail and may be marked. An intradermal bleb of local anaesthetic should be administered in the conscious patient, and this syringe and needle can also be used as a seeker to confirm correct identification by easy passage though the membrane and aspiration of air. Intratracheal lidocaine (lignocaine) is not essential because the catheter tends not to irritate the airway.

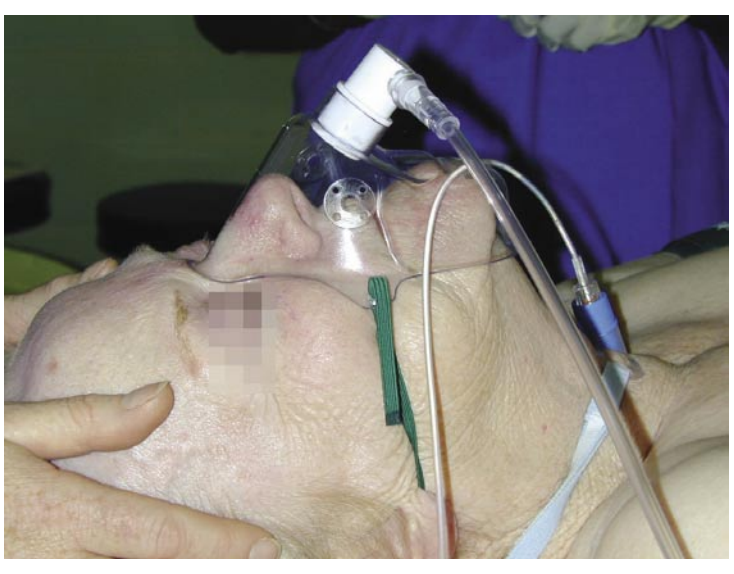
A 5 ml syringe is attached to the catheter/needle assembly which is inserted in a slight caudad direction with negative pressure maintained on the syringe plunger (Figure 4). A slight 'give' followed by further easy passage and aspiration of air signifies entry into the trachea. The catheter should advance easily off the needle, which is then removed (Figure 5). Further free aspiration of air from the catheter and a perfect end-tidal carbon dioxide trace on gas sampled from the catheter in the breathing patient confirm its position (Figure 6). The injector is then connected using Luer-Lock tubing and a single test breath should be administered to test the integrity of the system. The awake patient usually coughs at this stage, and all patients must be carefully observed for chest deflation after each breath. If air cannot be aspirated from the catheter it must be resited.



4 Needle insertion.



5 Withdrawal of cannula.

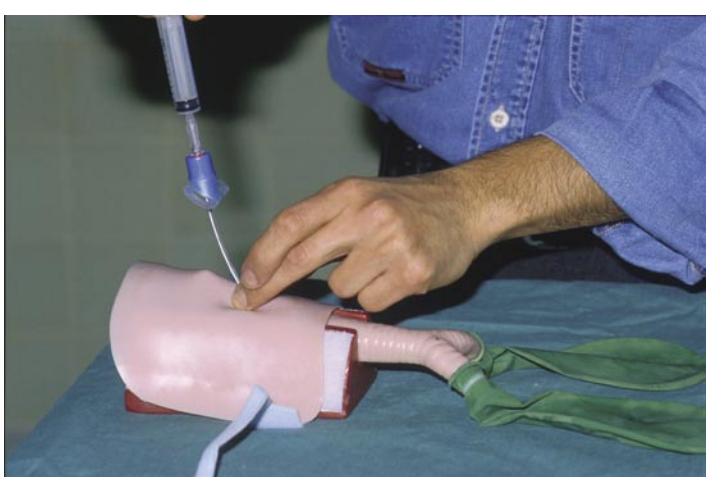


6 Checking catheter position.

In the elective situation anaesthesia can be induced, and jetting may proceed with the following provisos. 'Pre-oxygenation' guards against desaturation in the interval between induction of anaesthesia and the onset of paralysis and jet ventilation. Neuromuscular paralysis ensures there is no jetting against a forcibly closed glottis risking barotrauma.

Appropriate craniocervical extension and/or jaw thrust allows an adequate expiratory airway in most patients, even those with obstructing glottic lesions. An oral, nasopharyngeal or laryngeal mask airway (LMA) may also be needed. There is no record of a patient needing a second needle for gas escape, though this remains an option. It is important not to ventilate while the airway contains anything that may occlude the upper airway (e.g. the passage of a tracheal tube over a fibre-optic endoscope).

A mannequin or dummy neck can be used to practise the technique (Figure 7).



7 Practising the technique on a dummy neck.

Applications
TTJV, using a small diameter cannula, is preferable to tracheostomy in an emergency because it is faster and simpler to perform and involves fewer complications.

Assuming the anterior neck can be accessed in an elective patient in the absence of significant overlying tissue swelling or infection, TTJV may be indicated as an interim manoeuvre (surgical access for tracheostomy is not impeded by TTJV) or as the definitive airway management technique. The categories are not mutually exclusive.

Emergency/resuscitation: TTJV can be used in the 'can't ventilate, can't intubate' situation; where there is failure to intubate the trachea and established failure to ventilate the lungs by other means (such as face mask or LMA) owing to abnormal anatomy, trauma or disease.

Elective: TTJV alone is appropriate for airway management for suspension microlaryngoscopy, endoscopy, tracheal surgery, or laser surgery of the airway.

If there is uncertainty about the ability to maintain airway competence following induction of anaesthesia TTJV may be used as an alternative to awake intubation. Siting a TTJV catheter in the awake patient secures the ability to ventilate the lungs following induction. This does not require confidence with local anaesthetic techniques or patient cooperation and allows safe, unhurried and comfortable airway instrument-ation for patient and anaesthetist. In children with orofacial tumours for example, the cannula may be sited under ketamine sedo-analgesia allowing fibre-optic intubation under general anaesthesia with muscle relaxation. This combination constitutes a powerful technique.

TTJV may be used as an alternative to a surgical airway if fibre-optic intubation is inapplicable, for example because of airway soiling by blood or obstructing laryngeal tumours with 'pinhole trachea'. Awake tracheostomy is a difficult procedure even for the experienced head and neck surgeon; it may be impossible in the patient needing to sit to struggle to breathe or spit out blood. Siting a TTJV catheter is easier and permits tracheostomy or tumour resection to be carried out under general anaesthesia. Debris and blood tend to be blown out of the oropharynx.

Complications
The most common problem is failure to cannulate the trachea. Use of curved cannulas and other manoeuvres aimed at getting the catheter to lie axial to the trachea tend to make cannulation more difficult, but ultimately increase safety and success.

There are no reports of problematic haemorrhage, though TTJV is not advised if there is involvement of the anterior neck or trachea in vascular malformations. A small dried rivulet of blood in the trachea on endoscopy is not uncommon following catheter insertion.

The sequence of barotrauma, pneumothorax, pneumo-mediastinum and subcutaneous emphysema usually follows failure to ensure a clear expiratory pathway during surgical instrumentation and is more common in children. Meticulous technique, a high index of suspicion and prompt treatment mitigate against this complication becoming a catastrophe.

A dry cough is often reported after TTJV. The tiny puncture site normally seals on removal of the catheter. Pressure should be applied to the site to prevent subcutaneous emphysema.

There are no specific recognized late complications of perioperative TTJV. ◆

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Ethics

Anaesthesia
and intensive care medicine
on CD-ROM

Clinical Governance

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Britain's National Health Service (NHS) was constituted in 1948 as a universal system, funded predominantly by taxation, to provide healthcare without financial barriers to access. At its inception it was essentially a paternalistic service where the professionals delivering the care defined the needs of patients and set up services to meet those needs. The expectation was that high individual professional integrity and competence would lead to a high quality service. This system served the country well for several decades, however, various attempts have been made by successive governments to improve the NHS. These initiatives have been driven by rising public expectations over the lifetime of the service. In recent years, added impetus for change has developed as a consequence of high profile failures within the NHS (e.g. paediatric cardiac surgery in Bristol).

Clinical governance is the centrepiece of the latest government initiative aimed at improving the NHS. It was first described in the White Paper of 1997 *The New NHS*. It builds on several previous national quality initiatives (Figure 1). While high individual professional standards remain essential for a good quality service, clinical governance aims to instil an overall ethos of corporate responsibility to improve quality of care in the NHS.

History of national quality initiatives

Resource management	1980s
Medical audit	1989
Patient's Charter	1993
Clinical guidelines	1993
Clinical effectiveness	1995
Clinical governance	1997

1

Definition

Almost anything done under the name of quality in the NHS may now come under the clinical governance umbrella. As a result of a lack of an intuitive meaning to the term, and partly owing to its enormous scope, it has proved difficult to give a clear definition of clinical governance. The most widely used definition, and the one quoted by government agencies is 'Clinical governance is a system through which NHS organizations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish'.

Alternatively, in 1998, Sam Galbraith MP gave a statement, which touches on the role of clinical governance in meeting the rising public and political expectations of the NHS. 'Clinical governance is the vital ingredient that will enable us to achieve a health service in which the quality of healthcare is paramount. The best definition that I have seen of clinical governance is simply that it means corporate accountability for clinical performance. Clinical governance will not replace professional self-regulation and individual clinical judgement, concepts that lie at the heart of healthcare in this country. But it will add an extra dimension that will provide the public with guarantees about standards of care.'

A more succinct definition is 'Clinical governance is corporate responsibility for clinical performance'.

Responsibility

Clinical governance applies to all patient services in the NHS. The statutory duty to seek quality improvement through clinical governance rests with Trust chief executives. The government's aim is to ensure that quality of care is as important as financial matters at Trust board level. Trust chief executives are now expected to:

- ensure a culture in which the highest standard of clinical care is the responsibility of everyone in the organization
- introduce structures and processes that allow this to happen.

These duties are considerable and delegation is required. A degree of local discretion is allowed in how this is achieved but a common model is as follows.

- Individual doctors remain responsible for their clinical decisions.
- Departmental heads and clinical directors have responsibility for quality of care in their directorate and they report on quality issues to a clinical governance committee.
- This committee assumes oversight of the clinical governance activities of the Trust. It should ensure that the appropriate structures for clinical governance are in place and that they work well.
- The clinical governance committee reports directly to the Trust board and chief executive.
- Trusts are assessed by the national bodies described below.

Key components of clinical governance at Trust level

It is hoped that by adherence to the key tenets of clinical governance (reviewed below) at a local level, Trusts will have well trained and motivated staff producing safe and effective evidence-based care; and as a consequence of good communication, patients will be well informed and involved in the decisions regarding their care.

Education, training and professional development of staff: good quality healthcare depends on the quality of staff. Time should be set aside for staff education, training and continuing professional development. This has important resource implications for Trusts.

Evidence-based clinical practice: Trusts should ensure that the care they deliver is based on the best available evidence. Systems should be in place for receiving, distributing and implementing evidence-based guidelines as they are published. Adherence to evidence-based practice must be audited (see below).

Clinical audit requires:

- structured review by clinicians of their practice and results against agreed standards
- sharing of audit results across clinical teams
- modification of care as dictated by the results of audit
- remonitoring to ensure quality of care has improved.

Trusts should ensure that good audit systems are in place. This requires investment in information technology systems and extra staff to facilitate the process.

Risk management: Trusts must have established protocols to identify adverse events. A blame-free culture in which to report adverse events should be cultivated. Structures to allow identification of patterns, and the initiation of prompt change should be in place. Risk management within Trusts should be pro-active and lessons painfully learnt in other parts of the health service should be applied locally. Risk management staff may be useful in designing systems to minimize risk. Trusts should also aim to reduce problems and complaints by means of good communication.

Communication with patients and relatives: poor communication is regularly highlighted as a cause of patient dissatisfaction. Trusts should provide training in communication skills for their staff and ought to factor in the time required for good communication when planning staffing levels. The development and provision of information leaflets can aid staff in this activity. Trusts should encourage comments and suggestions from patients and relatives regarding the services they provide and institute change as necessary.

Complaints procedures: there should be accessible, well-publicized complaints procedures available to patients and relatives. Good clinical governance requires thorough investigation of complaints in an environment that is supportive of the staff involved.

Tackling poor clinical performance: while only a part of clinical governance, this is the area most associated in doctors' minds with the concept. It has been widely recognized that the pre-existing regulatory systems have, on occasion, failed to detect and correct poor clinical performance at an early stage. Extensive new national regulatory measures are being developed to reduce this problem. Despite these measures it remains probable that other doctors in a department will be the first to note a colleague's poor performance or conduct. Anaesthetic departments should aim to be vigilant in detecting, correcting and supporting their poorly performing members. If good structures are in place it may be possible to correct poor performance before it has a major impact on standards of care. The Royal College and the Association of Anaesthetists have published useful guidance for departments in this area.

Support structures for clinical governance: Trusts should have a simple clinical governance chain of command so there is clarity about who is doing what within the Trust. Clinical governance support staff have in the past been appointed in a rather scattergun fashion (e.g. separate staff for clinical audit, risk management and clinical effectiveness). Such staff should be integrated into a single clinical governance department to increase their effectiveness.

Major national components

With the inception of clinical governance a significant regulatory and support industry has developed. These structures are not fully established and continue to evolve. The major organizations with associated websites are listed in Figure 2. Their present roles are described below.

Organizations with major roles in clinical governance

• General Medical Council Revalidation	www.gmc-uk.org www.revalidationuk.info
• Royal College of Anaesthetists	www.rcoa.ac.uk
• Association of Anaesthetists of Great Britain and Ireland	www.aagbi.org
• Department of Health Appraisal National Service Frameworks Clinical Governance Support Team	www.doh.gov.uk www.appraisaluk.info www.doh.gov.uk/nsf www.cgsupport.org
• National Clinical Assessment Authority	www.ncaa.nhs.uk
• National Institute for Clinical Excellence	www.nice.org.uk
• Commission for Health Improvement	www.chi.nhs.uk
• National Patient Safety Authority	www.npsa.org.uk
• Scottish Intercollegiate Guidelines Network	www.sign.ac.uk
• Health Technology Board for Scotland	www.htbs.co.uk
• Clinical Standards Board for Scotland	www.clinicalstandards.org
• Clinical Resource and Audit Group	www.show.scot.nhs.uk/crag
• Clinical Resource Efficiency Support Team	www.n-i.nhs.uk/crest

2

Appraisal

Appraisal was introduced by the Department of Health with the support of the medical profession in April 2001. On an annual basis, trained appraisers will review the activities of the doctor being appraised; agree with him key objectives for the following year and outline the doctor's requirements of his employer to allow him to achieve these objectives.

The main objective of appraisal is to encourage continuing professional development but it also incorporates elements of performance review. The appraisal is based around the main tenets of the General Medical Council document *Good Medical Practice*.

All consultants in England should have undergone appraisal by April 2002. This deadline was not met, but following the completion of consultant appraisal it is planned to introduce appraisal for all other grades of NHS doctor.

General Medical Council (GMC) and revalidation

The GMC was set up in 1858 and its regulatory role in maintaining standards in the medical profession is long established. More recently, disquiet has been expressed by the profession, government and the public that the GMC could be more effective. In response, the GMC has examined its structures and proposes to develop an additional regulatory system for doctors. The GMC plans that all doctors will have to demonstrate, on a regular basis, that they remain fit to continue in medical practice – a process it has termed revalidation.

Revalidation involves an assessment against a standard fit-ness to practise and will result in the renewal or withdrawal of a doctor's licence to practise medicine after each revalidation process. Revalidation will take place every 5 years. The full details of revalidation are yet to be decided. As appraisal and revalidation will be based largely on the same sources of information, appraisal summaries are likely to be used in the revalidation process.

Government and the GMC expect the legislation to make revalidation mandatory to be passed in December 2002. If pilot schemes are successful revalidation will commence 2 years after this date.

The medical Royal Colleges

The individual Royal Colleges have long guided and supervised consultants and trainees in achieving and maintaining high standards – activities that now come under the clinical governance umbrella.

The Royal College of Anaesthetists, often in conjunction with the Association of Anaesthetists of Great Britain and Ireland, has been active in this regard. Major examples of their clinical governance activities include:

- assessment of trainees' core competencies as they progress through training
- the good practice guide for departments of anaesthesia
- publication of guidelines for anaesthetic practice
- an obligatory continuing educational and professional development programme for consultants
- publication of patient information materials (e.g. on pain relief in labour)
- support for critical incident reporting.

The new clinical governance ethos should put more weight behind College initiatives. In theory, as a result of clinical governance, managers will be more willing to fund the quality of care and safety measures that the College advocates (e.g. the removal of anaesthetic machines that can deliver a hypoxic mixture).

National Clinical Assessment Authority (NCAA)

The NCAA was established in April 2001 as a support service for employers of doctors whose performance is giving cause for concern. Its budget for 2002–2003 is £10.1 million.

The NCAA will consider referrals from employers (or self-referrals by doctors) on the full range of potential performance difficulties (i.e. clinical, behavioural and health matters). When a referral is received, the NCAA will:

- offer support and advice aiming for a local solution
- if this fails it will move to a formal assessment of the doctor's performance
- after assessment, a plan of action is recommended which might involve, for example, re-education or a change in working environment
- while it would hope to facilitate local resolution of problems, appropriate referral will be made if its assessment reveals matters that require investigation by the GMC or CHI.

Formal assessment of doctors began only in April 2002 and the role of the NCAA is not yet fully established. However, it does appear to have the advantage of being a 'half-way house' where problems can be identified and tackled at an early stage before a major breakdown in quality of service occurs or before suspension and referral to the GMC become mandatory.

National Institute for Clinical Excellence (NICE)

NICE was set up in April 1999. Its budget in the tax year 2001–2002 was £10.6 million. It is the main national facilitator for clinical governance issues. The functions of NICE are to:

- issue guidance on the full range of health technologies including drugs, medical devices and surgical techniques
- produce guidelines on the management and care of specific conditions
- oversee the four confidential inquiries (Confidential Inquiry into Maternal Deaths, Confidential Inquiry into Stillbirths and Deaths in Infancy, National Confidential Inquiry into Perioperative Deaths, Confidential Inquiry into Homicide by People with Mental Illness)
- advise on audit methodology and in particular to advocate audit of how well the advice it gives is adhered to.

The guidance produced by NICE is based on cost and clinical effectiveness. Adherence to its advice should contribute to an improvement in standards of care nationally and reduce regional variations in care.

National Service Frameworks (NSF)

The Department of Health instituted a rolling programme of NSF in 1998 as part of the clinical governance initiative. NSF set national standards to be attained in a particular area. There are, for example, NSF for coronary heart disease and for the elderly. They are broad in scope and of strategic importance. Usually only one new framework is published a year. They aim to drive improvement in standards of care across the country. NSF can impact on anaesthetic services by setting objectives that departments need to plan for and accommodate, for example the Older People NSF states that patients with fractured hips should have repair carried out by experienced staff within 24 hours of admission.

Commission for Health Improvement (CHI)

The CHI was established in November 1999 as the principal regulator of the clinical governance initiative in England and Wales. Its budget in the year 2001–2002 was £24.5 million. Its main roles are to:

- assess every NHS organization on a 4 yearly basis by means of a detailed clinical governance review, the results of which are published
- monitor the implementation of the national guidelines produced by NICE and NSFs
- investigate system failures within the NHS at local, regional and national level. One of CHI's strengths is that its reports achieve national prominence, particularly when they include adverse findings. They are a strong impetus to improvement when services are found wanting. CHI's recommendations have to be enforced by Health Authorities and the National Assembly of Wales.

Clinical Governance Support Team (CGST)

The CGST was established in September 1999 to support the implementation of clinical governance across the NHS in England. To date it has educated 400 teams from NHS organizations on clinical governance issues under its Clinical Governance Development Programme. Among other activities, it publishes on its website the details of successful local clinical governance schemes, and operates a Trust board level development programme.

National Patient Safety Authority (NPSA)

The NPSA was established in July 2001 to provide national leadership on patient safety and adverse event reporting. Its budget for 2002–2003 is £15 million. It will establish and operate a mandatory national system for reporting adverse events and near misses. This information will be collated and distributed to allow the early initiation of preventative measures throughout the NHS. It is hoped by these means to prevent recurrence of tragedies such as the intrathecal injection of vincristine (at least 13 patients are known to have died or been paralysed since 1985).

Organizational variations in the UK

- Appraisal, under the auspices of the Department of Health, applies to doctors in England. Similar appraisal systems are being instituted in the rest of the UK.
- The GMC and the Royal College of Anaesthetists operate throughout the UK.
- NICE, CHI and the NPSA operate in England and Wales. NSFs apply to England.
- The CGST and NCAA apply to England only, but it is probable the Welsh Assembly will accept their roles.
- In Scotland, though there is not an exact duplication of systems, similar roles to CHI and NICE are performed by the Clinical Standards Board for Scotland, aided by the Scottish Intercollegiate Guidelines Network, the Health Technology Board for Scotland, and the Clinical Resource and Audit Group. In 2003, these bodies, with the exception of the Scottish Intercollegiate Guidelines Network, together with the Scottish Health Advisory Service and the Nursing Midwifery Practice Development Unit will amalgamate to form NHS Quality Improvement Scotland.
- In Northern Ireland, the Clinical Resource Efficiency Support Team has published guidelines and audited services since 1988. An extensive review of health service provision is nearing completion which may lead to the introduction of further clinical governance measures. ◆

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Consent: Ethical Considerations

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The relationship between doctor and patient is not uniform. Ethical codes of conduct and laws of consent, confidentiality and negligence vary according to the role played by the doctor and the objective of the contact between patient and doctor.

- In the therapeutic model the relationship is therapeutic and the doctor's main objective is the well-being of the patient and improvement in that patient's health.
- In the research model the relationship changes and the doctor's aim is the accumulation of medical knowledge. The benefits are designed to aid future patients, though there is potential for the research subject to obtain benefit.
- In the relationship between an occupational health doctor and a patient, the doctor's duty is to his employer and not necessarily to the patient.

Rapid developments in medicine have been accompanied by a tendency for patients to ask for greater involvement and control over what happens to them. Physicians and other healthcare professionals do not have a right to do anything to patients without their consent because the right to consent to or to refuse treatment is grounded in the ethical principle of respect for autonomy. A feature of our society is the emphasis on the value and dignity of the individual. Principles of inherent natural rights dictate that a competent person should decide what happens to his or her body. All medical codes of ethics now hold that physicians must obtain the informed consent of patients and subjects before undertaking procedures.

Informed consent

The concept of informed consent needs clarification. Various commentators have reduced the concept to shared decision-making between doctor and patient, so that informed consent and mutual decision-making are identical ideas. The British Medical Association, for example, states that the relationship between doctor and patient is based on the concept of partnership and collaborative effort. Decisions should be made through frank discussion, in which the doctor's clinical expertise and the patient's individual needs and preferences are shared, resulting in the selection of the best treatment option. Patients are therefore actively involved in deciding what is to be done to them.

For the patient's consent to be a valid authorization for the professional to proceed, it must be based on understanding and must be voluntary. Because of the unequal distribution of knowledge between professionals and patients the principle of respect for autonomy entails that professionals have a prima facie obligation to disclose information, to ensure understanding and voluntariness, and to foster adequate decision-making. Thus, the information component can be said to consist of adequate disclosure followed by the understanding and comprehension of what is disclosed. The consent component, in turn, refers to a voluntary decision-making process which is followed by authorization. Therefore, informed consent can be analysed in terms of the elements in Figure 1.

The elements of informed consent

Threshold element
- Competence

Information elements
- Disclosure of Information
- Understanding of information

Consent elements
- Voluntariness
- Authorization

1

Competence

Competence is a precondition of being able to give consent. It is closely tied to autonomy. Law, medicine and to some extent philosophy presume a context in which the characteristics of the competent person are also the properties possessed by the autonomous person. Although autonomy and competence are different in meaning (autonomy meaning self-governance and competence meaning the ability to perform a task), the criteria of the autonomous person and of the competent person are strikingly similar. Thus an autonomous person is necessarily a competent person. A person is thus generally competent to authorize or refuse to authorize an intervention if and perhaps only if that person is autonomous.

Disclosure

There is a requirement for doctors to inform the patient about the material risks of a planned procedure or intervention. However, the patient is not compelled to accept or refuse the treatment that is offered. The patient should be allowed to choose the type and scope of treatment and to base this choice on adequate information about success rates and risks. It is impossible for a health professional to give all available information to the patient. It is not the doctor's role to provide a list of alternatives from which the patient selects options, according to their need and desires. Ideally, the doctor should inform the patient about any risks in the treatment that may be particularly important to that patient, as well as explaining the risks and benefits of alternatives and of non-treatment. Without an adequate transfer of information from doctor to patient there is insufficient information for decision-making. However, the professional's own perspective, opinions and recommendations are often essential for the patient's deliberation, as well as for mutual understanding.

Professionals are generally obliged to disclose a core set of information. This includes:

- those facts or descriptions that patients or subjects usually consider material in deciding whether to refuse or consent to the proposed intervention or research
- information the professional believes to be material
- the professional's recommendation
- the purpose of seeking consent and the nature of consent as an act of authorization.

Despite these general recommendations, controversy surrounds the issue of what should be disclosed about a procedure's risks and negative consequences, as well as about the nature and purpose of the procedure, its benefits and alternative procedures. Should a health professional discuss all the alternatives, including those considered too risky? For example, consider an operation in which a Tenckhoff catheter is inserted into the abdomen to allow peritoneal dialysis in a patient with renal failure. Several anaesthetic techniques may be used to allow this operation to proceed including general anaesthesia, infiltration of local anaesthetic by the surgeon, or an epidural or spinal anaesthetic administered by the anaesthetist. If the general anaesthetic option is taken, should one insert a laryngeal mask airway (LMA) or intubate the patient? If an LMA is inserted, should one use muscle relaxants? Time does not allow a detailed discussion of all the available options with the patient. Thus, the usual attitude is to discuss none of the options, possibly infringing the requirement for information disclosure and thus infringing the patient's autonomy. However, a recent personal audit has shown that patients require very little information from their anaesthetist. Indeed, the most common preoperative question concerned the duration of the anaesthetic. Despite this, it is clear that the more serious the risk or harm done to the person the greater the degree of information required. The legal standards that govern disclosure of information are discussed on page 426.

Understanding

Informed consent implies a duty to disclose information; however, it may be better to use the term comprehend because the information disclosed may not be understood. Increasingly, the ethical focus is changing from the doctor's obligation to disclose information to the quality of a patient's or subject's understanding and consent.

Understanding, therefore, is a more important element than disclosure and arguably the most important element in the process of obtaining informed consent. The key to effective communication, understanding and decision-making is participation by patients in an exchange of information. Ordinarily, a professional has only limited insight into the distinct values, fears, hopes and information needs of others. Asking questions, eliciting the concerns and interests of the patient, and establishing a climate that encourages the patient to ask questions may be more important to the person's understanding than a mass of disclosed information.

Clinical experience and empirical testing indicate that patients exhibit wide variations in their understanding of information about diagnoses, procedures, risks and prognoses. For example, in one study up to 44% of postoperative patients who signed consent forms were unaware of the exact nature of the procedure they had undergone. This also highlights the dubious usual practice of allowing the most inexperienced member of the surgical team to explain the operation to the patient and 'get consent'.

Although some patients are calm, attentive and eager for dialogue, others are nervous or distracted in ways that impair or block understanding. Many conditions, other than lack of sufficient information, can limit their understanding, such as illness, irrationality and immaturity.

It has been argued that patients cannot comprehend enough information or appreciate its relevance sufficiently to make informed decisions about medical care. Ingelfinger stated that 'the chances are remote that the subject really understands what he has consented to'.

There may be many reasons for this. Doctors and patients may use the same word but it may have different meanings to them. Fasting, for example, may mean to the patient 'do not take any food', thereby allowing them to drink as much liquid as they like. Enabling a patient to comprehend and appreciate risks and benefits can be a formidable task. It can be difficult for patients to appreciate the projected expectations of, for example, pain in labour or following surgery.

Patients presenting at antenatal clinics often state they wish to have a completely natural childbirth. This is clearly documented in the case notes, with the staff forbidden to use painkillers or epidural injections. However, once the contractions (and pain) set in, all that was previously stated is quickly forgotten and pain relief demanded. In this situation, can the previous refusal (illustrating respect for autonomy) be overridden? Let us assume for a moment that severe pain can make one's choices irrational and hence make one incompetent (a debatable point). It could be claimed that, because of the pain, the patient is no longer able to make a rational decision and, from a respect for autonomy, the healthcare staff should not administer painkillers. In such a situation, clearly, the principles of beneficence (do good) and non-maleficence (do not cause harm) would overcome any principle for respect for autonomy, leading to painkillers or an epidural being administered, to the obvious comfort of the patient. The point is that it may be difficult for patients to appreciate the nature and degree of pain in advance and thus they cannot fully understand what they are refusing.

Similar arguments can be applied to the appreciation of risks. The general public has a poor understanding of the probabilities of something occurring. Indeed, preferences can be affected simply by framing outcome in terms of probability of survival instead of probability of death, described as a cognitive illusion. If a misconception occurs regarding a particular risk which is material to decision-making, it implies that adequate understanding was not attainable and thus an autonomous authorization was not given. Even the amount of information that can be meaningfully processed is limited. Information overload may be as likely to lead to uninformed decisions as failure to disclose. This is the reason research ethics committees request research information sheets to be as short as possible and written in layman's terms.

Thus, the requirement of an ideal standard of full disclosure and full understanding cannot be attained. However, because actions are never fully informed, voluntary or autonomous, it does not follow that these actions are never adequately informed, free, or autonomous. It is clear that understanding does not need to be full or complete, because a substantial grasp of central facts and other descriptions is often sufficient.

It is also interesting to note what Beauchamp and Childress claim would be ethically acceptable if a patient has an unreasonable belief. For example, a patient may refuse a life-saving operation because of an irrational belief that he or she will die under anaesthesia, based on the fact that a relative died in similar circumstances. There may be overwhelming medical evidence that such a belief is unjustified. 'The position does not imply that we should never coerce patients or subjects to change their beliefs or to process information differently. If a patient's or subject's autonomy is limited by his or her ignorance, as in the case of a false belief a patient has difficulty in surrendering, it may be legitimate and even obligatory to promote autonomy by attempting to impose the information on a patient who finds it unwelcome. And if this proves impossible, the principles of beneficence and non-maleficence may still justify overriding the patient's non-autonomous choices.'

Voluntariness

Voluntariness is the condition of a patient being independent of manipulative and coercive influences exerted by others in order to control that person. There are degrees of influence and three primary categories have been described: coercion, manipulation, and persuasion. Coercion occurs when one person intentionally uses a credible and severe threat of harm or force to control another. This entirely compromises autonomy.

At the other end of the spectrum lie weak forms of influence such as rational persuasion. Here a person is convinced to agree to something through the merit of reasons advanced by another person. Such situations are probably common in the doctor–patient relationship. Manipulation means getting people to do what the manipulator wants by means other than coercion or persuasion. For the purposes of decision-making in healthcare, the most important form of manipulation is informational manipulation, a deliberate act of managing information that successfully influences a person by non-persuasively altering the person's understanding of a situation and thereby motivating the person to do what the agent of influence intends. Some forms of informational manipulation are incompatible with informed consent. For example, this could occur if clinicians withhold information not because of non-maleficence but to manipulate patients into agreeing to their recommendations.

It is easy to inflate the threat of control by influence beyond its proper significance. Most decisions in life are made in the context of competing influences, such as wants, needs, familial interests, legal obligations and persuasive arguments. Although significant, these influences may not be controlling to any substantial degree.

From a clinician's point of view, although there is an obligation to abstain from controlling influences, there can be occasions when doctors are blameworthy if they do not attempt to persuade resistant patients to pursue treatments that are medically essential. This reasoned argument may be vital to ensuring understanding and should never be considered an unjustified form of influence.

The future

The issue of informed consent within medical practice is coming to the fore as the balance of power in the doctor–patient relationship moves relentlessly towards patients. Doctors will have to learn to inhabit the complicated world in which philosophers feel comfortable. The question whether contemporary medicine and research should always be held to the standard of autonomous decision-making is not easy to answer. Respect for patient autonomy is generally regarded as one of the central ethical principles in medical practice. Many would claim a moral imperative of respecting human autonomy in almost all circumstances, and that failing to respect the autonomy of competent people is to inflict harm on them that is just as morally unacceptable as direct physical or mental harm. However, making respect for autonomy a trump moral principle, rather than one principle in a system of principles, places an inappropriately high premium on autonomy. It is not the only principle and should not be overvalued when it conflicts with other values. In certain situations it may take on a secondary importance and other moral principles may outweigh it. However, it is clear that such situations are limited. ◆

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Consent and Malpractice Litigation

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Malpractice litigation has numerous functions. It provides an incentive to practitioners to maintain a high standard of care, though the law is mainly concerned with guaranteeing that a minimal level of competence is achieved. It allows injured parties to bring a malpractice action as a way of gaining retribution against health professionals, who they believe, need to be punished for harming them. It may also lead to compensation. One of the most important reasons that leads to a legal action being brought is a quest for an explanation of what went wrong.

To win a negligence case the plaintiff (i.e. the patient) is required to prove three things:

- that a duty of care existed and the professionals sued were responsible for the victim's care at the time of the mishap
- that the professionals failed to reach the accepted standard of practice required by law
- that the injuries they suffered were caused by the failure to practise properly. If successful, the patient is entitled to damages.

Duty of care

Establishing a duty of care is not usually a problem when patients are in hospital. The anaesthetist is clearly responsible and has a duty of care to the patient being anaesthetized. However, there are limits to duty of care. For example, in the UK, professionals who pass a road traffic accident have no legal obligation to stop and assist anybody who has been injured, though they may have a professional obligation to do so.

Accepted standard of practice

In most cases of medical negligence the key question is whether the professional failed to reach the standard of care required of them by law. That standard was first established in Scotland in the case of Hunter v. Hanley (1955) and 2 years later in England in the case of Bolam v. Friern HMC (1957). In the Hunter case a hypodermic needle broke during an injection and the plaintiff alleged failure to use a suitable needle. The Bolam case concerned the failure of use of muscle relaxants to control the violent convulsions and spasms during ECT. In both cases it was held that a doctor was not guilty of negligence if he acted in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art. In other words, doctors are judged against the standards of their peers. Therefore, if experts from the defendant's profession are prepared to accept that the actions were proper, the negligence claim will fail. The experts merely have to regard the defendant's actions as being within the range of acceptable practice. This means a minimal level of acceptable practice, not what the expert would have liked to happen.

This implies that medical experts establish the standard of care and not the courts, with determination of the legal duty being left to the judgement of doctors. However, there are suggestions that the law is slowly moving away from this view. In the case of Sidaway v. Bethlem Royal Hospital Governors (1985; discussed later) the court reserved the right to decide that even standard practice may be negligent. Similarly, the recent court of appeal case of Bolitho v. Hackney HA (1993) indicated that judges are becoming less reluctant to set standards for doctors. Here Farquaharson noted the possibility of an accepted medical practice being held to be negligent because it put the patient unnecessarily at risk.

Current interpretation seems to be that the fundamental principle is that medical negligence is to be judged against the standards of the medical profession through the evidence of medical experts. This expertise is to be overridden when the medical experts hold views that the judges believe no reasonable doctor could hold.

The rule of acceptable practice applies to other areas of practice. For example, when professionals attempt to do something that they are not qualified to do, the failure to refer the patient to someone properly skilled may be negligence (Wilsher v. Essex AHA, 1996). The development of hospital policies may also have a significant impact on the way in which the standard of care is defined. It is easier to prove that health professionals have been negligent if they have failed to follow policies or protocols. Such protocols are usually designed to clarify acceptable practice and guard against risks by incorporating suitable safeguards. However, a departure from such a guideline or policy does not automatically mean that the person is negligent. It suggests that unless the circumstances indicate that there were good reasons for departing from the usual practice the professional will be found liable. Failing to provide such a justification indicates negligence.

In certain cases, the fact that a particular accident happened is held to be so obviously negligent that it requires the defendants to rebut the presumption that they were in breach of their duty. This maxim, *res ipsa loquitur* (the mishap is said to speak for itself), can be of particular significance in cases were the treatment is complex or the plaintiff is unconscious and is thus of particular importance to anaesthetists. In Saunders v. Leeds Western Health Authority (1985), a 4-year-old child suffered a cardiac arrest during an operation to correct a congenitally dislocated hip and became quadriplegic, mentally retarded and blind. At the trial, evidence was given that the heart of a fit child does not arrest under anaesthesia if proper care is taken. The plaintiff did not need to show what act or omission had caused the arrest. The defendants' explanation of a paradoxical air embolism was rejected and the court found in favour of the plaintiff. The defendants had been negligent.

Cause of the injuries

The third step in proving a negligence claim is showing that the failure to provide a satisfactory standard of care was the cause of the victim's injuries. Unless this can be proved, the claim will fail, even if the defendants were clearly at fault. Where the injury is caused by the care a health professional gives, such as severing a nerve during the course of an operation, it is easy to show that the professional's actions caused the injury. However, it is more difficult in cases in which the patient claims their underlying complaint should have been cured or alleviated but was not. Often it cannot be proved that the patient's injuries were not a result of natural causes, such as the underlying medical problems or an unavoidable accident.

Criminal charges

In most circumstances, malpractice is the concern only of the civil law. However, in extreme cases there may also be criminal implications. For example, if a mistake causes the death of a patient, the health professional could be prosecuted for manslaughter. For this to occur, there must have been gross negligence not merely negligence. A recent determination has been that of the anaesthetist Dr Adomako in the House of Lords. He failed to notice that for over 4 minutes a tracheal tube had become disconnected during an operation under general anaesthetic. An alarm sounded but the connection of the tube was not checked until the patient had suffered a cardiac arrest. One expert prosecution witness stated that a competent anaesthetist should have spotted the problem within 15 seconds. The defendant accepted that he had been negligent, but denied that he was grossly negligent so as to be guilty of involuntary manslaughter. The House of Lords held that the question of whether the degree of culpability was such that the anaesthetist should be liable to criminal sanctions was a matter for the jury. It also approved tests from earlier cases that adopted a suggestion that gross negligence describes cases where the defendant has shown such disregard for the life and safety of others as to deserve punishment. This focuses attention on the recklessness of the professional's behaviour, that is, the failure to concentrate on the patient's interests. Thus, where health professionals have shown an obvious indifference to the risks to the patient, they may be charged with manslaughter.

Consent

A more contentious area regarding malpractice litigation arises when dealing with issues of consent. The consent of the patient legalizes medical examination and treatment. Significant case law has arisen owing to doctors failing to communicate adequately with their patients, either because there had been no proper consultation before treatment or because the medical practitioner failed to disclose the risks inherent in the proposed treatment.

If an individual wants to buy a car, the vendor is not obliged to point out defects in the car. If specifically questioned, the vendor commits fraud if he answers dishonestly, but he is not obliged to volunteer information that may be detrimental to the sale. On the other hand, the relationship between patient and doctor is one known in law as a 'fiduciary relationship.' Any person such as a physician, attorney, priest or other who enters into a relationship of trust and confidence with another has a positive obligation to disclose all relevant facts. The essence of a professional relationship is that the professional knows more about his subject than the person who seeks his help, therefore an affirmative duty of disclosure has always existed.

Patients need to be given a clear explanation of any treatment proposed, including any risks and alternatives, before they decide whether they agree to the treatment. Although consent, expressed or implied, must be given in most cases before treatment is lawful, this does not mean that consent needs to be fully informed. Indeed, the author does not believe that 'fully informed consent' can ever be achieved. Lord Donaldson has pointed out that consent plays two quite different functions in the doctor–patient relationship. One, which he called the legal function, is to provide a legal justification for care. Without such consent health professionals would commit a crime (battery) and a tort (trespass to the person) when they touch their patient. The other function, termed clinical by Lord Donaldson, is to secure the patient's trust and cooperation. This aspect of consent may involve more extensive counselling on the implications, risks and side-effects of treatment than the laws of trespass and battery require.

Battery

A battery is an intentional or reckless unlawful application of force to another person and is a crime as well as a tort at common law. Theoretically many procedures a doctor performs might be batteries (e.g. injections, surgery, manipulations) if done without the consent of the patient. The touching of a person in this manner without consent violates an individual's right of self-determination and constitutes an act of trespass to the person.

The main importance of battery lies in its role in emphasizing that patients are entitled to refuse the care provided by health professionals. They have a right to refuse treatment. In the words of Justice Cardozo from 1914: 'Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without the patient's consent commits an assault.'

The common law has long recognized the principle that every person has the right to have his bodily integrity protected against invasion by others. The seriousness with which the law views any invasion of physical integrity is based on the strong moral conviction that everyone has the right to self-determination with regard to his body.

The distinction between an action based on battery and one for negligence is important. Battery, which is a non-consensual touching, is itself a legal wrong, whether or not any specific damages can be shown to result. Thus, a patient may bring a successful action for battery even when the procedure that was carried out without consent was clearly for his or her benefit. By contrast, in negligence, in addition to showing that the professional fell below the required standard the patient must prove that some damage resulted. This means a patient will lose their case if the procedure benefited them or where the carelessness of the professional did not cause the damage.

Lawyers acting on behalf of patients have argued that, if the patient's consent for an operation or a mode of treatment was given on the basis of inadequate information, either of the risks of the treatment or of the extent of the treatment, the case should be heard in battery and thus have a right to compensation under the laws of battery. However, the UK courts have been intolerant of attempts to try these cases under the laws of battery. Any such attempt has been seen as a device to side-step difficulties in sustaining an action for negligence based on failures to communicate proper information, and the courts have been consistent in holding that actions for battery should play a limited role in healthcare law. Although this position has been criticized, it is unlikely to be altered in the foreseeable future. As a result, battery can normally be successfully alleged only when there was no consent to the procedure. This usually occurs when there has been a blatant error by healthcare staff, such as when the wrong leg is amputated, or when no consent was obtained. Liability in such cases is virtually always admitted and usually settled out of court. In the case of Allan v. New Mount Sinai Hospital (1980) the patient told the anaesthetist not to use the left arm for injections. Unfortunately, the anaesthetist forgot this, and the injection into the left arm leaked out causing tissue damage. The patient successfully sued under an action for battery.

Disclosing information

On the other hand, it is clear that if professionals fail to counsel patients in a way recognized by their peers as appropriate they may be negligent. Thus, patients who allege that they have been given insufficient information must argue that the professionals have been negligent in carrying out their duty to advise them about the decision. This means that this important aspect of consent is governed by the same principles that apply to ordinary malpractice cases. Furthermore, the extent and quality of information that should be provided depends on whether the standard is based on the patient's expectations, that is a patient standard, or on a professional standard.

The professional standard test is the standard of disclosure that the profession would be expected to tell the patient, that is, in accordance with the Bolam test or Hunter v. Hanley. If a responsible body of medical opinion would not have disclosed what was not disclosed by the defendant the doctor would not be found guilty of negligence. Thus, even a significant minority of doctors in agreement will leave the plaintiff in difficulties.

Lord Scarman has attacked this reasoning. Although he would permit the medical experts to establish the standard of care in relation to diagnosis and treatment, he found it unacceptable in relation to informed consent. He has commented that the law's standard is, in effect, set by the medical profession. If a doctor can show that his advice or his treatment reached a standard of care that was accepted as adequate by a respectable and responsible body of medical opinion he cannot be made liable in damages if anything goes wrong. It is a totally medical preposition erected into a working rule of law.

The patient-centred standard, on the other hand, can be subdivided into two, the particular patient standard and the prudent patient standard, corresponding to subjective or objective standards.

The particular patient (subjective) test defines what the plaintiff would have done if notified of all relevant facts. This test suffers from the use of hindsight and since the relevant facts exist only in the mind of the individual an accusation is hard to refute. However, it is a desirable standard in so far as it embodies personal factors, including many that are non-medical, which might affect a particular person's decision.

The prudent patient test requires the plaintiff to establish that a reasonable person would not have undergone a recommended procedure after having been advised of all significant risks. This suffers from the impossibility of defining a reasonable person for each case. However, it appears fair to both sides in that a reasonable doctor and a reasonable patient are meeting on comparable terms.

Other views: if the Bolam test is assumed to be representative of the current law, the doctor would have to warn of all risks that a responsible body of medical opinion considers the patient should be warned of, as opposed to every possible risk. The British Medical Association (BMA) claims that how much or how little is considered adequate varies with each patient. 'It must also be a matter of clinical judgement and the standards set by other doctors. From an ethical viewpoint, the criteria should be as much information as the patient needs or desires. It is interesting to note that in the Bolam case, the law set the level at the standard adopted by the medical profession and a doctor who gives as much detail as a recognized body of medical opinion considers appropriate would be unlikely to be held liable in law.'

It is interesting to note that the BMA considers it unlikely doctors would be held liable in law. The reason for this is that Bolam has been softened by various statements made in cases such as Sidaway v. Bethlem Royal Hospital Governors (1985). In this case the plaintiff suffered from persistent pain in her arms. Preoperatively the surgeon decided that an operation to relieve pressure on the fourth cervical nerve root was required. During the course of the operation the patient's spinal cord was damaged and she suffered severe disability. She sued the hospital and the surgeon, not for negligence in performing the operation, but for failing to warn her of the risk of damage to the spinal cord. Evidence was presented at the trial that this risk was less than 1%. Medical witnesses stated that, in keeping with a practice common to other neurosurgeons, they would also not mention the risk of paralysis or death in order not to frighten the patient. The trial judge therefore dismissed the claim.

The Court of Appeal affirmed the trial judge's view that the law in relation to failures in diagnosis and treatment also applied to failures in the realm of advice. Lord Donaldson, the Master of the Rolls, reviewed the leading transatlantic cases giving rise to the prudent patient test in the doctrine of informed consent, but declined to incorporate those principles: '…what information should be disclosed and how and when it should be disclosed is very much a matter for medical judgement, to be exercised in the context of the doctor's relationship with a particular patient in particular circumstances. It is for this reason that I would reject the American formulation of the duty by reference to a 'prudent patient test'.'

However, the adoption of the medical standard implicit in Bolam was not seen by him as abdicating responsibility to the medical profession. The practice held by the body of responsible practitioners had to be one that was rightly and properly held, and the court would not: 'stand idly by if the profession by an excess of paternalism denies their patients real choice.' In the same case, Lord Justice Browne-Wilkinson formulated a proposition that a doctor was under a duty to disclose to the patient information relevant to the decision the patient would have to take.

It is therefore clear that the courts and medical literature in the UK have suggested that disclosure is the key item and chief condition in the act of giving an informed consent. This allows medical authority and physician responsibility to take preference over patient autonomy. This is not in keeping with the meaning of informed consent which is better analysed in terms of autonomous authorization. Furthermore, good practice is not necessarily interchangeable with the legal minimum. However, it is very clear that the UK, when considering standards of information disclosure, differs significantly from other jurisdictions, such as Australia, Canada and the USA. Indeed, the position is at odds with that in most other common law countries and is notably isolated within the European Community. ◆

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Ethics of Research

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Research is vital in improving the health and healthcare of the population; patients have the right to expect the best available prophylactic, diagnostic and therapeutic methods. At present, research involving human participants is not governed by legislation, but doctors involved in research have an ethical duty to show respect for individual rights and follow good research practice.

Patients want to receive the best possible treatment based on evidence derived from previous clinical trials. It could therefore be argued that there is an obligation on current patients to participate in the procurement of this evidence for future patients. However, the interests of the research subject are paramount. Even if research may lead to advances in medical knowledge, the outcome may not justify the risk to the participants. Respect for human life and individual autonomy of the research participant is the primary aim of the ethical review of research.

Ethical approval

All human research should follow ethical principles and be approved by an ethics committee. Ethical review of medical research has had a protracted development since World War II following the inhumane procedures carried out by Nazi doctors in the name of medical research. At the Nuremberg trials, 23 doctors were convicted and the exposure of their deeds led to adoption of the first internationally recognized code of medical ethics, the Nuremberg Code. The rights of research subjects were highlighted in the code, in particular the right of an individual to withdraw from a study at any time.

The formation of ethical review by committee followed the World Medical Association Declaration of Helsinki in 1964, the publication of Pappworth's *The Human Guinea Pig* in the UK and Beecher's *Experimentation in Man* in the USA. They all added weight to the discussion of the ethics of clinical trials, creating a framework for the principles for biomedical research. The Royal College of Physicians issued reports in 1967 and 1973, making various recommendations for the setting up and structure of ethical review committees. In 1975, the Department of Health and Social Security produced guidance, though the resulting system was varied in quality.

In 1991, a revised set of guidelines was issued by the Department of Health reconstituting all Research Ethics Committees (REC) to a standardized structure. Every health district required a local REC and detailed guidance on their composition and function was given. These RECs are convened to provide independent advice to participants, researchers, employers and care organizations on the extent to which proposals for research studies comply with recognized ethical standards. The purpose in reviewing study proposals is to protect the dignity, rights and safety of research participants. In addition, RECs have an obligation to society and researchers to encourage research that will improve healthcare and health.

The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH Guidelines) was established in 1990 as a joint regulatory project to improve the efficiency of the process for developing and registering new medical products in Europe, Japan and the USA. The guidelines describe internationally accepted principles and practices for the conduct of individual clinical trials and overall development strategies for new medical products.

Aim of research

Research is often categorized as therapeutic or non-therapeutic, though this is increasingly challenged. In therapeutic research, the subject may benefit from being involved in the research project. In non-therapeutic research there is no clinical benefit to the subject. The distinction is useful when discussing ethical issues and is one of a number of factors that RECs consider.

The aim of research is the generation of knowledge, not the improvement of the health of the research subject, though it may lead to this. Research must be capable of identifying and confirming improvements in clinical management, however small, or improving medical knowledge. Research is justified only if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research. Duplicate or redundant research is unethical because it involves finite risk to the participant with no beneficial outcome. The REC must reassure itself that the research project will lead to a meaningful result. Pre-recruitment statistical analysis must show, for example, that sufficient numbers of participants will be recruited to allow valid results to be produced.

The risks involved with research apply to the participant during the research period. The benefits accrue to future patients if the therapy or diagnostic test being researched is then implemented. This unequal distribution of risk (to the subject) and benefit (to future patients) requires the protection of the research participant who may receive no benefit from the research. The REC must be satisfied that the risks to participants are minimized. However, significant risks may be acceptable under certain circumstances. For example, patients who are critically ill may participate in research involving novel treatment despite known or suspected serious side-effects.

In non-therapeutic research it is essential that all risks should be mentioned and all foreseeable risks kept as low as possible. Potential benefits must greatly outweigh the risks of participation. Although it may be possible to define risk, whether the balance between risk to the individual and the benefit to others is acceptable is difficult to determine. Often the balance is subjective and some suggest the research subject could make the decision. However, this is unethical for several reasons. The REC has more experience and access to advice and knowledge than research subjects and is better able to assess the degree of risk. Also, research subjects may feel they owe a duty to the researchers looking after them and thus subtle coercion may come into play (see later). The REC can come to a collective judgement using individual expertise rather than individual judgement. Furthermore, the cumulative experience of the REC allows identification of serious risks. It is essential to ensure that involvement in the research project is not contrary to the subject's interests.

Consent

Ethical review of research not only considers what risks are acceptable but also ensures that the participants' autonomy is respected. Proper mechanisms for consent must be in place. The principles governing consent are provision of sufficient information to allow choice and freedom to decide without influence from the researcher.

Each participant must be adequately informed of the aims, methods, anticipated benefits, and the potential risks of the study. The participant must be informed of the right to abstain from participation in the study or to withdraw participation at any time without reprisal. Once the researcher has ensured that this information has been understood the participant's freely given informed consent must be obtained. This presents a problem in some areas of research, namely, day surgery, emergency medicine and ICU.

Day surgery: the time available for consent is restricted and there is inadequate opportunity for the patient to process the information, reflect on the risks and benefits, and discuss the proposals with relatives. Efforts should be made to discuss the research with the patient before the day of surgery, allowing formal written consent to be obtained on their arrival for surgery. This may increase the workload for the researcher but failure to do this is deemed by some RECs to be unethical.

Emergency medicine: obtaining consent in emergency medicine and ICU is further compromised because patients are unable to comprehend the information provided owing to their clinical condition. Treatment that is part of a research project may be permitted if the risks of the treatment being studied are not thought to be greater than standard treatment. This causes an ethical dilemma. The benefit to future patients must be balanced against the risks to the research participant and the protection of autonomy. There are no rules governing this balance and individual RECs must assess each study individually. However, it is generally accepted that it is ethical to involve adults who lack capacity, such as in the ICU, in therapeutic research. The situation for non-therapeutic projects is less clear and potentially illegal in England and Wales, though probably not in Scotland through a recent law giving relatives the right to consent on behalf of their incompetent relative. Paradoxically, it is increasingly regarded as ethical throughout the UK, provided certain safeguards are applied. RECs have a major part to play in such decisions and researchers are strongly urged to seek their views.

Recruitment

During recruitment, principles of consent, provision of information and freedom to decide, can be compromised because of the vulnerability of participants. During illness, comprehension and decision-making can be difficult. The research subject can be influenced by a desire to show gratitude and obligation to the doctor, which may make them susceptible to pressure from the researcher, however unintentional. This sense of gratitude can also prohibit a patient's voluntary withdrawal from the research. A suggestion to the patient that they will benefit by participating in research may be an inducement to participate. During recruitment, patients must be protected from pressure to participate and reassured if they decide to refuse participation. Any issues that arise during the research must be addressed and the imbalance of power between researcher and participant minimized.

Despite these problems, it is ethical to recruit from vulnerable groups. The vulnerability of different groups must be anticipated, recognized and taken into consideration by the researcher during recruitment. Participants must be correctly identified and exclusion criteria established. Efforts must be made to ensure that the research could not be carried out on a less vulnerable group. This is a general moral requirement for all research and precludes individuals who are less mature, frail, severely ill or confused from participating in research unless there are special circumstances.

Ethical errors

All research must be based on a properly developed protocol that has been approved by an REC (Figure 1). The aims, design, and methodology of the study must be justifiable, verifiable, scientifically valid and ethical.

Basic components of a Research Ethical Committee proforma

Purpose of the study
- Background of the work
- Information to be obtained
- Proposed benefits

Details of the procedure
- Explain how the study will be executed
- Duration of research
- Treatment allocation
- Procedures undertaken

Recruitment
- Age range of participants
- Principal inclusion and exclusion criteria
- Minimum number of subjects and justification for these numbers, with power calculations where appropriate
- How patients will be approached

Trial products
- Description of all drugs used, stating their known pharmacology, side-effects and toxicity
- If a new drug is to be used, a copy of the Clinical Trials Certificate or Clinical Trials Exemption Certification from the Committee on Safety of Medicines must be included
- List approved and new indications

Patient information
- Purpose of study, nature of procedure, discomfort and possible risks in terms that the subject can understand

Consent
- A standardized form should be used

Finances
- All sources of support for the work should be stated including details of all payments to be made to investigators, patients and healthy volunteers

The aims of the study determine the benefit, and therefore, must be clear, focused and reflected in the study design. The temptation to obtain as many answers as possible from the same number of participants can lead to serious methodological problems. The normal level of statistical significance is that there be no more than one chance in twenty that a given result is due to random variation. Clearly, the more outcomes that are measured the greater the chance that the researchers will identify a false-positive observation. Poor methodology is unethical because it subjects participants to risk for possibly invalid results.

Control groups

Research is susceptible to bias. The outcome measured can be influenced by participant characteristics that are independent of the process being tested. The variability of different individual patients must be overcome by using controls. These are research participants who are closely matched to those in whom the new treatment is being investigated. Thus, variables such as age, weight and diet are similar in both groups; the only difference is the therapy and therefore any difference between the groups can be assumed to be due to the therapy.

An ethical dilemma presents if the control group also requires treatment. This is overcome by giving this group the best current therapy and comparing its benefits, risks and effectiveness to the new treatment. This does not exclude the use of placebo or no treatment in studies where no proven method exists. No trial design should prevent a patient who needs active treatment from receiving it, though the trial therapy may be less effective than the standard treatment.

To eliminate bias, the allocation of controls and study patients must be done in a manner that reduces the introduction of un-recognized but influential factors. The researcher should not choose the controls but use a valid method of randomization.

Blind procedures

Researchers and subjects must be prevented from introducing their own expectations and hopes, which could influence outcome. The effects of a placebo are well documented. Similarly, researchers may be influenced during the measurement of the effect if they know which treatment has been given. Therefore, it is important that neither the researcher nor the subject knows to which group subjects have been allocated. Blinding of patients and researchers is crucial if bias is to be minimized and the results of a trial accepted. It is essential that randomization, the nature of the process and reasons for it are mentioned to the research subjects before their consent (contrary to the Zelen design). In a double-blind trial neither the researcher nor the subject knows whether the subject is receiving treatment or is in the control group.

The ethical problem with randomization and blinding is that the standard treatment is no longer prescribed by the doctor to the patient, but is chosen by a random decision process. The normal doctor–patient relationship is thereby compromised. This problem can be intensified if the clinician is blinded and unaware of the treatment the patient is receiving. If the patient subsequently becomes worse than expected during a trial, it is the responsibility of the researcher to provide a quick and effective means for withdrawal from the study and identification of the treatment received.

Sample size

Essential to the planning of a randomized trial is estimation of the required sample size. The investigator should ensure that there is sufficient power to detect, as statistically significant, a treatment effect. If a trial with negative results has insufficient power, a clinically important effect may be ignored or taken to mean that the treatment under study made no difference. Such a trial may be scientifically useless, and deemed unethical because patients may be put at risk with no apparent benefit. Likewise, studies that are too large are unethical because they involve supernumerary participants and incur unnecessary costs.

Placebos

Care should be taken in the use of placebos. Section 29 of the revised declaration of Helsinki states that ‘the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, where no proven prophylactic, diagnostic or therapeutic method exists.’

This is highly contentious and seems to rule out some vital uses of placebo-controlled trials in areas where proven treatment already exists. However, failure to use placebos may occasionally reduce the reliability of trial conclusions and increase the proportion of wrong decisions. Placebo-controlled trials are generally more reliable, providing their own check of internal validity and more conclusive proof of efficacy. Using placebos does not mean that the subject receives no treatment, because other medications are permitted in both groups. Rescue medication is also prescribed for specific circumstances.

Epidemiological research

Epidemiological research and disease registers involve collecting and analysing data from large numbers of patients, often without identifying individuals or their clinical involvement. The main aim is the investigation of the incidence and prevalence of diseases, often determining environmental and social factors. This is vital to protect and enhance public health. However, the investigators are bound by the principles of respect for the patient’s autonomy. Records made for one purpose (e.g. anaesthetic charts) should not usually be disclosed for another purpose without the patient’s consent.

The Data Protection Act 1998 requires researchers to make sure that patients are clear how their personal health information may be used and to give them an opportunity to opt out. The Act does not require the use of formal consent forms or signatures from patients before information is shared. However, the Act does require reasonable steps to be taken. A summary of the main principles of the Act is given in Figure 2.

Data Protection Act and Caldicott Guardians

Data Protection Act 1998
This brings into UK law European Directive 95/46/EC on the processing of personal data. It came into effect on 1 March 2000 and, in comparison with the 1984 Act, it is concerned with both records on paper and records held on computers. The act is based on eight principles

1. Personal data shall be processed fairly and lawfully
2. Personal data shall be obtained only for one or more specified and lawful purposes, and shall not be further processed in any manner incompatible with that purpose or those purposes
3. Personal data shall be adequate, relevant and not excessive in relation to the purpose or purposes for which they are processed
4. Personal data shall be accurate and, where necessary, kept up to date
5. Personal data processed for any purpose or purposes shall not be kept for longer than is necessary for that purpose or those purposes
6. Personal data shall be processed in accordance with the rights of data subjects under this Act
7. Appropriate technical and organizational measures shall be taken against unauthorized or unlawful processing of personal data and against accidental loss or destruction of, or damage to, personal data
8. Personal data shall not be transferred to a country or territory outside the European Economic Area unless that country or territory ensures an adequate level of protection for the rights and freedoms of data subjects in relation to the processing of personal data

Caldicott Guardians
In 1997, the Caldicott Committee reported on its review of information that identifies NHS patients.

Following the recommendations, a new system of data protection officers, ‘Caldicott Guardians’, was established.

Each Health Authority, Trust and Primary Care Group required a guardian to agree and review internal protocols for the protection and use of identifiable information obtained from patients

2

Systems of information collection should be constructed to balance public need and the rights of privacy of the individual. Consent should be obtained where practical, with anonymization of data if possible. However, data that have been encoded are regarded by the Data Protection Act as personal if the key for decoding remains in existence. Thus, coded data fall within the Data Protection Act and the researchers’ ethical responsibility, even if the key is not readily available to the researcher. If full anonymization is impossible, the use of pseudonymous data (creating codes and restricting access to them) should be considered, though this can still be interpreted as personal data.

The issues of consent and anonymization are complex, and uncertainties about the interactions between researchers, data protection officers, RECs and the new Caldicott Guardians are not yet clarified. ◆

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Jehovah's Witnesses

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The Jehovah's Witness Christian movement was founded in the north-eastern USA about 120 years ago. There are more than 5.9 million Jehovah's Witnesses in over 230 countries. The headquarters of the church organization, the Watchtower Bible and Tract Society, is based in Brooklyn, New York. In general, Jehovah's Witnesses are obliged to refuse blood transfusions or other blood-based products. This is based on the prohibition of the consumption of blood as outlined in the Bible (*Genesis* 9:3–4, *Leviticus* 17: 11–12 and *Acts* 15: 28–29). Accepting banned blood products is a serious offence and may lead to excommunication and 'enforced shunning'. This leads to social isolation because friends and family are instructed to avoid the 'offender's company'.

Changes in policy

Vaccinations for Jehovah's Witnesses were banned from 1929 to 1952, as were organ transplants from 1967 to 1980. The policy of refusal of blood dates back to 1945 and was enforced in 1961 with the threat of judicial sanctions and excommunication.

In June 2000, the Watchtower Society announced a change in procedure for 'offenders' and in the 'blood policy'. If through personal choice members accept blood transfusion they automatically disassociate themselves from the religion. If they repent, spiritual support is offered with the possibility of redemption. In other words, members resign from the religion rather than being expelled by a judicial committee.

The more important change from the medical community's view is the expansion in what are acceptable blood products. The ban on primary components (defined as red and white blood cells, platelets and plasma) and whole blood is still upheld. However, it now appears that the Society permits the use of all fractions of so-called 'primary components', the so-called 'secondary components'. At what point a primary blood product becomes a secondary product is open to debate and becomes an individual decision. It appears that nearly all components can be transfused as long as they are given piecemeal or processed (e.g. albumin, all clotting factors, immunoglobulins). Red cells stripped of their outer membrane may be transfused in the form of haemoglobin transfusions. Haemoglobin-based blood substitutes have entered phase 3 clinical trails and may become an acceptable treatment. Bone marrow transplants and the use of peripheral stem cells for autografting are often considered as transplants rather than infusions of primary blood products.

The current blood policy is confusing and complex and not every Jehovah's Witness is aware of the official position of the Watchtower Society. Therefore, in most major cities, Jehovah's Witness Hospital Liaison Committees have been set up to resolve these medical issues. An anonymous group within the Jehovah's Witnesses is trying to reform the blood policy of the Watchtower Society. Until this happens, more premature and avoidable deaths will occur.

Informed consent

As with any other competent adult, Jehovah's Witnesses are entitled to accept or refuse treatment or even only certain aspects of it (e.g. the administration of blood products). Many Jehovah's Witnesses leave copies of detailed healthcare advance directives (a living will concerning all kinds of personal matters) with their general practitioner, family and friends. In addition, Jehovah's Witnesses may carry a signed advanced directive declining blood in all circumstances and releasing the treating doctor from liability for the consequences. Doctors who knowingly give the patient blood despite the presence of an advanced refusal are likely to be held guilty of assault.

Each Jehovah's Witness must decide individually if he or she can accept the blood-derived products mentioned above. Doctors should discuss acceptable treatment, and the medical consequences of not receiving blood products, with the patient.

Blood transfusion

Jehovah's Witnesses believe that blood removed from the body should be disposed of. They object to techniques involving intra-operative blood collection, storage and haemodilution. However, provided the extracorporeal circulation is uninterrupted, many Jehovah's Witnesses agree to autotransfusion as a continuous blood salvage with reinfusion (e.g. during cardiac bypass). Isovolaemic haemodilution may be performed provided a closed continuous loop is maintained. Even epidural blood patches may be accepted provided the injecting syringe remains connected to the circulation. A long extension line from the venous cannula to the syringe and injection via a three-way tap into the epidural space maintains continuity. The use of pre-donation, storage and re-transfusion of blood is unacceptable.

Emergency situations

If a patient is incapable of giving consent (e.g. following trauma) and his or her views as a Jehovah's Witness are unknown, life-saving transfusions should not be delayed. This intervention is not subject to the religion's sanction or judicial process because the individual has not conscientiously accepted blood. If time permits, the patient's relatives or general practitioner can be contacted to establish the patient's views, though they do not have a legal right to refuse transfusions in England and Wales. However, the law in Scotland may be changing shortly, giving relatives legal authority to make treatment decisions. Evidence must be provided, for example in the form of an advance directive, that the patient would not accept blood even if that resulted in death. An advance directive is legally binding, but concerns have been raised because it is often unclear if, at the time of signing, the person was adequately informed of the risk and benefits of blood transfusion and the obligation to comply with church rules may have influenced their decision.

Child of Jehovah's Witness

In the UK, children under the legal age of consent, but capable of understanding the issues, can refuse transfusion without the consent of the parents or legal guardian, though the legal standing of such a refusal is unclear. If blood transfusions are required for an elective procedure and the parents refuse to consent, it may be necessary to apply to a court to make the child a ward of court. At this stage, a second opinion should testify that the child's life or long-term wellbeing is in danger unless it receives blood products during the proposed procedure. A court decision may become necessary to clarify who can give lawful consent, for example, if the child opposes the parental decision or if the parents are divorced and have different views.

In an emergency with the immediate requirement for blood transfusions, there is insufficient time to wait for a court order and blood should be transfused irrespective of the parent's wishes. A second medical opinion, confirming the necessity of immediate requirement for blood should be documented. The courts are highly likely to uphold the decision of the doctors.

Managing Jehovah's Witnesses

Anaesthetists and refusal to treat: in the elective situation individual anaesthetists may decide not to get involved in the care of a Jehovah's Witness, but in an emergency they are obliged to provide appropriate care and to respect the wishes of the patient if known.

Preoperative management: a preoperative consultation should be done early, before the planned procedure, to discuss and document acceptable treatment. Private consultations may be necessary because peer pressure is exerted on members to refuse transfusions. If a Jehovah's Witness accepts blood transfusions it is essential to maintain medical confidentiality. It is important to avoid transfusions during visiting hours and to keep fluid and prescription charts away from the patient's bedside. Access to medical notes should be restricted to the treating medical team. These precautions allow patients to remain silent about the medical treatment if they wish and avoid sanctions or disassociation from the church. Agreed procedures should be signed by the patient and kept in the medical records. Failure to respect the patient's wishes is unlawful and ethically unacceptable and may lead to criminal or civil proceedings. Preoperative anaemia is an important determinant of operative outcome, particularly in patients with underlying ischaemic heart disease. Anaemia should be investigated and treated. The use of iron tablets combined with erythropoietin is effective.

Intra-operative management: surgery under regional anaesthesia can be associated with major blood loss, especially in obstetrics. Confronted with major haemorrhage and the need for urgent transfusion, Jehovah's Witnesses may accept life-saving blood products. This change of consent has to be accepted and life-saving transfusion given, even if the patient had sedation and may not strictly meet the legal standards to give informed consent. Any change in the pre-existing consent should be documented and witnessed in the notes.

Managing anaemia and blood loss: haemoglobin levels of 8–10 g/dl are safe, even in the presence of cardiorespiratory disease. Critical levels of oxygen delivery in fit, healthy and resting adults are reached at about 5 g/dl. For elective procedures, a course of vitamin K, iron, folic acid and erythropoietin can be given. Strategies to reduce intra-operative and postoperative haemorrhage include cell savers and the use of antifibrinolytic drugs (e.g. tranexamic acid, aprotinin). Desmopressin (DDAVP) a synthetic analogue of antidiuretic hormone (ADH) may be used to control bleeding associated with acquired disorders of haemo-stasis, including chronic renal failure and liver diseases and some platelet disorders. In addition, elective ventilation, paralysis and sedation minimize oxygen consumption. Hyperbaric treatment, perfluorochemicals and active cooling have been described, though the latter may impair homeostasis. Recently, Sn-meso-porphyrin, a potent inhibitor of haeme oxygenase, has been used as therapy for severe hyperbilirubinaemia in Jehovah's Witness newborns as an alternative to exchange transfusions. ◆

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Transplantation Ethics

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There have been ethical dilemmas about transplantation since the first successful human kidney transplant in 1954. That transplantation proceeded in the belief that the psychological benefit of live donation outweighed the unknown outcome. Advances in transplant biology and technology have produced new ethical issues. These vary between individuals, countries and cultures, but many arise owing to the scarcity of suitable donor organs.

Allogenic (same species but different genetic constitution) solid organ transplantation is now an established treatment for end-stage organ failure (kidney, heart, lung, liver, pancreas), and a successful transplant results in improved duration and quality of life for the recipient. Unmet demand means patients die waiting for heart, lung and liver transplants because there are no alternative treatments. The success of long-term renal replacement therapy creates growing waiting lists for renal transplantation.

Most societies, and the main religions, accept that organ donation and transplantation is justified by the good it brings.

Transplant organ supply

Brainstem death

Brainstem death (BSD) is a product of modern intensive care. The concept is now well established in most societies. Acceptance took place in several stages and was central to the development of transplantation. In the UK, BSD heart-beating donors have been the main donors since the mid-1970s. Maintaining ventilation and circulatory support on these dead patients allows time for discussion with relatives, screening of donor, and a controlled approach to organ retrieval, allowing the use of the kidneys, heart, lungs, liver and pancreas with short warm ischaemic times.

BSD criteria provide an important demarcation between medical care for the patient (including the determination of death) and the separate involvement of transplant teams. Despite this, there is often discomfort at performing a 'lethal' operation on a body with 'signs of life' even though they are secondary to techno-logical interventions.

Some cultures hold beliefs about death that make it difficult to equate brain death with death. Organ harvesting from BSD donors was not permitted in Japan until 1997 because of the belief that death was not complete until funeral rituals were concluded. This was combined with a loss of trust in the medical community when the initial heart harvest led to a murder charge. Japanese citizens may now elect to permit their death (for the purposes of organ donation) to be elicited using BSD criteria.

Anencephalic donors

It has been suggested that brain death could be extended to anencephalic infants who could become organ donors byplacing them in a special category of death. This might be justified by prolonging life for the recipients, however, anencephalic infants have a functioning brainstem and are not brain dead. Moreover, transplanted organs from anencephalic infants have not worked well. Altering the definition of death in specific cases may also present risks to other patients (e.g. those in a persistent vegetative state).

Elective ventilation

In 1988, the Royal Devon and Exeter Hospital developed an elective ventilation protocol. Dying patients in deep irreversible coma were transferred to the ICU to allow artificial ventilation to be instituted immediately after respiratory arrest. This support continued until brainstem death ensued. The purpose was to increase the donor pool and optimize the condition of organs in preparation for transplantation. Strong arguments have since been made that it was wrong to prolong life and alter the mode of dying only for the benefit of others. The practice also risked patients entering a vegetative state. This practice was abandoned and the Department of Health forbids it. Treating patients for the purposes of organ donation rather than for their benefit risks charges of assault under the Criminal Offences Against the Person Act 1861. Calls for permissive legislation in this area, with patient consent given through an advance directive, must also be balanced against possible damage to the existing BSD programme from loss of public trust.

Non-heart-beating donors

Non-heart-beating donors are being increasingly considered as an important source of organs because demand is unmet by BSD donors. Non-heart-beating donors are declared dead after the irreversible cessation of circulation and respiratory function.

Irreversible brain damage

Patients with profound irreversible brain damage (not BSD) for whom continued support is considered futile by relatives and doctors often have life-sustaining treatment removed and die soon afterwards. In such cases it is possible to harvest organs in controlled conditions (with short warm ischaemic times) shortly after circulatory arrest, with the consent of the patient or relatives. Contentious issues include *pre mortem* placement of femoral catheters and *pre mortem* administration of drugs (e.g. heparin, phentolamine) to optimize retrieved organ function that cannot benefit the patient and may cause harm.

Patients dying in hospital

Other patients dying in hospital may also be potential donors but in a less controlled manner (e.g. death following resuscitation). Delay caused by lack of prior consent has sometimes led to measures such as *post mortem in situ* cooling of the body via percutaneous catheters until relatives are contacted and consent to harvest obtained. Is it justifiable to perform these extraordinary procedures without consent in order only to benefit others? Some argue there is an obligation to help others and such actions offer the family this chance. The limited time in which consent and harvest must be carried out risks misunderstandings. When has irreversible cessation of circulation occurred? Is prolonged resuscitation necessary first, or always ethical itself? Should there be a minimum period between the declaration of death and harvesting? The traditional loose definitions and timings of cardiac death are challenged in the context of non-heart-beating donors. The conflicting interest of reducing warm ischaemic damage must not influence good medical care (appropriate resuscitation, care and respect for the dying) and it is clear that there must be transparent separation between the medical and transplant teams. Likewise the transplant community should avoid any changes in definitions of death. It has been suggested that such a programme should only follow education of, and general acceptance by, the community in which it is to operate. Donor and family wishes and values must be taken into account at all times.

Poor graft survival from so-called marginal donors is also a concern, and the recipients must be made aware of differences in outcome from different sources. Recent evidence suggests that kidneys retrieved with warm ischaemic times of about 30 minutes (with no percutaneous cooling), have delayed initial function but similar long-term survival to those obtained from heart-beating cadavers.

Executed prisoners

In some countries, organs are retrieved from prisoners after execution. This is condemned by many, as is the involvement of physicians. Others argue that it is immoral not to use such organs if they exist, given the benefit they can provide.

Living donors

Before BSD criteria were accepted, living donors provided many kidneys for transplant. Living donation (kidney, liver lobe and lung lobe) has increased as cadaveric organs remain scarce. In Norway and the USA, about 50% of kidney transplants involve living donors compared with 27% in the UK (2001). The benefits to the recipient include reduced waiting time, scheduled procedure, healthy donor organ, reduced cold ischaemic time and longer graft survival. The main benefits to the donor are psychological.

The risks of morbidity and mortality to the donor vary depending on the organ (or partial organ) donated. The magnitude of these risks should alter the way in which decisions are made. Adult-to-adult transplantation of the right liver lobe has a donor mortality of about 1%, while kidney donation has a mortality of 0.03%. The risk to the donor may contradict the obligation to cause no harm. The donor must be aware of all risks and alternatives, and allowed an informed decision free from coercion. The doctrine of free consent allows this non-therapeutic surgery provided the consequences are not against the public interest. What role does the transplant community have in deciding if the risks are unacceptable to a particular donor? It is also worth considering the benefits that individuals and institutions gain from running such programmes and the distinction between allowing a person to risk harm and actively encouraging it.

Living emotionally related donors are not related by blood but by a close relationship such as friendship or marriage. The reward of seeing the recipient in better health is thought to justify their altruistic and risky donations. Most countries permit such donations.

Living unrelated donors: in the USA there have been recent cases of unrewarded altruistic kidney donation from live donors to unknown recipients. They are also known as 'undirected' donors. Concerns include difficulties in accepting that a true understanding of risk has been made; and what should be done if conditions are attached.

Consent for cadaveric organ donation

Opt in: in the UK, individuals are asked to register their intention to be an altruistic donor to society on the NHS donor register. The number of donors from this pool has diminished owing to improved road safety and a shortage of neurosurgical facilities. Over the last 10 years, the 20% reduction in the number of cadaveric organ donors has been matched by a 3% increase per year in patients listed for transplantation. The UK cadaveric kidney transplant rate of 24/1 million population is about half that required to service the waiting list. Spain achieves about 48 cadaveric kidney transplants per 1 million population. The current opt-in system may fail the utilitarian principle of maximizing benefits for society because about half of potential donors fail to become donors.

Opt-out – presumed consent: an alternative strategy of presumed consent assumes an individual wants to donate unless they have 'opted out' by previously registering an objection. An individual's silence is equated with assent whereas there may be a lack of understanding or ambivalence. 'Opt-out' laws, with registers that can be accessed quickly, have advantages in permitting early cooling of potential non-heart-beating donors. Presumed consent laws are accompanied by an obligation to ensure widespread understanding in society and ease of opting out.

Consent from relatives: many countries using 'opt-in' or 'opt- out' systems still seek consent from relatives. Allowing relatives to veto wishes made by a potential donor offends the principle of self-determination. Donor rates may not be increased in 'opt- out' countries taking this 'softer' approach. Countries taking less account of relatives' wishes may demonstrate higher rates but this may not be transferable to other countries without risking loss of trust.

Required request: failure to ask the relatives of suitable donors because of discomfort or antipathy may be a common reason for losing organs, resulting in policies of 'required request'. Disconnecting a ventilator from a BSD individual without making inquiries into the possibility of their organs being used for transplantation is thereby identified as unethical. The individual's and family's right to donate may be denied, and the potential benefit to society lost if relatives are not approached. In the USA, financial penalties have been used to enforce this approach.

Conditional donation occurs when agreement to donation is made dependent on who may receive the organs. A recent UK case involved relatives stipulating the skin colour of the recipient; the conditions were accepted and transplantation proceeded. Review by the Department of Health ruled that organs should not be allocated on the basis of race and that such practice would breach the Race Relations Act 1976. Organs should be accepted when freely given, as a gift, to society. Society has not extended to the donor or their family the right to decide who receives it.

Rewards for donation

Commercialization of organ transplantation is illegal in most countries, however, trade in organs occurs. This may seem unethical and distasteful to those in developed countries, especially those not exposed to a market healthcare system. It may be socially accepted in some countries without a cadaver transplant programme. An individual may argue it is his or her right to sell their organs and undergo non-therapeutic surgery while knowing and understanding the risks. To prevent such transactions may be paternalistic and attack autonomy. The financial pressures to sell may be as important as other moral pressures such as donating an organ within the family. Altruistic donation may be unable to meet demands and the alternative for the recipients may be death. However, the facts suggest that hospitals and doctors undertaking this provide poor quality grafts and poor continuing care, and thus exploit donor and recipient. Such rewarded donation may inhibit the development of sustainable transplant programmes. It is also clear that organ tourists visit poorer countries for transplantation.

Compensation: the boundary between sale and other rewards such as compensation may be blurred. Living donors in the USA are entitled to receive compensation for loss of earnings and expenses. In the USA, the introduction of ethical incentives (Figure 1) to increase living and cadaveric donation has been suggested. There have also been arguments for regulated reward systems to benefit donors and increase organ quality. However, this undermines the principle that one should not sell one's body, and would promote organs as products for sale. Some argue that non-commercialism of the body is paramount and commercialization can never be justified even if it increases the number of organs for transplant. Others point out that payments are often made for blood and gametes.

Proposed 'ethical incentives'

- Medals of honour for bereaved families
- Reimbursement of funeral expenses
- Allowing regulated organ exchanges
- Donors receive highest priority if organ failure develops
- Donor insurance in case of morbidity/mortality

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Should ICUs be given bonuses or other incentives, in an effort to encourage requests to relatives for organ donation? Does this differ from penalizing them for failing to make a required request?

Access to transplantation

The corollary of demanding that cadaveric organs be unconditionally donated to society is that a just system must exist to distribute this scarce resource.

Access: in the UK, geographical differences in the referral rates for liver transplant may reflect true differences in referral practice and thus inequitable access. Likewise, not all patients may have the same access to living donor programmes. In some health systems, funding for lung transplant is dependent on health insurance. Thus the lung is effectively donated to the part of society that can afford insurance. Without equity of access it could be argued that the best allocation schemes are unjust.

Allocation: UK Transplant controls organ allocation in the UK. Other countries have similar organizations. They aim to maximize overall benefit while meeting individual need in a fair and unbiased way (efficacy, utility, equity, urgency). The exact system differs with organ but includes blood group, and scoring systems for tissue matching, age, urgency of transplantation and location.

To what extent should prognosis after transplantation be taken into consideration? Should continuing alcohol, or other drug misuse be a contraindication for organ transplantation or alter position on a waiting list? Should young recipients have priority? What should be done about differences in outcome that are race dependent? Equity would stress that these factors not be taken into account, but what about using scarce organs for new indications with unknown efficacy? The balancing of utility with justice is a duty for all of society and not just for the transplantation community. It is essential that the criteria for organ allocation are transparent and debated by the public.

Legislation and the Regulation of Transplantation

In the UK, the Human Tissue Act 1961 and the Human Organ Transplants Act 1989 govern organ donation and transplantation.

The Human Tissue Act 1961 allows the person in lawful possession of a body to authorize the removal, from the body, of any part that the person wished to be used for therapeutic, education or research purposes. If no such wish was made then the person lawfully in possession may still authorize such removal, after having made reasonable enquiries that there is no reason to believe that the deceased had expressed an objection or that the surviving spouse or any relative objects.

The Human Organ Transplants (HOT) Act 1989 permits anyone suitable to donate all or part of a vital organ to a close blood relative. It was enacted to regulate transplantation of living donor organs after a scandal involving the purchase of kidneys from Turkish living donors. The Unrelated Live Transplant Regulatory Authority (ULTRA) was set up under this Act to approve all transplant operations involving a living donor who is not a close blood relative of the recipient. The purpose is to ensure that no payment is involved, other than expenses, and that full understanding and consent is obtained without coercion. The process includes the donor being interviewed by an independent assessor. The HOT Act does not apply to transplants of regenerative tissues.

Other legal issues

Domino transplants require ULTRA approval. This refers to organs becoming available from a recipient during a transplant procedure which could be used for someone else (e.g. a healthy heart, during a heart–lung transplant). The necessity for ULTRA approval in domino transplants has been questioned because the opportunity for organ trafficking is effectively non-existent. However, this would require an amendment of the HOT Act.

Paired exchange involves one donor/recipient pair donating to, and receiving from, another donor/recipient pair to resolve tissue incompatibilities, which would prevent transplant within a pair. A variation is an incompatible living donor donating to the general recipient pool in exchange for their relative going to the top of the cadaveric waiting list. In the UK, these swaps are forbidden because they involve elements of coercion (e.g. I will donate only if X receives) while the HOT Act supports only altruistic donation.

Xenotransplantation is transplantation between different species. It offers the possibility of unlimited organ supply. Failed attempts have been made with great controversy, and remain experimental. Immunological problems remain the main barrier to efficacy. The collective risk of trans-species infection is currently considered greater than the potential benefits to individuals and has led to a moratorium on further xenogeneic organ transplants by the UK Xenotransplantation Interim Regulatory Authority (UKXIRA). There is a wide diversity of opinion on the issue of animal rights and welfare. One opinion is that animals are not people and have no value in their own right and human needs should be given precedence because of our special moral status. A counter-argument is that we are animals ourselves, part of nature, not set apart from it and that animals have their own rights as sentient beings. ◆

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History

Anaesthesia
and intensive care medicine
on CD-ROM

Chloroform à la reine

Neil Adams

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On Thursday 7 April 1853, John Snow administered chloroform to Queen Victoria during the birth of Prince Leopold, hence the expression, 'chloroform à la reine.' The three casebooks of John Snow survive in the library of the Royal College of Physicians in London and document his activities as an anaesthetist from 1848 to 1858. The late Dr Richard Ellis transcribed these books as a supplement to *Medical History.* The use of chloroform by Queen Victoria is described in Snow's own words. Ellis notes the particular care Snow took with this entry and the possible slip of the pen (marked with an asterisk) where the word 'after' should have appeared.

Administered chloroform to the Queen in her confinement. Slight pains had been experienced since Sunday. Dr Locock was sent for about nine o'clock this morning, stronger pains having commenced, and he found the os uteri had commenced to dilate a very little. I received a note from Sir James Clark a little after ten asking me to go to the Palace. I remained in an apartment near that of the Queen, along with Sir J Clark, Dr Ferguson and (for the most part of the time) Dr Locock till a little a(*) twelve. At a twenty minutes past twelve by a clock in the Queen's apartment I commenced to give a little chloroform with each pain, by pouring about 15 minims by measure on a folded handkerchief. The first stage of labour was nearly over when the chloroform was commenced. Her Majesty expressed great relief from the application, the pains being very trifling during the uterine contractions, and whilst between the periods of contracting there was complete ease. The effect of the chloroform was not at any time carried to the extent of quite removing consciousness. Dr Locock thought that the chloroform prolonged the intervals between pains, and retarded labour somewhat. The infant was born at 13 minutes past one by the clock in the room (which was 3 minutes before the right time); consequently the chloroform was inhaled for 53 minutes. The placenta was expelled in a very few minutes, and the Queen was cheerful and well, expressing herself much gratified with the effect of the chloroform.

With regard to the historical context of this case, it is possible that two myths have passed down through history. Firstly, was the doctrine of a campaign opposing the use of chloroform in midwifery and surgery by the Church. This idea arose after the publication in 1848 by Sir James Young Simpson of *The Answer to the Religious Objections Advanced Against the Employment of Anæsthetic Agents in Midwifery and Surgery.* Secondly, was the idea that the use of chloroform by Queen Victoria provided an impetus to the general acceptance of the use of anaesthesia in midwifery. For example, Cartwright states that it was the acceptance of the Queen herself that changed the minds of the opponents, while Longford's biography of Queen Victoria states "It was fitting that the battle royal should be won forDr Simpson by the Queen herself."

Queen Victoria photographed by Charles Clifford.
©National Portrait Gallery.

In examining the use of chloroform by Queen Victoria, Connor and Connor throw considerable doubt on the claim of public acceptance following the Queen's usage, noting that the event was largely ignored by the lay newspapers, and that Snow's own obstetric practice did not increase proportionately after April 1853. Turning to religious objection, again much doubt exists because no single piece of evidence has yet been found in contemporary religious writings confirming such opposition.

Snow's services were to be required at the Palace, once again, on Tuesday 14 April 1857 to administer chloroform to Queen Victoria in her ninth confinement for the birth of Princess Beatrice. ◆

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Curare, and Griffith and Johnson's use in 1942

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Curare appears in European writing as early as 1516, when Peter Martyr d'Anghera described the arrow poison of the South American Indians. In 1595, Hakluyt also describes it in his work on Sir Walter Raleigh's voyage to South America.

The explorer Waterton brought a curare extract back from the Amazon and in 1814 demonstrated, with the help of Sir Benjamin Brodie and Mr Sewell of the London Veterinary College, that its paralysing effects were transient. They injected a curare extract into a she-ass and kept it alive by ventilation of the lungs with a bellows inserted into the animal's windpipe through a tracheotomy.

The attempted use of curare in clinical practice goes back at least as far as 1858, when Sayres and Burrall attempted, unsuccessfully, to use the drug locally to treat tetanus. Beigel described the clinical effects in man in 1868, using calabash curarine. In 1935, Harold King, working with Sir Henry Dale, isolated the pure curare alkaloid from a specimen in the British Museum, but it took until 1943, for Wintersteiner and Dutcher, working in the laboratories of Squibb, to demonstrate that the curare alkaloids could be extracted from the plant *Chondrodendron tormentosum*. Squibb then went on to produce the first commercial preparation of curare under the trade name *Intocostrin*.

Squibb were able to manufacture the drug in a known strength by the 'rabbit head drop test' being calculated from the smallest amount that would cause a rabbit's head to drop without affecting respiration. The first clinical use was in Omaha, Nebraska, where McIntyre and Bennett were assessing the effect of intravenous *Metrazol* to produce convulsions in the treatment of schizophrenic patients. The violence of the convulsions caused 50% of the patients to suffer spinal compression fractures, but a small dose of *Intocostrin* significantly reduced the fracture rate.

Samples of *Intocostrin* were sent to Professor Rovenstine at Columbia Medical School, where his assistant E M Papper spent the night resuscitating the two patients who received the drug. This led Rovenstine to believe that *Intocostrin* was not safe for clinical use. Cullen, in Iowa, used the drug on dogs, but bronchospasm ensued and he came to the same conclusion as Rovenstine.

Harold Griffith, Professor in Montreal, was approached by Squibb's medical representative, Lewis Wright. He reviewed the work of McIntyre and Bennett, including a film they had made. Noting that the psychiatric patients had not died, he reasoned that the worst possibility was to ventilate a paralysed patient, a technique with which he had gained confidence under the training of Ralph Waters in Madison, Wisconsin (with whom, interestingly, Rovenstine and Cullen had also worked). Griffith agreed to try the drug.

Harold Randall Griffith 1894–1985.
© Osler Library of the History of Medicine, Montréal, Québec, Canada.

On 23 January 1942, Griffith and his assistant Enid Johnson, used *Intocostrin* on a 20-year-old man undergoing appendicectomy. The result is reported as dramatic, the abdominal muscles were completely relaxed, and the surgeon was able to remove the appendix with ease. The anaesthetic record survives, intact, in the Sir William Osler Library in Montreal.

Remarks: *Intocostrin, Squibb (Curare) 3.5 cc given intravenously in 1½ minutes as operation started – no appreciable effect on pulse or respiration. After 5 minutes another 1.5 cc of Intocostrin given. Apparently complete relaxation of abdominal muscles resulted and continued for 20 minutes, during which time cyclopropane was lightened. At the end of this period muscle tone returned, probably from wearing off of curare effect. Cyclopropane was then increased in concentration and anaesthesia continued in the usual way. There was no demonstrable change in pulse, blood pressure or respiration*

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Shortly afterwards, Griffith and Johnson submitted a series of 25 cases of the use of curare to the journal Anesthesiology and so began a new chapter in the history of anaesthesia. ◆

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Punch Drunk

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Following the introduction of inhalational anaesthesia in 1846, it did not take long for the humorous possibilities to be explored. The cartoon shown here and nine articles appeared in *Punch* during 1847 and 1848.

Given that society in 1846 was very different from that of today, with child labour, slavery in America, and literacy rates of about 20% in some socioeconomic groups, it is interesting to see that a humorous perspective was already well developed.

WONDERFUL EFFECTS OF ETHER IN A CASE OF SCOLDING WIFE

Patient – "This is really quite delightful – a most beautiful dream"

Animal rights

Clearly concerned for the welfare of animals in 1847, *Punch* reports that the inhalation of ether had been resorted to professionally by various pork butchers with great success. "The chief difficulty they experienced had consisted of the opposition of the patient; but when the natural obstinacy of the pig had been overcome, and he had been persuaded to inhale the ether, he had been killed with comfort to himself, and without disturbance to the neighbourhood." Other uses reported include the opening of oysters, and the skinning of eels.

Punch noted that in France, bees had been etherized so as to be able to take their honey while they were in a state of inaction, without the necessity of destroying their lives. The article extrapolates to find a method of etherization that would render John Bull insensible to the operation of income tax!

Stages of anaesthesia

An article of 1847 suggests that the first description of the stages of anaesthesia may not be from Snow or Guedel, but from a fictional character, Cimabue Potts, a historical painter.

Potts writes: ''Sir – I have imbibed ether, and shall continue to do so till I have painted a work destined for immortality, which I confidently expect to do next week. I subjoin what I remember of my feelings during the ethereal state.

First stage: Imagined myself in Rome, in company with Rafaelle, Mr. Etty (RA), and the editor of *Art-Union*, the latter in chains, and trampled upon by us in succession (you are aware that I have been the butt of his malignant criticism for years).

Second stage: Felt immortal, and was congratulated by the daily and weekly papers.

Third stage: Produced an historical picture, 25 feet by 15, representing the discovery of the dead body of Harold after the Battle of Hastings; received the premium of £700 from the Fine Arts Commissioners, and was dragged home by the populace in my own carriage!

Last stage: Recovered and found myself, with the bladder empty, in the Goose and Gridiron."

Politics

The absence of items in *Hansard* suggests that Parliament was indifferent to the introduction of anaesthesia. The *Times*, reporting from an article in *Punch* points out political possibilities.

"However desirable this invention may be in a surgical point of view, we have every hope that it will soon be applied to the more delicate operations of politics. How useful would it have been during the last session, when the Conservative body had to undergo the painful process of the cutting off of so many members! Had the new process been known, the political amputations might have taken place without any pain. Considering the frequent severings that Sir Robert Peel has been obliged to undergo, and the numerous occasions upon which he will again most probably feel it necessary to submit to amputations, the new process must be most welcome. As the plan is calculated to prevent pain in all cases of removal, we should recommend its being tried on the next occasion of a removal from office by Her Majesty's Ministers. This has always been a most distressing operation, from the suffering it has inflicted on the parties concerned; and all the friends of humanity must be delighted at the prospect there is of its becoming an entirely painless proceeding." ◆

The Royal Humane Society Resuscitation Guidelines – 1774

Neil Adams

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It is impossible to define when the techniques of resuscitation began. They may have ancient origins, for example, there is archaeological evidence of trephining – removing a piece of bone from the skull. Another example is found in the Bible, the Second Book of Kings, Chapter 4, verses 34 and 35, in which the Prophet Elijah is described as bringing back the dead child of the Shunamite woman by warming and mouth-to-mouth resuscitation. In this long history, the work of the Royal Humane Society is fascinating.

In the 18th century, drowning was one of the main causes of death following the development of the canal system as a means of transport. In the UK, the Royal Humane Society had its origins in a meeting held on 18 April 1774 at the Chapter Coffee House, St Paul's Churchyard, London, between Dr William Hawes and Dr Thomas Coggan. Each invited 16 of their friends to help found the Society. Initially 'The Society for recovery of persons apparently drowned', this became 'The Humane Society' in 1776 and 'Royal' in 1787.

The remarkable instructions of the Society as to how revival of the apparently dead may be achieved are printed below. Figure 1 shows the apparatus of the Society; this example is kept in the Museum of the Association of Anaesthetists.

1 The apparatus used by the Royal Humane Society. © The Association of Anaesthetists of Great Britain and Ireland.

Cautions

1 Lose no time

2 Avoid all rough useage

3 Never hold the body up by the feet

4 Nor role the body on casks

5 Nor rub the body with salt or spirits

6 Nor inject tobacco smoke or infusion of tobacco

Restorative means

Send quickly for medical assistance: but do not delay the following measures.

i Convey the body carefully, with the head and shoulders supported in a raised position, to the nearest house.

ii Strip the body, and rub it dry, then wrap it in hot blankets and place in a warm bed in a warm chamber.

iii Wipe and cleanse the mouth and nostrils.

iv In order to restore the natural warmth of the body:
- 1 Move a covered warming pan over the bed.
- 2 Put bladders or bottles of hot water, or heated bricks to the pit of the stomach, the armpits, between the thighs, and to the soles of the feet.
- 3 Foment the body with hot flannels, but if possible,
- 4 Immerse the body in a warm bath, as hot as the hands can bear without pain, as this is preferable to the other means for restoring warmth.

v In order to restore breathing, introduce the pipe of a common bellows (where the apparatus of the Society is not available) into one nostril, at the same time drawing downwards and pushing gently backwards the upper part of the windpipe, to allow more admission of air; blow the bellows gently, in order to inflate the lungs, till the breast be a little raised and make a moderate pressure with the hand upon the chest. Repeat the process till life appears.

vi Inject into the stomach, by means of an elastic tube, half a pint of warm brandy and water, or wine and water.

vii Apply sal volatIle or hartshorn to the nostrils.

If apparently dead from noxious vapours etc.

1 Remove the body into a cool fresh air.

2 Dash cold water on the neck and face and brush frequently.

3 If the body be cold, apply warmth as recommended.

4 Use the measures recommended for inflating the lungs.

5 Let electricity (particularly in accidents from lightening) be early employed by a medical assistant.

Some of these themes would be familiar to those engaged in resuscitation in the 21st century, demonstrating a repeated historical cycle of methods discovered, then forgotten, then re-discovered. ◆

Informatics

Anaesthesia
and intensive care medicine
on CD-ROM

Anaesthetic Records

Tim Peachey

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For almost as long as anaesthetics have been given, a comprehensive system of recording their conduct and effect has been emerging. When John Snow was practising anaesthesia in the 1850s he kept comprehensive notes on the conduct of his anaesthetics in a notebook. Although less systematized than 'modern' anaesthetic records this approach had the advantage that all the records were in a central location and were available for review. Contrast this with today's method of filing anaesthetic records among a plethora of other documents in a case file. All anaesthetists are aware of the limitations of the modern approach, the usefulness of each record, for tracing the anaesthetic history is dependent on the availability of the case file and a record having been filed. Even in Snow's time, the anaesthetic records contained histories of previous anaesthetic episodes. In the search for a good record-keeping solution, the merits of manual and computer-based systems should be considered.

Purposes of the anaesthetic record

Anaesthetics are probably documented to a greater degree than any other aspect of medical practice. Manual systems of data recording, document the effects of anaesthesia and surgery on the patient at a time resolution typically 12-fold greater than that of manual data recording systems in critical care units. The purpose of such detailed record keeping is multiple. Several authors have tried to define the optimum content of the anaesthetic record, but its format has remained a matter of local preference and has not been standardized. Various functions have been agreed by a number of authors.

Facilitating clinical care during anaesthesia – in designing, or compiling an anaesthetic record, the facilitation of clinical care should be the primary consideration. Although records from two centres are seldom the same, most have similar features. All are based on a time-based chart of physiological observations, drug and fluid administration, events and notes. All should contain information about the patient and their preoperative status together with an operative procedure description (proposed and actual). Most records contain elements of a preoperative checklist and all contain some description of the anaesthetic methodology or technique. As the chart is created during anaesthesia, patterns of response may emerge and trends may be noted. An ideal record should contain all the information required for another anaesthetist to continue the conduct of anaesthesia safely, though this goal is seldom achieved in practice. It follows that the recording of adverse events is as important, if not more important, than recording a series of normal values. However, adverse events are less likely to be recorded than normal occurrences. Other features may be included, which are specifically designed to improve care or avoid an adverse outcome, for example a tick box labelled 'Throat pack removed'.

Augmenting the handover processes – the handover of any anaesthetized or recovering patient from one person to another is a potentially hazardous process break. There are protocols for the handover of patients in post-anaesthesia care areas or recovery rooms and recent guidance has been issued in the UK. The presence of an anaesthetic record does not diminish the obligations of anaesthetists in this regard; a well-kept record should answer most questions that arise during the care of the patient.

Advising the providers of future care – implicit in the safe conduct of anaesthesia is the ability to predict difficulties in management or the likelihood of adverse outcomes. One of the most valuable pieces of information sought from patients in preoperative assessment is their anaesthetic history, particularly any previous problems. A previous anaesthetic record greatly assists in planning another episode of care. A section of the record that documents warnings to future care providers has been advocated. Also, the certain knowledge that a patient is straightforward to intubate is of much greater value than the patient's own recollection of there having been no problems with a previous anaesthetic.

Informing statistical processes – collective sets of anaesthetic records may be used to assess the quality of care offered by a group of anaesthetists as well as providing activity data that may be useful in service planning. Anaesthetics are administered in huge numbers, with a low risk of a negative outcome. The serious adverse effects of anaesthesia are now so rare that their prediction and assessment of probability is difficult. Variations in outcome are subject to a large number of variables, the individual effects of which may be quite subtle. For example, the number of variables that affect the rate of postoperative nausea and the uncertainty that any one approach to the problem will be effective may make the analysis of anaesthetics in large numbers desirable.

Reviewing clinical care – anaesthetic records are the only method by which the quality of anaesthetic care can be evaluated after the passage of time from the episode. Memory of events deteriorates, therefore accurate documentary evidence is essential if retrospective reviews of care are to be possible. Many of these reviews are for clinical audit and clinical governance but some records will be used for complaint investigation and even litigation. Poorly kept and incomplete records may be eliminated from group audits, but such records will reflect poorly on the standard of care delivered when subject to legal scrutiny.

Optimum content

The anaesthetic record set suggested by the Royal College of Anaesthetists is shown in Figure 1. Recommendations from the Australia and New Zealand College of Anaesthetists are similar, but slightly broader in scope, less detailed and emphasize the recording of problems and their management. Documentation of the name of the supervisor and the level of supervision, when trainees are administering anaesthesia, is advocated.

The list in Figure 1 is not an exhaustive account of everything that could be included, but offers sound guidance. The inclusion of information regarding the checking of anaesthetic equipment is controversial. An anaesthetic record that contains the question 'Anaesthetic machine checked – Yes / No' is most unlikely to be answered in the negative. Nor can it be inferred from looking at a given record that the equipment was checked immediately before the anaesthetic in question. The documentation of critical incidents (especially those where no harm results) in the anaesthetic record has not been widely adopted, nor, in the author's opinion, is it likely to be in the near future. In the UK, printed anaesthetic records vary considerably from the suggested record set.

Suggested anaesthetic record set [1]

Pre-operative information
Patient identity
- Name/ID no./gender
- Date of birth

Assessment and risk factors
- Date of assessment
- Assessor, where assessed
- Weight (kg) (height (m) optional)
- Basic vital signs (blood pressure, heart rate)
- Medication (including contraceptive drugs)
- Allergies
- Addiction (alcohol, tobacco, drugs)
- Previous general anaesthesia, family history
- Potential airway problems
- Prostheses, teeth, crowns
- Investigations
- Cardiorespiratory fitness
- Other problems
- ASA grade ± comment

Urgency
- Scheduled – listed on a routine list
- Urgent – resuscitated, not on a routine list
- Emergency – not fully resuscitated

Peroperative information
Checks
- Nil by mouth
- Consent
- Premedication, type and effect

Place and time
- Place
- Date, start and end times

Personnel
- All anaesthetists named
- Qualified assistant present
- Duty consultant informed
- Operating surgeon

Operation planned/performed
Apparatus
- Check performed, anaesthetic room, theatre

Vital signs recording/charting
- Monitors used and vital signs (specify)

Drugs and fluids
- Dose, concentrations, volume
- Cannulation
- Injection site(s), time and route
- Warmer used
- Blood loss, urine output

Airway and breathing system
- Route, system used
- Ventilation: type and mode
- Airway type, size, cuff, shape
- Special procedures, humidifier, filter
- Throat pack
- Difficulty

Regional anaesthesia
- Consent
- Block performed
- Entry site
- Needle used, aid to location
- Catheter yes/no

Patient position and attachments
- Thrombosis prophylaxis
- Temperature control
- Limb positions

Postoperative instructions
- Drugs, fluids and doses
- Analgesic techniques
- Special airway instructions, including oxygen
- Monitoring

Untoward events
- Abnormalities
- Critical incidents
- Preoperative, peroperative, postoperative
- Context, cause, effect

Hazard flags
- Warnings for future care

[1]Reproduced with permission from the *Royal College of Anaesthetists Newsletter* 1997; **36**

Manual records

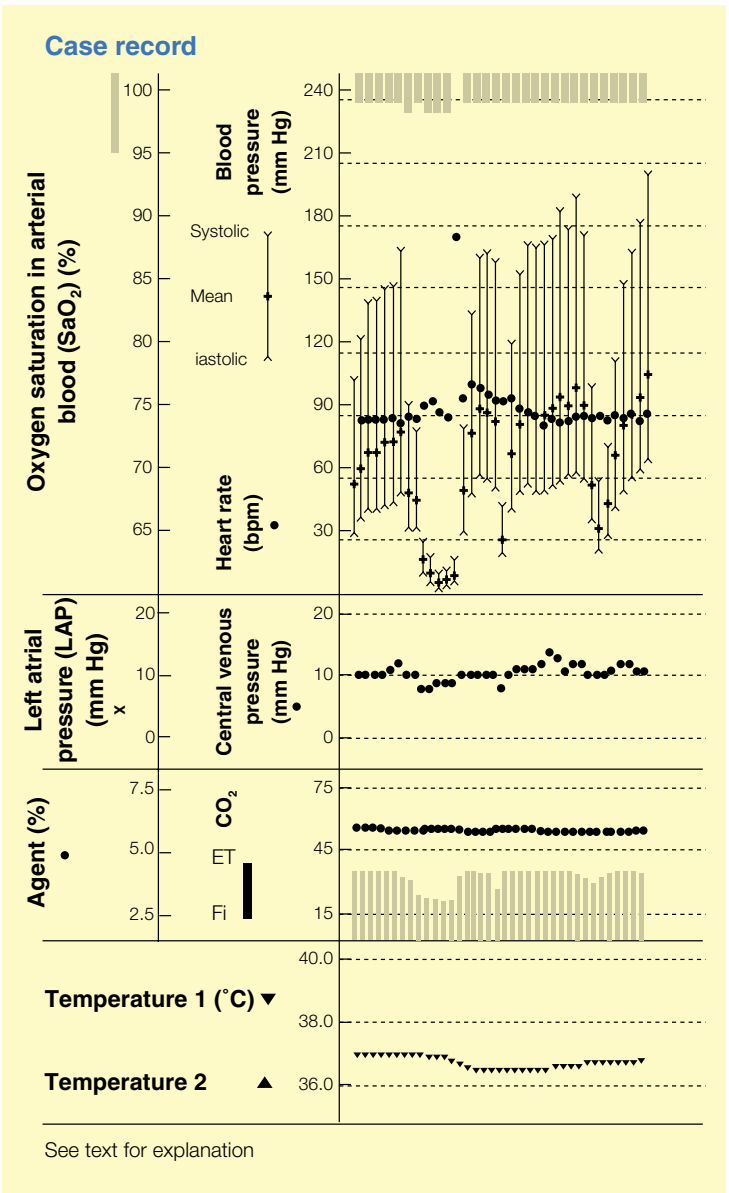
About 10% of an anaesthetist's time is spent making records during anaesthesia. This might be regarded as time that could have been spent being more vigilant, considering options for the patient, or planning ahead, but the act of record keeping probably ensures that the anaesthetist has mentally registered the values of the parameters he is recording. Attention to the chart may make the detection of trends more likely. However, when critical events occur, the first task that is lowered in priority is record keeping. The value of an anaesthetic record after a critical event may be seriously compromised by inaccuracies in time and recorded values. One study (using simulation) found that over 20% of values recorded during critical incidents were in error by at least 25% and some by 100%. The variability between recorded values and actual values has been known for some years, as has the tendency for real data to be smoothed before they are recorded, so that extreme values and sudden changes are attenuated. It is perhaps not surprising that we feel the desire to make things look good but every anaesthetist knows that most patients have some measurable physiological disturbance during the course of an anaesthetic. The lack of objective evidence for this is a failure of documentation rather than reflection of reality. If records are misfiled, lost or inaccessible the value of keeping them is largely negated.

Computerized records

Computerized anaesthetic records have been in use for over 20 years and commercial systems have been available for at least 10 years, but they have yet to gain widespread acceptance. The medical profession is now embracing electronic patient records but anaesthesia has been passing up the opportunity for at least 10 years. This may be due to the perception among hospital managers that anaesthesia is expensive enough as it is and that computerized record-keeping systems do not save money. (Failure to save money has been a feature of most medical informatics projects and is a poor test of benefit.) The profession has also been slow to accept the benefits of such systems and associates some risk with their adoption. Computerized recording systems offer a number of benefits. They are more accurate than manual data recording systems and offer more detailed data collection for no additional effort. Some systems can now offer documentation of an anaesthetic, even for the shortest of cases, in less time than it takes to write it down. However, there is a perception that the accurate recording of data and the possible recording of monitoring artefacts, may make the defence of the conduct of anaesthesia more difficult. In a sense this is illogical because physiological variability and monitoring artefacts are normal occurrences during anaesthetic practice, not faults of individual anaesthetics or anaesthetists. However, because anaesthetists do not generally record them, this is difficult to prove. Perhaps the most persuasive argument in favour of computerized systems is that all records are kept by the anaesthetic department in a central store and can be recovered instantly for reference, collective statistical analysis, comparison, quality control, transmission to other interested parties or for defence.

Legal aspects

The law does not prescribe any particular format or content for an anaesthetic record. In fact, there is no statutory requirement for a record to be kept. Common law, however, provides that the standard of care offered to a patient has to be higher than 'that which could not be condoned by a reasonable body of one's peers' (the Bolam principle). Therefore, as most anaesthetists keep records, it must be regarded as required in common law to do so. Powers has stated: 'As a matter of evidence, medical records do not prove themselves any more than a newspaper article is proof of the facts to which it relates'. It would seem reasonable though, to assume that a record compiled electronically by automatic collection of data from a vital signs monitor would gain higher standing as evidence of fact than a manual set of notes that are known to suffer from inaccuracies in transcription. While the possibility of tampering with computerized data exists, in reality it is highly unlikely. If an anaesthetic is properly conducted and accurately recorded, it is difficult to see how the anaesthetist's legal position could be damaged by this, almost incontrovertible, evidence. The strength of such evidence is related to the likelihood that a set of data fit with each other and with the story they are asked to support. Figure 2 shows data taken from a real case record. The fall in end-tidal carbon dioxide associated with a period of hypotension, and the subsequent after-drop in temperature fit well with sudden massive blood loss and fluid resuscitation. ◆



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Clinical Service and Audit

Ranjit Verma

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The purpose of audit is to provide an efficient, safe and reliable healthcare service that offers the best quality patient care achievable under the circumstances. By looking critically at the processes, mechanisms and quality of healthcare delivery, areas of deficiency can be identified and improvements made or remedial action taken. To facilitate this, various organizations have been formed and many processes created. National Health Service (NHS) Trusts are now required to implement these processes and can be severely penalized if they fail to comply with them.

Patient expectations have also changed following a series of highly publicized events including problems at the Bristol surgical cardiac unit, which resulted in two surgeons being struck off the medical register in 1998 and Dr Harold Shipman's conviction for murder in January 2000. Therefore, it is imperative that a culture of self-examination, accountability and openness is established and becomes part of normal clinical practice.

King's Fund Organizational Audit

King's Fund is an independent charitable organization that was founded in 1897. Its aims are to support health, mainly through improving the quality of health and social care services. It supports research, addressing issues relating to funding of the NHS and the inequalities of access to healthcare, and promotes development work in service provision, such as implementing clinical effectiveness, better services to carers and education in NHS management.

In 1989, it launched a project called the King's Fund Quality Programme, which looked at the quality of healthcare delivery in NHS hospitals based on specified standards. In 1990, this became the King's Fund Organizational Audit and most organizations delivering healthcare, both NHS and private, subscribed to its standards. In 1998, the King's Fund Organizational Audit was relaunched as the Health Quality Service.

Health Quality Service

The Health Quality Service is an independent charitable organization and is the successor to the King's Fund Organizational Audit. It gained accreditation from the UK Accreditation Services as an ISO9002 certified body in 1999. This means that it can award ISO9002 certification to health organizations that fulfil its criteria. It has developed accreditation criteria for acute hospitals, community, mental health, learning difficulties, palliative care and hospices. Its programme for accreditation is voluntary and several NHS Trusts and many private hospitals subscribe to its quality standards.

Audit Commission

The Audit Commission was first established in 1983 to regulate auditors of local authorities in England and Wales. In 1990, its role was extended to include the NHS. Its remit now covers over 13,000 bodies who, between them spend nearly £100 billion of public money annually. The Audit Commission is an independent body which appoints auditors to assess and monitor the way the money is spent and to determine if the various bodies get value for money. Its most recent project involving clinical services is the Acute Hospital Portfolio. This is a collection of audits available for auditors to undertake at acute hospitals. They focus on key service areas or resources within the Trusts. Each year the Commission plans to select up to four topics from the portfolio to survey across all the Trusts in England. The topics are clinical and non-clinical.

National Institute for Clinical Excellence (NICE)

NICE was established as a Special Health Authority of the NHS in 1999. Its purpose is to provide authoritative, robust and reliable guidance on current 'best practice' to patients and their carers and to health professionals and the general public. Projects are undertaken at national level and evaluated by a panel of experts, which includes NHS professionals and members of the lay public, including clinical professionals, patient and carer representative groups, NHS managers, members from industry and research bodies and from the Royal Colleges and professional societies and associations. NICE produces three types of guidance.

Technology appraisals are independent reviews of the clinical usefulness and cost-effectiveness of specific technologies such as the use of a drug, equipment, diagnostic technique, surgical procedure or health promotion activity. Technology appraisal can take up to 12–14 months to produce.

Clinical guidance is produced for healthcare professionals and patients to help them make the right decisions about healthcare in specific clinical circumstances. These guidances are intended to be used in conjunction with current knowledge to help make the right decision for a given scenario. Clinical guidance can take about 2 years to produce.

Interventional procedures relate to the efficiency or effectiveness of new procedures, for example the use of a new surgical technique and its implications in the wider context.

Commission for Health Improvement (CHI)

CHI was launched by the Government in April 2000 aimed at improving the quality of patient care in the NHS. One of its most significant aspirations is to abolish the inequality of standards that exists throughout the NHS. CHI aims to achieve this by undertaking clinical governance reviews, by visiting every NHS Trust and Health Authority including Primary Care Groups, Local Health Groups and General Practices in England and Wales on a rolling programme every 4 years. It investigates any serious failures and checks that the NHS is following national guidelines. It makes its findings public. A typical review takes 17 weeks and has clear objectives and deadlines, which include consultation, data collection and analysis.

Commission for Healthcare Audit and Inspection (CHAI)

CHAI is the next step in the Government's plans to monitor quality of healthcare delivery in the NHS and is planned to be implemented by 2004. It will have appropriate legislation from Parliament and its purpose is to inspect every part of the NHS and private healthcare. It will monitor and review the quality of healthcare delivery and assess how well the NHS is using its funds. It will report to Parliament. It will take over all of CHI's current functions and the National Care Standards Commission's (NCSC) responsibilities for inspecting the private health sector. The Audit Commission's value-for-money studies relating to healthcare, as well as some of its other functions, will also come under CHAI's umbrella, and it will be responsible for a star rating system for NHS hospitals and for instigating special measures in those organizations that fail.

The NHS Litigation Authority (NHSLA)

The NHS Litigation Authority is a Special Health Authority that handles claims and indemnifies NHS bodies in respect of both clinical negligence and non-clinical risks. Clinical negligence claims are handled through the Existing Liabilities Schemes for pre-1995 claims, and the Clinical Negligence Scheme for Trusts for incidents after April 1995.

The incidence of claims against clinical negligence continues to rise. In 1999/2000, the NHS spent £386 million in settling negligence claims and it is estimated that the net value of claims outstanding against the NHS alleging clinical negligence is about £2.6 billion. There is also an estimated liability of a further £1.3 billion for negligent episodes that are likely to have occurred, but for which claims have not yet been received. On average, claims take over 5 years to resolve and there were 23,000 claims outstanding in 2002.

Clinical governance

Clinical governance strives to improve and assure a high standard of clinical practice. It was first described by the Government in 1998 as 'a new system in NHS Trusts and primary care to ensure that clinical standards are met, and that processes are in place to ensure continuous improvement, backed by a new statutory duty for quality in NHS Trusts'. The responsibility for clinical governance rests with the chief executive of each Trust, but it is usually implemented jointly by consensus between senior management and clinicians. The process is open to public scrutiny and every clinician is required to take part. It is a multifaceted process and involves participation in several activities such as clinical audit, education and training, research and development and risk management.

Evidence-based medicine

Evidence-based medicine is a process of systematically reviewing, appraising and using clinical research findings to aid the delivery of optimum clinical care to patients. It is seen as increasingly important in assuring clinical effectiveness in terms of treatments and of cost-effectiveness. Evidence is gathered from existing sources such as research and scientific reviews, and is subjected to a critical appraisal. Critical appraisal is a method of assessing and interpreting the evidence by systematically considering the validity, results and relevance to the problem being considered. Following the appraisal process, evidence-based guidelines are produced and disseminated for implementation.

Clinical effectiveness

Clinical effectiveness is the extent to which specific clinical interventions do what they are intended to do (i.e. maintain and improve health and maximize health gain from available resources). It consists of obtaining evidence (e.g. from journals, national guidelines or other sources), implementing changes based on the evidence, and assessing the effect of the changes.

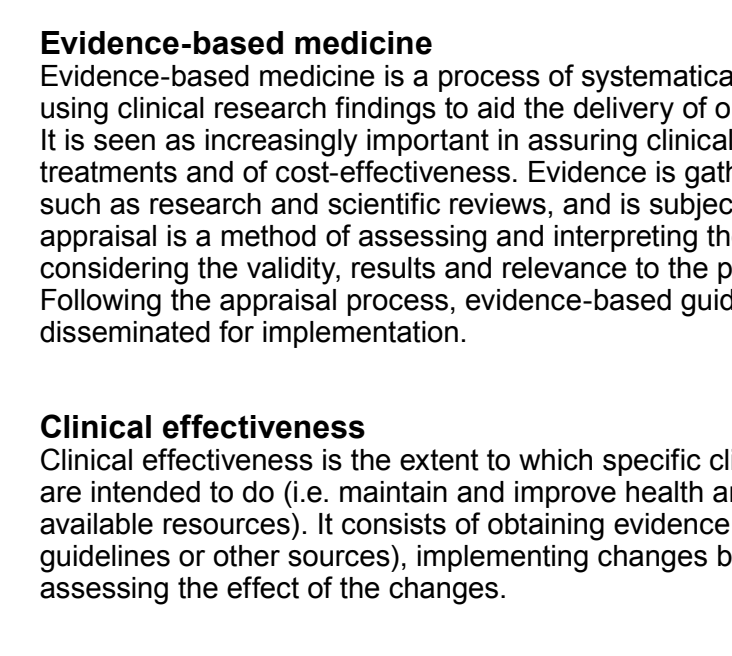
Risk management

No activity is without risks. In healthcare delivery there can be risks to the patients, to the practitioners and to the organization providing the healthcare service. Risk management is a process that tries to keep these risks to a minimum. If things go wrong, the process attempts to find out why and ensures that it does not happen again. A risk management strategy should ensure a safe working environment. Training should be appropriate for the tasks being undertaken and untoward or critical incidents should be easily identified and reported. There should be an effective claims management mechanism in place.

Clinical audit

The NHS Executive defines clinical audit as 'the systematic critical analysis of the quality of healthcare, including the procedures used for diagnosis, treatment and care, the use of resources and the resulting outcome and quality of life for patients. It embraces the work of all healthcare professionals'.

Clinical audit can be retrospective, prospective or related to significant events. It is a cyclical process in which standards are agreed and data collected. Analysis of the data shows if the standards are being met. If not, changes are planned and implemented and data collected for a second time and analysed to see if any improvements have resulted from these changes (Figure 1). It is important to realize that data are collected and analysed on two occasions. The first data collection is to establish the current position and the second is to see if any improvements have been made. The audit process should allow sufficient time for the changes to take effect and it may be necessary to repeat the audit cycle several times before the benefit is seen.



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Clinical audit is likely to be successful if it is done voluntarily rather than being imposed. The topic selected should be relevant and potentially beneficial to the patient or to the organization and amenable to improvement. The whole process should be trans-parent. The criteria being measured should be meaningful and clearly defined. The standard against which the criteria are measured should be realistic and based on what is right for the local circumstances. Careful planning of how the audit will be done is critical and the methodology should be kept as simple as possible. Only data that are relevant to the topic should be collected (collection of superfluous data is time-consuming and wasteful). Data collected for clinical audit, unlike clinical research, is not usually subjected to rigorous statistical techniques, simple percentages are usually sufficient.

If the first run shows that the stipulated standards have been met, it is important to consider if this is because the performance is genuinely satisfactory or whether the standards were set too low. If the analysis shows that standards are not being met, changes need to be agreed and implemented and the process repeated to see if the changes have achieved an improvement.

PDSA (Plan, Do, Study, Act) cycle

The PDSA cycle (Figure 2) is a tool for bringing about change in an organization by breaking it down into small manageable elements. It consists of looking at small areas to see if improvement can be made to benefit the whole. Large numbers of individuals involved in small, simple PDSA cycles are more productive in terms of seeing the process through and instigating minor changes that make a significant difference to the whole.

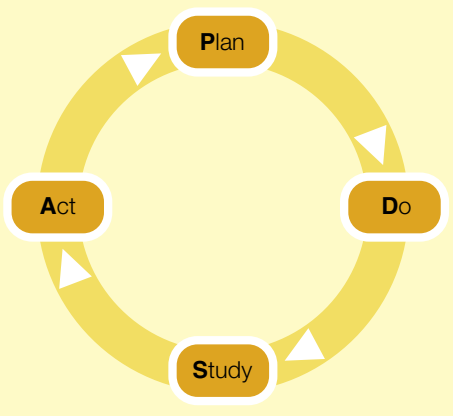
Plan – a small area of perceived benefit is identified by any individual working in a given environment. A change in working practice is planned with clear objectives in mind. It is important to be aware of who might be affected by this change.

Do – the plan is executed over a short period of time. Careful documentation and unexpected observations are recorded. Analysis of the results as they are collected may be started.

Study – the analysis is completed and results compared with predictions.

Act – if the original precept is justified, the proposed changes are incorporated as a matter of policy and disseminated throughout the organization. If there is no significant gain, the cycle may be repeated or the idea for that particular change dropped.

The PDSA cycle



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Informatics

The Government has committed itself to an expenditure of £1 billion over a 7-year period to modernize the NHS inform-ation technology (IT) infrastructure. The programme, which was started in 1998, focuses on five main areas:

- NHS Direct
- NHS Net
- National Booked Admissions Project
- National Electronic Library for Health (NeLH)
- Electronic Health Record.

All Trusts have been building up their IT infrastructures to enable them to exploit these developments. As these technologies come on stream it should make audit of clinical services easier, simplifying data collection, analysis and report generation. The use of e-mail to facilitate communications in the NHS is already well established. Medline and Embase offer excellent electronic access to peer journals while the Cochrane Collaboration, through their network of collaborative review groups, provide objective reviews of various topics to enable healthcare professionals to improve clinical management of patients. ◆

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Communication: Health Records

Roger M Tackley

Roger M Tackley is Consultant Anaesthetist at Torbay Hospital, Torquay. He is devoting increasing amounts of time to developing electronic patient record systems for the South West region. He has been involved in the NHS Clinical Terms Project, Headings Project and Maternity Data Care Project, and is currently the Chairman of the Society for Computing and Technology in Anaesthesia.

Treating and caring for patients usually involves a team of clinicians who work different shifts and may work in different locations. Unless there are good methods of communication, clinical care will be delayed or compromised. The limitations of holding health records on paper are becoming more obvious as the throughput of patients increases, staff work shorter shifts with more handovers, patients demand access to their records and new rules for confidentiality are introduced. In response to this, the NHS published *Information for Health* in 1998, which outlined its plans to computerize hospitals and the benefits that would follow to patients, staff and public. A key target is that all acute hospitals will have an Electronic Patient Record by 2005. This was supported by another White Paper in July 2002 entitled *Delivering 21st century IT support for the NHS*.

Health records

The importance of clinical records is often underestimated. According to the Audit Commission report *Setting the Record Straight* in 1995, clinicians spend at least 25% of their time recording, reading or manipulating information. Health records are kept for several reasons.

Record care given – to monitor progress and reaction to different treatments. It also records what has been explained to the patient.

Communication – information is shared among the clinical team and, increasingly, with the patient.

Source of data for aggregate analysis – information for audit and clinical governance is often extracted manually from notes.

Archive – notes are kept as an historical record.

Legal record – notes are often used to support or refute complaints and medico-legal actions.

Standards for clinical record keeping: guidelines for record keeping have been developed by The General Medical Council (GMC) (Figure 1), the Clinical Negligence Scheme for Trusts (CNST), Royal College of Anaesthetists Good Practice Guide (Figure 2), CASPE Accreditation and Development of Health Records and many other clinical bodies. It is the clinician's responsibility to keep good records because so much depends on them. The NHS Litigation Authority uses the standards developed by the CNST to accredit hospitals into different categories of medico-legal risk. This affects the insurance premium each Trust has to pay. It is clear from the standards (see NHSLA web site) that there is less risk, for instance, when different clinical disciplines all use the same health record.

GMC Good Medical Practice 2001 (extract)

In providing care you must:

- 'keep clear, accurate, and contemporaneous patient records which report the relevant clinical findings, the decisions made, the information given to patients and any drugs or other treatment prescribed'
- 'keep colleagues well informed when sharing the care of patients'

1

RCA Good Practice Guide 1998 (abbreviated)

'The record must be such that if another doctor were required to take over the case this record would give him/her systematic and ready access to all the information required'

Points to include

- Basic data: names of surgeon(s) and anaesthetist(s), date, proposed operation
- Patient identification: name, age, gender, hospital number
- Preoperative assessment: relevant history, physical examination, drugs, allergies
- Anaesthetic technique
- Intravenous drugs administered
- Relevant equipment monitoring
- Patient monitoring used: recommendations of the Association of Anaesthetists
- Physiological variable recorded: not less frequently than every 15 minutes
- Fluid balance: evidence of venous cannulation and record of fluids
- Postoperative pain relief: clear and appropriate postoperative analgesic orders
- Other postoperative instructions
- Critical incidents and complications must be accurately documented
- Handover from one anaesthetist to another should be noted

2

Archiving NHS records: in the UK, there are statutory requirements for how long health records must be kept. In the case of hospital records some examples are:

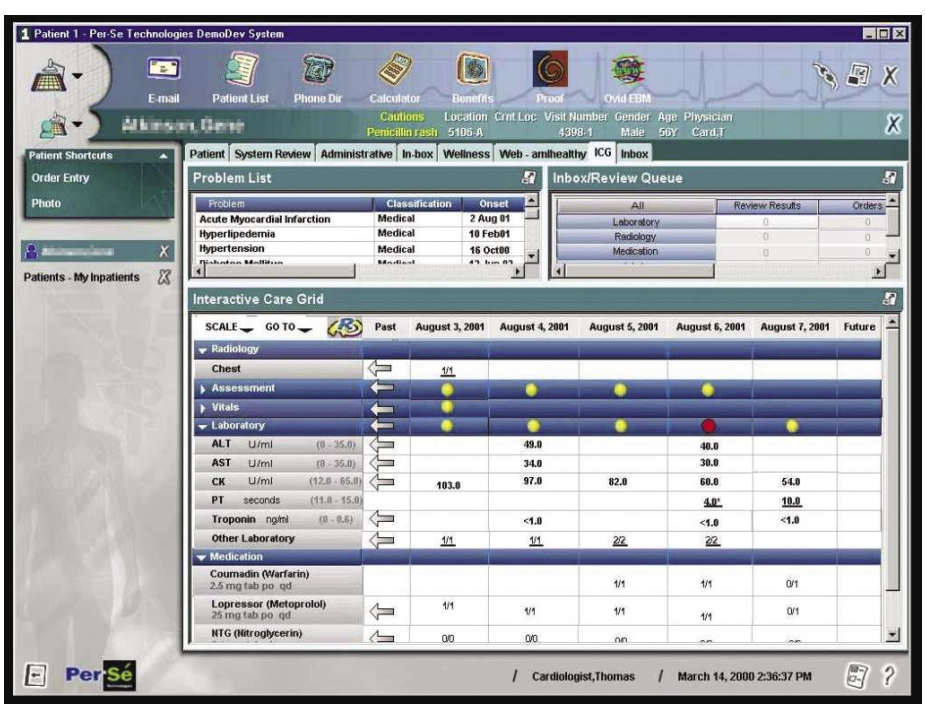
- 8 years, in general, unless specified below
- children – up to 25th birthday
- donor records – 11 years post-transplantation
- maternity – 25 years
- mentally disordered – 20 years after last treatment
- patients in clinical trials – 15 years after end of treatment
- litigation – 10 years
- audit documents – 2 years
- theatre registers – local decision in consultation with health professionals.

Electronic patient records (EPR)

The NHS defines EPR as 'A record containing the patient's personal details (demographics), their diagnosis or condition, and details about the treatment/ assessments undertaken by a clin-ician. Typically it covers the episodic care provided mainly by one institution.' In practice, there are separate EPRs for a patient in a number of Trusts, GP surgeries and specialist clinical systems (e.g. anaesthetic record keeping systems). The NHS has defined six levels for EPR; each builds on the previous level:

- clinical administrative data
- integrated clinical diagnosis and treatment support
- clinical activity support
- clinical knowledge and decision support
- specialty specific support
- advanced multimedia and telematics.

Telemedicine allows clinicians in remote areas to access expert advice from specialists. Other multimedia applications allow the storage of video or sound clips in the patient's notes. Well-designed EPR screens allow a user-defined composite view of patient information. Figure 3 shows a problem list, an in box of current messages and a timeline summary of clinical results. The screen is interactive so the clinician can click on any item and find more details, and if security allows, edit or add further orders.



3 Example of electronic patient record screen.

Electronic health record (EHR)

The NHS defines EHR as 'the concept of a longitudinal record of patient's health and healthcare – cradle to grave. It combines the information about patient contacts with primary healthcare as well as subsets of information associated with the episodic elements of care held in EPRs'. EHRs will probably follow the introduction of EPRs; pilot sites are expected to be running by 2005.

The use of an EHR is epitomized in the following scenario. There is an emergency admission of a confused, semiconscious patient with abdominal pain following a road traffic accident. Using the details found in his wallet, it is realized that he is not on the hospital patient administration system, and so the EPR software is used to access the National Strategic Tracing Service (NSTS) to obtain his NHS number. Doctors treating this patient will then have access to the EHR and using the patient's NHS number can look up his:

- current medication (e.g. insulin)
- current diagnoses (e.g. diabetes, porphyria, angina)
- previous contacts – shows current GP and last admission to hospital.

It is then possible to contact the last hospital for details of any previous anaesthetic and possibly obtain an electronic reply. Even without it, the anaesthetist is forewarned about many aspects that improve the patient's care.

Clinical language

If information is to be shared, clarity is essential. To share information, clinicians must use the same language. For instance, there are many ways of recording a prolonged suxamethonium effect:

- suxamethonium apnoea
- sux apnoea
- scoline apnoea
- prolonged succinylcholine block
- dual block.

All of which can be further confused by spelling mistakes. This problem is exacerbated by the use of computers, which are very good at legible recording and rapid display, but can interpret only what they have been programmed to recognize. Therefore a search for all the 'scoline apnoeas' will not automatically find the 'sux apnoeas'. To improve communication between disciplines and to allow computerization of health records a comprehensive, but flexible, set of terms must be used.

Statistical classifications

For many years, the NHS has been compiling statistics based on diagnoses and operations recorded during a hospital admission. For accuracy, there are strict rules about which codes must be used for which concepts. The International Classification of Diseases (ICD, now in version 10) and the Office of Population Censuses and Surveys (OPCS) classification of operations and procedures (version 4) have been used for many years to code diagnoses and operations which are then sent to the Department of Health hospital episode statistics (HES) department for aggregation.

One disadvantage of these classifications is that the terms used are often unsuitable for clinical use; for example, 'Epidural anaesthetic using sacral approach', 'Biopsy of cerebellum NEC'. Despite this, many electronic systems incorporate these terms and expect clinicians to use them. Another disadvantage is that OPCS4 (about 7000 terms) does not include procedures for nursing or physiotherapy, and is revised so seldom that newer techniques have to be included as OS (otherwise specified). ICD10 (about 11,000 terms) includes very few symptoms and signs so that it is impossible to record a full clerking or nursing assessment.

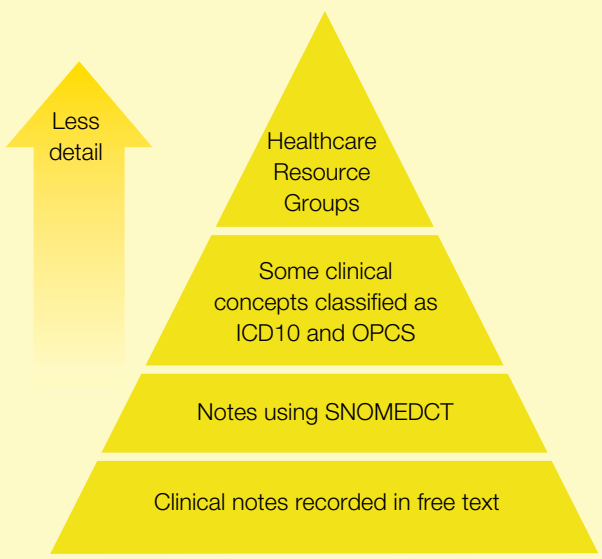
Clinical terminologies

In the UK, over half of GPs use computerized record systems. They need to be able to record symptoms and signs, treatments and operations. In the 1980s, a GP called Dr Read developed a coding system that covered most of what a GP needed to record. This was bought by the Department of Health in 1990 and expanded to include what hospital clinicians needed. The resulting clinical terms (CTV3) were comprehensive (nearly 300,000), but at the time too complex for most system suppliers to take on.

In 1999, the NHS formed an alliance with the College of American Pathologists to merge CTV3 with SNOMEDRT (Systematized NOmenclature for MEDicine Reference Terminology), a terminology in use in the USA. The NHS expect that this new terminology (SNOMEDCT) will be in use in clinical systems by mid-2003. Being an international terminology there are many advantages to clinical system suppliers in using it. SNOMEDCT has 325,000 concepts and over 800,000 terms including synonyms and so it has to be used in a computerized environment.

SNOMEDCT maps to other coding systems (e.g. ICD10 and OPCS4) which means that even if clinical information is recorded only in SNOMEDCT, it can be semi-automatically mapped to other classifications, saving many hours of coding work. Figure 4 shows the progression from recording notes in free text, which is unreliable to analyse, to using SNOMEDCT which allows recording of clinical detail in a reproducible format, and then classifications (e.g. OPCS4) which can be used to generate Healthcare Resource Groups for management purposes.

Aggregation of clinical terminology



Abbreviations: ICD, International Classification of Diseases; OPCS, Office of Population Censuses and Surveys; SNOMEDCT, Systematized Nomenclature for Medicine

Team working

Communication with other members of the clinical team may be by sharing the health record, by correspondence or by conversations (face to face or by telephone). The members of the clinical team may be based on one site but more often are not. Each discipline tends to use their own structures for recording patient assessments; for example, doctors use history and examination headings and nurses use activities of daily living. In order to share information effectively, there must be a structured handover. This may be face to face, but often staff are too busy to do this for all patients. It is recommended that clear summaries of the patient's problems and progress are kept so that any clinician can quickly understand the relevant issues.

Laurence Weed has written many papers on the benefits of Problem Oriented Medical Records. Out of this has come the concept of a shared problem list which is much easier to maintain in an electronic patient record, and is accessible to all authorized staff, at any time and simultaneously if necessary.

Structured notes and discharge summaries

Many studies have shown that doctors prefer to use semi-structured notes for clerking, discharge summaries and anaesthesia. They speed the entry of information, reduce omissions and make it easier to find important facts. GPs prefer to receive discharge summaries set out with sections for: reason for admission, diagnoses, investigation results, operations performed and drugs on discharge. As yet there are no standard headings but the National Headings project (see NHSIA website) has proposed a set that has worked well in many pilot sites and should be used as guidance when designing any structured clinical notes. ◆

FURTHER READING

Audit Commission. *Setting the Record Straight*, 1995.

Burns F. *Information for Health*. NHS Executive, 1998.

Coiera E. *Guide to Medical Informatics, the Internet and Telemedicine*. London: Chapman & Hall Medical, 1997.

NHS Information Authority **www.nhsia.nhs.uk.** This has links to the Headings Project, Clinical Terminology and SNOMEDCT, Electronic Records Development.

NHS Litigation Authority. *CNST Standards.* **www.nhsla.com**

Royal College of Anaesthetists. *Good Practice Guide*. **www.rcoa.ac.uk.**

Weed L L. Medical Records that Guide and Teach. *New Eng J Med* 1968; **278:** 593–600.

Confidentiality and Security of Information

David Jones

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Keeping patient information confidential is not a new issue (it is one of the professional responsibilities placed on doctors by the GMC), but because of the rapid rise in electronic processing it has acquired greater emphasis. In addition, there has been increasing dependence on information technology in healthcare and a greater need for information to be made more widely available. To address the consequent security implications, the UK government has produced new guidelines and there have been changes to the law. While much of the provision of security may lie at a corporate level, individual health workers have obligations dictated by these guidelines and laws.

Information security is about preserving confidentiality, integrity and availability of information (Figure 1). Security can never be perfect and there is an element of mutual incompatibility with this triad. Making information more easily available, even for authorized access, can compromise confidentiality and the more the information is made available by accessing, updating and transmitting, the more likely its integrity may suffer. Failure of these three principles can cause problems. Service disruption can occur if vital data are unavailable; there can be loss of privacy; patient harm can result if vital information is incorrect or unavailable, and financial loss can be incurred with the replacement of lost equipment and information. There are also the wider issues of falling foul of the law and loss of public confidence.

Information security

- **Confidentiality** a ‘for your eyes only’ principle, access is confined to those who have authority
- **Integrity** relates to the preservation of information in the form that it was recorded
- **Availability** involves ensuring that information can be provided to the right person when required

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Department of Health directives

In the UK, a number of government documents relate to information technology. The most relevant are the Department of Health’s prescription for the future use of information technology *Information for Health* and the more technical *Building the Information Core*. They describe computer systems using lifelong electronic records, and are available round the clock to health workers in all disciplines across the whole NHS. The security implications of this are recognized in the documents. It is acknowledged that patients must be made aware of the intention to share information and their objections respected and that all systems should have access controls to preserve confidentiality and adhere to legislation.

Growing confidentiality problems led to the government convening a committee chaired by Dame Fiona Caldicott with the purpose of reviewing the confidentiality issues of patient-identifiable information. This Caldicott Committee identified principles of good practice that NHS Trusts are obliged to adopt for all information flows. Each Trust is required to appoint a Caldicott Guardian, a board-level healthcare professional, whose role is to supervise the production and execution of local policies ensuring confidentiality. Every use of patient-identifiable information must be justified and where possible excluded in information flows. Trusts are responsible for ensuring that only those with authorization and a need to know should have access and even then only to those items that they need to see. Trusts must regularly review their practice and institute appropriate security, ensuring that all uses of information are legal and that those with access are aware of their responsibilities and legal obligations.

Legislation

The 1998 Data Protection Act came into force in the UK on 1 March 2000, replacing the 1984 version and incorporating the 1990 Access to Health Records Act. It defines data processing as collecting, using, modifying, storing and disclosing information. It uses the terms data controller to describe those responsible for processing information and data subject as the person whose information is recorded. It is designed to protect individuals by preventing misuse of their personal information and defines situations in which those who process personal information should register their use. It applies to living persons; the 1990 Access to Health Records governs access to records of the dead.

The Act uses the word ‘data’ where the word ‘information’ might be preferable. In precise terms ‘data’ is a pure collection of values or terms without meaning and as such has no confidentiality issue. Information is data with meaning. I have used the word ‘data’ where it is used in reference to the Act. The Act has eight principles.

Data shall be obtained and processed fairly and legitimately – the criteria given for fairness are that the common law duty of confidence is complied with and that the data subject was not misled into providing information. The data subject should be aware of how the information will be used and who will use it. To be legitimate, either consent must be given or there must be a valid reason as described by the Act. Two schedules define valid use (schedules 2 and 3). Schedule 3 describes the use of sensitive information such as health records, defined by the Act as information relating to the physical or mental health or condition of an individual which have been made by or on behalf of a health professional in connection with the care of that individual.

Data shall be obtained only for specified and lawful purposes – the information cannot be used for a purpose other than that specified without consent of the data subject.

Data shall be adequate, relevant and not excessive – pro-cessed information must be sufficient to perform the specified task but no more than the minimum required data items must be used.

Data shall be accurate and where appropriate up to date – it is a duty of the controller to take reasonable steps to ensure information remains accurate.

Data shall be kept for no longer than necessary – they should be retained only for the duration of the specified purpose.

Data shall be processed according to a data subject’s rights – subjects have a right to see what is recorded about them (subject access), though the Act provides an exception if awareness could be considered harmful to their physical or mental health. For a small fee (£10; though documents such as radiographs can cost up to £50) they are entitled to a description of the information, its purpose, who may use it, a copy in a form they can understand (but not the original) and how it was obtained. Where processing contravenes the Act a subject has the right to prevent processing and demand rectification. There is a right to control use of data where it is used for automated decision making, for instance, where patients may be placed on a waiting list. In such circumstances they have a right to demand a manual analysis. The Information Commissioner, formerly known as the Data Protection Registrar (currently Elizabeth France), can be asked to make an assessment if there is a dispute and, where appropriate, take action against the data controller.

Data shall be protected by appropriate security – the Act does not define appropriate. There is considerable scope for interpretation of what is reasonable.

Data shall not be transferred without adequate protection – this principle governs international transfer. Personal data must not be transmitted ‘unless that country or territory ensures an adequate level of protection of the rights and freedoms of data subjects in relation to the processing of their personal data.’

Consent

The Data Protection Act does not require consent for using personal information in healthcare. The important criterion is that the data controller can show that the specified purpose could not readily be achieved without its use. In any other instance, anonymized information should be used or explicit informed consent obtained from the data subject. The Commissioner interprets healthcare quite broadly to include preventative medicine, medical diagnosis, medical research, the provision of care and treatment, and the management of healthcare services. If patient information is disclosed to others, the data controller has a duty to ensure that those to whom the information is disclosed have the same justification. Because of the proposed wider use of health records in the NHS and potential disclosures the safest option would be to obtain explicit consent to that wider use. While Trusts generally produce leaflets for patients on the use of health records, obtaining explicit informed consent does not seem the norm.

The Act defines other valid processing purposes which could apply to doctors: for the performance of a contract; where required by statute (e.g. infectious disease notification); and circumstances that are considered to be for the greater public good. The latter is open to interpretation. There are many potential consequences of the Act that have yet to be tested in Court. For their own protection, health service employees who record and use patient information should ensure they do so within local guidelines based on Caldicott recommendations, which are governed by the law. These guidelines will develop as the NHS implements technological strategies.

The Computer Misuse Act 1990 protects information systems from the acts of individuals. It makes it an offence to access a computer system without authority and an offence to cause modification to that system.

Other laws relate to information security, but the two described above are the most relevant.

Security measures

Security breaches fall into three categories:

- denial of access
- unauthorized disclosure
- unauthorized destruction or modification of data.

Appropriate countermeasures to deal with these issues require resources, and their cost has to be considered relative to the cost of the assets to be protected and the risk of harm.

Theft prevention is a major security problem in any large organization and loss of equipment is a common cause of denial of access. Controlling physical access to secure areas by ensuring locks are used is essential. There is a need for a cultural change in the NHS where open access to areas that should be secure has been the norm.

Information security covers all communication, even what is spoken, therefore general office security must cover information given over the telephone or sent by fax, in both cases the recipient may not be the intended person. Media containing confidential information should be locked away and sensitive documents shredded when no longer needed.

Network security

Access to hospital systems is generally made over a network and the logging in process attempts to restrict access to those authorized. Each user has a user name provided by the system administrator. This identifies the user to the system for the purpose of determining to which parts of the network and to which processes the user has valid access. This can also offer accountability because an automated system log records the actions of individual users. User names are not secret and a password is also used to authenticate an individual. The password is provided by the system initially, but should be changed to the user’s choice as soon as possible. User names and passwords should not be shared; each user must have their own.

There are some simple basic rules for the choice and use of passwords. Passwords should be memorable and not a random sequence of characters; they should be kept secret and not written down. Personal details such as family member names are too easily guessed. Ideally they should be eight characters or more in length and contain at least one non-alphabetic character. Passwords should be changed from time to time and always changed if compromised. Some of these rules, particularly those relating to length, characters used and the frequency of changes may be enforced by the system.

Different processes, accessible via the same network, may require additional user identification and passwords, though sometimes a single log in provides access to all. The former is more secure, but the latter is more convenient. Users are required to log out of systems when finished and this should be done when leaving the computer to avoid unauthorized access. Monitors should face away from public areas and have a facility for screen blanking or a screen-saver to protect information from prying eyes.

E-mail communications can be read on any of the servers on the electronic route from sender to receiver and therefore are not very secure. Patient-identifiable information should be encrypted in e-mails. The NHS began rollout of encryption tools in March 2002.

Privacy enhancing technologies (PETs)

Access control and encryption are examples of PETs. The term has also been associated with features designed to protect identities that substitute identifiers such as names, addresses and registration numbers with pseudonyms. If it is never necessary to know the identity of the individuals to whom personal data relates, then all personal identifiers should be removed. However, this can lead to problems if future cross-references are needed. Pseudonymization is the process by which pseudonyms replace the true personal identifiers. The latter are not discarded but retained in a secure part of the computer system allowing the original data to be retrieved if appropriate. Normally, only the pseudonyms are visible which allows administrative tasks to be performed on the data by those who have no need to identify an individual patient. It could allow researchers to make more extensive use of medical records without confidentiality becoming an issue.

Logbooks and private practice

The greatest problem for individual doctors is managing the security of patient information that they have sole control of, such as their personal logbooks and private practice accounts. A complete logbook database is often carried around, in many cases on a portable computing device, which is easy to lose. The easiest and safest way to achieve confidentiality is to remove all patient identifiers, although this precludes cross-referencing to other information or authentication of individual records later.

Maintaining a copy of the database is essential; it is surprising how often no backup of essential documents exists. Backup floppy disks or CDs should be verified as a true copy and kept secure. Electronic logbooks have an advantage over paper logbooks because they can be protected by a password and encryption. Therefore, even if others obtain access to the device, the information can be kept secure.

There is no guaranteed way to avoid viruses, but the worst of their effects, destruction of information, can be resolved by having backups. The risks can be reduced by using anti-virus software, which must be used regularly and kept up to date.

Research

In the UK, patient information processed for the purposes of medical research has some exemptions from the Data Protection Act, provided it is not processed to support measures or decisions relating to an individual patient or in such a way that they may suffer damage or distress. These exemptions are that personal data may be kept indefinitely and data may be processed further, provided this is for research purposes. In addition, subject access is not obligatory provided an individual patient will not be identified in the results of the research.

Doctors who independently use databases containing patient-identifiable information must notify the Information Commissioner of that use. This can be done on-line ***(http://www.dpr.gov.uk/notify/4b.html)*** or by telephone (01625 545740) at a cost of £35 per annum. The doctor has an obligation to ensure that patients know what is recorded, who will use it and for what purpose. The duty of confidence requires that reasonable steps are taken to keep information secure. ◆

FURTHER INFORMATION

Confidentiality General Medical Council, 178 Great Portland Street, London W1W 5JE. 2000.
http://www.gmc-uk.org/standards/secret.htm dpa

Information for Health NHS Information Authority, Aqueous 2, Rocky Lane, Aston, Birmingham B6 5RQ
http://www.nhsia.nhs.uk/def/pages/info4health/contents.asp

Building the Information Core Implementing the NHS Plan. NHS Information Authority
http://www.nhsia.nhs.uk/def/pages/info_core/contents.asp
NHS Information Authority provides a help desk on security issues and an Information Security Manual – 01392 251289

Caldicott Report Department of Health 1997
http://www.doh.gov.uk/confiden/crep.htm

Caldicott Guardians Manual The NHS Information Policy Unit, NHS Executive, Quarry House, Quarry Hill, Leeds LS2 7UE. 1998.
http://www.doh.gov.uk/ipu

Data Protection Act 1998 The Stationery Office Ltd, PO Box 276, London SW8 5DT
http://www.hmso.gov.uk/acts/acts1998/19980029.htm

The Information Commissioner
http://www.dataprotection.gov.uk

BS 7799 – Standard for Information Security Management British Standards Institute, 389 Chiswick High Road, London W4 4AL. 2002.
http://emea.bsi-global.com/InformationSecurity/Standards/index.xalter

Databases

John Fairfield

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A database is any collection of data or information, that is specially organized for rapid search and retrieval by a computer (Figure 1). Databases are built to facilitate the storage, retrieval, modification, and deletion of data in conjunction with various data-processing operations.

Database

One or more large structured sets of persistent data, usually associated with software to update and query the data. A simple database might be a single file containing many records, each of which contains the same set of fields where each field is a certain fixed width.

A database is one component of a database management system.

Source: The Free On-line Dictionary of Computing, © 1993–2003 Denis Howe (http://wombat.doc.ic.ac.uk/)

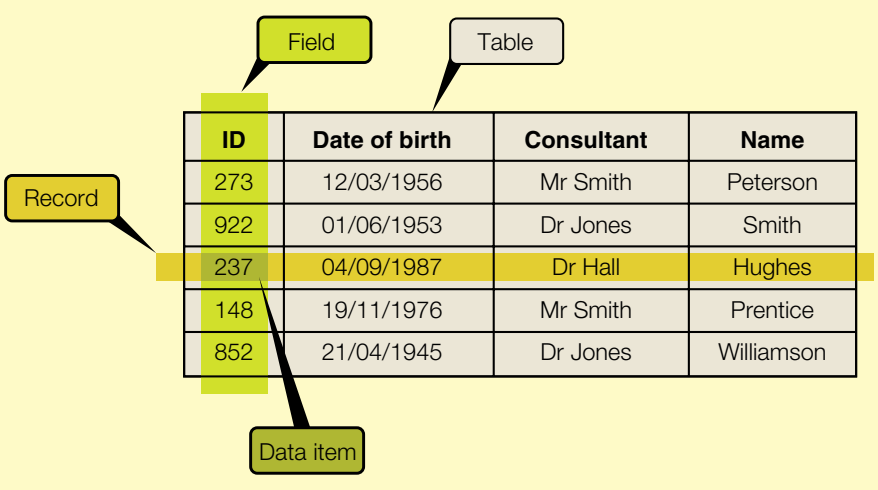
1

A database consists of a table or set of tables. The information in the tables may be broken down into records, each of which consists of one or more fields. Fields are the basic units of data storage, and each field typically contains information pertaining to one aspect or attribute of the object described by the database. Using keywords and sorting commands, users can rapidly search, rearrange, group and select the fields in many records to retrieve or create reports on particular aggregates of data.

Databases are designed to manage and manipulate structured information. For example, the telephone book contains several items of information (name, address, telephone number) about each telephone subscriber in a particular area. Each subscriber's information takes the same form. In terms of a database, the telephone book is a table, which contains a record for each subscriber. Each subscriber record contains three fields: name, address, and telephone number. The records are sorted alphabetically by the name field, which is called the key field.

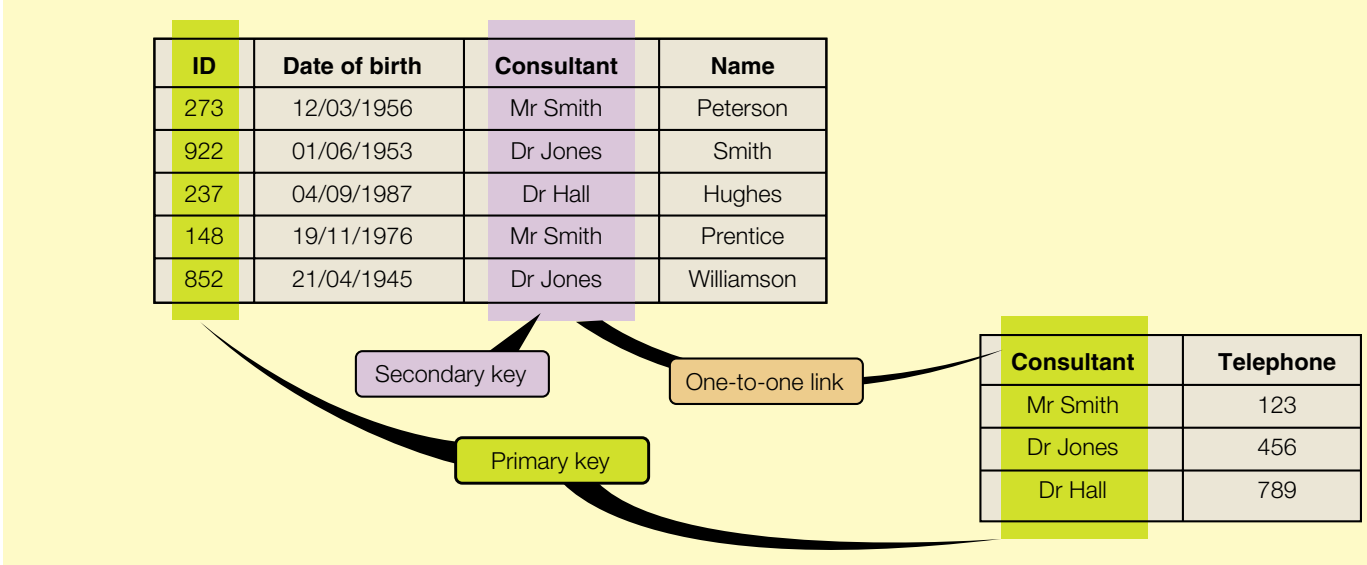
Figure 2 shows a small section of a table from a medical database used to store a list of patients and their doctor; the table, a field, record and data item are marked. It can be seen that a table is basically a collection of data with a name. The name is usually equivalent to some object (e.g. patient, resource, procedure). One of the main features of a database table that differentiates it from a spreadsheet is that each record must be unique. The specific field (or in some cases combinations of fields) that guarantees that uniqueness is known as the primary key (Figure 3). It is inevitable therefore that the primary key must be unique.

Components of a database table



2

Extra fields and links



3

If it is necessary to store more information in the database, it is possible to increase the number of fields in the table. In the medical database, for example, the telephone number that each patient needs to call to contact their doctor could be added as an extra field (Figure 3). The use of a database using only a single table to contain all the data is known as a flat file database. Although adding extra fields is simple, it can lead to problems. The most important of which is data duplication, for example each doctor and their telephone number occurs in the table many times. Therefore, there is an increased need for storage space that can become significant in large tables and cause slowing of the system. Also, if a doctor changes their telephone number, all the entries in the table must be changed. A more efficient solution is to add a new table containing the names of the doctors and their telephone numbers, then to link the new table to the original one as shown in Figure 3. Each table has its own primary key, and the primary key of the subsidiary table is linked to a secondary key in the master table.

Databases with linked tables, some of which are related to other tables, are known as relational databases. The process of moving data into separate related tables is known as normalization. In real-life databases the number of tables often increases dramatically. One of the most important aspects of database design is deciding which fields should go into which table. Normalization and object modelling facilitate this process.

The object that the table as a whole represents (i.e. what its name stands for such as 'doctor') plays some part in determining the fields, however, the fields must be subjected to a formal process known as normalization to ensure whether they should be included in the table or would be better included in a different one. If the tables are designed from an object model they are often already normalized.

Object modelling

The purpose of modelling is to provide a description of a system of some type. It is a method for distilling the associations between 'things', and requires a good understanding of the real-world system that the database is attempting to represent. The model requires only enough detail to describe the processes and the information to be represented and it is always context specific. In database modelling terms, a hospital patient is a different entity from the doctor, the finance manager and the hospital chaplain.

Normalization ensures that a database can work. Anyone can come up with all sorts of tables and sets of fields within each of them, but this is ineffective if the data are not structured in the correct way. A relational database is designed to work with normalized data and if presented with non-normalized (i.e. unstructured) data it will fail to work correctly.

Normalization has its origins in mathematical set theory. It was first developed by Edger Codd in the late 1960s, it is a process that consists of several clearly defined stages and requires an understanding of functional dependency. Data are said to be in first, second, third, etc. form indicating how structured they are. Data in first normal form are said to be less normalized than those in second normal form which, in turn, is less normalized than those in third normal form. Data can be in one of these normal forms or be made to conform to one of them by applying a number of strategies, which usually involves splitting a table up into several smaller ones.

It may sound as if something as technical as normalization should be left firmly in the hands of experts (often referred to as knowledge domain experts) however, it is important that data normalization is undertaken by someone who understands database design as well as the data and their relationships in the real world. Normalization applied by data processing staff is often done badly, because it depends on a detailed understanding of the data used by the organization and such an understanding is seldom held by these staff. Rather, the data are best understood by managers and users who work with the data on a day-to-day basis. To them, normalization represents 'common sense'.

The definitions of the forms of normalization are beyond the scope of this article but are well explained at the web site of DataModel.Org (http://www.datamodel.org/DataModelReference.html) and in several of the books listed in the Further Reading.

As a result of normalization, the number of tables is often increased dramatically. This process of increasing the number of tables, but not the number of fields, should not be seen as increasing the complexity of the database, but the opposite. After normalization, tables are simplified in terms of conceptual clarity (the tables often relate more closely to real-world objects) and database operations (updating, deleting and searching).

Resources

The following websites contain a wealth of information and links to many other resources.

- British Computer Society
  http://www.bcs.org.uk
- British Healthcare Internet Association
  http://www.bhia.org
- Datamodel.org (Data modelling made easy!)
  http://www.datamodel.org/DataModelReference.html
- Relational Database Management Systems
  http://cbbrowne.com/info/rdbms.html
- What you need to know about databases
  http://databases.about.com/mbody.htm

Database management systems

If a database is a collection of data in its component tables then the computer program that organizes and manipulates the database is a Database Management System (DBMS). Many computer programs called databases are in reality DBMSs, for example Access (®Microsoft Corporation), FileMaker Pro (®FileMaker, Inc.) and Paradox (®Corel Corporation) are designed to work on desktop computers while Oracle (®Oracle Corporation) and SQLServer (®Microsoft Corporation) are designed to work in a networked environment.

A DBMS:
- contains metadata (the structure of the data)
- allows actions to be performed on the data (e.g. adding, editing, deleting, sorting)
- supports queries
- produces reports based on queries.

Queries and reports

Queries are the main way users retrieve database information. Typically, the user provides a string of characters and the computer searches the database for a corresponding sequence and provides the source materials in which those characters appear. A user can request, for example, all records in which the contents of the field for a patient's last name is the word Smith. More complex queries can be constructed, for example to list all patients who failed to attend Dr Smith's outpatient clinic in the last 6 months.

Most DBMSs use a standard system called Structured Query Language (SQL) to query their tables, although most provide a graphical interface to generate the SQL itself. SQL resembles many programming languages, and is a structured form of English. For example, the SQL to find which of Dr Smith's patients did not attend would look something like:

```
Select * from patients
where surgeon = Smith
and clinic date >( now()-183)
and DNA = True
```

The result of the query is placed into a new answer table.

Having performed a query to select the data required, DBMSs have the ability to format the data in the answer table, together with many other complex elements such as other text and graphics, to produce a report that is easier to use than the raw data. In the example given above it could be used to produce letters to send to the patients who failed to attend giving them a new clinic appointment. ◆

Computers let you make more mistakes faster than any other invention in human history, with the possible exception of handguns and tequila

Mitch Radcliffe

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Knowledge Management

Chris Barham

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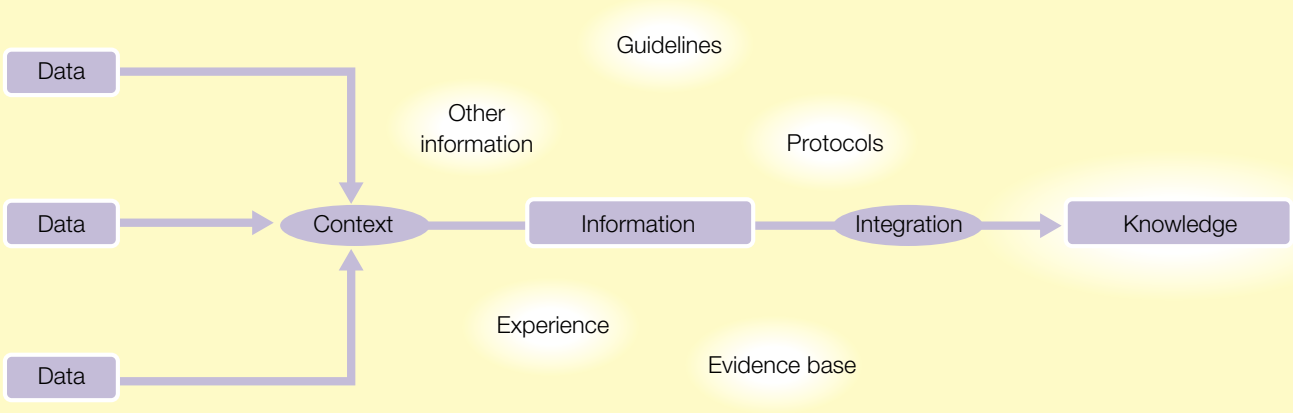
A little learning may be 'a dang'rous thing', but our problem today is a seemingly limitless supply of information.

Data: an item of data (a datum) consists of a label and a value. Thus, pulse = 80, systolic blood pressure = 120 are data. They convey facts, but tell you little unless you know their context.

Information: if the above data are known to be from an adult, ASA 1 patient this provides information. Clearly the information would be different if the data were from a neonate.

Knowledge can be defined as the information one has acquired through learning or experience. This implies conscious awareness and is the result of processing information and assimilating it with other information from the environment. For example, the doctor may decide to treat hypertension based on information on the patient, the likely pathology, the pharmacology of antihypertensive drugs and many other factors. All these integrate to produce knowledge (Figure 1).

Decision-making process



1

Knowledge may be explicit (e.g. guidelines, protocols, evidence base) or tacit (e.g. experience, intuition). The former may be written down, but the latter is more difficult to record because it is 'in the head'. In time, it may be codified, and so become explicit, for example, the development of algorithms to manage difficult airway problems.

This process of making tacit knowledge explicit is used in decision support. This may be any method that takes input information about a clinical situation and then produces inferences that can assist practitioners in their decision making. For example, a prescribing system might present advice based on information about the patient and the drugs. It may alert one to potential hazards or interactions, and suggest alternatives. It may tell you things you already know, but it will not overlook or forget things, as we are prone to do.

Wisdom is required for knowledge to be useful practically. This is the ability to make sensible judgements and decisions based on one's knowledge, experience, prudence and common sense.

Knowledge acquisition: the two main sources are the spoken word and books, but some others are shown in Figure 2. The textbook is accessible but expensive and quickly becomes out of date. This journal combines the accessibility of a textbook with currency of information.

Sources of knowledge acquisition

- Books
- Lectures
- Multimedia
- Ask a colleague (Phone a friend)
- Survey (Ask the audience)
- Guidelines
- Journals
- Internet

2

Problem-based learning: using a problem-based approach to learning influences the recall and application of knowledge. The method is based on using a problem (real or simulated) and access to the knowledge required for its solution. Context is also important – if the environment is real, knowledge retrieval is better. Thus, learning in the operating theatre is better than using a simulator, but that is better than the classroom. Learning is most effective when we have access to answers to questions at the point of patient care. A useful strategy is to develop a personal mission statement for learning, based on what we need to know and what we are happy to look up.

Information for patients: patients are expressing an increasing desire for information. The implicit trust placed in the medical profession has been dented in recent years, and concerns have led patients to search for their own information. They seek it from a variety of sources, including family and friends, chemists, NHS Direct, the Internet and medical consultations. The Royal College and Association of Anaesthetists has recently developed a series of information sources on anaesthesia for patients (www.youranaesthetic.info).

Information technology: the Internet is a source of knowledge, and the worldwide web has become the most accessible source of information for many. Email has also revolutionized information exchange, but it is important to be aware of the security and confidentiality implications. Email discussion lists can be a useful means of rapidly seeking the views of a number of colleagues.

Most hospitals now have an intranet, which is a mini-Internet accessible only within the organization. It can provide access to locally developed information, for example policies and guidelines. The NHS is committed to giving desktop access to all clinicians, but this has yet to be achieved. To the anaesthetist, the 'desktop' means the anaesthetic machine as well as the office. ◆

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(This is the first of a series of 10 articles on *Knowledge for the Clinician* published in the succeeding issues of the journal.)

Secondary Uses of Clinical Information

John Fairfield

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Information about patients is collected in huge quantities in the health service. Although some of this information is general (e.g. patient demographics) most is clinical, relating to the patient's medical condition. This information is stored in a host of systems, some paper based and some electronic. Much of the information is duplicated.

The primary use of this information is to aid the management of the healthcare of the patient to whom it relates; to achieve a diagnosis and then to plan and provide treatment for the patient. Uses for the data that are not concerned with the day-to-day management of an individual patient's illness are termed 'secondary uses of clinical information'. In general, these are the use of personal information for the benefit of the community (in its widest sense) rather than the individual. They include:

- planning services at local, regional and national levels
- record keeping for legal reasons
- teaching (including logbooks)
- performance management
- adverse incident and risk management
- complaints and litigation
- research
- audit
- clinical governance, including benchmarking of performance of individuals, teams, hospitals and regions.

Data aggregation

Many, though not all, of the secondary uses of clinical inform-ation use data that have been aggregated (data that relate to many patients or have been taken from many sources). For example, when estimating the number of deaths following myocardial infarction (MI), the data may be taken from many patients, in many hospitals, following MI from a number of different aetiologies. This aggregation can be used to define prognosis, to measure performance, and for research. However, data aggregation is prone to many problems.

Case-mix – in order for the results of the aggregation to be accurate it is important that all the cases are similar. For example, the mortality following MI complicated by left ventricular failure is different from uncomplicated MI, and it is relatively easy to separate these two groups. It is harder to understand the difference in mortality following MI in patients treated by two cardiologists, unless one knows that one of the cardiologists has a special interest in diabetic patients.

Data collection – using the example of MI, it might seem simplest to use data from death certification, but this is prone to error. Following MI, many patients die from heart failure, if only patients whose primary cause of death is recorded as MI are included in the data, then those suffering MI followed by heart failure will be missed. If heart failure as the primary cause of death is used, then many patients who suffered heart failure without MI will be included. The diagnosis at the time of admission could be used, but many patients have the diagnosis of chest pain made on admission, only to have MI confirmed later. The number of patients whose diagnosis is obscure on admission varies between hospitals, invalidating comparison between them.

Using different terms for the same clinical entity – the potential for confusion is clear if one doctor in a hospital records all MIs as 'myocardial infarction' but another uses 'coronary thrombosis'. It would be difficult to store the full English or Latin name of every diagnosis and operation. For example, myocardial infarction could be spelt incorrectly, other words having the same meaning could be substituted, or the doctor's handwriting could be difficult to read. Even if there was unlimited capacity to retain and search text, it would be impossible to take account of all the possible descriptive variables that clinicians might use.

Coding

The problem of multiple clinical terms, and that of recording the correct primary diagnosis, is addressed by using sets of alphanumeric codes. In the UK, the diagnosis is coded using the International Classification of Diseases, 10th revision (ICD10). The code for myocardial infarction is I21.9. These codes use less space, are easier to search and are specific for each disease or diagnosis. ICD also allows certain codes to be paired to convey more information. Operations and procedures are coded using the Office of Population Censuses and Surveys Tabular List of the Classification of Surgical Operations and Procedures; normally referred to as OPCS4. In OPCS4, percutaneous transluminal balloon angioplasty of the aorta is neatly reduced to L26.1.

Hospital Episode Statistics

Each NHS hospital is required to return data about each patient treated to the Department of Health. This data set forms the basis of the Hospital Episode Statistics (HES) system, which is a powerful database containing personal, medical and administrative details of all patients admitted to, and treated in, NHS hospitals in England. This information has a host of uses including:

- policy development
- illustrating variations in health status and health delivery through time and across geographical areas
- production of comparative statistics to assist in performance management
- medical research – HES contains information of use to clinicians and others who are developing new treatments, investigating causal factors and monitoring trends.

Some technical terms

Benchmarking
The process of measuring the results of a service at a known point and position and then evaluating that point-position on a comparative basis with other similar services on an appropriate and repeatable basis

Case-mix
The mix of people, patients, treatments or services. It is used to understand the needs, provision and resource uses associated with healthcare

Core Data Sets (CDS)
The core information that health professionals need to exchange and share about the treatment of a patient with a specific condition (e.g. the national cancer data sets)

Cochrane Library
An electronic publication designed to supply high quality evidence to inform people providing and receiving care, and those responsible for research, teaching and funding and administration at all levels. It is an international endeavour that prepares, maintains and promotes the accessibility of systematic reviews of the effects of healthcare interventions

Electronic Health Record (EHR)
The concept of a longitudinal record of a patient's health and healthcare – from birth to death. It combines both the information about patient contacts with primary care as well as subsets of information associated with the episodic elements of care held in EPRs

Electronic Patient Record (EPR)
Contains a patient's personal details (e.g. name, date of birth), their diagnosis or condition, and the details about the treatment/ assessments undertaken by a clinician. Typically covers episodic care provided mainly by an institution

Health Benefit Groups (HBG)
A method of linking health needs with service delivery and the expected health benefit to assist in health needs assessment and planning service delivery

Healthcare Resource Groups (HRG)
A way of grouping the treatment of patients to allow analysis of the appropriateness, efficiency and effectiveness of care. It is based on clinically meaningful hospital inpatient episodes and the level of resources

Informatics
Covers all aspects of information management, information systems and information technology for professional practice

Information management (IM)
The way in which data and information are collected, stored, processed and used

Information technology (IT)
The equipment and the mechanics of information systems

Performance Assessment Framework (PAF)
A group of 6 areas (health improvement, fair access, effective delivery of appropriate healthcare, efficiency, patient and carer experience, outcomes of healthcare) by which the performance of all NHS Trusts is measured

Tables summarizing the data are published annually by the Department of Health and are available from the NHS Executive web site. The records are collected from all hospital providers in England (Scotland and Wales have their own systems) and are amalgamated annually. There are 40 items of information (fields) (Figure 1), including some of the patient's personal details (e.g. age, gender, place of residence), information about their admission to hospital (e.g. elective or emergency) and11 fields provide clinical data (e.g. diagnoses and details of any operations).

Some data fields in the Hospital Episode Statistics

Dates
- When admitted
- When operated on
- When discharged

Cause of accident
- E-codes (ICD10)

Hospital Episode Statistics numeric codes
- Method of admission
- Method of discharge

Surgical procedures
- OPCS4 codes

Provider and area codes
- Hospital Unit or Trust
- Health Authority
- Area of residence

Periods in days
- Duration of episode
- Waiting time

Diagnosis
- ICD10 codes

1

Diagnostic analysis

When using systems such as HES to provide answers to questions such as: "How many in-patients were diagnosed as suffering from MI during 2001?" it is necessary, for the sake of consistency, to use common standards when deciding which episodes to count. Also, it is important to qualify answers with an explanation of how the figures were produced. In some cases it may be impossible to give an answer because, in HES for example, information is divided into consultant episodes, it does not deal directly in 'patients' or 'stays in hospital'. Each record has space for seven separate diagnoses, which can present another problem. Unless the questioner specifically demands something different, it is standard to look only at the primary diagnosis field of those episodes that finished during the year. Counting finished episodes includes some patients who were admitted the previous year, but this is counterbalanced by those who remain in hospital until the following year. It is important to understand, for example, that if a patient's primary diagnosis was heart failure, but they also suffered a MI, the MI will be missed if only the primary diagnosis field is searched.

NHS Performance Assessment Framework

One of the uses of HES data is to generate the information used to produce indicators of the quality and effectiveness of NHS Trusts. This is known to the NHS as the NHS Performance Assessment Framework (PAF) and to the media as league tables. It enables Hospital Trusts to assess and compare their performance against a range of measures. It has four areas:

- clinical effectiveness and outcomes
- efficiency
- patient/carer experience
- capacity and capability.

Of most relevance to HES data are the measures relating to clinical effectiveness and outcomes (Figure 2). Bearing in mind the problems associated with using aggregated data, with coding some diagnoses and procedures, and with the variable quality of the information systems in parts of the NHS, it is easy to see how the performance for individual Trusts is easily misrepresented. ◆

NHS Performance Assessment Framework for acute Trusts, clinical components

i Percentage of patients discharged to usual place of residence within 56 days of emergency admission to hospital with a stroke, aged 50 and over (age and gender standardized)

ii Percentage of patients discharged to usual place of residence within 28 days of emergency admission to hospital with a hip fracture, aged 65 and over (age and gender standardized)

iii Emergency readmissions to hospital within 28 days of discharge (all ages), as a percentage of live discharges (age and gender standardized)

iv Emergency readmissions to hospital within 28 days of discharge following treatment for a fractured hip, as a percentage of live hip fracture discharges (age and gender standardized)

v Emergency readmissions to hospital within 28 days of discharge following a stroke, as a percentage of live stroke discharges (age and gender standardized)

vi Deaths within 30 days of surgery for non-elective admissions to hospital, per 100,000 patients (age and gender standardized, includes deaths in hospital and after discharge)

vii Deaths within 30 days of a coronary artery bypass graft, per 100,000 patients (age and gender standardized, includes deaths in hospital and after discharge)

viii Deaths within 30 days of emergency admission to hospital with a hip fracture, of patients aged 65 and over, per 100,000 patients (age and gender standardized, includes deaths in hospital and after discharge)

ix Deaths within 30 days of coronary artery bypass graft, per 100,000 patients (age and gender standardized, includes deaths in hospital and after discharge)

Resources

British Computer Society	http://www.bcs.org.uk
British Healthcare Internet Association	http://www.bhia.org
Centre for Evidence Based Medicine	http://cebm.jr2.ox.ac.uk/
Cochrane Library	http://www.update-software.com/cochrane
Education Training and Development Programme (NHS)	http://www.nhsia.nhs.uk
Health Centre Index	http://www.healthcentre.org.uk/
Medical Information Group (MIG)	http://www.hull.ac.uk/mig
National Electronic Library for Health	http://www.nelh.nhs.uk/
National Health Service Executive	http://www.doh.gov.uk/nhs.htm
NHS Performance Indicators	http://www.doh.gov.uk/nhsperformanceindicators

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Telemedicine

Sophie M Jones

Sophie M Jones is Research Registrar in Plastic Surgery at Salisbury District Hospital, Wiltshire, UK. She qualified from Oxford University and UMDS before completing her surgical training in Norwich. She was involved in the development of a telemedicine system at the Queen Victoria Hospital, East Grinstead, and carried out research in this field.

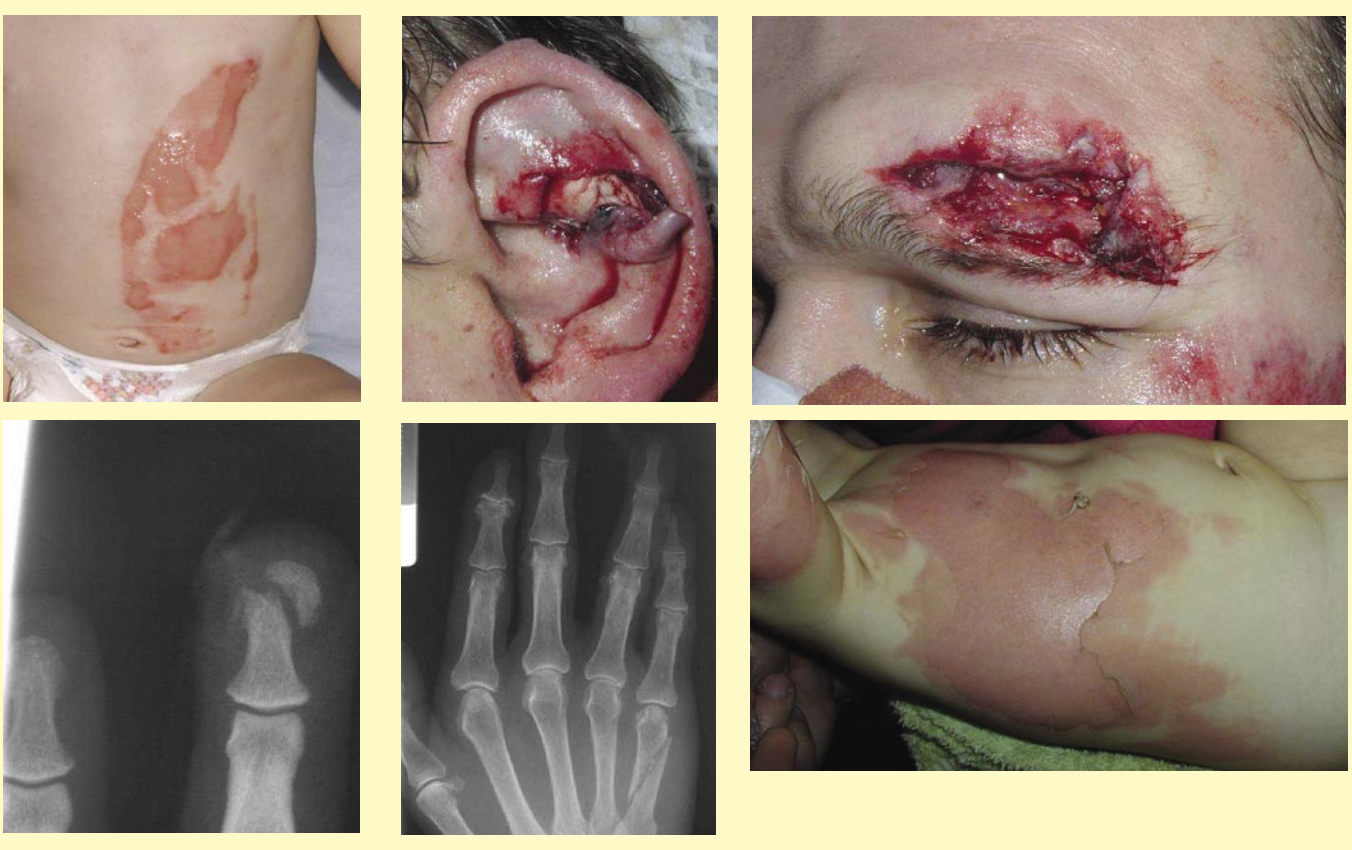
Telemedicine is the assessment and review of patient information (history, examination or investigations) by a health professional who is separated temporally and/or spatially from the patient. It is 'the practice of medicine from a distance'; from the Greek *tele* meaning far.

Telemedicine is not new; it has been practised since the invention of the telephone. However, the development of technology, specifically the Internet, has increased the means whereby information can be acquired and transmitted over large distances. Virtually any information relevant to patient treatment can now be shared with colleagues over large distances in a short time. Telemedicine diminishes inequalities in service provision, improves access to healthcare and reduces costs.

Components of telemedicine

Telemedicine requires communication between two or more sites. The fundamental components of a telemedicine system are means of information capture, transport and display.

Information capture: in the medical consultation it is essential to ensure privacy and security of data using technology that is accurate, reliable and simple to use. Generally, the patient's informed consent is necessary, particularly if identifiable information (e.g. a recognizable photograph) is to be transferred. There are no standards for photographic technique and referring practitioners receive little or no training in clinical photography. However, modern digital cameras are easy to use and attention to detail can result in excellent images (Figure 1).



Digital images taken by staff and transmitted for expert opinion.

1

Information transmission: telemedicine can be practised almost anywhere, given the right equipment. Satellite systems enable access from the most remote locations. Most systems use telephone networks, digital networks (e.g. Integrated Services Digital Network (ISDN), Local Area Networks (LANs), Global System for Mobile communications (GSM), mobile phones, asynchronous transfer mode (ATM)) or the Internet. Fast, sophisticated and automated telemedicine using intuitive interfaces and powerful information management systems is possible using these methods of transmission and current technology. However, simple telemedicine systems can be just as effective.

Most systems use some form of encryption or exclusive LANs to transmit data securely. In the UK, the NHSnet is an exclusive intranet which allows communication across the National Health Service (NHS) while providing maximum security of its contents. However, no system is completely safe against intruders.

Information display: software used to display the information should be accurate, reliable and simple to use. Images can be displayed in a variety of formats; the most common are BMP and JPEG files. JPEG files are smaller than most others, containing about 300 kB. This is important because the number of pixels used for each image influences its quality and size and therefore the download time of each file. Having conveyed the information to an expert, the referring doctor can receive an opinion in real-time or store-and-forward. In real-time telemedicine at least two individuals communicate synchronously using a video-conference or a telephone call (e.g. telepsychiatry). Store-and-forward telemedicine (Figure 2) refers to the transfer of pre-recorded information that can be assessed in a time-independent fashion (e.g. teledermatology, teleradiology).

2 Using a store-and-forward telemedicine system.

History

Telemedicine has been in existence through radio and telephones since their invention. One of the earliest examples of modern telemedicine was the monitoring of astronauts' physiological functions (blood pressure, respiratory rate, ECG and temperature) by the US National Aeronautics and Space Administration (NASA) in the late 1960s. Also in the USA, in 1967, doctors were invited to bring radiographs to Logan Airport in Boston where they were scanned by a black-and-white camera and transmitted to a video monitor in the radiology department of Massachusetts General Hospital. Physicians could then discuss the case by telephone.

The first real-time interactive link was also set up in 1967 between the Nebraska Psychiatric Institute in Omaha and the Norfolk State Hospital (112 miles apart). The first use of satellite communications took place in 1976 when the Communications Technology Satellite *Hermes* was launched by NASA as part of a joint project with Canada's Department of Communications to serve remote areas of Canada; it was used in several telemedical studies. Telemedicine continues to play an important role in Canadian Healthcare (NORTH Network, Ontario).

Cost

Implementation of telemedicine systems has been resisted partly because of the cost of purchasing the hardware. However, with the advancement of technology, costs have fallen. Setting up a telemedicine system is now cheaper and running costs are relatively low, especially for store-and-forward systems.

Education

Telemedicine enables fast and easy access to medical information and guidance. Initially, the quality of health information on the Internet was poor, but the quality and quantity has increased over the last few years and much of it is available to health consumers as well as clinicians. The Internet allows clinicians to keep up to date with the latest medical advances, consult online textbooks and share clinical problems. Increasing numbers of hospital departments and universities arrange interactive tutorials and case discussions via videoconference. Patients can access information online about their disease, its management, research trials and support groups.

Legal challenges

The medico-legal implications of telemedicine have been debated extensively. Most legal and ethical issues are similar to those in general medicine (e.g. security of data, confidentiality, risk). The specific implications of telemedicine will be revealed by litigation as they arise. The Health Guidance Note on Telemedicine published by NHS Estates states that the medico-legal issues are not fully resolved.

Research

The Telemedicine Information Exchange (TIE) (http://tie.telemed.org) is a US-based database of current research in telemedicine throughout the world. In the UK, the Telemedicine Information Service (TIS) (www.tis.bl.uk) monitors current research and is a good source of information.

Implementation

Implementation of telemedicine into routine health services has been impeded by lack of scientific evidence about its clinical and cost effectiveness. The British government stated that, without such evidence, telemedicine will not be introduced widely. The Information Technology departments in UK hospitals are also ill-equipped to cope with the exponential advancements in medical technology. The integration of telemedicine into mainstream conventional healthcare is one of the greatest challenges facing the NHS over the coming years. If met, it will change our way of thinking about the delivery of primary and secondary care in the next millennium.

Telemedicine holds the promise of improving access to healthcare, especially in areas where there are geographical barriers. It is evolving into a valuable, but underused, resource for the delivery of healthcare to patients at a distance, particularly where patient transport is impractical, expensive, complicated, and/or urgent. Progress in its use has been slow, it is only in the last few years that telemedicine has moved from development and evaluation of prototype systems to use in clinical practice. Today, over 250,000 telemedicine consultations are generated annually in military and civilian health delivery systems. Thus, slowly but surely, telemedicine is advancing and changing the practice of medicine. ◆

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Working Clinical Systems

Anthony P Madden

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Computerization of healthcare is unavoidable. All clinicians, including anaesthetists, need to understand what computers can do for them, and what may be involved in the procurement and implementation of such systems.

In the UK, the NHS has a clear vision and strategy for the implementation of clinical computer systems, which is set out in documents such as *Information for Health*, the *NHS Plan*, *Delivering the NHS Plan*, the *Wanless Report*, and the *National Specification for Integrated Care Records Service*.

The problem for clinicians worldwide has been that until recently most of the effort that has gone into computerization of healthcare has been aimed at supporting departmental functions (e.g. pathology, radiology, pharmacy) or at supporting the political need for information about the performance of publicly funded healthcare systems, including the need for clinical governance.

Why computerize?

There are four main reasons for introducing computers into clinical practice.

- Paper-based clinical data recording cannot effectively support new models of care.
- Often the information contained in paper records is not available to clinicians when they need it.
- Paper is an inefficient way of providing the information needed for clinical governance.
- Paper processes cannot support clinical decision-making in the way that computers can.

The way healthcare is provided is constantly evolving. The introduction of ambulatory centres or diagnostic and treatment centres, remote from the main hospital, and the requirement that patients should not have to travel long distances for a consultation, means that clinicians have to travel and may see the same patient in different places on different occasions during a single episode of care. In this system, there is considerable risk of paper records going astray and not being available when needed. Computerization can solve this problem, as well as the associated processes of booking the patient into outpatient clinic and operating theatre slots, ordering tests, scheduling transport, booking a bed, transmitting test results, keeping their GP informed and ensuring the patient is not lost to follow-up (Figure 1).

Some reasons for implementing electronic patient records (EPRs)

"…making the fundamental and lasting changes that will have a major impact on patient safety is much more difficult than simply installing new technologies…We must re-examine all that we do and redesign our many and complex systems to make them less prone to human error"
Editorial, *BMJ*, 18 March 2000

"If we managed travel like we manage healthcare then travel agents would book flights on the basis of the flight schedules they could remember"
Lawrence L Weed

Paper clinical notes are "poorly legible, ill-structured, bulky and untidy"
***Audit Commission*, 1995**

Anyone who has spent time trawling through a pile of paper clinical records trying to extract data for clinical audit will know that this is an inefficient way to gather data for clinical governance and for central government returns. Paper cannot advise, guide, or support clinical decision making in an active way. There is no guarantee that the relevant paper document will be available when needed, for example, a hospital protocol for the management of insulin-dependent diabetics undergoing surgery. Computerization can help.

Classification of modern EPR systems

There is no accepted single classification of electronic patient record (EPR) systems. Systems have a variety of origins and most are undergoing constant development. User interfaces are being changed, and in some cases the underlying databases and data structures are evolving. All this makes classification difficult. No single EPR system can do everything, so a useful primary classification for the core functions of a modern system is into:

- integrated
- interfaced 'best of breed' solution.

Even this is slightly false because it begs the question of what functions are 'core' and what are not. An integrated EPR will need interfaces to secondary or feeder systems (e.g. pathology, radiology) and these interfaces are typically managed by an integration engine that translates the output of one system (e.g. pathology) into a form that is 'understood' by the EPR or *vice versa*. HL7 is an international standard for transmitting such structured messages, but some manufacturers have enhanced the standard so that a degree of translation is required.

A secondary classification is:

- designed from scratch using modern technology
- based on fundamentally old technology with a user front end that has been updated over the years
- developed from a patient administration system or a departmental system (e.g. pharmacy).

All modern EPR systems are patient-centric. This means that when a user logs on to the system the first thing they do is identify the patient or patients in whom they are interested. This contrasts with older systems, in which a user typically logs in to the functional area of interest (e.g. patient administration, radiology, pathology) and then identifies the patient. A system that is not patient-centric cannot provide the integration of appointment scheduling, bed management and clinical functions demanded of a modern system.

In terms of technical architecture, modern systems are either based on a 'client-server' model (where the EPR software resides on the user's PC) or a 'thin client' model (where all the processing is performed on a central server). The clients in this environment typically use a web browser for the user interface. This may run on a relatively lowly specified PC, or on a personal desktop assistant (PDA), tablet or laptop device. Screen size can be a problem with PDAs because it is impossible to display all the required information on a screen with a diagonal of 8–10 cm. Thin client environments are theoretically easier to maintain because enthusiastic users cannot interfere with the EPR software and thin client devices can be cheaper to buy than a conventional well-specified PC. The network bandwidth may also be less demanding. However, 'client-server' architecture can be set up to run in a thin client mode using special software. This may be useful for running these applications in places that are remote from the main hospital, such as primary care health centres or community hospitals.

Core EPR functions

The main EPR functions are:

- patient administration
- scheduling and tracking
- clinical documentation
- order communications, including laboratory and radiology requests and results, pharmacy and electronic prescribing
- clinical decision support
- analysis.

Jargon buster

ADT	Admissions, discharges and transfers, see PAS
AIMS	Anaesthetic Information Management System
Arden syntax	A programming language for medical logic modules/sophisticated clinical decision support
DICOM	A communication standard for handling digital images, mostly relevant to diagnostic imaging (e.g. radiographs)
EHR	Electronic Health Record, a term introduced in IfH and now superseded by ICRS. The concept of a cradle-to-grave record of health and healthcare maintained in the primary care arena
EPR	Electronic Patient Record. Superseded by ICRS but still in common use. The electronic equivalent of the hospital notes folder but with added functions
GUI	Graphical User Interface (e.g. Microsoft Windows)
HL7	Health Level 7. A standards group in the USA. Often used in the context of 'structured messages' used to send clinical information between computer systems (e.g. EPR and RIS)
HTML	Hypertext Markup Language. The language of the World Wide Web. A small subset of SGML
ICRS	Integrated Care Records Service. A new term encompassing the concepts of both EPR and EHR
IfH	*Information for Health*. The UK Government's Information Strategy for the NHS for the period 1998–2005. Updated in *Building the Information Core*
LIMS	Laboratory Information Management System. Computer system used to manage laboratory processes and outputs
LIS	Local Implementation Strategy for IfH
Order Comms	Order communications. The electronic equivalent of 'requesting' a radiograph or blood test or almost anything else that may be required for a patient (e.g. a theatre slot, dietetic advice)
PACS	Picture Archiving and Communication System. Uses DICOM standard. Electronic store for digital images, mostly diagnostic
PAS	Patient Administration System. Deals with appointments, waiting lists, admissions, discharges, transfers and provides information for Government returns regarding hospital activity
PDA	Personal Desktop Assistant. A handheld computer designed to be used in conjunction with a desktop PC (e.g. Palm or Pocket PC devices)
RIS	Radiology Information System. Computer system used to manage radiology processes and outputs
SGML	Standard Generalized Markup Language, a page markup language that was initially developed in the late 1960s by the US Graphic Communications Association to permit the electronic transfer of page formatting and layout instructions from publishers to printers. Adopted as an international standard in 1986
UML	Universal Modelling Language. A technique for modelling processes that is universally applicable and facilitates the subsequent computerization of those processes
URL	Universal Resource Locator. An internet address (e.g. www.doh.gov.uk/ipu). Also used to identify 'resources' such as PCs or printers on a local area network
XML	Extensible Markup Language. A subset of SGML. More flexible than HTML. Can be used to transmit structured messages (e.g. pathology results)

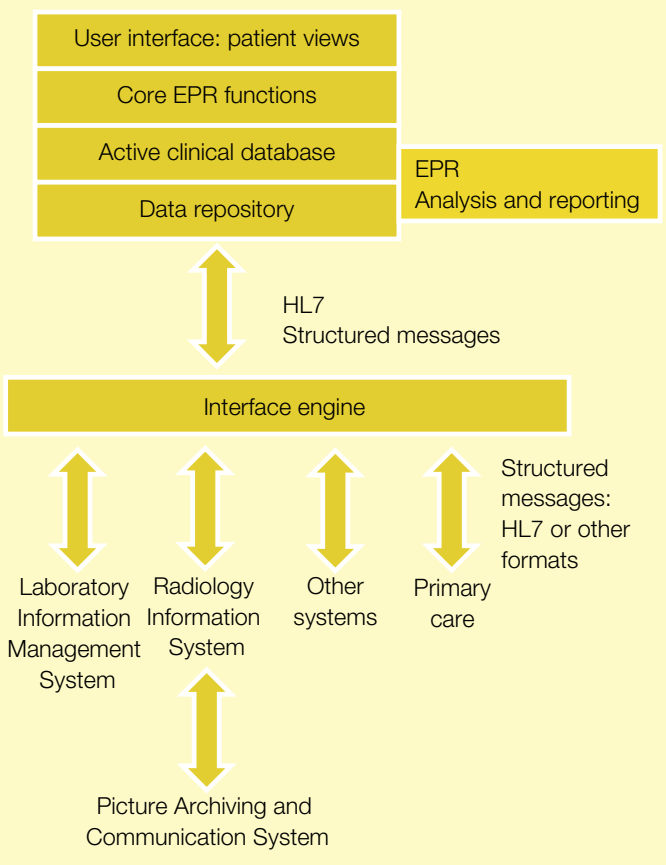
Most modern EPRs have weak areas and none that the author is aware of does everything really well, despite the claims of the software companies. Most have a comprehensive set of patient administration system (PAS) functions, and nearly all have good order communications functionality, though electronic prescribing can be a weakness, largely because the software has not yet been fully developed and tested in clinical use. The ability to document clinical findings and record clinical observations varies from system to system. Active decision support is an area that all companies recognize as something that must be supported, though most require work to be done during implementation to tailor the decision support module to local needs. Analysis is best performed on an off-line copy of the database, because running reports on the active copy can result in unacceptably slow response times for clinical users.

Some EPRs have scheduling and tracking functions integrated into their core, thus permitting a close link to order communications, PAS and care pathways. This close linkage is not easy if patient scheduling and tracking functions are provided by a separate system that has to be interfaced to the EPR. Laboratory information management system (LIMS) and radiology information system (RIS) functions are also sometimes available as part of the core, though it is more common for these to be provided separately and interfaced to the EPR (Figure 2). PACS is always separate.

Modernization

Most clinicians can think of ways to improve the service they provide. The jargon term for this is business process re-engineering, and when it involves the re-design of clinical processes it needs a formal process to ensure that patients are not put at greater risk.

Technical structure of a typical electronic patient record (EPR)



2

Process re-engineering is an essential component of implementing an EPR, and the stages comprise:

- analysis of the existing process
- design of the new computerized process
- configuring the EPR to deliver the new process
- testing the software and running clinical scenarios *in vitro* before going live
- piloting the new clinical processes in a limited clinical area (e.g. a single ward or department) with careful supervision and collecting audit data if applicable
- formally reviewing the outcome of the pilot and making changes if necessary
- rolling out the new process and the EPR to other clinical areas.
  All this requires input from clinicians if it is to work well.

Anaesthetic considerations

Information for Health specified six levels of increasing sophistication of EPRs. NHS hospitals have some flexibility in choosing which functions in which of the six levels they implement and when. However, there are target dates for the implementation of some functions (e.g. electronic prescribing).

The data recording and reviewing requirements of anaesthesia are similar to those of many other specialties. Preoperative assessment and investigation, intraoperative recording of physiological data and drug and fluid administration, along with details of anaesthetic technique, and postoperative data recording are not fundamentally different from the processes that are undertaken by clinicians in many other specialties. EPRs should be able to handle these requirements, though special anaesthetic screens may need to be designed when the EPR is being configured following the analysis phase and before piloting the system in a clinical environment.

Automatic downloading of physiological data from anaesthetic monitors has been technically possible for many years. Difficulties encountered in linking all the different devices in use in a typical anaesthetic department to an AIMS, and the fact anaesthesia is now so safe (making the economic justification weak) may explain why these systems are not more widely available.

It is likely that the small number of AIMS manufacturers will be squeezed as equipment manufacturers provide devices with outputs that comply with international communication standards and protocols, and EPRs are provided with the ability to incorporate the data streams from critical care monitors using ‘plug and play’ technology. ◆

FURTHER READING

Information for Health: **http://www.doh.gov.uk/ipu**

The NHS Plan: **http://www.doh.gov.uk/nhsplan**

Delivering the NHS Plan: **http://www.doh.gov.uk/deliveringthenhsplan**

The Wanless Report: **http://www.hm-treasury.gov.uk/Consultations_and_Legislation/wanless/consult_wanless_final.cfm?**

Building the Information Core: **www.doh.gov.uk/ipu**

National Specification for Integrated Care Records Service: **http://www.doh.gov.uk/ipu/whatnew/specs_12d.htm**

Note: any Internet search engine will provide URLs for further reading on topics referred to in this article. Particularly recommended is www.google.com

Intensive care

Anaesthesia
and intensive care medicine
on CD-ROM

Acid–Base and Blood Gas Analysis

Peter J McQuillan

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Acid–base homeostasis is important because protein structure and function, ionic dissociation and all chemical reactions are pH dependent. Whereas plasma sodium is controlled within a few mmol/litre, $[H^+]$ is controlled within a few nmol/litre. Acid load comes from both respiratory sources (i.e. carbon dioxide via carbonic acid) amounting to 15–20,000 mmol H^+/day, and metabolic sources (i.e. metabolism of sulphates, phosphates, nitrates, lactate and ketoacids; 40–80 mmol/day). Acute changes in acid–base state are minimized by buffering systems (which minimize the change in $[H^+]$) and other compensatory mechanisms, before excretion of acids or alkalis.

Definitions

$$pH = -\log[H^+] = \log \frac{1}{H^+}$$

(p stands for power from German *Potenz*)

- pH is the negative logarithm (i.e. the logarithm of the reciprocal) of the hydrogen ion concentration. In a logarithmic scale, a unit change in pH represents a 10-fold change in H^+ concentration.
- Normal ranges: pH = 7.34–7.43 (i.e. ≈ 7.40); H^+ = 46–37 nmol/litre (i.e. ≈ 40 nmol/litre)
- Figure 1 gives the rule of thumb for interconversion of pH and $[H^+]$
- Acidaemia/alkalaemia occur when pH or H^+ are outside the normal range.
- Acidosis/alkalosis are the processes tending to produce an acidaemia/alkalaemia.
- An acidosis or alkalosis may exist in the absence of an acidaemia/alkalaemia if:
  - the primary process is not sufficiently severe to change pH beyond the normal limits
  - compensation may have occurred to bring pH back within the normal range
  - mixed processes alter pH in different directions.

A rule of thumb for easy translation between pH and H^+

$[H^+]$ nmol/litre	$[H^+]$ nmol/litre	pH
10^{-7}	100	7.00
$10^{-7.2}$	63	7.20
$10^{-7.3}$	50	7.30
$10^{-7.4}$	40	7.40
$10^{-7.5}$	32	7.50
$10^{-7.6}$	25	7.60
$10^{-7.8}$	16	7.80

If pH =7.ab and H^+ = cd, then ab+cd ≈ 83
pH 7.23 => H^+ = 83 – 23 = 60
H^+ = 25 => pH = 7.(83–25) = 7.58
The error is small and inconsequential for clinical purposes between pH 7.1 and 7.6.

1

Henderson and Hasselbalch equation

This equation describes the relationship between concentrations of dissociated and undissociated acid or base, dissociation constant and pH. The carbonic acid system is of fundamental importance. The reaction of carbon dioxide with water forms carbonic acid, which dissociates to form bicarbonate and hydrogen ions:

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^- \qquad 1$$

Henderson noted that according to the law of mass action:

$$\frac{[H^+][HCO_3^-]}{[H_2CO_3]} = k \quad \text{where k is a constant}$$

$$\Rightarrow 24.\frac{40\ (\text{mm Hg})}{24} = 180.\frac{5.3(\text{kPa})}{24} = 40\ \text{nmol/litre}$$

This simple formula allows the validity of blood gas results to be checked easily.

Hasselbalch took the logarithm of the reciprocal to produce the classical Henderson–Hasselbalch equation:

$$= pK_a + \log \frac{HCO_3^-}{0.03 \times PaCO_2\ (\text{mm Hg})} \quad \text{or} \quad \frac{HCO_3^-}{0.23 \times PaCO_2\ (\text{kPa})}$$

The pK_a value at 37°C is 6.1. Thus pH depends on the ratio of bicarbonate to carbonic acid or the ratio of bicarbonate to dissolved carbon dioxide. Changes in pH or H^+ occur through a change in this ratio. Compensatory mechanisms exist to return this ratio towards 20.

Alterations to pH

'Metabolic' processes change HCO_3^-, which alters the numerator and hence the pH.

Metabolic acidosis

$$pH = 6.1 + \log \frac{HCO_3^-}{0.23 \times PaCO_2} \qquad \downarrow\downarrow \ \downarrow$$

The primary change is a fall in bicarbonate (acidosis, metabolic). Compensation produces a fall in $PaCO_2$ to return the ratio (and pH) towards normal.

Respiratory compensation occurs quickly in spontaneously breathing patients. Ventilated patients may have ventilation limits imposed, thereby precluding adequate compensation. A patient with diabetic ketoacidosis may develop a $PaCO_2$ of 1.7 kPa to compensate: intubation and ventilation requires the use of a high minute volume to maintain the compensated state.

Metabolic alkalosis

$$pH = 6.1 + \log \frac{HCO_3^-}{0.23 \times PaCO_2} \qquad \uparrow\uparrow \ \uparrow$$

The primary change is a rise in bicarbonate (alkalosis, metabolic). Compensation produces a (small) rise in $PaCO_2$ to return ratio (and pH) towards normal. This hypoventilatory ability is very limited in humans.

'Respiratory' processes change $PaCO_2$, which alters the denominator and hence the pH.

Respiratory acidosis

$$pH = 6.1 + \log \frac{HCO_3^-}{0.23 \times PaCO_2} \qquad \uparrow \ \uparrow\uparrow$$

The primary change is a rise in $PaCO_2$ (acidosis, respiratory). Compensation produces a rise in bicarbonate to return the ratio (and pH) towards normal.

An acute rise in $PaCO_2$ moves Equation 1 to the right prod-ucing an increase in HCO_3^- (as H^+ is buffered by haemoglobin) as a change in equilibrium of the reaction, rather than a compensation. Chronically, renal retention of HCO_3^- is a compensatory process taking hours to days. The expected level of HCO_3^- can be calculated using the formula in Figure 2 giving an indication of the acuteness of the process. If the HCO_3^- is other than the predicted value (for acute or chronic change), another process must be involved.

Respiratory alkalosis

$$pH = 6.1 + \log \frac{HCO_3^-}{0.23 \times PaCO_2} \qquad \downarrow \ \downarrow\downarrow$$

The primary change is a fall in $PaCO_2$ (alkalosis, respiratory). Compensation produces a fall in bicarbonate to return the ratio (and pH) towards normal.

Compensatory mechanisms move the pH back towards normal but seldom completely normalize it.

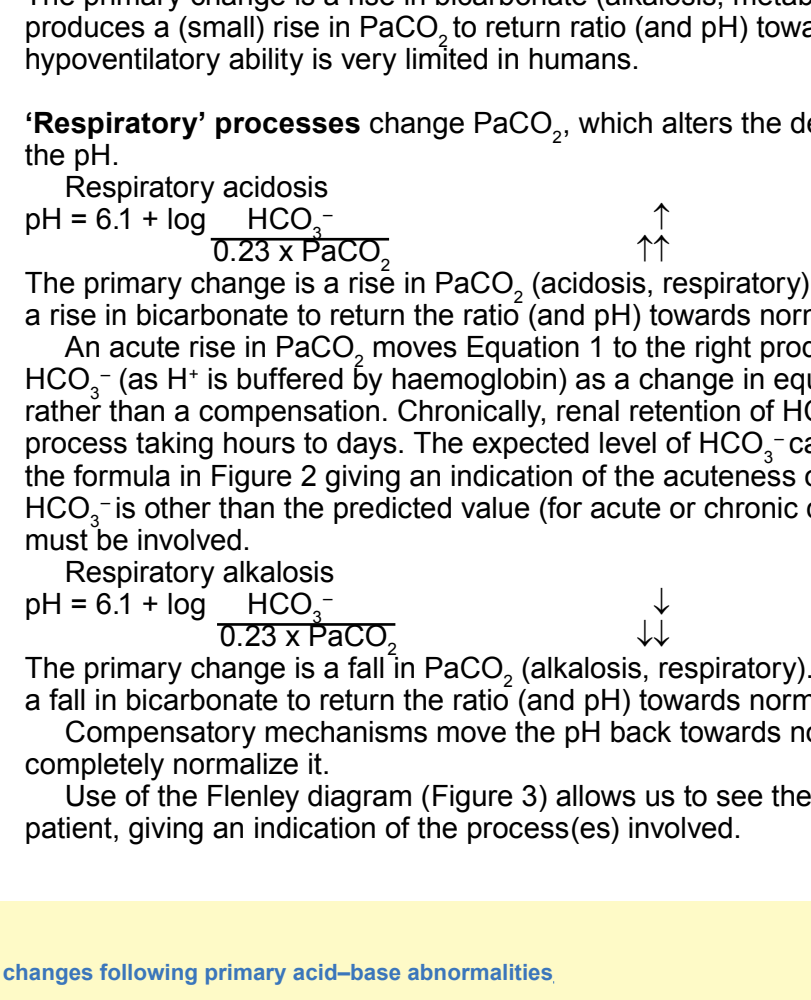
Use of the Flenley diagram (Figure 3) allows us to see the acid–base status of the patient, giving an indication of the process(es) involved.

Expected changes following primary acid–base abnormalities

kPa	Standard base excess (SBE) (mmol)	ΔHCO_3^- (mmol)	$\Delta [H^+] / PCO_2$	pH
Respiratory acidosis: acute	$\Delta SBE = 0\ \Delta PCO_2$	$\Delta HCO_3^- = 0.75\ \Delta PCO_2$	$\Delta[H^+] = 5.5\ \Delta PCO_2$	$0.06\ \Delta PCO_2$
Respiratory acidosis: chronic	$\Delta SBE = 3\ ^*\Delta PCO_2$	$\Delta HCO_3^- = 3\ \Delta PCO_2$	$\Delta[H^+] = 2.3\ \Delta PCO_2$	$0.023\ \Delta PCO_2$
Respiratory alkalosis: acute	$\Delta SBE = 0\ \Delta PCO_2$	$\Delta HCO_3^- = 1.5\ \Delta PCO_2$	$\Delta[H^+] = 5.5\ \Delta PCO_2$	$0.06\ \Delta PCO_2$
Respiratory alkalosis: chronic	$\Delta SBE = 3\ ^*\Delta PCO_2$	$\Delta HCO_3^- = 4\ \Delta PCO_2$	$\Delta[H^+] = 2.3\ \Delta PCO_2$	$0.023\ \Delta PCO_2$
kPa	**PCO_2 (kPa)**	**PCO_2 (kPa)**	**PCO_2 (kPa)**	**pH**
Metabolic acidosis	$\Delta PCO_2 = 0.13\ \Delta SBE$	$\Delta PCO_2 = (0.17\ ^*\ HCO_3^-) + 1$	$PCO_2 = -0.1H^+ + 9.3$	$7.(\ HCO_3^- + 15)$
Metabolic alkalosis	$\Delta PCO_2 = 0.08\ \Delta SBE$	$\Delta PCO_2 = (0.1\ ^*\ HCO_3^-) + 2.8$	$PCO_2 = -0.2H^+ + 13$	$7.(\ HCO_3^- + 15)$

2

Flenley diagram



Plotting the measured parameters of H^+ (or pH) against PCO_2 allows a graphical illustration of the observed acid–base status and the processes involved.

3

Metabolic acidosis and acidaemia

Blood contains anions (negatively charged) and cations (positively charged) and electrical neutrality dictates that:

$$(Cl^- + HCO_3^- + \text{albumin}^- + \text{phosphate} + \text{sulphate} + \text{lactate} + \text{ketones}) = (Na^+ + K^+ + Ca^{2+} + Mg^{2+})$$

If we measure only Na^+, Cl^- and HCO_3^- and UC^+= unmeasured cations and UA^- = unmeasured anions, the above equation becomes:

$$Na^+ + UC^+ = Cl^- + HCO_3^- + UA^-$$

$$\text{The anion gap (AG)} = Na^+ - (Cl^- + HCO_3^-)$$
$$= UA^- - UC^+ = < 12\ \text{mmol/litre}$$

Another version of the formula uses Na^+ and K^+ with a normal value of ≈ 15 mmol/litre. Hypoalbuminaemia reduces the AG and can be corrected using the formula AGc = AG – 0.25 (normal – actual albumin).

A metabolic acidosis involves a primary fall in HCO_3^-. Assuming there is no change in cations, the fall in HCO_3^- must be balanced by either an increase in UA^- or Cl^-.

High anion gap metabolic acidosis: an increase in UA^- implies a gain of acid. $Na^+ - [Cl^- + \downarrow HCO_3^-]$ implies an increase in AG. HCO_3^- falls and Cl^- is unchanged, UA^- is increased.

The causes include:

- lactic acidosis
- ketoacidosis (diabetes, alcohol, starvation)
- renal failure
- salicylates, ethanol, methanol, ethylene glycol.

Normal anion gap metabolic acidosis: normal AG plus increased Cl^- implies a loss of HCO_3^-.
$Na^+ - [\uparrow Cl^- + \downarrow HCO_3^-]$ means a normal AG with no change in unmeasured anions.
The causes include:
- gain of acid (ammonium chloride ingestion; lysine, arginine HCl in TPN)
- reduction in renal H^+ elimination (renal tubular acidosis (type 1, distal or type 4, hypoaldosteronism))
- an increase in HCO_3^- loss which may be gastrointestinal (diarrhoea, ileostomy, ureteroenterostomy) or renal (carbonic anhydrase inhibitors: acetazolamide, renal tubular acidosis (type 2, proximal) or renal tubular damage).

Metabolic alkalosis

Generation of a metabolic alkalosis is associated with a net gain of HCO_3^- via:
- loss of acid via gastrointestinal or renal routes
- administration of HCO_3^- or its precursors (e.g. citrate in blood, lactate or acetate in haemofiltration fluid)
- loss of fluid with disproportionately more Cl^- than HCO_3^-: sometimes called a contraction alkalosis, a decrease in extracellular volume with little HCO_3^- loss leads to an increase in $[HCO_3^-]$ and hence a metabolic alkalosis.

Maintenance of metabolic alkalosis requires impairment of renal HCO_3^- excretion because the kidney normally excretes HCO_3^- easily. This may occur in
- hypovolaemia
- potassium depletion
- mineralocorticoid excess
- hypercapnia.

Metabolic alkalosis may be:
- saline (Cl^-) responsive (urinary $Cl^- < 10$ mmol/litre) due to vomiting, chloride diarrhoea, diuretics or alkali ingestion
- saline (Cl^-) unresponsive (urinary $Cl^- > 10$ mmol/litre) due to mineralocorticoid excess, potassium depletion or renal Cl^- wasting (Bartter's syndrome)

Interpreting blood gases

Only PaO_2, $PaCO_2$ and $[H^+]$ or pH are measured in blood gas analysers. $PaCO_2$ defines the magnitude of the respiratory component but there is debate about the usefulness of the derived variables that describe the metabolic component (bicarbonate, standard bicarbonate, base excess and standard base excess (SBE)). This is in part because changes in $PaCO_2$ alter bicarbonate. The following system may be useful in assessing acid–base status.
- Is the pH normal, acidaemic or alkalaemic?
- pH or $[H^+]$ in normal range suggests one of the following:
  – no acid–base disorder exists
  – two or more disorders tending to offset pH or $[H^+]$ in opposite directions
  – partial compensation has occurred.
- Does the $PaCO_2$ change in the direction that would explain the pH change?
  – if it does then there is (at least) a respiratory abnormality.
  – if not, there must be a metabolic abnormality driving the pH change.
- Does HCO_3^- change in the direction that explains the pH change?
  – if it does there is a metabolic abnormality.
  – if not and it changes in the same direction as the change in $PaCO_2$ then it may represent a compensatory change.
- After identifying the primary or major abnormality ($\Delta PaCO_2$ for respiratory or ΔHCO_3^- for metabolic), what value would you expect for the other component if this were the only acid–base abnormality present (Figure 2)? If the value is different from the predicted value there must be another abnormality (i.e. a mixed picture). Alternatively, if an acute respiratory abnormality exists, are the actual and predicted pH or $[H^+]$ the same? If not, another metabolic abnormality exists.
- In a metabolic acidosis, the anion gap helps to identify the cause. If the deviation in the HCO_3^- from normal is different from the change in the anion gap from normal, another abnormality may exist.

Stewart physicochemical approach of acid–base balance

Stewart suggested changes in $[H^+]$ occur from dissociation of water into H^+ and OH^- rather than additions of acid or alkali. This dissociation potentially produces an inexhaustible source of H^+ and is bound by the laws of physical chemistry, in particular the principles of electroneutrality and of the conservation of matter. Three independent fundamental determinants of $[H^+]$ are the strong ion difference (SID), $PaCO_2$ and the total weak acid concentration (A_{TOT}). Stewart pointed out that the correlation of HCO_3^- with metabolic changes in $[H^+]$ is not evidence of causation, any more than the ECG changes in myocardial infarction represent the cause.

A strong ion is one that is (nearly) completely dissociated. SID is the net charge balance of all strong ions in solution, i.e. $(Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + lactate^-) =$ 40–42 nmol/litre = apparent SID (SIDa). This is similar to the old 'buffer base' concept. Neither H^+, nor HCO_3^- are strong ions. Weak acids, A^- (albumin and phosphate) contribute the remaining charge to satisfy electroneutrality. A rise in SID causes less water dissociation and an alkalosis and a fall in SID produces greater dissociation and an acidosis (Figure 4).

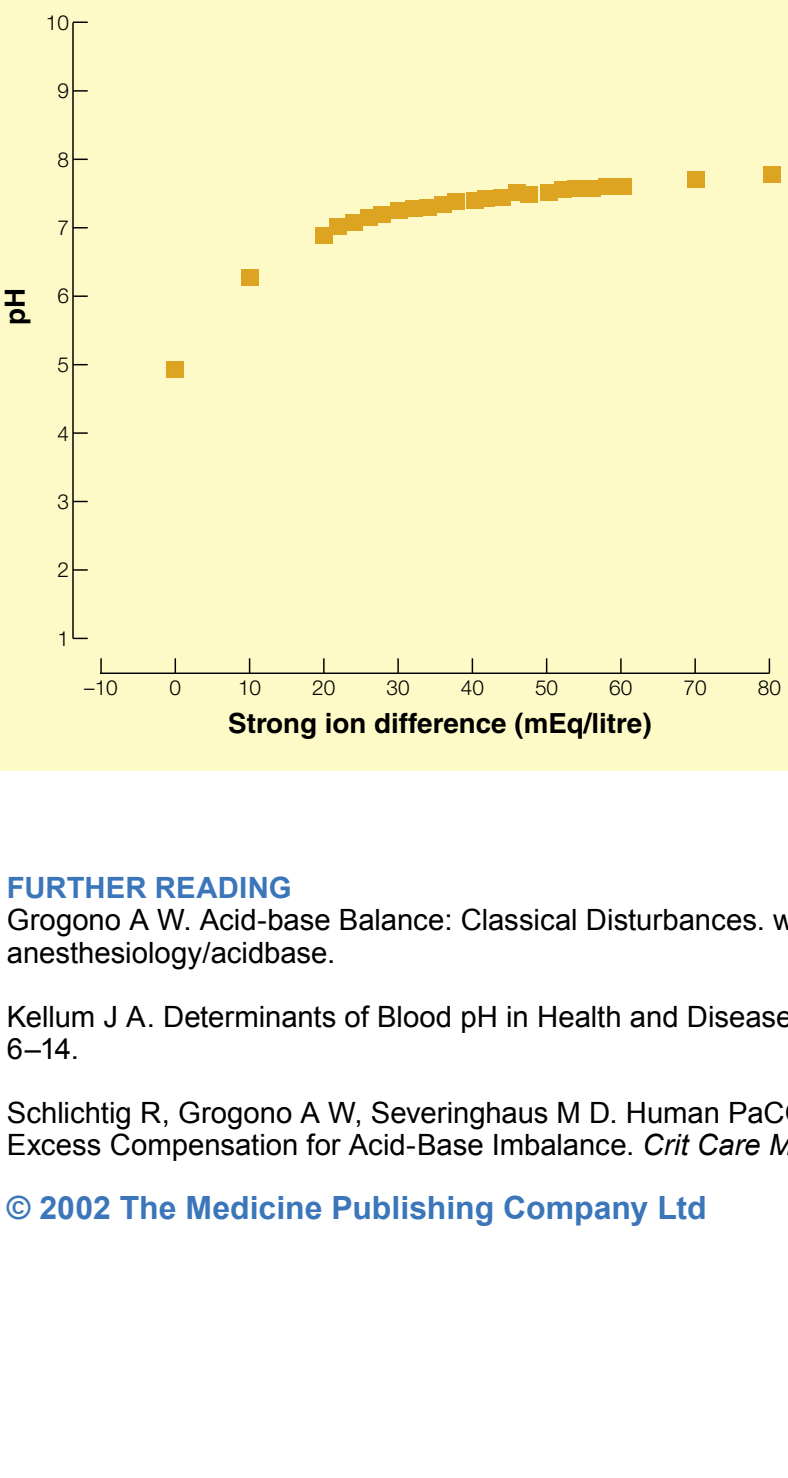
SID ↓
↓

$H_2O \rightleftarrows H^+ + OH^-$

↑

SID ↑.

Effect of strong ion difference on pH due to dissociation of water



4

FURTHER READING

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Kellum J A. Determinants of Blood pH in Health and Disease. Crit Care 2000; **4(1):** 6–14.

Schlichtig R, Grogono A W, Severinghaus M D. Human $PaCO_2$ and Standard Base Excess Compensation for Acid-Base Imbalance. *Crit Care Med* 1998; **26:** 1173–9

Acute Liver Failure

Kevin E J Gunning

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Acute liver failure (ALF) is an uncommon condition characterized by jaundice, coagulopathy and encephalopathy in a patient with previously normal liver function. In the USA, there are 2000 cases a year and in the UK there are 400. The main aims of treatment are the control of cerebral oedema and supportive management of multiple organ failure until hepatic regeneration occurs. Sepsis and cerebral oedema are the main causes of death.

Aetiology – in the UK, paracetamol (acetaminophen) overdose is the most common cause (70%) of ALF, but worldwide it is viral hepatitis (Figure 1).

Pathology – there is centrilobular necrosis of hepatocytes with activation of macrophages and liberation of cytokines, specifically tumour necrosis factor and interleukins 1 and 6.

Causes of acute liver failure

- Infection (hepatitis A, B, C, E, non-A non-B, cytomegalovirus, herpes simplex virus, Epstein–Barr virus, varicella)
- Drugs (paracetamol (acetaminophen), isoniazid, monoamine oxidase inhibitors (MAOIs), non-steroidal anti-inflammatory drugs (NSAIDs), halothane, Ecstasy, gold, phenytoin)
- Metabolic (Wilson's disease, Reye's syndrome)
- Cardiovascular (Budd–Chiari syndrome, ischaemic hepatitis)
- Miscellaneous (acute fatty liver of pregnancy, lymphoma, amanita phalloides, herbal medicines)

1

Clinical presentation

ALF usually presents with malaise, nausea and jaundice. The interval between the onset of jaundice and the onset of enceph-alopathy depends on the aetiology and is used to classify ALF:

- hyperacute liver failure (7 days between onset of jaundice and encephalopathy)
- acute liver failure (8–28 days)
- subacute liver failure (5–12 weeks).

This classification has implications for the prognosis and incidence of cerebral oedema, which is more common in hyperacute failure. As liver failure progresses, encephalopathy becomes the characteristic feature. The grading of encephalopathy is described in Figure 2. The mechanism of encephalopathy is not fully understood. Ammonia, false neurotransmitters and endogenous benzodiazepine ligands that enhance the effect of the inhibitory transmitter γ-aminobutyric acid have been proposed as causes.

Grades of encephalopathy

- Grade I: altered mood, impaired concentration and psychomotor function, rousable
- Grade II: drowsy, inappropriate behaviour, able to talk
- Grade III: very drowsy, disorientated, agitated, aggressive
- Grade IV: coma, may respond to painful stimuli

2

Diagnosis and investigations

There is no specific diagnostic test for ALF, however specific tests to identify the cause may include:

- viral serology for the hepatitis viruses
- plasma caeruloplasmin and 24-hour urinary copper to diagnose Wilson's disease
- hepatic ultrasound to demonstrate hepatic vascular occlusion in Budd–Chiari syndrome.

There will be elevation of:

- serum bilirubin (a level over 300 μmol/litre implies severe disease)
- plasma aspartate aminotransferase (AST) and alanine amino-transferase (ALT) reflecting hepatocellular damage
- prothrombin time (PT) (used as an indicator of the severity of the disease). Other common abnormalities are hypoglycaemia, hyponatraemia, hypomagnesaemia, respiratory alkalosis and metabolic acidosis.

Management

Paracetamol (acetaminophen) overdose results in the accumulation of the hepatotoxic metabolite N-acetyl-p-benzoquinonimine which is normally inactivated by conjugation with glutathione. N-acetylcysteine should be given as soon as possible after the overdose according to the standard treatment nomogram, to re-plenish hepatic stores of glutathione. The management of patients who meet the clinical indicators of poor prognosis (Figure 3) should be discussed with a regional liver centre and they should be transferred urgently for transplant assessment. Elective intubation and ventilation should be considered before transfer for patients with Grade II encephalopathy and it is mandatory for patients with Grade III or IV encephalopathy. The patient should be transferred with full monitoring by experienced personnel.

King's College Hospital criteria for liver transplant-ation in acute liver failure

Paracetamol (acetaminophen) overdose

- H^+ > 50 nmol/litre

Or all of the following:

- Prothrombin time > 100 seconds
- Creatinine > 300 μmol/litre
- Grade III–IV encephalopathy

Non-paracetamol (acetaminophen)

- Prothrombin time > 100 seconds

Or three of the following:

- Age < 10 years or > 40 years
- Prothrombin time > 50 seconds
- Bilirubin > 300 μmol/litre
- Time from jaundice to encephalopathy > 2 days
- Non-A, non-B hepatitis, halothane or drug-induced acute liver failure

3

The basis of intensive care management is to provide support for failing organs while allowing time for hepatic regeneration.

- Omeprazole or ranitidine are given as prophylaxis against gastrointestinal bleeding.
- Early enteral nutrition is recommended but there is no need to restrict protein or calories.
- Hypoglycaemia is common and an infusion of 10% glucose should be administered to keep the blood glucose level above 3.5 mmol/litre.
- Agitated or aggressive patients may need ventilation to enable care to be given.

Those with grade III or IV encephalopathy should be electively ventilated, because of the risk of cerebral oedema.

- High levels of positive end-expiratory pressure (PEEP) should be avoided because they may increase hepatic venous pressure and intracranial pressure (ICP).
- Pulmonary complications such as acute respiratory distress syndrome, aspiration or pneumonia occur in 50% of cases.
- Cardiac output is high (> 5.0 litre/minute) in 70% of cases, with a reduced systemic vascular resistance. Relative hypotension is therefore common and should be treated by volume loading with colloids. A pulmonary artery catheter or PiCCO should be inserted to guide therapy. Vasopressors (e.g. noradrenaline (nor-epinephrine)) may be needed to maintain mean arterial pressure, despite adequate volume replacement.
- N-acetylcysteine may be beneficial in the management of ALF even if paracetamol (acetaminophen) is not the cause. The evidence is conflicting, but it has been shown to increase cardiac output and oxygen delivery and is given as a loading dose of 300 mg/kg followed by an infusion of 150 mg/kg/hour.
- Coagulopathy is a major feature of ALF, because the liver synthesizes all the coagulation factors apart from factor VIII. Sepsis, reduced protein C and antithrombin III levels contribute to low- grade disseminated intravascular coagulation (DIC). The PT is a good measure of the severity of the disease and should not be corrected unless the patient is actively bleeding. Thrombocytopenia should be corrected if the platelet count falls below 50 x 10^9/litre.

Infection

Infection is common as a result of neutrophil and Küpffer cell dysfunction and sepsis is the cause of death in 11% of cases. Bacterial infections with Gram-positive organisms are seen in the first week and fungal infections after 2 weeks. The usual signs of infection (e.g. pyrexia, leucocytosis) may be absent and infection surveillance must be rigorous. Prophylactic fluconazole, 100 mg/day, should be started.

Cerebral oedema

Cerebral oedema develops in 80% of patients with Grade IV encephalopathy and is the cause of death in about 30–50% of patients with ALF. There is now evidence to suggest that it is the result of the high level of ammonia, which leads to an increase in the synthesis of intracellular cerebral glutamine. This increases osmotic pressure in astrocytes, resulting in cerebral oedema. The patient should be nursed with a 20° head-up tilt to improve cerebral perfusion pressure; there should be minimal intervention to prevent surges in ICP. Hyperventilation should be avoided and the $PaCO_2$ should be maintained at 4.7–5.2 kPa. Systolic hypertension and sluggish pupillary responses are the most reliable clinical signs of raised ICP, which should be treated with an intravenous bolus of mannitol 20%, 0.5 g/kg, which takes 20–60 minutes to act. The boluses may be repeated provided that the serum osmolality is less than 320 mOsmol/litre.

Some centres measure ICP using extradural, subdural or parenchymal monitors. However, the benefits must be balanced against the risk of haemorrhage, which occurs in about 15%. Coagulation should be corrected before the insertion of the monitor. Cerebral perfusion pressure should be maintained above 60 mm Hg. Thiopental (thiopentone) as a 50 mg bolus or an infusion of 50 mg/hour can be used to treat intractable intracranial hypertension, but may cause a fall in systemic blood pressure and a reduction in cerebral perfusion pressure. Moderate hypothermia (32–33°C) reduced ICP in one study.

Renal failure

Renal failure occurs in 70% of patients after paracetamol (acet-aminophen) overdose due to its nephrotoxic effect. Sepsis and hypovolaemia also contribute to renal failure. Haemodiafiltration may be necessary to maintain fluid balance and to correct hyponatraemia, hyperkalaemia and acidosis. A lactate-free replacement fluid should be used, because the failing liver can not clear lactate.

There has been considerable research into the development of an artificial liver. Trials of systems using extracorporeal perfusion of blood through columns of hepatocytes, or dialysis against an albumin-coated membrane have been undertaken, but most studies are small and experimental.

Prognosis

Overall survival with medical treatment is 10–40%. The prognosis depends on the aetiology and is best after paracetamol (acetaminophen) overdose and hepatitis A, and worst for non-A, non-B hepatitis and idiosyncratic drug reactions. The time to the onset of encephalopathy also affects prognosis, hyperacute failure has a 35% survival and subacute failure has a 15% survival. The outcome from transplantation for ALF is improving and is now 65–75%. ◆

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Acute Lung Injury and the Acute Respiratory Distress Syndrome

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Acute lung injury (ALI) and its extreme manifestation, the acute respiratory distress syndrome (ARDS), complicate a wide variety of medical and surgical conditions. Mortality remains high (40–70%) and survivors often require extensive periods of intensive care, representing a considerable clinical and fiscal burden.

ALI and ARDS are defined by refractory hypoxaemia associated with lung inflammation and increased pulmonary vascular permeability. The commonly accepted radiological and physiological criteria were first established at an American–European Consensus Conference in 1993 (Figure 1). ALI and ARDS were defined as separate, yet related, states on a pathophysiological continuum of pulmonary damage. Standardization of the criteria required to diagnose these conditions greatly facilitated the design of clinical trials allowing comparison between patient groups in various studies. However, these definitions take no account of the prognostic significance of the precipitating condition, and fail to specify the ventilatory strategy to be used when the presence and severity of hypoxemia are established. It is also increasingly recognized that individual interpretation of chest radiographs can vary widely, even among experienced clinicians. The Consensus Conference therefore met again in October 2000 to address these concerns in revised criteria.

Definitions of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

- Appropriate clinical setting with one or more recognized risk factors
- New, bilateral, diffuse, patchy or homogeneous pulmonary infiltrates on chest radiograph
- No clinical evidence of heart failure, fluid overload, or chronic lung disease (pulmonary artery occlusion pressure < 18 mm Hg)
- PaO_2:FiO_2 ratio of < 40 kPa (< 300 mm Hg) for ALI or < 26.6 kPa (< 200 mm Hg) for ARDS

1

Incidence and aetiology
Historically, the incidence of ARDS is estimated as 1.5–75 cases per 100,000 population. However, the only study to use the 1993 consensus criteria to define ALI and ARDS using a prospective cohort study identified 17.9 and 13.5 cases of ALI and ARDS, respectively, per 100,000 population. Many serious medical and surgical conditions may precipitate ALI/ARDS, not all of which involve the lung (Figure 2). Prognosis depends in part on the nature of the precipitating insult. Thus, trauma-induced lung injury is associated with a more favourable outcome than that precipitated by sepsis. The presence of multiple risk factors further increases the likelihood of developing ARDS, as do co-morbid factors such as chronic alcohol abuse. A recent study has suggested that a history of diabetes reduces the risk of developing ARDS in patients with septic shock.

Causes of acute lung injury and acute respiratory distress syndrome

Pulmonary causes
- Pneumonia
- Aspiration of gastric contents
- Inhalational injury
- Hypoxia/reperfusion injury
- Fat emboli
- Pulmonary contusion
- Near-drowning

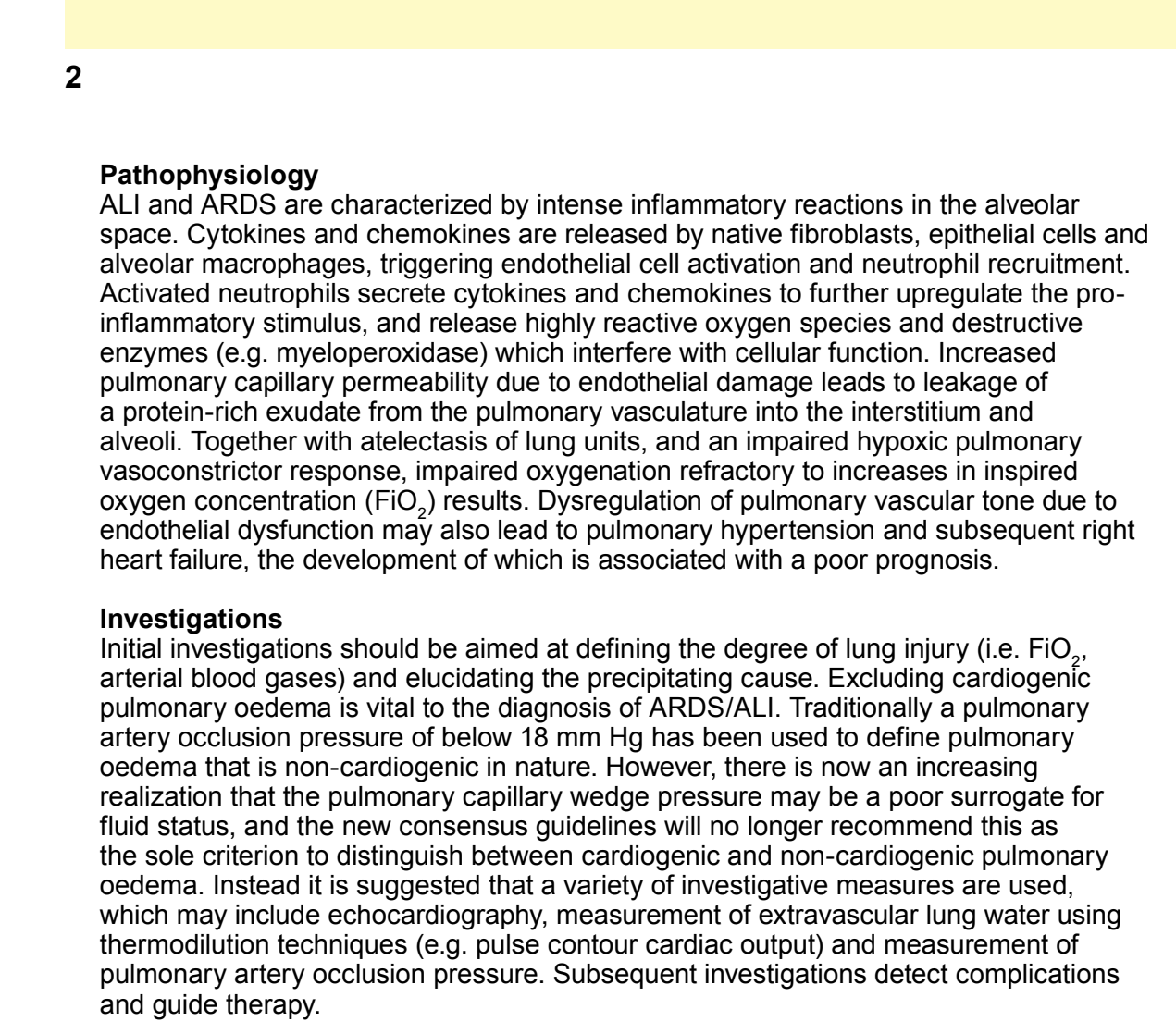
Non-pulmonary causes
- Sepsis
- Severe trauma
- Cardiopulmonary bypass
- Massive transfusion
- Drug overdose
- Acute pancreatitis

2

Pathophysiology
ALI and ARDS are characterized by intense inflammatory reactions in the alveolar space. Cytokines and chemokines are released by native fibroblasts, epithelial cells and alveolar macrophages, triggering endothelial cell activation and neutrophil recruitment. Activated neutrophils secrete cytokines and chemokines to further upregulate the pro-inflammatory stimulus, and release highly reactive oxygen species and destructive enzymes (e.g. myeloperoxidase) which interfere with cellular function. Increased pulmonary capillary permeability due to endothelial damage leads to leakage of a protein-rich exudate from the pulmonary vasculature into the interstitium and alveoli. Together with atelectasis of lung units, and an impaired hypoxic pulmonary vasoconstrictor response, impaired oxygenation refractory to increases in inspired oxygen concentration (FiO_2) results. Dysregulation of pulmonary vascular tone due to endothelial dysfunction may also lead to pulmonary hypertension and subsequent right heart failure, the development of which is associated with a poor prognosis.

Investigations
Initial investigations should be aimed at defining the degree of lung injury (i.e. FiO_2, arterial blood gases) and elucidating the precipitating cause. Excluding cardiogenic pulmonary oedema is vital to the diagnosis of ARDS/ALI. Traditionally a pulmonary artery occlusion pressure of below 18 mm Hg has been used to define pulmonary oedema that is non-cardiogenic in nature. However, there is now an increasing realization that the pulmonary capillary wedge pressure may be a poor surrogate for fluid status, and the new consensus guidelines will no longer recommend this as the sole criterion to distinguish between cardiogenic and non-cardiogenic pulmonary oedema. Instead it is suggested that a variety of investigative measures are used, which may include echocardiography, measurement of extravascular lung water using thermodilution techniques (e.g. pulse contour cardiac output) and measurement of pulmonary artery occlusion pressure. Subsequent investigations detect complications and guide therapy.

Chest radiography is easy to perform and may help in the detection of barotrauma or superadded infection. However, CT of the thorax is more sensitive for detecting pneumothoraces, pleural collections or pulmonary infiltrates, and is increasingly used as a routine investigation in ALI and ARDS. CT has also contributed to the understanding of the pathophysiology of ARDS by demonstrating patchy involvement of lung parenchyma rather than the homogeneous appearance seen on chest radiographs (Figure 3). Attempts have been made to use CT to predict responsiveness to interventions, one study correlating a response to inhaled nitric oxide with CT evidence of alveolar recruitment following increased positive end-expiratory pressure (PEEP).



Chest radiographs and CT scans for two patients with established acute respiratory distress syndrome. The radiographs show characteristic ground-glass shadowing bilaterally. Both CT scans demonstrate areas of interstitial ground-glass shadowing (w) with dense opacification (x) in the dependent regions. Patient 2 has extensive barotrauma and a pneumothorax (y) and an intercostal drain (z) are seen on the CT.

3

Fibre-optic bronchoscopy is often used to obtain microbiological samples to rule out pulmonary infection. Analysis of bronchoalveolar lavage fluid can also provide information concerning neutrophil infiltration and cytokine levels, which may have implications for prognosis.

Management

Treatment of the precipitating condition and the complications of ventilation (e.g. barotrauma, nosocomial infection) are essential in managing ALI and ARDS.

General supportive measures
Nutrition: adequate nutrition introduced early in the clinical course is now regarded as crucial to the management of patients with ARDS. Whenever possible, nutrition should be administered via the enteral route, and the use of prokinetic drugs, avoidance of agents that impair gastric emptying (e.g. dopamine) and the use of post-pyloric feeding tubes can help to achieve this. Recent research has suggested that feeds rich in certain fatty acids and antioxidants may be of benefit in ARDS, presumably via changes in the host immune response. Eicosapentaenoic acid (EPA) modulates production of pro-inflammatory eicosanoids, and γ-linoleic acid (GLA) may suppress production of leukotrienes while being metabolized to prostaglandin E_1. A recent randomized controlled trial of feeds supplemented with EPA/GLA in patients with ARDS has shown improvements in oxygenation, and shorter periods of ventilation and ICU stay. Further investigation in this area is required.

Fluid management: pulmonary oedema in ALI/ARDS is caused by increased pulmonary vascular permeability in the face of 'normal' pulmonary capillary pressures. Several studies have shown an association between a persistent positive fluid balance and poor outcome in ARDS, but it is not clear whether this represents administration of unnecessary fluid or greater haemodynamic instability in a group with a pre-existing poor prognosis. One clinical trial has shown that patients managed using the more restrictive of the two had shorter periods of ventilation and reduced ICU stays.

Ventilation and gas exchange

Protective ventilatory strategies: most patients with ARDS require mechanical ventilatory support to achieve adequate gas exchange. One study indicated that satisfactory oxygenation can be achieved in a proportion of patients by using positive pressure ventilation applied via a face mask, however, most patients require tracheal intubation.

The traditional strategies of ventilation used in these patients may have contributed to the propagation of lung injury. Experiments in animals showed that ventilation using large tidal volumes caused disruption of the pulmonary epithelium and endothelium, lung inflammation and impaired oxygenation. Excessive stretching of the lung parenchyma together with cyclical opening and closing of damaged lung units is thought to generate pro-inflammatory mediators, which exacerbate pulmonary damage, and if disseminated into the systemic circulation also contribute to the development of distant organ failure to which many patients succumb. As a result, ventilatory strategies now aim to limit the shear forces applied to the lung parenchyma, and reduce the cyclical recruitment and derecruitment of alveolar units. Thus, tidal volumes are set at lower levels than have traditionally been thought necessary. This reduces carbon dioxide clearance, often resulting in a respiratory acidosis. A large multi-centre trial in the USA has shown a convincing reduction in mortality (from 40% to 31%, p = 0.007) associated with this approach (using tidal volumes of 6 ml/kg) compared with conventional (12 ml/kg) ventilation.

High levels of PEEP can also be used to ensure recruitment and retention of damaged lung units. PEEP can also be transiently increased in a step-wise manner to high levels (e.g. 35–40 cm H_2O) before step-wise reduction to a maintenance level above the lower inflection point of the pressure–volume curve. CT images during such manoeuvres have demonstrated recruitment of atelectatic regions especially in dorsal areas of the lung, which remain inflated after the PEEP is reduced, with an associated improvement in gas exchange. A large multi-centre trial in North America is currently investigating the effect of different levels of PEEP and transient recruitment manoeuvres on outcome following ARDS.

Prone positioning: mechanical ventilation in the prone position is often used in the management of patients with ARDS. About 60% of patients respond with significant improvements in gas exchange, which may persist after the patient is returned to the supine position. Response cannot be predicted, therefore a trial period is often used to identify patients who are likely to benefit. There have been no controlled studies to establish whether this technique is associated with an improved outcome, although a large (over 300 patients) Italian study is soon to report.

Extracorporeal gas exchange is performed using veno-arterial bypass and can be used in the absence of conventional forms of ventilation as the sole mechanism of gas exchange, or coupled to mechanical ventilation (in which case its principal function is to enhance carbon dioxide clearance). Neither of the two randomized trials of extracorporeal gas exchange carried out to date revealed a survival advantage. An increased understanding of the most appropriate way to ventilate patients with severe ARDS is likely to lead to this technique being used less often.

Novel ventilatory techniques

High-frequency ventilation (HFV) is a mode of mechanical ventilation that employs rapid respiratory rates (more than four times those used in conventional techniques). Tidal volumes are reduced, and are often smaller than the anatomical deadspace. The two modes of HFV most widely used are high-frequency jet ventilation (HFJV) and high-frequency oscillator ventilation (HFOV). HFJV involves the intermittent delivery of high-pressure gas jets into the tracheal tube. However, optimal gas warming and humidification are difficult to achieve, leading to problems with airway secretions and debris, which coupled with a reliance on passive expiration can lead to air trapping. HFOV involves the delivery of a continuous distending pressure to the tracheal tube, which is then modified by the movement of a vibrating loudspeaker. Humidification and warming of the fresh gas flow are easier to achieve, and an active expiratory phase leads to less gas trapping. The only randomized controlled trial of HFJV in patients with severe acute respiratory failure did not show a significant improvement in gas exchange or a survival benefit. However, recent evidence suggesting that low tidal volumes reduce ventilator-associated lung injury, and that high levels of continuous airway pressure (PEEP) improve recruitment and retention of lung units, has renewed interest in HFV (especially HFOV) as an appropriate mode of ventilation in ARDS.

Liquid ventilation involves filling the lungs with biologically inert fluids called perfluorocarbons through which oxygen and carbon dioxide readily diffuse. Ventilation occurs either through a specialized ventilator, or if the lungs are only partially filled (partial liquid ventilation) by using a conventional ventilator. The results of a phase II study of partial liquid ventilation in patients with ARDS are awaited.

Pharmacological therapies

Vasoactive agents: nitric oxide is an endogenous vasodilator, which can be given by inhalation at concentrations up to 20 parts per million. It has been shown to improve oxygenation in ALI and ARDS through effects on ventilation–perfusion matching, and to decrease pulmonary vascular resistance. Only a proportion of patients with ARDS benefit from nitric oxide and randomized controlled trials in patients with ALI and ARDS have failed to show an improvement in mortality or a reduction in the duration of mechanical ventilation. Improvements in oxygenation are transient, disappearing after 24 hours of therapy.

Prostacyclin (PGI_2) is another endogenous vasodilator that may have beneficial effects in ARDS. Like nitric oxide it is thought to redistribute pulmonary blood flow to ventilated lung units, thus improving ventilation–perfusion matching. A sequential trial of nitric oxide and PGI_2 in patients with ARDS showed the two treatments to have identical effects on oxygenation and shunt flow, but as PGI_2 is easier to monitor and deliver than nitric oxide, it is often used in its place.

Surfactant supplementation has proved effective in neonatal respiratory distress syndrome, and surfactant deficiency and dysfunction has been demonstrated in adult patients with ARDS. A number of randomized controlled trials have failed to demonstrate an effect on either mortality or length of ventilation or ICU stay. More recently, a smaller trial has shown a survival benefit following use of bovine surfactant, but further large-scale trials are necessary.

Antioxidants: oxidative stress is thought to be central to the pathogenesis of ARDS. Alveolar macrophages and recruited activated neutrophils release highly reactive oxygen species, which cause injury through interactions with proteins, lipids and DNA. It is thought that excessive production overwhelms the endogenous antioxidant systems that normally regulate the redox state within the lung. Attempts have therefore been made to introduce antioxidants to redress this balance, in particular using N-acetylcysteine, but none has shown a survival benefit nor a reproducible effect on pulmonary physiology.

Anti-inflammatory agents: ketoconazole is an imidazole used primarily for its antifungal effects, but which also has immune modulating functions that may be of benefit in preventing the development of ARDS. Although a large multi-centre trial showed that ketoconazole had no effect on mortality or duration of ventilation in patients with established ALI or ARDS, two smaller studies in critically ill surgical patients demonstrated a significant reduction in the incidence of ARDS.

Corticosteroids have been used to treat ARDS since the 1960s. However, several multicentre trials in the 1980s failed to show a beneficial role for corticosteroids, either in the prevention of ARDS in at-risk groups or in the treatment of established ARDS. Recent meta-analyses have concluded that corticosteroids do not improve, and may worsen, mortality in patients with sepsis (a high-risk group for ARDS). However, despite this evidence, there has been a recent resurgence in enthusiasm for the use of corticosteroids in the late (fibroproliferative) phase of ARDS. The only controlled data to support such therapy randomized patients on day 7 of ARDS to receive methylprednisolone or placebo for 32 days. Despite the small numbers of patients studied (24), there was an impressive reduction in ICU and hospital mortality (p = 0.002 and p = 0.03, respectively) associated with corticosteroid use. However, care must be taken to exclude continuing infection before the introduction of corticosteroids in this setting.

Prognosis and future developments

Few interventions in ALI and ARDS have been demonstrated to improve outcome. This may be, in part, because only about 5% of patients die as a result of respiratory failure, and thus therapies that improve oxygenation or other ventilatory parameters are unlikely to impact significantly on mortality. The heterogeneity of patients entered into trials as a result of the broad definitions of ALI/ARDS may preclude the demonstration of outcome benefit. New definitions of ALI/ARDS and an increasing focus on aetiological subgroups of patients are needed.

Despite this, an improvement in the outcome of ARDS in single centres has been reported in recent years, one study reporting a reduction in mortality from 66% to 34% over the years 1990 to 1997. Large-scale clinical trials (coordinated by the ARDS network in North America) are investigating the use of late steroids, the optimal settings of PEEP, and the effects of recruitment manoeuvres in ARDS. There is also increasing interest in genetic polymorphisms that may predict susceptibility to develop these conditions and thus allow early identification of high-risk patients.

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Acute Pancreatitis

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Aetiology and pathogenesis

Acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems.

Gallstones and high alcohol intake are associated with about 80% of cases. 10% of cases are idiopathic. Other causes include:

- hypertriglyceridaemia
- hypercalcaemia
- trauma
- endoscopic retrograde cholangiopancreatography (ERCP)
- drugs (e.g. sodium valproate, tetracycline, thiazides, furosemide (frusemide)).

The incidence of acute pancreatitis appears to be rising. Figures as high as 200/1,000,000 population have been quoted; a ten-fold increase since 1970. High alcohol intake accounts for much of this rise. The disease is most common in women aged 50–60 years.

The cellular mechanisms involved in the development of acute pancreatitis are unclear, however, a key step appears to be intra-acinar activation of trypsinogen. This causes activation of other enzyme systems including lipase, phospholipase A2, elastase, chymotrypsin and the kallikrein-kinin system, resulting in fat and tissue necrosis, coagulation, vascular damage, haemorrhage, oedema formation and inflammation.

Diagnosis and assessment of severity

The clinical presentation is of rapid onset of upper abdominal or back pain, vomiting, fever and tachycardia. Occasionally Grey Turner (bruising in the loin) and Cullen (bluish discoloration near the umbilicus) signs may be present. In about 80% of cases the course is mild and resolves spontaneously.

Diagnosis is most commonly made using serum amylase estimation, though there are limitations to its specificity and sensitivity. The serum lipase level is more accurate and a better marker for alcoholic pancreatitis. However, the laboratory measurement of lipase was, until recently, more complicated and it is not available in many centres.

Assessment of severity – the most common scoring systems are those of Ranson and Glasgow (or Imrie). The criteria for the Glasgow system are:

- patient aged over 55 years
- white blood cell count over 15 x 10^9/litre
- serum glucose over 10 mmol/litre
- serum urea over 16 mmol/litre
- partial pressure of oxygen in arterial blood (PaO_2) less than 60 mm Hg (8.6 kPa)
- serum calcium less than 2 mmol/litre
- serum albumin less than 32 g/litre
- serum lactate dehydrogenase over 600 units/litre
- serum aspartate transaminase over 100 units/litre.

Three positive criteria within 48 hours indicate severe disease. The disadvantage of the above systems is that data collection is not complete until 48 hours after patient admission. Evidence suggests that APACHE II (Acute Physiology and Chronic Health Evaluation) scoring at 24 hours is at least as accurate.

Biochemically, C-reactive protein (CRP) is a useful test to assess severity, but only 72 hours after disease onset. An earlier marker is urinary trypsinogen activation peptide (TAP) which is valuable at 24 hours. It has an 86% sensitivity for identifying patients who will develop severe disease.

Imaging may be necessary to diagnose the disease or its cause. Ultrasound is useful in suspected pancreatitis only for diagnosing gallstones. Contrast CT scanning is the imaging procedure of choice to diagnose and monitor acute pancreatitis.

Management

General care: the basis of management is:

- bed rest
- analgesia
- intravenous fluids
- withholding of oral intake
- support of failing organ systems
- identification of severe cases
- identification of complications.

In episodes with complications, or those predicted to be severe, the patient should be managed in a critical care area. Physiological supportive care is required because systemic inflammatory response syndrome (SIRS) or multiple organ failure may result.

Specific therapies include:

- aprotinin
- glucagon
- somatostatin
- octreotide
- gabexate mesilate (an antiprotease agent)
- fresh frozen plasma
- lexipafant (an inhibitor of platelet activating factor)
- peritoneal lavage.

None of these have any impact on the mortality rate, though there is weak evidence that lexipafant, commenced within 48 hours of disease onset, can reduce complications and organ failure.

Nutrition: in severe or prolonged cases total parenteral nutrition is commonplace. Total parenteral nutrition seldom causes release of pancreatic enzymes, except when there is a high lipid load. Enteral nutrition promotes pancreatic enzyme production unless feed is delivered into the jejunum or below. Elemental feeds seem to stimulate the pancreas even if delivered directly to the jejunum, whereas standard feeds do not.

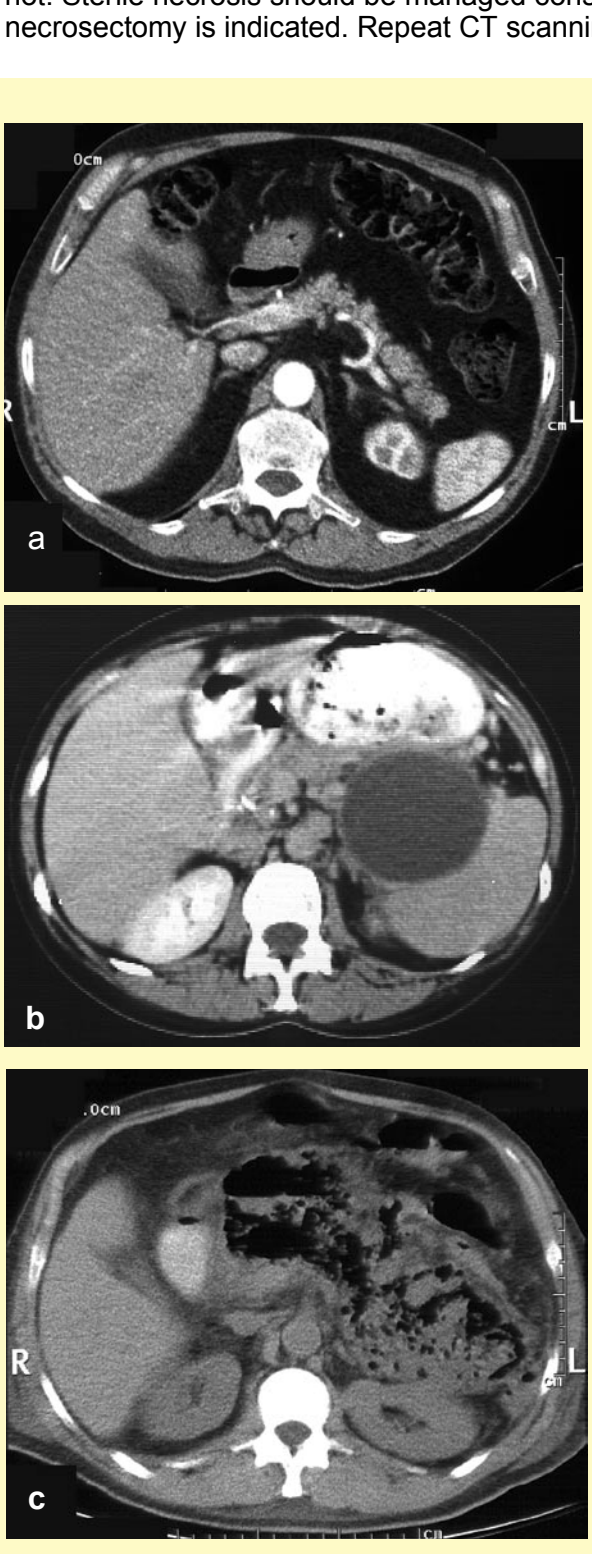
ERCP and sphincterotomy may be necessary in the case of gallstone pancreatitis even in the acute phase of the illness. It is recommended if there is evidence of obstructive jaundice, or for severe pancreatitis with gallstones that does not settle within 72 hours.

Complications: the main complications of pancreatitis are:

- infection and/or abscess formation
- pancreatic necrosis
- multiple organ failure
- hypocalcaemia
- pseudocyst formation
- chronic pancreatitis.

The mortality from infected severe pancreatitis is over 50%. There is evidence to support the use of prophylactic antibiotics in severe pancreatitis. Where there is proven infection, but a specific organism is unknown, treatment with imipenem, 500 mg 8 hourly, is suitable, because of its spectrum and pen-etration into pancreatic tissue.

CT scanning is used to recognize abscess or pseudocyst formation or necrosis (Figure 1). Even if a CT scan is not required for diagnostic purposes, it should be performed 3–10 days after the start of a severe attack. If signs of necrosis are seen, a fine needle aspirate of the pancreatic fluid is indicated to identify whether the tissue is infected or not. Sterile necrosis should be managed conservatively but, if there is infection, open necrosectomy is indicated. Repeat CT scanning is recommended every 1–2 weeks.



a Normal pancreas (CT with contrast);
b Inflamed pancreas with pseudocyst;
c Extensive pancreatic necrosis with gas trapping (emphysematous pancreatitis).

1

Acute respiratory distress syndrome and multiple organ failure are common sequelae of severe pancreatitis and require supportive care. Specifically, hypocalcaemia may result, owing to hypoalbuminaemia, abnormal parathyroid activity, or form-ation of intraperitoneal soaps with released free fatty acids. Other metabolic complications include hyperlipidaemia and hyperglycaemia.

Prognosis and further management

80% of cases are mild attacks that settle in a few days with conservative management. Mortality in such cases is less than 2%. In severe cases, mortality is about 10% overall; 20% where there is necrosis and over 50% with infected necrosis. Data from the Intensive Care National Audit and Research Council case-mix programme indicate a hospital mortality of 44% for patients with pancreatitis admitted to ICU.

Although the spectrum of severity is similar with different aetiology, there may be a difference in outcome. If pancreatitis is associated with alcohol there is often evidence of chronic fibrosis and inflammation, but with acute biliary pancreatitis the gland usually returns to histological normality. Gallstone pancreatitis is likely to recur if the stones are not treated, and it is recommended that cholecystectomy and clearance of the common bile duct is performed within 4 weeks of the attack. ◆

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Acute Renal Failure and Renal Replacement Therapy in the ICU

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Acute renal failure (ARF) is a sudden and sustained fall in the glomerular filtration rate (GFR) associated with a loss of excretory function and the accumulation of metabolic waste products and water. It leads to rising serum urea and creatinine, usually with a fall in urine output. Definitions such as a doubling of the serum creatinine or daily urine volumes of less than 400 ml have been used as diagnostic markers for ARF. The absence of a universally accepted definition for ARF makes determining its incidence difficult, but up to 10% of all patients admitted to the ICU receive some form of renal replacement therapy.

Patients with hospital-acquired ARF are more likely than those with community-acquired ARF to be admitted to ICU. In critically ill patients, renal failure is often a component of multiple organ failure, and its aetiology is likely to be multifactorial. Different incidence rates between ICUs are a reflection of their case-mix as well as different attitudes to renal replacement therapy. Renal failure in patients on the ICU is unlikely to resolve with conservative management; up to 70% of patients with ARF require renal replacement therapy. In many cases this is started within 24 hours of admission to the ICU.

The main causes of ARF (Figure 1) can be categorized as pre-renal, intrinsic or obstructive.

Mortality – in ICU, ARF alone has a mortality of 20–30% but this rises if another organ failure exists. When associated with ARF, failure of two organs leads to death in about 50% of patients, rising to over 90% if ARF accompanies three or more organ failures.

Outcome – following discharge from the ICU, about 70% of those who have developed ARF recover renal function completely. 5–10% of patients with previously normal renal function remain on long-term renal replacement therapy. The figure is much higher (about 30%) if there is a background of pre-existing renal impairment.

Causes of acute renal failure on the ICU

Pre-renal (renal hypoperfusion)
- Intravascular volume depletion (e.g. dehydration, blood loss, redistribution of fluid between body compartments)
- Severe hypotension (e.g. sepsis, drugs)
- Reduced cardiac output (e.g. pump failure post myocardial infarction, myocardial ischaemia)

Intrinsic renal failure
- Acute tubular necrosis (ATN)
  Ischaemic (the extreme end of pre-renal failure, also seen with pancreatitis, burns, sepsis)
  Exogenous toxins (e.g. radiocontrast, nephrotoxic drugs – usually occurs on a background of volume depletion, sepsis or pre-existing renal impairment)
  Endogenous toxins (e.g. rhabdomyolysis, massive haemolysis, tumour lysis syndrome)
- Hepatorenal syndrome
- Acute glomerulonephritis/interstitial nephritis (with multi-system involvement)
- Increased intra-abdominal pressure
- Vascular (e.g. malignant hypertension, atheroembolic conditions)

Obstructive renal failure
- Unusual to be main cause of acute renal failure on the ICU

Renal replacement therapies

In an ICU, renal replacement therapies can be categorized as continuous or intermittent. In the UK, continuous therapies predominate (Figure 2). There are few randomized controlled trials comparing intermittent with continuous therapies, but continuous renal replacement therapy (CRRT) is associated with reduced mortality. CRRT usually involves the removal and return of blood through a single cannula placed in a large vein (veno-venous therapy); arteriovenous therapies are seldom used. CRRT causes less haemodynamic instability, because fluid removal is slower and there is time for fluid to re-equilibrate between body compartments.

Continuous renal replacement therapies used on ICUs

Mode of therapy	Principal method of solute clearance
Continuous veno-venous haemofiltration (CVVH)	Convection
Continuous veno-venous haemodiafiltration (CVVHDF)	Convection and diffusion
Continuous veno-venous haemodialysis (CVVHD)	Diffusion
Slow continuous ultra-filtration (SCUF)	Fluid removal by ultrafiltration
High flux dialysis (HFD)	Convection and diffusion

Principles of CRRT

In CRRT, solutes are removed from blood by diffusion or convection. Different processes remove different sized molecules (Figure 3).

Diffusion is the movement of solutes down a concentration gradient across a semipermeable membrane. This is the main physical process occurring during haemodialysis. Solutes (e.g. urea, creatinine) cross the dialysis membrane from the blood to the dialysis fluid compartment. Fluid in the dialysis compartment moves in a counter-current direction, thereby maintaining a concentration gradient. It is also possible for solutes (e.g. bi-carbonate) to move in the opposite direction (e.g. from dialysate to blood).

Convection – if a pressure gradient is set up across the dialysis filter, water is pushed across the membrane and carries dissolved solutes with it; this is known as the solvent drag. The movement of fluid across the membrane as a result of this transmembrane pressure is ultrafiltration, and the fluid produced is ultra-filtrate. The process by which solutes move across the membrane is convection.

Size of molecules cleared by continuous renal replacement therapies (CRRT)

Type of molecule	Size	Example	Mode of removal
Small	< 500 Da	Urea, creatinine, amino acids	Convection, diffusion
Middle	500–5000 Da	Vitamin B_{12}, inulin, vancomycin	Convection better than diffusion
Low molecular weight proteins	5000–50,000 Da	β_2 microglobulin, cytokines, complement	Convection or absorption (on to filter)
Large proteins	> 50,000 Da	Albumin	Only minimal removal by standard CRRT

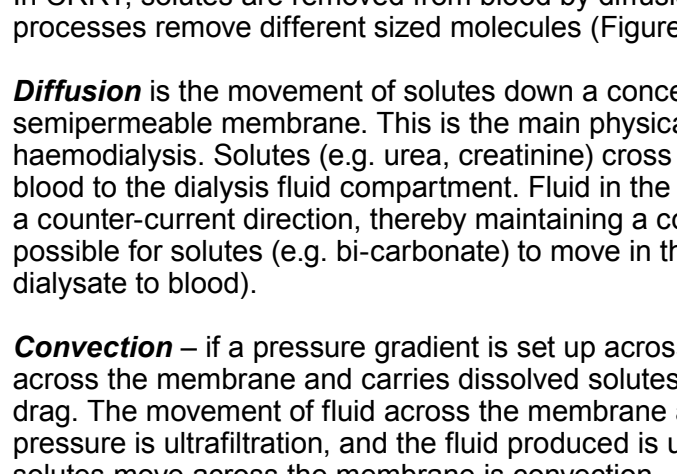
Da = Daltons

Types of CRRT

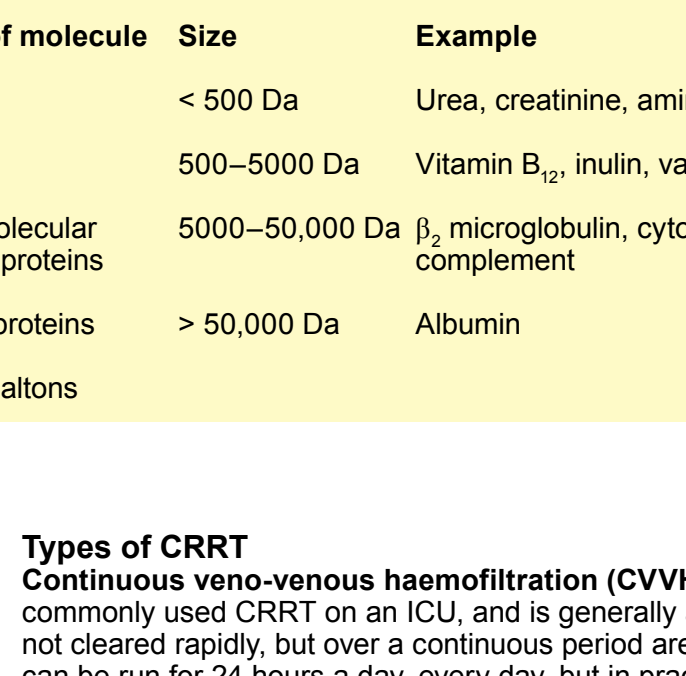
Continuous veno-venous haemofiltration (CVVH) (Figures 4a and 5) is the most commonly used CRRT on an ICU, and is generally a continuous process. Solutes are not cleared rapidly, but over a continuous period are cleared efficiently. The process can be run for 24 hours a day, every day, but in practice it is often run for 24–72 hours at a time. 'Down time' occurs to change the filter (either electively or because the filter has clotted) or for procedures to take place. It is stopped when there is evidence of a return of renal function.

Types of continuous renal replacement therapies

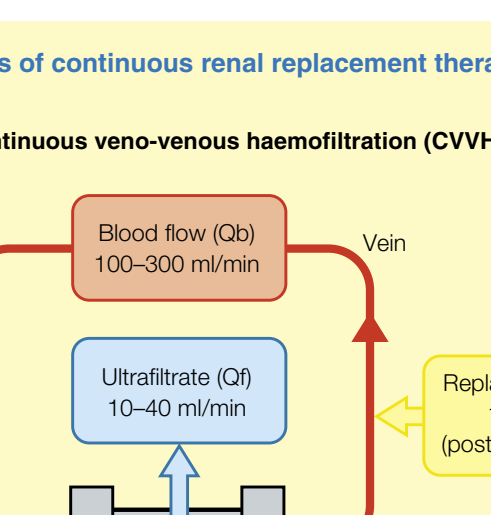
a Continuous veno-venous haemofiltration (CVVH)

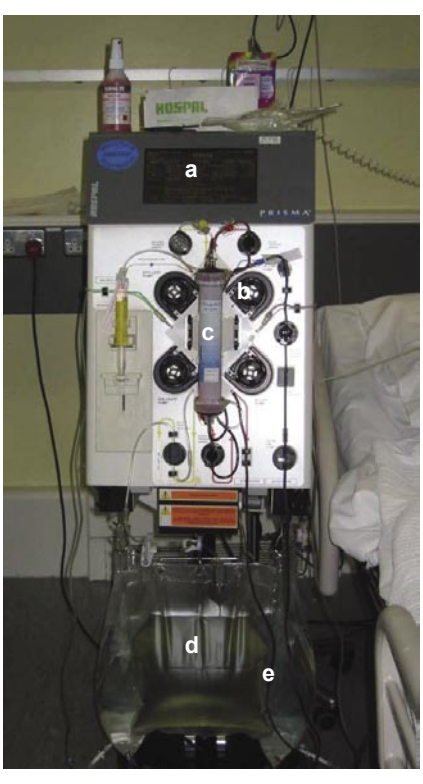


b Continuous veno-venous haemodiafiltration (CVVHD)



c Slow continuous ultrafiltration (SCUF)





5 The Prisma (Hospal) continuous renal replacement therapy machine. **a** Information screen; **b** four pumps (dialysate, blood, replacement fluid, effluent); **c** filter; **d** effluent bag; **e** replacement fluid.

Blood is usually pumped through the dialysis circuit at the highest achievable flow rate (100–200 ml/minute); this depends on the quality of vascular access and the patient's haemodynamic state. A specialized, sterile fluid (replacement fluid) replaces the large volume of ultrafiltrate removed. There is no consensus on how long or how fast haemofiltration should be undertaken, but an ultrafiltration rate of at least 35 ml/kg/hour has been associated with improved survival compared with 20 ml/kg/hour. In practice about 2 litres of ultrafiltrate are removed each hour. Either all or part of the ultrafiltrate is replaced depending on the desired overall fluid balance.

Continuous veno-venous haemodiafiltration (CVVHD) (Figure 4b) is similar to CVVH but combines diffusion and convection. Blood and dialysate fluid are circulated in a counter-current fashion. As with CVVH, a transmembrane pressure is applied, producing large volumes of ultrafiltrate. Replacement fluid is reinfused at a rate dependent on the volume of fluid to be removed.

Haemodialysis almost exclusively uses diffusion to remove solutes from plasma but can be combined with ultrafiltration to remove fluid. As with CVVHD, blood and dialysis fluid are circulated in a counter-current fashion, but no replacement fluid is reinfused. This treatment is generally performed intermittently for patients with end-stage renal failure needing chronic dialysis. It can be performed continuously on the ICU, but its use is not widespread.

Ultrafiltration can be applied alone as a slow and continuous therapy, termed slow continuous ultrafiltration (SCUF) (Figure 4c). Ultrafiltrate is formed at a rate of less than 300 ml/hour and replacement fluid is not infused. It can be useful when there is volume overload, but no solute accumulation (e.g. congestive cardiac failure).

Continuous high flux dialysis uses a highly permeable dialysis membrane with blood and dialysate circulating in a counter-current fashion. The production of ultrafiltrate is controlled by pressure, and is reinfused by backfiltration in the blood system, therefore a separate replacement fluid is not needed. This process is seldom used on the ICU.

Indications for starting renal replacement therapy

It is better to start renal replacement therapy early rather than wait for complications of ARF to develop (Figure 6). Fluid balance is a major stimulus for starting CRRT in critically ill patients because large volumes of daily intravenous fluids are required to maintain intravascular volume, and for drug delivery and nutrition.

Indications for starting renal replacement therapy

Indication	Comments
Anuria or oliguria	Urine volumes < 200 ml/12 hours
Hyperkalaemia	Serum potassium persistently > 6.5 mmol/litre
Severe acidaemia	pH < 7.1
Serum urea > 30 mmol/litre or creatinine > 300 μmol/litre	Values are not absolute, only a guide
Refractory fluid overload	Especially if compromising lung function
Uraemic complications	Encephalopathy, pericarditis, neuropathy or myopathy
Temperature control	Hyper- or hypothermia
Drug overdose	See Figure 7
Sepsis	

Convection removes low molecular weight proteins of 5000–50,000 Da. Many of the septic mediators (e.g. cytokines, complement) lie within this group. These mediators are absorbed onto the filter membrane and so removed. Interest surrounds the use of high volume haemofiltration to remove these inflammatory mediators to improve outcome from severe sepsis. High volume filtration is defined as ultrafiltration of over 2 litres/hour, and there is evidence that filtrate volumes up to 6 litres/hour are associated with a significantly lower mortality in septic patients.

Vascular access

Most renal replacement therapy is veno-venous in nature, therefore vascular access is usually via a double-lumen vascular catheter placed in a central vein. Blood is withdrawn from the proximal lumen ('arterial side') and returned through the distal lumen ('venous side').

The site of insertion is determined clinically, because critically ill patients often have other central venous catheters in place. The subclavian route is usually avoided in patients who may need an arteriovenous fistula for long-term haemodialysis, because the incidence of subclavian vein stenosis following cannulation is high.

Blood flow through the catheter should be good. Poor access should not be treated by reducing blood flow rates, because this leads to ineffective solute clearance.

Dialysis filters

As blood comes into contact with the filter (membrane) surface, complement and leucocytes can become activated, triggering the coagulation cascade and inflammatory pathways. The degree of activation is variable with some filters having more 'membrane biocompatibility' than others (more biocompatibility means less activation). It is suggested that biocompatible membranes are associated with an improved outcome from ARF, but the evidence is not robust.

Filter membranes are either cellulose-based or synthetic. Cellulose-based filters (e.g. cuprophane, cellulose acetate) are very thin and strongly hydrophilic. They are generally low flux membranes and are poor at removing middle molecules. Synthetic filters (e.g. polysulfone, polyamide, polyacrylonitrile) are high flux membranes and are generally more biocompatible than cellulose membranes. The flux of a membrane refers to its hydraulic permeability and how much convective transport can take place across it. Most filters used for CRRT are synthetic, high flux membranes with a surface area of 0.6–1.2 m^2.

Replacement fluid

A sterile replacement fluid replaces the ultrafiltrate removed by haemofiltration and haemodiafiltration. The fluid is infused either before the filter (pre-dilution) or into blood leaving the filter (post-dilution). Pre-dilution lowers the haematocrit of blood passing through the filter thus reducing anticoagulation requirements, but leads to a 10% reduction in solute clearance.

The main buffers in replacement fluid are lactate or bicarbonate. Many critically ill patients already have a lactic acidosis or are unable to handle lactate appropriately. In these patients, a paradoxical worsening of the acid–base balance may be seen with a lactate buffer.

The concentration of sodium, potassium and glucose in the replacement fluid can be varied depending on the clinical need. However, the fluid does not contain phosphate or amino acids and these may have to be supplemented.

Anticoagulation during renal replacement therapy

During CRRT, blood is continually in contact with the circuit tubing and the filter, with consequent stimulation of the coagulation cascade. Recurrent clotting of the circuit renders treatment inadequate and is a drain on nursing and financial resources.

Often, CRRT can be performed in critically ill patients without the use of anticoagulants because they often have deranged clotting, thrombocytopenia or both. Anticoagulation-free CRRT is made easier with good venous access, good blood flow rates and pre-dilution.

If anticoagulation is required, unfractionated heparin at doses that do not alter the activated partial thromboplastin time (e.g. 5–10 IU/kg/hour) can be used. Full systemic heparinization is seldom needed. Other options include low-molecular-weight heparin, recombinant hirudin, regional heparinization and the use of prostacyclin. The latter inhibits platelet aggregation but has no effect on coagulation parameters. Its side-effects include vasodilatation, but this is seldom a contraindication, even in patients with an unstable cardiovascular system.

Pharmacokinetics on CRRT

The high flux haemofilter membranes used in CRRT are per-meable to most non-protein-bound drugs (Figure 7). While receiving CRRT, the doses of drugs should be given on the assumption that the GFR is 10–50 ml/minute. When a patient with ARF is not receiving renal replacement therapy, the GFR should be assumed to be less than 10 ml/minute. With pre-dilution, the concentration of the drug entering the membrane is reduced by dilution. During CRRT, the highest drug clearances occur with drugs that are not protein-bound or when post-dilution is used. ◆

Pharmacokinetics

Drugs removed on haemodialysis
- Salicylates
- Methanol
- Barbiturates
- Lithium
- Aminoglycosides
- Cephalosporins

Drugs not removed on haemodialysis
- Digoxin
- Tricyclic antidepressants
- Phenytoin
- Benzodiazepines
- β-blockers
- Oral hypoglycaemic agents

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www.adqi.net/Acute Dialysis Quality Initiative

Antibiotic Prescribing in the ICU

Richard Brindle

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Choosing an appropriate antibiotic

Patients in the ICU displaying signs of sepsis belong to one of the following categories:

- infected with a known organism from an identified site
- infected with a known organism from an unidentified site
- infected, but no causal agent has been identified
- uninfected.

Occasionally the clinical signs of an infection suggest the causal organism and the appropriate antibiotic. However, the choice of antibiotic is often guided by the results of microbiological investigation. Ideally, specimens for culture should be taken before antibiotics are given. Appropriate specimens include:

- blood cultures (preferably from different sites)
- urine
- respiratory secretions (non-bronchoscopic lavage samples are preferred)
- wound swabs or aspirates from skin lesions
- drain, fistula or other fluids or pus
- other relevant specimens.

Cultures should be repeated every few days, even if the patient is improving or stable. This allows empirical therapy to be rationalized and provides information about patterns of resistance.

If the organism is known, a decision can be made about the most suitable antibiotic, the most appropriate dose and dosing schedule, the ideal duration of therapy and the need for adjunctive therapy. If the source of infection is unknown, the site can often be suggested on the basis of an organism isolated from blood (Figure 1).

Correlation between organism and site of infection

Isolate from blood	Likely sites	Action
Staphylococcus aureus	Infected intravenous line site Deep sepsis (abscesses) Endocarditis	Remove source, if possible, and give at least 14 days' therapy All *S. aureus* infections need treating
Staphylococcus epidermidis (coagulase-negative *Staphylococcus*)	Contaminant Colonized lines (venous and arterial) Infected prosthesis	Remove source Treating colonized tunnelled lines may be successful
Enterococcus spp.	Colonized lines Intra-abdominal sepsis Endocarditis	Remove source Drain collection Treat, if source cannot be removed
Coliforms	Urinary tract Gall bladder Intra-abdominal sepsis Lines Chest	Treat Drain any collections Remove lines
Anaerobes	Intra-abdominal sepsis Necrotizing cutaneous infections	Drain collection Debridement Treat
Pseudomonas aeruginosa urinary catheter)	Colonized lines Urinary tract Chest	Remove source if possible (line or Treat
Yeasts	Colonized lines Intra-abdominal sepsis Urinary tract	Remove source Drain collection and give at least 14 days' therapy

Antibiotic combinations

Combinations of antibiotics are recommended when:

- the cause of the infection is unknown
- multiple bacteria are involved
- resistance develops easily on monotherapy
- the outcome is known to be improved with combinations of antibiotics.

The most common ICU situation in which combination therapy is appropriate is in the treatment of ventilator-associated pneumonia (VAP). This is characterized by the onset of an inflammatory response, radiographic changes, purulent secretions and hypoxaemia after a patient has received positive-pressure ventilation for a few days. The organisms causing VAP are varied and depend on the patient's previous pulmonary history and previous use of antibiotics. Late onset VAP is generally caused by *Pseudomonas aeruginosa* or *Staphylococcus aureus*. Most UK hospitals have high levels of methicillin-resistant *S. aureus* (MRSA), therefore a high proportion of *S. aureus* VAP is caused by MRSA. Consequently, when empirical therapy for VAP begins it should include an agent directed against both *Ps. aeruginosa* and MRSA.

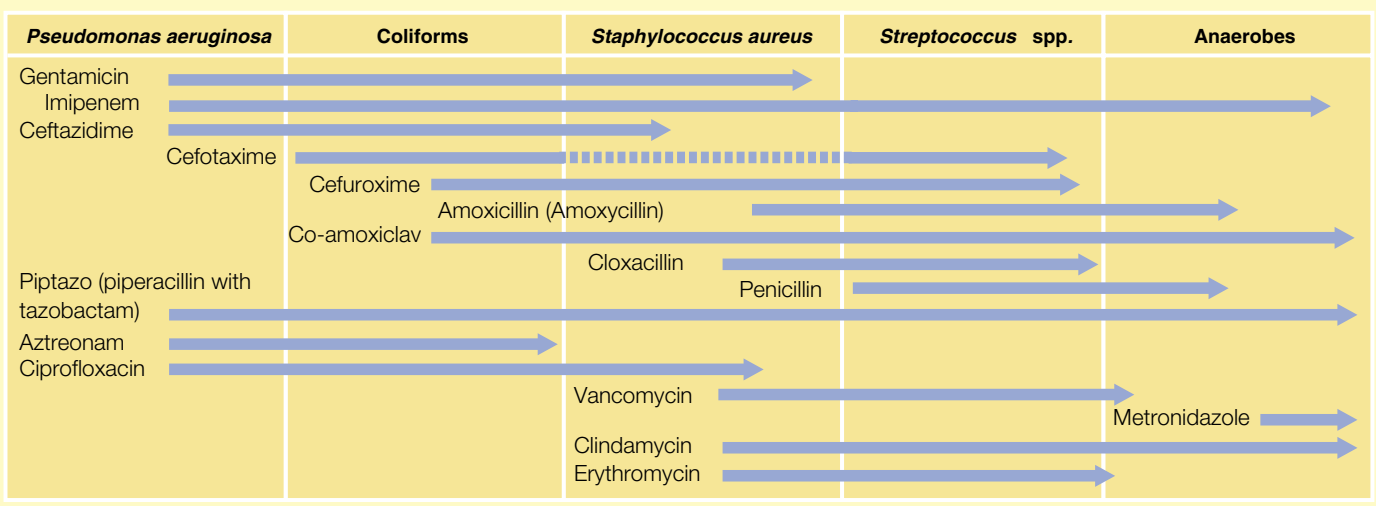
While the development of vancomycin resistance by MRSA with monotherapy is rare, the development of resistance to anti-pseudomonal antibiotics while taking anti-pseudomonal monotherapy is common. One way of reducing resistance developing in *Ps. aeruginosa* is to use two anti-pseudomonal antibiotics, of different classes.

Combinations of antibiotics are also of value when resistance is high or unpredictable and they ensure that at least one anti-biotic will be effective. Antibiotic combinations can also be more effective than monotherapy, for example an aminoglycoside and acylureidopenicillin (azlocillin or piperacillin) in the treatment of *Ps. aeruginosa* infections. However, the risk of toxicity increases with the number of antibiotics used and, if adequate levels of both antibiotics are not maintained, resistance to one agent can develop. This is commonly seen with rifampicin and *S. aureus* infections.

Broad-spectrum and narrow-spectrum antibiotics

Most antibiotics used as empirical therapy in the ICU have a broad antibacterial spectrum which is useful if the cause of sepsis is uncertain. However, broad-spectrum agents are generally more expensive, have significant effects on the patient's normal flora and are more likely to lead to *Clostridium difficile*-associated diarrhoea, fungal overgrowth and colonization with resistant organisms. Therefore, it is sensible to change to a narrow-spectrum agent as soon as possible, though whether this reverses the effect of an initial broad-spectrum agent is uncertain. Figure 2 illustrates the spectrum of activity of commonly prescribed antibiotics.

Spectrum of activity of some antibiotics



Only vancomycin or teicoplanin are suitable for empirical treatment of *Staphylococcus epidermidis* (coagulase-negative *Staphylococcus*) and methicillin-resistant *Staphylococcus aureus* (MRSA). Bacteria such as meningococci, *Haemophilus*, *Listeria*, enterococci and the 'atypicals' do not fit neatly into the scheme.

Selective decontamination of the digestive tract

There is strong evidence that by reducing the bacterial load on a patient on admission to the ICU, infection can be reduced. This can be accomplished using broad-spectrum antibiotics and antifungals and seems to be particularly effective following trauma. The regimen should include antibiotics active against resistant enterobacteria, *Ps. aeruginosa* and MRSA. However, there is a reluctance to use the limited armoury of antibiotics as prophylactic agents, despite the lack of evidence that selective decontamination has increased superinfection with resistant organisms.

Early and late infections

The acquisition by patients of ICU flora is a function of their length of stay in the ICU and, more importantly, their previous antibiotic treatment. Many patients admitted to ICU will have received antibiotics and most ICU patients receive antibiotics at some stage during their stay, and will also have been in hospital for some time before admission to the ICU. For example, respiratory specimens from a patient admitted directly to the ICU with a community acquired pneumonia may contain *Streptococcus pneumoniae*. Treatment with a narrow-spectrum antibiotic is characterized by initial clinical improvement, however, if assisted ventilation continues beyond a few days, this flora is commonly replaced by ICU flora and the development of VAP.

Sites of infection

Line-associated sepsis and bacteraemia is common in the ICU. Blood or intraluminal cultures identify the organism. Catheters impregnated with antibiotics or antiseptic reduce the infection rate, but are more expensive than standard ones. If the catheter entry site is infected, or cultures from the line are positive, the line should be removed. *S. aureus* or yeast blood infection associated with a line require therapy and are absolute indications for line removal. Bacteraemia associated with other organisms generally resolves following line removal.

VAP therapy may need to be continued for as long as the patient is mechanically ventilated. Empirical therapy is discussed above.

Intra-abdominal sepsis – infection seldom resolves without drainage and corrective surgery. Antibiotics such as co-amoxiclav or the combination of cefuroxime and metronidazole are generally adequate in community-acquired infections with early surgery. If the patient has been in hospital and taking antibiotics for more than a few days, a broader spectrum antibiotic (e.g. piptazo, imipenem) is recommended.

Urinary tract – though a high proportion of ICU patients are catheterized, and the bladder urine may become colonized, the urinary tract is seldom the source of clinical infection, if catheter patency is maintained. Candiduria is relatively common but may be a reflection of colonization or a sign of candidaemia.

Diarrhoea

The widespread use of broad-spectrum antibiotics is a significant cause of diarrhoea. *C. difficile*-associated diarrhoea and colitis need early recognition and treatment, because infection may require colectomy. The current endemic strains of *C. difficile* are resistant to most antibiotics and this allows their preferential survival. Withdrawal of antibiotics may allow resolution but, if diarrhoea persists, it should be treated with metronidazole (oral or nasogastric is preferred). If the diarrhoea does not resolve, or has developed while taking metronidazole, oral vancomycin should be administered.

Dose

It is important to use appropriate doses because too little antibiotic may not have a therapeutic effect and allows resistant organisms to persist; too much antibiotic may cause toxicity. Dose needs to be individualized and knowledge of the mode of excretion is vital. In general, the highest dose that is safe to use should be administered.

Duration

The duration of antibiotic therapy depends on the organism isolated, its source and the clinical response. Studies of relapse and complications suggest a minimum of 2 weeks' therapy for *S. aureus* and *Candida* spp. blood infections, but there are few data on minimum duration of therapy for other ICU-acquired infections. The duration of therapy for VAP depends on the clinical and laboratory response. Antibiotics should be reviewed after 5 days' therapy. Some patients, particularly with MRSA pneumonia, may require repeated courses. If there is a poor clinical response, the antibiotics should be stopped for 12 hours and cultures taken; a new empirical treatment can then be commenced. ◆

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Assessment and Stabilization of the Critically Ill Patient Outside the ICU

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ICU medical staff are often required to assess and stabilize patients referred for ICU admission. They may also be asked to assess patients for the following reasons:

- difficult venous access
- analgesic techniques
- fluid balance
- tracheostomy care
- inter-hospital transfer
- intra-hospital transfer to a high dependency unit or the operating theatre
- as a member of the cardiac arrest or medical emergency team.

The assessment and stabilization of all such patients follows similar lines, but this contribution focuses on the patient who is referred and accepted for ICU admission.

Referral process

ICU referrals are traditionally made by doctors; however, they are increasingly being made by nurses and physiotherapists acting on guidelines (e.g. physiological abnormalities) previously agreed with ICUs. The ICU staff require a range of referral details (Figure 1). If the patient has a potentially life-threatening illness, the caller should be given simple instructions regarding therapy to be undertaken before the ICU team arrives. Before leaving to assess the patient, the ICU doctor should share the collated data with the senior ICU nurse and check whether an ICU bed is available.

Information required during referral to the ICU

- Patient's name
- Patient's gender
- Patient's age
- Current location of patient
- Date of referral
- Time of referral
- Name, grade and contact details of person making the referral
- Whether the referral has been discussed with the consultant responsible for the patient's care
- Whether the referral has been discussed with the patient or the patient's relatives, and their wishes
- The patient's diagnosis and prognosis
- Relevant past medical history
- Relevant social history, including quality of life
- Patient's current condition, especially vital signs, urine output
- Patient's current therapy, especially fractional inspired oxygen concentration, fluid therapy, drugs
- Patient's current monitoring
- Presence of intravenous lines and central venous access
- Presence of a nasogastric tube, wound drains or thoracocentesis tubes
- Results of recent laboratory investigations
- Patient's resuscitation status
- Any agreed limitation of therapy

1

ICU retrieval team

In some ICUs, a dedicated retrieval nurse attends the patient with the ICU doctor, in order to provide expert assistance. He/she can also support the patient during stabilization and transfer, and provide an initial contact for the patient's family. The ICU team usually takes the necessary stabilization drugs and equipment to the patient's bedside, possibly attached to the patient's stretcher.

Assessment and stabilization

Traditional history-taking and examination is often inappropriate when attending critically ill patients, where life-saving measures must often precede diagnosis. Initially, assessment and stabilization occur together, focusing on the rapid detection and simultaneous treatment of potentially life-threatening emergencies. Simple questions to the patient can establish whether the patient has a patent airway, is breathing and perfusing his/her brain. Patients who can speak only in short sentences, or with one or two words at a time, are usually in extreme respiratory distress and at risk of sudden respiratory arrest. As stabilization proceeds, important aspects of the patient's medical history can be obtained from ward staff, the patient's case notes and charts (e.g. temperature, pulse, respiration, blood pressure, neurological observation chart, fluid balance, drug prescription chart) or the patient's family. Co-morbid conditions may have a significant impact on the response to critical illness.

Throughout the period of assessment and stabilization, the ICU team should observe good hygiene and infection control measures. In order that patients are examined properly, full exposure may be necessary. This should be done in a way that respects the dignity of the patient and prevents heat loss.

Airway

Assessment of airway patency involves the steps given in Figure 2. If the airway is obstructed, immediate clearance is mandatory before assessing breathing. Simple adjuncts (e.g. oropharyngeal or nasopharyngeal airway) suffice initially, but tracheal intubation under general anaesthesia is usually required in the critically ill. Anaesthetic agents invariably reduce cardiac output and vascular resistance, therefore a 200–500 ml fluid bolus should be given before induction. Occasionally, vasoactive drug infusions (e.g. adrenaline (epinephrine), noradrenaline (norepinephrine), dobutamine) are also required. In extremely rare circumstances, a surgical airway is required. In all patients, a chest radiograph should be undertaken as soon as possible to confirm correct tracheal or tracheostomy tube placement.

Assessing airway patency

Look for

- Foreign bodies, secretions or blood within the mouth
- Obstruction of the pharynx by the tongue
- Use of the accessory muscles of respiration
- Chest expansion
- Paradoxical breathing

Listen for

- Abnormal upper airway sounds (e.g. stridor, gurgling, snoring); if obstruction is complete, breath sounds will be absent

Feel for

- Expired air

2

Breathing

Breathing is assessed as described in Figure 3. Unilateral chest movement suggests underlying unilateral disease (e.g. pneumothorax, pneumonia, effusion). A high (> 20), or rapidly rising, respiratory rate usually indicates severe illness or impending deterioration. Small pupils may reflect excessive opiate administration.

Respiratory interventions are often based on clinical signs rather than arterial blood gas analysis. All critically ill patients must receive oxygen via a face mask with a reservoir bag or bag–valve–mask manual resuscitator, sufficient to maintain a minimum peripheral saturation of haemoglobin by oxygen of 90% (arterial oxygen tension = 8 kPa). Inadequate minute volume requires assisted ventilation, possibly with intubation. Positive end-expiratory pressure may be required. Pneumothoraces or large pleural fluid collection should be treated using tube thoracocentesis. Wheezing should be treated with inhaled bronchodilators. If the patient is in pain, initiation of an appropriate analgesic regimen may improve ventilation.

Assessing breathing

Look for or observe

- Cyanosis
- Chest deformity
- Respiratory rate, pattern and depth
- Equality of chest expansion
- Fractional inspired oxygen concentration
- Peripheral saturation of haemoglobin by oxygen
- Jugular venous pressure
- Abdominal distension

Listen for

- Wheeze, crackles, bronchial breathing
- Bilateral breath sounds

Feel for or palpate

- The position of the trachea
- Chest wall (for surgical emphysema or crepitus)
- Depth and equality of movement on each side of the chest

Percuss

- To elicit dullness or hyper-resonance

3

Circulation

Lung or pleural pathologies (e.g. tension pneumothorax) that can compromise the circulation, should have been treated during the respiratory system assessment. Figure 4 describes how to assess circulation. In shock, the blood pressure may be normal, because compensatory mechanisms increase peripheral resistance as cardiac output falls. A low diastolic blood pressure suggests vasodilatation (as in sepsis). A narrowed pulse pressure suggests vasoconstriction (cardiogenic shock or hypovolaemia). A thready pulse suggests poor cardiac output; a bounding pulse may indicate sepsis. The presence of a carotid or radial pulse implies systolic blood pressures are greater than 70 and 90 mm Hg, respectively.

The nature of cardiovascular resuscitation is determined by the cause, but should be directed at replacing fluid, controlling haemorrhage and restoring tissue perfusion. Massive or continuing haemorrhage and cardiac tamponade (diagnosed by hypotension, raised jugular venous pressure, muffled heart sounds, cardiomegaly on chest radiography, or electromechanical dissociation) are life-threatening conditions and must be treated urgently. Massive or continuing haemorrhage requires transfusion and may require urgent resuscitative surgery. Cardiac tamponade requires pericardiocentesis or pericardiotomy. All critically ill patients require at least one large (16 G) cannula, preferably two, placed in large veins.

Hypovolaemia contributes to circulatory dysfunction in almost all medical and surgical emergencies. Fluid challenges of warmed crystalloid should be given over 5–10 minutes to all patients, as follows:

- 10 ml/kg in normotensive patients
- 20 ml/kg in hypotensive patients
- 5 ml/kg in patients with known cardiac failure, in whom closer monitoring should be initiated (listen for crepitations after each bolus, consider a line).

The goal of therapy is to improve tissue perfusion. Although blood flow is more important than blood pressure, a minimum mean blood pressure of 70 mm Hg should be sought (higher in hypertensive patients). If perfusion does not respond to fluids alone (i.e. central venous pressure rises after fluid boluses without evidence of improved cardiac output), vasoactive drugs such as dobutamine, > 5 μg/kg/minute, adrenaline (epinephrine),> 0.05 μg/kg/minute, or noradrenaline (norepinephrine), > 0.05 μg/kg/minute, should be commenced.

Reassessment of circulatory status is essential. If there is no improvement, the fluid challenge can be repeated. In a few patients, fluid administration leads to cardiac failure. If this occurs, fluid administration should be stopped and vasoactive drugs (see above) commenced.

Disability
Rapid assessment of a patient's neurological status involves:
- examining the pupils (size, equality, reaction to light)
- the 'AVPU' system (A, alert; V, responds to vocal stimuli;P, responds to painful stimuli; U, unresponsive).

Common causes of unconsciousness include profound hypoxaemia, hypercapnia, cerebral hypoperfusion, hypoglycaemia or recent administration of sedatives, analgesics or anaesthetic drugs. Reversible causes should be treated immediately. Spontaneously breathing, unconscious patients are at risk of airway obstruction and aspiration of secretions, vomit or blood. Consequently, unconscious patients are better nursed in the lateral recovery position until intubated.

Assessing circulation

Look for or observe
- Conscious level
- Capillary refill (normally < 2 seconds)
- Colour and temperature of digits (cyanosed, pale, cold and clammy in shock)
- Venous filling (including jugular venous pressure)
- Urine output
- Nasogastric, stoma or drain output
- Evidence of concealed or overt haemorrhage

Listen for
- Heart sounds
- Blood pressure (systolic, mean, diastolic); note patient's normal values

Feel for or palpate
- Presence, rate, quality, regularity and equality of peripheral and central pulses

End of the initial assessment and stabilization period
At the end of the initial assessment, the patient should be showing signs of improvement. The following minimum monitoring devices should already be attached or inserted:
- pulse oximeter
- capnograph (if intubated)
- ECG
- blood pressure measurement (usually invasive).

Other devices that may be used include: urinary catheter, central venous catheter, nasogastric tube, and pulmonary artery catheter. Before moving the patient from the ward, the patient's oxygen saturation in arterial blood, heart rate, blood pressure, central venous pressure, end-tidal carbon dioxide tension, ventilator settings and performance should be noted. Actions taken during stabilization should be documented in the patient's notes. All invasive devices should be firmly secured to the patient. The patient should be sedated to an appropriate level for transfer; muscle relaxation may be required. Finally, the ICU should be notified of the impending arrival of the patient.

Brainstem Death

Suzie J Tanser
Gary B Smith

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Death has traditionally been diagnosed using the triad of Bichat – 'the failure of the body as an integrated system, associated with the irreversible loss of circulation, respiration and innervation'. However, the development of techniques to maintain respiration and circulation artificially, and the fact that dead patients may look alive, have a heart beat and feel warm, has led to conceptual and practical problems with the diagnosis of death.

The brainstem comprises the midbrain, pons and medulla oblongata. It contains the respiratory and cardiovascular centres and integrated sensory and motor functions. It is necessary for spontaneous respiration, consciousness and cortical activation. Death of the brainstem is equivalent to death of the individual, even if heart, lung and spinal cord function persist. Eventually all organs fail and asystole occurs. There has never been a documented recovery following properly conducted brain death testing that indicated brainstem death. It is agreed that permanent functional death of the brainstem constitutes brain death and, once this has occurred, further artificial support is fruitless and should be withdrawn. It is good medical practice to recognize when brain death has occurred and to act accordingly, sparing the relatives from futile hope and freeing valuable intensive care resources.

Incidence and aetiology

Up to 10–15% of deaths in UK ICUs are brainstem deaths. In adults, the most common primary diagnoses are trauma and intracranial haemorrhage; in children, they are trauma and the anoxic encephalopathies (e.g. drowning). Other causes include intracranial malignancy, intracranial abscesses, hydrocephalus and meningitis. Cardiac arrest may lead to brainstem death, but more often, leads to a persistent vegetative state.

Diagnosis of brainstem death

The UK code for the diagnosis of brainstem death was defined by the Conference of Medical Royal Colleges in 1976 and has been updated subsequently. The three stages of diagnosis are preconditions, exclusions and clinical testing.

Preconditions

- The patient is in an unresponsive coma.
- The patient's condition is due to irreversible brain damage of known aetiology.

Exclusions

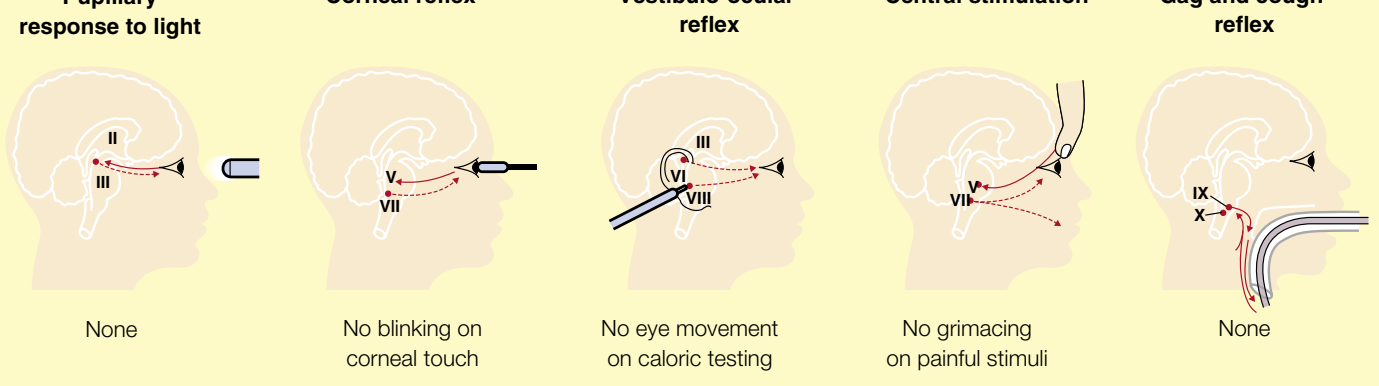
All the following reversible causes must be excluded:

- drugs (e.g. narcotics, hypnotic, tranquillizers, muscle relaxants)
- primary hypothermia (core temperature must be above 35°C)
- circulatory (including recent circulatory arrest)
- metabolic (e.g. hyponatraemia, hypoglycaemia)
- endocrine (e.g. hypothyroid state).

Clinical tests

- Clinical tests are performed by at least two doctors (one a consultant, the other at least 5 years' post registration) who are unconnected with the family and, if organ donation is an option, the transplant team.
- These tests are repeated twice by both doctors either indep-endently or together. The time interval is not specified.
- The tests involve reflexes involving the brainstem (Figure 1) and an apnoea test. There should be no pupillary response to light, no corneal reflex, no vestibulo-ocular reflex, no motor response to central stimulation, no gag and cough reflex and no spontaneous breathing.

Clinical tests for brainstem death



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Pupillary response to light – the pupils do not respond directly or consensually to sharp changes in light intensity. This tests cranial nerves II (afferent) and III (efferent).

Corneal reflex – there is no response to direct stimulation of the cornea. This tests cranial nerves V (afferent) and VII (efferent). Care should be taken to avoid damage to the cornea. Gentle pressure using a cotton bud is the preferred method.

Vestibulo-ocular reflex – there are no eye movements following slow injection of 20 ml of ice-cold water over 1 minute into each external auditory meatus in turn. A normal response is deviation towards the stimulus. Before this a visual inspection of each tympanic membrane must be made to ensure clear access. Local injury or disease does not invalidate the diagnosis. This tests cranial nerves VIII (afferent) and III, IV and VI (efferent).

Motor response to central stimulation

- No motor response within the cranial nerve distribution to sustained painful stimuli to limbs or the supraorbital notch. This tests cranial nerves V (afferent) and VII (efferent).
- Spinal reflexes may occur after stimulation of the trunk or extremities. Occasionally these can be dramatic, such as back arching or extensor posturing (Lazarus' sign). These movements may be upsetting but since they originate below brainstem level, they do not rule out the diagnosis of brainstem death.
- No reaction should be seen following painful stimulation in the cranial nerve distribution.

Gag and cough reflex – there is no contraction of the soft palate when stimulated or response to bronchial stimulation. This tests cranial nerves IX and X.

Spontaneous breathing – this tests the ability of the patient's brainstem to initiate spontaneous respiration. Before testing, the following should occur:

- preoxygenation of the patient with 100% oxygen for 10 minutes
- the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) should be allowed to rise to 5 kPa (40 mm Hg) or above.

To test the function of the respiratory centre:

- the patient is disconnected from the ventilator
- oxygen at 6–10 litres/minute is insufflated into the trachea using a catheter (to maintain adequate oxygenation)
- the $PaCO_2$ is allowed to rise to over 6.65 kPa (50 mm Hg) – this requires arterial blood gas analysis
- the lack of spontaneous respiratory effort is confirmed.

Following apnoea testing, the patient is reconnected to the ventilator if:

- only one set of brainstem function tests has been completed
- two sets of tests have been completed, which show lack of brainstem function and the patient is to become an organ donor.

Time of death

The legal time of death is the time of completion of the first set of brainstem tests. Death is certified after completion of the second set of tests, regardless of when active support is withdrawn.

Special circumstances

Neonates and young children – clinical brainstem tests alone cannot be applied to children with a conceptual age of less than 52 weeks or less than 2 months post-term delivery. Ancillary testing such as cortical electrical activity (EEG), sensory evoked potentials (SEP), evaluation of brain blood flow (cerebral angiography, radionuclide scanning or Doppler ultrasonography) or MRI has been suggested, but no tests are foolproof. Therefore, no single method should be relied on and any clinical or ancillary test used should be repeated two or three times over a period of up to 24 hours.

Respiratory disease – apnoea testing may be invalid in patients with chronic pulmonary disease and carbon dioxide retention. For such patients, their usual $PaCO_2$ levels should be taken as baseline and the $PaCO_2$ allowed to rise during apnoea testing to at least 2 kPa above baseline or until a respiratory acidaemia can be demonstrated. Oxygen supplementation should be reduced accordingly.

Inability to apply clinical criteria – in some cases, such as severe facial trauma, profound metabolic or endocrine disturbances, it may be impossible to apply all the preconditions, exclusions or clinical tests. Under these circumstances, all possible tests should be completed and supplemented with the additional tests described below. Great care should be taken under these circumstances when declaring death because the additional tests have not been legally validated in the UK.

Additional tests

Cerebral angiography – a selective four-vessel angiography is done with contrast media injected into both the anterior and posterior circulation. A minimum mean arterial pressure of 80 mm Hg is required for this test. In brain death, no intracranial perfusion other than occasional filling of the superior sagittal sinus is seen.

Radionuclide scanning – a radioactive-labelled substance that readily crosses the blood–brain barrier can be used to image parenchymal uptake activity. In brain death there is lack of uptake into parenchymal tissues.

Transcranial Doppler ultrasonography – the intracranial arteries can be insonated using a 2 MHz pulsed Doppler instrument. Absent diastolic flow has been reported in brain death. However, interpretation of these tests can be difficult.

Neurophysiological tests – the electroencephalogram (EEG) can be a useful confirmatory tool especially in young children. It should not be used in isolation, because it does not adequately assess brainstem function. Auditory and sensory evoked potentials have also been used.

Social and religious issues

The concept of brainstem death is difficult for many relatives and has been made more so by media reporting of so-called medical errors. It should be emphasized that brainstem death is irrefutably death and the act of switching off the ventilator is not 'killing the patient' but merely ceasing to ventilate a corpse.

Allowing relatives to witness the brainstem tests may help them to understand that death has occurred. However, witnessing the spinal reflexes tests may cause distress and it is important to explain the process continually throughout the testing.

Some religious groups (e.g. Orthodox Jews) do not believe in the concept of brainstem death and may refuse to allow withdrawal of ventilatory support, which they consider to be tantamount to murder. Published data indicate that asystole results within days of brainstem death. Therefore, to respect religious or cultural sensitivities, it may be appropriate to wait for asystole to occur before certifying death. ◆

Cannulation of Central Veins for Resuscitation and Monitoring in the ICU

Carl Waldmann

Carl Waldmann is Consultant Anaesthetist and ICU Director of the Royal Berkshire Hospital, UK. He qualified in medicine from Cambridge University and the London Hospital and trained in anaesthesia in the RAF. His main interests are the setting up of ICU follow-up programmes, and head injury management in a district general hospital.

Central venous catheters (CVCs) are integral to current medical practice, but complications are associated with their insertion. Placement of CVCs used to be the preserve of surgeons using general anaesthesia but the success rate was only about 75% and the vein was compromised for future use. The introduction of the percutaneous method led to uncontrolled use of CVCs by a variety of inadequately trained staff with serious, potentially avoidable, complications that were sometimes fatal. Recent advances in CVC manufacture, better training in insertion techniques, the use of ultrasound, the development of hospital nutrition teams, and the increasing involvement of interventional radiologists in the ICU should all ensure that CVC placement becomes safer. Interventional radiologists should be more involved in the management of ICU patients because they are familiar with ultrasound and fluoroscopic techniques, have extensive experience with advanced catheter and guidewire techniques, and are adept at retrieving catheters or parts of catheters inadvertently lost within the vascular system.

Figure 1 lists the indications for using CVCs. Originally CVCs were of fine bore, but newer, wide-bore, high-flow, central venous pressure lines and pulmonary artery catheter introducers permit rapid volume replacement. Multilumen catheters allow concurrent CVP monitoring and multiple drug infusion.

Indications for central venous catheterization

- Replacement of circulating volume
- Haemodynamic monitoring
- Monitoring of jugular bulb venous oxygen and mixed venous oxygen saturation
- Administration of vasopressors
- Repeated or frequent blood sampling
- Parenteral nutrition
- Chemotherapy
- Insertion of pacing wires or pulmonary artery catheters
- Endoluminal intervention (e.g. endocardial biopsy)
- Haemofiltration

1

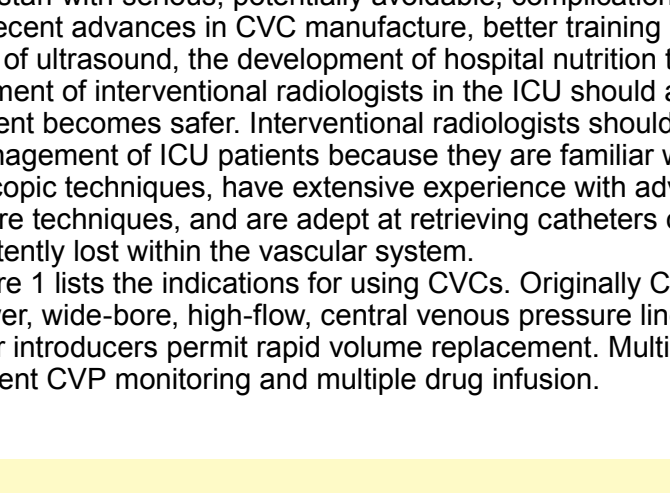
Insertion

In general, internal jugular, subclavian and femoral veins can be cannulated using standard anatomical landmarks (Figure 2).

The technique most often used was described by Seldinger in 1953. A small needle is inserted through the vein wall, a wire guide is advanced through the needle into the vein and the needle replaced by a dilator over the guide. A small incision is made close to the wire and the dilator replaced by the catheter. After cannulation of the internal jugular vein and subclavian vessels a chest radiograph should be taken to confirm correct CVC positioning and to ensure there is no pneumothorax.

Access sites of choice

1. High internal jugular
2. External jugular
3. Low internal jugular
4. Supraclavicular
5. Infraclavicular



a Clavicle
b 1st rib
c Suprasternal notch
d Sternal angle
e Right atrium
f External jugular vein
g Internal jugular vein
h Subclavian vein
i Left innominate vein
j Superior vena cava
k Suggested catheter tip positioning zone

2

Femoral vein
The most common use of the femoral vein in an ICU is for placement of a double-lumen haemofiltration line. Traditional teaching suggests that the femoral vein lies medial to its artery. However, ultrasound studies have demonstrated that the artery and vein do not always lie side by side; the degree of overlap between vessels varies between patients and sides. It is recommended that the femoral vein should be accessed just below the inguinal ligament and that ultrasound-guided placement should be used in patients with difficult anatomy, coagulopathy or peripheral vascular disease.

The femoral approach is usually used only when central access is unfeasible by other routes, and usually only as a short-term expedient. The route is impractical for mobile patients. Other concerns are thromboembolism and groin sterility.

Subclavian vein
The subclavian vein is the most comfortable cannulation site for patients, and is the best for long-term parenteral nutrition, pacing wires and Hickman lines. However, there are significant concerns because of the proximity of the subclavian vein to the subclavian artery (pressure cannot be exerted here if the artery is punctured), lung (risk of pneumothorax) and, on the left, the thoracic duct. Successful placement may be impossible unless the patient is placed head-down, which they may not tolerate.

Various approaches have been described. The author prefers infraclavicular puncture with a small needle introduced 2 cm inferior to the junction of the middle and medial thirds of the clavicle (see Figure 2). The needle is advanced medially in the direction of the suprasternal notch in a horizontal plane.

Internal jugular vein
Cannulation of the internal jugular vein may be difficult in obese patients or those with goitre or neck rigidity. This route, especially the high approach, is favoured for cannulation in the ICU because the insertion site is distant from the lung apex and haemorrhage from an inadvertent puncture of the carotid artery is easily controlled. However, damage to the brachial plexus, phrenic nerve and sympathetic chain are possible.

There are several well-described approaches to the internal jugular vein (see Figure 2). Success is increased by positioning the patient head-down with a pillow under the shoulders. The needle is inserted laterally to the palpated carotid artery, under the clavicular head of the sternomastoid at the apex of the posterior triangle. It is directed caudally and anteriorly towards the ipsilateral nipple. Normally the internal jugular lies anterior and lateral to the carotid artery; however, it may be unilaterally absent in up to 2.5% of patients. In 5.5% of patients the internal jugular lies outside the path predicted by anatomical landmarks.

Coagulopathy
Although insertion of CVCs in the presence of a coagulopathy is a relative contraindication, a recent series of 658 cannulations in patients with liver disease and coagulopathy demonstrated a low incidence of haemorrhagic complications. The presence of a raised international normalized ratio alone is not a contraindication to CVC insertion, and there is little evidence that transfusion of fresh frozen plasma is required before insertion. Nevertheless, caution is recommended in patients with combined coagulopathies, thrombocytopenia, or those on haemofiltration.

Aids to successful CVC insertion

Correct positioning of a patient, and the use of various manoeuvres, during central vein cannulation may increase the chances of success. The diameter of the internal jugular vein can be increased by using a Valsalva manoeuvre, abdominal binder and increasing head-down tilt. Carotid artery palpation and full neck extension reduce the vein's diameter.

Venography reduces the number of attempts to insert CVCs in patients with occluded or absent central veins.

Hand-held Doppler probes avoid multiple attempts in patients with unilateral absence or narrow diameter veins.

Portable ultrasound machines – the use of two-dimensional (B-mode) ultrasonography allows visualization of the anatomy both before and during cannulation. 100% success has been reported if a portable ultrasound machine is used as a 'bale-out' technique after failed attempts at 'blind' cannulation. It has recently been suggested that blind attempts at venous cannulation should be replaced by ultrasound-guided techniques. The use of a longitudinal view enables the operator to monitor the passage of the needle throughout the procedure as the needle enters the vein.

Complications
Complications may occur in up to 10% of central vein cannulations. Common complications are listed in Figure 3.

Complications of central venous catheterization

Local complications
- Failure to cannulate
- Arterial puncture
- Haematoma
- Local infection
- Thrombosis of vessel

Distant complications
- Perforation
- Haemorrhage
- Cardiac tamponade
- Pneumothorax
- Arrhythmias
- Damage to thoracic duct (subclavian)
- Brachial plexus damage (subclavian)
- Air embolism
- Catheter embolism
- Thrombus formation
- Bacteraemia, sepsis
- Respiratory obstruction

3

Line infection: catheter-related infections are potentially avoidable, yet account for about 25% of all nosocomial infections and 50% of nosocomial bloodstream infections in ICU patients. Consequently, there is considerable interest in determining whether CVCs need to be changed regularly in ICU patients, even in the absence of evidence of infection, and whether they should be changed routinely when an ICU patient has a persistent fever.

Recent data demonstrate that removal of the CVC in patients with suspected line infection is unnecessary in up to 90% of cases. In the absence of obvious infection at the skin entry site, one expedient would be merely to change the line over a guidewire with antibiotic cover and await microbiological advice following culture of the removed CVC tip. Replacement of the second catheter is recommended if the first is found to be significantly colonized. However, the first CVC is still often unnecessarily sacrificed to enable the diagnosis of catheter-related sepsis. To avoid this, using the very sensitive and specific technique of endoluminal brushing may be an alternative. The use of endoluminal brushing is regarded as safe and simple and eliminates the need for recatheterization with its attendant complications. This is particularly important in patients with long-term Hickman lines.

Catheter-related sepsis may also occur in the absence of pyrexia, leucocytosis and localized erythema at the insertion site. Line removal may be essential if severe systemic illness is to be avoided. Regular bacteriological surveillance with endoluminal brushing or by a technique known as 'time to positivity of hub-blood versus peripheral blood cultures' (in this technique an earlier positivity of central compared with peripheral venous blood cultures may be associated with catheter-related bacteraemia) may prove to be useful surveillance methods.

The incidence of bacteraemia due to infected CVCs has been estimated at 5.3 episodes per 1000 catheter days (ranging from 2.8 in cardiac surgical patients to 12.8 in patients in the burns units). The organism most commonly cultured is coagulase-negative *Staphylococcus*, though *Candida* is often reported. Colonization of lines may be associated with death, morbidity and a prolonged hospital stay. The essential elements of a strategy to prevent CVC-related infections include barrier precautions during insertion, strict aseptic technique during manipulation of lines, avoiding systematic change of dressings and catheters, and continuous surveillance.

Advances in catheter design

Material: the use of polyurethane virtually eliminates kinking. Soft catheter tips prevent vessel perforation.

Adjustable hubs permit the insertion distance to be altered after chest radiograph checks have been performed. In adults, the use of 15 cm CVCs often eliminates the need for hubs if the internal jugular vein site is used. Suturing the hub may not always ensure that a CVC is securely sited; it is preferable to suture the catheter itself.

Multilumen catheters reduce the possibility of drug interaction and bolusing of vasoactive drugs, allow rapid volume replacement and permit the introduction of a pulmonary artery catheter through the same catheter, thereby reducing the need for more than one venous puncture.

Heparin and antibiotic coating: non-thrombogenic lining of CVCs was described in 1971 as a method of preventing catheter blockage by fibrin deposits and avoiding bacterial growth on catheters. Some catheters are now coated with a combination of antimicrobial agents (e.g. minocycline, rifampicin) and heparin.

FURTHER READING

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Cardiac Arrhythmias in the Critically Ill

Kirsten J C Richards
Andrew T Cohen

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Cardiac arrhythmias are a common cause of potentially life-threatening, haemodynamic compromise in critically ill patients. This article describes a systematic approach to the management of the four general characteristics of arrhythmia – broad or narrow complex and tachycardia or bradycardia – because it is important to treat the patient and the general type of rhythm rather than considering each disturbance in detail.

Factors that predispose to the development of arrhythmias in peri-operative or critically ill patients include:

- cardiac disease
- hypoxia and hypercarbia
- electrolyte imbalance (particularly hypo- or hyperkalaemia, hypomagnesaemia)
- hypovolaemia
- extremes of temperature
- elevated catecholamine levels (endogenous and exogenous)
- pulmonary artery catheterization
- systemic inflammation (e.g. systemic inflammatory response syndrome)
- drugs.

Successful management should be approached in stages:

- rapidly assess the haemodynamic status of the patient
- identify the origin of the arrhythmia
- correct predisposing factors (e.g. hypoxia, electrolyte imbalance)
- consider specific therapy (e.g. drugs, DC cardioversion)
- prevent further arrhythmias.

Identification of the arrhythmia

A 12-lead ECG should be performed before treatment in all cases of arrhythmia except pulseless rhythms occurring during cardiac arrest. Identifying the precise rhythm is unnecessary but it is important to determine whether the complex width is narrow or broad, whether the patient is haemodynamically compromised, and in certain situations, whether the patient has known underlying structural heart disease.

A pulseless narrow complex tachycardia should be treated as pulseless electrical activity (electromechanical dissociation) if the rate is less than 200 beats per minute (bpm). However, if the rate is greater than 200 bpm, the initial treatment should be synchronized DC cardioversion (100 J, 200 J, 360 J). The Resuscitation Council (UK) Advanced Life Support guidelines for pulseless electrical activity should be followed if there is no response to initial DC cardioversion.

If a pulse is present, determine whether the rhythm is a tachycardia (> 100 bpm) or a bradycardia (< 60 bpm) and whether the complexes are broad (> 0.12 second) or narrow (< 0.12 second). Examples of the four types of arrhythmia are given in Figure 1.

Types of arrhythmia

Narrow complex bradycardias

- Sinus bradycardia
- Slow atrial fibrillation
- Mobitz type II heart block

Broad complex bradycardias

- Sinus bradycardia with pre-existing bundle branch block
- Mobitz type III heart block (complete heart block may be present if the ventricular rate is 30–40 bpm with complete dissociation of atrial activity)

Narrow complex tachycardias

- Irregular: atrial fibrillation
- Regular: supraventricular tachycardia (e.g. atrial tachycardia, atrial flutter, junctional tachycardia, supraventricular tachycardia with accessory pathway)

Broad complex tachycardias

- Ventricular tachycardia
- Supraventricular tachycardia with aberrant conduction (pre-existing inter-ventricular block)

1

Management of arrhythmias

Drug treatment
All antiarrhythmic drugs are also potentially rhythmogenic.

Electrolytes

Potassium – hypokalaemia commonly causes arrhythmias, especially ventricular tachycardia (VT). Patients at particular risk of hypokalaemia include those taking diuretics, post-operative patients, patients undergoing treatment for diabetic ketoacidosis, and those receiving intravenous fluid replacement therapy. An infusion of potassium chloride, 60 mmol in 60 ml normal saline, should be given via central access at a maximum rate of 30 mmol/hour.

Magnesium – magnesium deficiency tends to occur concurrently with hypokalaemia. Magnesium correction should be considered in all patients with VT. Intravenous magnesium sulphate, 2.5 g (5 ml 50%), should be given over 30 minutes. In patients with shock and refractory ventricular fibrillation (VF) an initial dose of magnesium sulphate, 1–2 g (2–4 ml 50%) may be given peripherally over 1–2 minutes.

Other antiarrhythmic drugs are listed in Figures 2 and 3.

Antiarrhythmic drugs

	Uses	Dose	Important side-effects
Adenosine • Blocks specific cardiac receptors • Slows conduction across AV node • Slows rate • Very short half-life (8–10 seconds)	• Terminates SVT • Facilitates diagnosis • Differentiation of broad complex SVTs from VT Identification of arrhythmia by revealing the underlying atrial rhythm (e.g. atrial flutter/ fibrillation/tachycardia)	6–12 mg via central access or large peripheral vein (can repeat 12 mg x 3) Immediately flush with saline. Monitor patient in a high dependency setting throughout administration. Reduce initial dose to 3 mg in heart transplant patients who are more sensitive to adenosine and to 0.5–1 mg in patients receiving dipyridamole. Effects are antagonized by theophylline and coffee	• Bradyarrhythmias • Bronchospasm (should be administered in high dependency facility and used with extreme caution in asthmatics) • Transient chest tightness, nausea, flushing • Avoid in heart block and sick sinus syndrome
Amiodarone • Blocks repolarizing potassium channels • Prolongs AP, refractory period and QT interval • Long half-life (50 days) • Minimally negatively inotropic	• Refractory VF • Pulseless VT • Haemodynamically stable VT, SVT and AF	• Refractory VF/pulseless VT: 300 mg in 20 ml 5% dextrose • Stable tachyarrhythmias: 150 mg in 20 ml 5% dextrose over 10 minutes, or 300 mg in 100 ml 5% dextrose over 1 hour followed by maintenance infusion of 900 mg in 250 ml 5% dextrose over 23 hours • Ideally use central access but large-bore peripheral vein may be used	• Hypotension, photosensitivity, slate-grey skin discoloration, corneal microdeposits, peripheral neuropathy, bradycardia, conduction disturbances of thyroid and liver, dysfunction of pulmonary and retroperitoneal deposits • Decrease digoxin and warfarin doses • Avoid in heart block
Atropine • Antimuscarinic • Blocks vagus nerve	• Bradyarrhythmias • Asystole	• 0.5–1 mg i.v., increasing to a maximum total dose of 3 mg	• Tachycardia, constipation, reduced bronchial secretions, urinary retention, dilated pupils
Digoxin • Cardiac glycoside • Inhibits Na/K-ATPase • Increases intracellular calcium • Increases vagal tone • Decreases sympathetic drive • Prolongs AV nodal conduction • Positive inotrope	• Slows ventricular rate in AF • Positive inotrope in congestive cardiac failure	• 250–500 μg in 50 ml 5% dextrose over 30 minutes i.v. Repeat once if necessary • Oral loading dose 1–1.5 mg over 24 hours in divided doses • Maintenance 62.5–250 μg/day • Therapeutic plasma range 0.8–2 ng/ml • Reduce dose in renal impairment, old age, low body mass • Antagonized by verapamil • Treat overdose with digoxin-specific antibody fragments	• Nausea, diarrhoea, dizziness, anorexia • Toxicity (nausea, arrhythmias) increased by hypokalaemia, hypomagnesaemia, hypoxia, hypercalcaemia, hypothyroidism • Avoid in heart block, Wolff–Parkinson–White syndrome, hypertrophic obstructive cardiomyopathy, recurrent ventricular arrhythmias
Esmolol • β-blocker • Short half-life (9 minutes) • Cardioselective at low doses • Decreases AV node conduction • Antagonizes circulating catecholamines • Decreases myocardial contractility	• Second-line therapy of SVT after adenosine	• 500 μg/kg i.v. over 1 minute • Follow with infusion of 50–100 μg/kg/minute	• Bradyarrhythmias, heart failure, hypotension • Avoid in impaired LV function, heart block, haemodynamic collapse • Administer with care in asthmatics
Flecainide • Sodium channel blocker • Slows conduction • Negatively inotropic • Metabolized in liver	• AF • SVT with accessory pathway	• 2 mg/kg i.v. over 10 minutes to maximum of 150 mg • Follow with infusion of 1.5 mg/kg/hour for 1 hour, then 0.1–0.25 mg/kg/hour for 24 hours	• Hypotension, bradycardia, blurred vision, paraesthesia • Avoid in heart block, sinoatrial disease, heart failure and pace-makers (pacing threshold may rise)
Lidocaine (lignocaine) • Sodium channel blocker • Shortens action potential • Metabolized in liver	• Haemodynamically stable VT if amiodarone is unavailable	• 1.5–2 mg/kg i.v. as a bolus (effective for 10 minutes only) • Follow with infusion of 4 mg/minute for 1 hour, then 2 mg/minute for 2 hours, then mg/minute • Decrease dose in liver or cardiac failure	• Dizziness, paraesthesia, hypotension, bradycardia, respiratory depression • Toxicity leads to anxiety, metallic taste, confusion and convulsions • Avoid in severe myocardial depression, AV block, porphyria
Verapamil • Calcium channel blocker • Slows AV nodal conduction • Peripheral and coronary vasodilatation • Significantly negatively inotropic	• Established SVT with good LV function	• 5–10 mg i.v. over 2 minutes followed by further 5 mg bolus if needed	• Flushing, hypotension, arrhythmias, headache, gastrointestinal upset, allergic reactions • Avoid in hypotension, broad complex tachycardias, history of heart failure or significantly impaired LV function, heart block, cardiogenic shock, Wolff–Parkinson–White syndrome, porphyria or i.v. in conjunction with β−blockers

Abbreviations: AF, atrial fibrillation; AP, action potential; AV, atrioventricular; LV, left ventricular; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

2

Vaughan-Williams classification of antiarrhythmic drugs

Class and site of action	Examples	Extra cardiac side-effects
Ia Block fast sodium channels, moderately prolongs conduction and repolarization	Quinidine	Gastrointestinal upset, thrombocytopenia, haemolytic anaemia, hepatic toxicity, lupus-like syndrome, psychosis
	Procainamide	Gastrointestinal upset, lupus-like syndrome, agranulocytosis, psychosis
Ib Block fast sodium channels, minimal effect on conduction and repolarization	Lidocaine (lignocaine)	Confusion, seizures, dizziness, paraesthesia, respiratory depression, reduce dose in hepatic failure
Ic Block fast sodium channels, marked prolongation of conduction	Flecainide	Dizziness, visual disturbances, headache, photosensitivity, ataxia, jaundice, peripheral neuropathy, pulmonary fibrosis
	Propafenone	Blurred vision, dry mouth, gastrointestinal upset, dizziness, headache
II β-blockers (decrease sympathetic stimulation on the cardiac muscle)	Propranolol Sotalol Esmolol	Bronchospasm, lethargy, attenuated hypoglycaemic response, peripheral vasoconstriction, gastrointestinal upset
III Block repolarizing potassium channels	Amiodarone	Vasodilatation, hypotension, photosensitivity, slate-grey skin discoloration, corneal microdeposits, tremor, ataxia, pulmonary fibrosis, liver and thyroid dysfunction, optic neuritis, peripheral neuropathy, gastrointestinal upset, metallic taste, dizziness, paraesthesia, benign intracranial hypertension
	Bretylium	Hypotension, gastrointestinal upset, tissue necrosis with intramuscular injection
	Sotalol	
IV Calcium channel blockers	Verapamil Diltiazem Nifedipine	Hypotension, constipation, gastrointestinal upset, flushing, dizziness, headache, myalgia, paraesthesia, fatigue, ankle oedema, abnormal liver function tests, rash

3

Temporary pacing
The indications for temporary pacing are given in Figure 4.

Indications for temporary pacing

Temporary pacing indicated

- Asystole
- Complete heart block
- Symptomatic bifascicular block (right bundle branch block + left axis deviation (LAD)
- Symptomatic trifascicular block (right bundle branch block + LAD + prolonged PR interval)
- Mobitz type II second-degree heart block
- Symptomatic bradycardia refractive to pharmaceutical therapy

Temporary pacing may be considered

- Mobitz type I second-degree heart block with hypotension not responsive to atropine
- Recurrent sinus pauses not responsive to atropine
- Atrial or ventricular overdrive pacing for recurrent ventricular tachycardia
- Sinus bradycardia with hypotension not responsive to atropine

4

Broad complex tachycardias

The management of broad complex tachycardias is summarized in Figure 5.

Ventricular tachycardia (VT)
It is safe to assume that any broad complex tachycardia is ventricular in origin unless the cardiac history suggests otherwise. Causes of VT include:

- ischaemic heart disease
- ventricular scarring following myocardial infarction or previous cardiac surgery
- right ventricular failure
- electrolyte disturbances in patients with a prolonged QT interval (drugs that prolong the QT interval include antiarrhythmic agents, erythromycin, antihistamines, tricyclic depressants and phenothiazines).

Features in the history and ECG that point to a diagnosis of VT rather than supraventricular tachycardia (SVT) with aberrant conduction include:

- history of ischaemic heart disease
- irregular cannon waves or variable S in V1 (atrioventricular dissociation)
- independent p waves, fusion or capture beats
- positive concordance in all precordial leads
- deep S wave in V6
- RSR pattern in V1
- QRS width greater than 0.14 seconds with right bundle branch block morphology
- QRS width greater than 0.16 seconds with left bundle branch block morphology
- extreme left axis deviation (–90 to 180°).

The patient should be assessed clinically for features of haemodynamic compromise including chest pain, heart failure, low systolic blood pressure (< 90 mm Hg), ventricular rate greater than 150 bpm, and decreased consciousness.

Management of broad complex tachycardias

- If in doubt assume all regular broad complex tachycardias to be ventricular in origin
- The differential diagnosis of a broad complex tachycardia is ventricular tachycardia (VT) or supraventricular tachycardia (SVT) with aberrant conduction. An irregular broad complex tachycardia is likely to be atrial fibrillation with bundle branch block
- Avoid verapamil in any broad complex tachycardia – it may cause haemodynamic collapse
- Intravenous adenosine may be used safely in broad complex tachycardia as a diagnostic aid. VT will be unaffected but an SVT with aberrant conduction will probably be terminated. Transient AV-nodal blockage will reveal the underlying rhythm in atrial flutter or atrial tachycardia
- The drug of choice in VT is amiodarone
- Potassium and magnesium deficiencies should be corrected where possible
- Synchronized DC cardioversion under sedation should be considered if there is any evidence of haemodynamic compromise
- Treatment of torsade de pointes should include magnesium and pacing rather than antiarrhythmogenic drugs

5

Treatment
If haemodynamic compromise is present:

- DC synchronized cardioversion under sedation (100 J, 200 J, 360 J)
- correct any potassium or magnesium deficiencies using potassium chloride, 60 mmol in 60 ml normal saline at a maximum rate of 30 mmol/hour, and magnesium sulphate, 5 ml 50% over 30 minutes
- if patient remains in broad complex tachycardia, administer amiodarone, 150 mg i.v. over 10 minutes
- consider repeated DC synchronized cardioversion
- consider other pharmacological agents (e.g. sotalol, lidocaine (lignocaine), amiodarone); overdrive pacing is a further possibility
- seek cardiological opinion if neccesary.

In the absence of haemodynamic compromise:

- correct potassium and magnesium deficiencies
- administer intravenous amiodarone, 150 mg over 10 minutes, or intravenous lidocaine (lignocaine), 50 mg over 2 minutes, repeated to a maximum of 200 mg
- consider synchronized DC cardioversion under sedation
- consider repeating amiodarone administration
- consider repeated DC cardioversion.

Torsade de pointes
Torsade de pointes is a polymorphic form of VT. It is characterized by beat-to-beat variation and a constantly changing axis. It may be self-limiting but can progress to VF. It may be caused by antiarrhythmic drugs associated with QT prolongation (e.g. Class Ia and Ic drugs, phenothiazines, butyrophenones, tricyclic antidepressants and antihistamines), congenital QT prolongation, electrolyte disturbances (hypokalaemia, hypomagnesaemia, hypocalcaemia), profound bradycardia, myocardial infarction or ischaemia, arsenic poisoning and neurological insults (e.g. subarachnoid haemorrhage, stroke, encephalitis).

Treatment:

- intravenous magnesium (even in patients without suspected magnesium deficiency)
- correct other electrolyte disturbances (e.g. hypokalaemia)
- withdraw precipitating drugs
- consider overdrive pacing at rate of 100 bpm, increasing the rate if needed
- consider use of β-blockers
- DC cardioversion in the event of haemodynamic collapse.

Narrow complex tachycardias

The management of narrow complex tachycardias is summarized in Figure 6.

Management of narrow complex tachycardias

- If the patient is haemodynamically compromised, proceed immediately to synchronized DC cardioversion under sedation
- When considering treatment options in a patient with uncompromised atrial fibrillation, consider whether the arrhythmia has been present for less than 24 hours
- Cardioversion of atrial fibrillation carries a significant risk of thromboembolism
- Intravenous adenosine should be administered rapidly via a large vein in a monitored patient, and followed immediately by a flush of normal saline
- Avoid adenosine in patients with asthma, atrioventricular block or known Wolff–Parkinson–White (WPW) syndrome
- In addition to adenosine, avoid verapamil and digoxin in patients with WPW syndrome. Flecainide or amiodarone may be used in WPW syndrome
- WPW syndrome may give rise to atrial fibrillation or atrioventricular re-entrant tachycardia. Signs of WPW syndrome on a 12-lead ECG in sinus rhythm include delta-waves and a short PR interval. The delta-wave is positive in lead V1 in left-sided accessory pathways, and positive in V6 in right-sided accessory pathways
- Consider the possibility of drug-induced myocardial depression, particularly with polypharmacy
- Consider digoxin toxicity as a cause of atrial tachycardia

6

Irregular narrow complex tachycardia
Atrial fibrillation often occurs in the critically ill patient, particularly in the presence of sepsis, inotropic support, underlying heart disease and in the elderly. Other causes of atrial fibrillation include impaired left ventricular function, hypertension, hypovolaemia, pulmonary embolism, cor pulmonale, thyrotoxicosis, pericarditis, cardiac trauma and toxins (e.g. alcohol). Although many patients tolerate rapid atrial fibrillation with few adverse symptoms, decompensation leading to cardiac failure is common. If the arrhythmia has been present for longer than 48 hours, thrombi may form in the fibrillating atria leading to the complication of systemic embolism. ECG evidence to support a diagnosis of atrial fibrillation includes an irregularly irregular rhythm with absence of p waves.

Choice of therapy depends on haemodynamic compromise and the duration of atrial fibrillation. In most patients, the aim of treatment should be cardioversion, using pharmaceutical or electrical methods. It is important to try to minimize the risk of systemic embolism.

Treatment

- Avoid precipitating factors (e.g. alcohol) and correct electrolyte imbalances. Treat underlying problems such as thyrotoxicosis, cardiac failure and sepsis.
- If there is severe cardiovascular compromise (rate > 150 bpm; systolic blood pressure < 90 mm Hg; critical perfusion or continuing chest pain), immediately give intravenous heparin or subcutaneous low molecular weight heparin, and attempt DC synchronized cardioversion under sedation (100 J, 200 J, 360 J). Amiodarone, 300 mg i.v. over 1 hour, may be given if electrical cardioversion is unsuccessful, repeat if necessary.
- If atrial fibrillation has been present for less than 24 hours in a haemodynamically stable patient, give heparin and attempt cardioversion. Pharmacological cardioversion should be attempted if there is no underlying structural heart disease. Amiodarone, 300 mg i.v. over 1 hour, or flecainide, 100–150 mg i.v. over 30 minutes, are the agents of choice. If pharmacological cardioversion fails or if structural heart disease exists, DC cardioversion with intravenous amiodarone if necessary should be used.
- If atrial fibrillation has been present for over 24 hours and the patient is haemodynamically stable, formal anticoagulation should be commenced and pharmaceutical agents (e.g. digoxin, β-blockers, verapamil or diltiazem) should be used to control the ventricular rate. Four weeks after anticoagulation, DC cardioversion should be attempted in patients without significant mitral valve disease or left atrial impairment. If cardioversion is successful, it is recommended that anticoagulation is continued for a further 4 weeks to avoid thromboembolism. Patients in whom cardioversion is unsuitable and those in whom cardioversion is unsuccessful should be maintained on digoxin and anticoagulation.

Regular narrow complex tachycardias

Sinus tachycardia is the most common rhythm disturbance in critically ill patients. Generally it requires no specific drug therapy, but it is usually one of the first warning signs of systemic illness. Common causes include hypoxaemia, hypercapnia, haemorrhage, thyrotoxicosis, pain, anxiety, infection, pulmonary embolism, cardiac tamponade, pneumothorax and drug or alcohol withdrawal.

SVT: although critically ill patients often develop a sinus tachycardia or atrial fibrillation, regular narrow complex tachyarrhythmias may also occur. These are likely to be caused by atrial flutter, atrial tachycardia, junctional tachycardias (atrioventricular nodal re-entry tachycardia) or the involvement of an accessory pathway (atrioventricular re-entry tachycardia). Management is principally the same, irrespective of the exact type of regular narrow complex tachycardia.

Treatment

- If the patient is haemodynamically compromised, immediate synchronized DC cardioversion under sedation should be considered (100 J, 200 J, 360 J).
- In the absence of cardiovascular compromise, vagal man-oeuvres should be attempted to abolish the arrhythmia or slow the conduction through the AV node in order to reveal atrial flutter. These include the Valsalva manoeuvre, application of cold water to the face and carotid sinus massage (avoid if patient has a carotid bruit).
- If there is no response to vagal manoeuvres, adenosine, initial dose 6 mg given rapidly followed immediately by a flush of 20 ml saline, should be administered via a central vein or large- bore peripheral cannula. The patient should be monitored closely during administration and should be warned to expect transient feelings of chest tightness, nausea and flushing. If the arrhythmia persists, adenosine, three doses of 12 mg, every 2 minutes, may be repeated. Adenosine should be avoided in patients with atrioventricular block and asthma, and care should be taken in patients with chronic obstructive pulmonary disease because it may provoke bronchospasm. Its use is contraindicated in patients with Wolff–Parkinson–White (WPW) syndrome because blockade of the artioventricular node may precipitate rapid atrial fibrillation. The effects of adenosine are potentiated by dipyridamole and antagonised by theophylline.
- If the patient has heart failure, chest pain, heart rate over 200 bpm or hypotension, synchronized DC cardioversion under sedation should be attempted (100 J, 200 J, 360 J). Amiodarone, 150 mg over 10 minutes, may be administered before repeating DC cardioversion if the initial three shocks are unsuccessful.
- If the patient remains cardiovascularly stable, alternative pharmacological therapy should be considered including esmolol, amiodarone, digoxin or verapamil. Verapamil should not be used in the presence of WPW syndrome, previous β-blockade or if signs of impaired LV function exist. Be wary of using multiple pharmacological agents.
- If the arrhythmia continues despite the above measures, a cardiological opinion should be sought regarding the possible indication for atrial overdrive pacing.

Bradyarrhythmias

The definition of a bradyarrhythmia is a heart rate less than 60 bpm. However, it should include patients whose heart rate is proportionally slow for their haemodynamic state. Causes of bradyarrhythmia include :

- acute myocardial infarction
- age-related degenerative disease of the conduction system
- atrioventricular nodal blocking drugs
- hypothyroidism
- hypothermia
- head injury.

Treatment: the management of bradyarrhythmias is summarized in Figure 7.

- Assess the patient for adverse signs including chest pain, heart failure, hypotension or a heart rate less than 40 bpm.
- If adverse signs are present administer atropine, 500 µg i.v. This may be repeated to a maximum total dose of 3 mg.
- If there is no response to atropine, consider an adrenaline (epinephrine) infusion at a rate of 2–10 µg/minute.
- Consider the need for temporary pacing. This may be initially in the form of external pacing leads with mild sedation but should subsequently be via an intravenous temporary pacing wire.
- If adverse signs are absent, it may be appropriate to monitor the patient in a high dependency environment.
- Patients with Mobitz type II atrioventricular block, complete heart block, ventricular pauses greater than 3 seconds, symptomatic bifascicular or trifascicular block or recent asystole may require pacing to avoid the risk of asystole.

Management of bradyarrhythmias

- Treat the patient rather than the ECG. If the patient is not haemodynamically compromised it may be appropriate to observe them in a monitored high dependency setting while removing any precipitating factors
- External pacing may save lives in patients whose bradyarrhythmias do not respond to atropine or adrenaline (epinephrine).

FURTHER READING

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Cardiogenic Shock and Congestive Cardiac Failure

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Cardiac failure occurs when the heart is unable to maintain an adequate cardiac output to meet the demands of the body despite adequate ventricular filling. A diagnosis of cardiac failure alone is inadequate and the cause and any precipitating factors should be determined (Figure 1).

Cardiogenic shock is a severe form of cardiac failure characterized by the triad of hypotension (systolic blood pressure < 90 mm Hg), low cardiac output, and signs of poor tissue perfusion (e.g. oliguria, delayed capillary return, cold extremities, impaired cerebral function). It may be differentiated from other forms of shock by having an elevated pulmonary capillary wedge pressure (PCWP). Even with intensive care, it has a high mortality (> 90%) because pump failure causes impaired coronary perfusion that further reduces cardiac contractility.

Causes of heart failure

Volume overload

Left ventricular failure
- Aortic regurgitation
- Mitral regurgitation
- Ventricular septal defect

Right ventricular failure
- Tricuspid regurgitation
- Atrial septal defect

Pressure overload (obstruction to cardiac output)

Left ventricular failure
- Hypertension
- Aortic stenosis
- Coarctation of aorta
- Cor pulmonale

Right ventricular failure
- Pulmonary hypertension
- Pulmonary embolus
- Mitral stenosis

Myocardial dysfunction
- Ischaemic heart disease
- Hypoxia
- Electrolyte imbalance
- Acidosis
- Septic shock (cytokines e.g. myocardial depressant factor, tumour necrosis factor-α)

Primary myocardial disease
- Cardiomyopathy
- Myocarditis
- Amyloidosis

Mechanical disadvantage
- Large ventricular aneurysm

Prevention of ventricular filling
- Pericardial tamponade
- Constrictive pericarditis
- Restrictive cardiomyopathy
- Diastolic dysfunction

High cardiac output
- Septicaemia
- Thyrotoxicosis
- Arteriovenous fistula
- Systemic-to-pulmonary shunt
- Paget's disease
- Beri beri

Factors aggravating or precipitating cardiac failure
- Arrhythmias
- Anaemia
- Fluid overload
- Corticosteroids, non-steroidal anti-inflammatory drugs
- Hypoxia
- Electrolyte imbalance
- Acidosis
- Infections
- Thyrotoxicosis

1

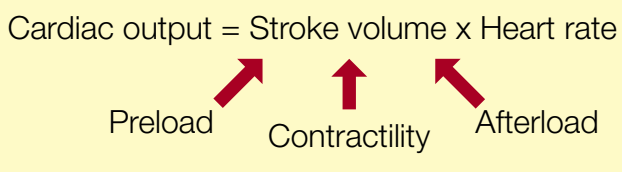
Aetiology

Although there are several causes of heart failure, the most common is ischaemic heart disease. Left heart failure is most often associated with left ventricular myocardial infarction or systemic hypertension. The causes of right heart failure include left heart failure and pulmonary disorders such as chronic obstructive pulmonary disease, pulmonary hypertension and pulmonary embolus. These pulmonary disorders cause an increased pulmonary vascular resistance against which the right ventricle must pump. Myocardial infarction of the right ventricle is uncommon (< 3%). Depressed cardiac function may be precipitated or exacerbated by infection, anaemia, fluid overload or dysrhythmias.

Regulation of cardiac function

Maintenance of an adequate cardiac output depends on stroke volume and heart rate (Figure 2). The essential factors that determine the performance of the heart are venous return (preload), inotropic state or contractility, outflow resistance (afterload) and heart rate.

Determinants of cardiac output



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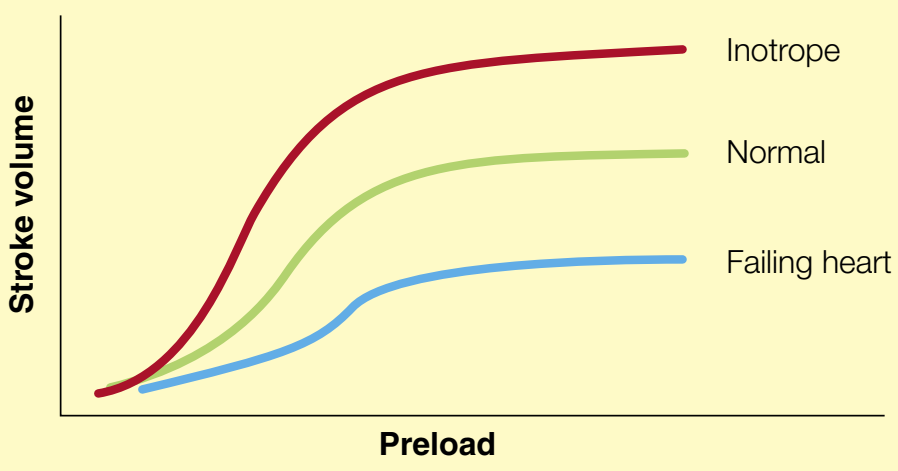
Venous return (preload): the increase in ventricular stroke volume (ventricular performance) that occurs with an enlargement of ventricular diastolic volume (preload) is known as the Frank–Starling relationship. In clinical terms, this represents the increase in cardiac output that accompanies an increase in PCWP. In the failing heart, the ventricular function curve is flattened and shifted to the right. Small degrees of myocardial depression are not necessarily associated with a reduction in cardiac output because it is maintained by an increase in venous pressure and tachycardia. However, the ejection fraction is reduced early in cardiac failure. In more severe myocardial dysfunction, cardiac output can be maintained only by a large increase in venous pressure and marked tachycardia. This eventually results in a further reduction in contractility. Despite symptoms caused by increased venous pressure, the cardiac output at rest may be only minimally depressed, but myocardial reserve is so compromised that cardiac output cannot be increased on exertion. In cardiogenic shock, the cardiac output at rest is depressed despite high venous pressures.

Inotropic state or contractility: increased contractility can result from increased sympathetic drive or the administration of inotropic agents. In the critically ill patient, contractility is often reduced, either as a result of pre-existing myocardial disease or the acute disease process itself (e.g. acidosis, hypoxia, sepsis). Changes in myocardial contractility alter the slope and position of the Frank–Starling curve (Figure 3).

Frank–Starling relationship



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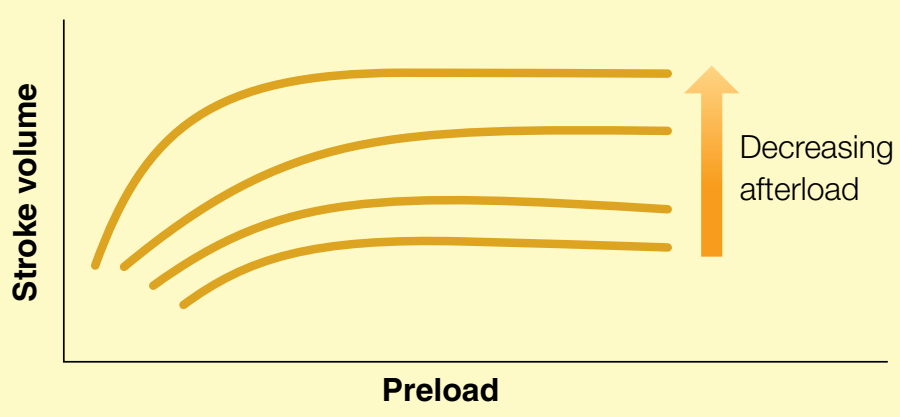
Outflow resistance (afterload): the afterload is the load or resistance against which the ventricle contracts. For the left ventricle it is determined by the resistance imposed by the aortic valve and the peripheral vasculature (systemic vascular resistance) and influenced by the elasticity of the major blood vessels. Decreasing the afterload can increase stroke volume at any given preload (Figure 4), while also reducing ventricular wall tension and myocardial oxygen consumption. The reduction in wall tension may lead to an increase in coronary blood flow, thereby improving the myocardial oxygen supply:demand ratio. On the other hand, an increase in afterload can cause a fall in stroke volume and an increase in myocardial oxygen consumption.

The effect of changes in afterload on the Frank–Starling curve



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Heart rate: extreme bradycardia or tachycardia can reduce cardiac output. When the heart rate falls, the increase in stroke volume eventually becomes insufficient to compensate for the bradycardia and cardiac output falls. When a tachycardia occurs the duration of systole is unchanged, whereas diastole, and thus the time available for ventricular filling and coronary blood flow, becomes progressively shorter. In the healthy heart this occurs above 160 beats/minute, but in those with cardiac pathology, stroke volume may fall at much lower rates. Alterations in heart rate are often caused by disturbances of rhythm. For instance, in atrial fibrillation or complete heart block, the absence of atrial contraction reduces stroke volume.

Clinical features

The clinical presentation depends on which ventricle is failing. The division of heart failure into syndromes of left, right and congestive cardiac failure is clinically useful, though it is uncommon for any part of the heart to fail in isolation. The left and right ventricles function in series and left heart failure may lead to right heart failure, the combination being termed congestive cardiac failure. In congestive cardiac failure there is a combination of the signs and symptoms of left and right heart failure.

Left heart failure (Figure 5) causes raised hydrostatic pressure within the pulmonary veins and capillaries. Fluid is forced from the capillaries into the interstitial and alveolar spaces, causing pulmonary oedema. Interstitial or alveolar oedema results in breathlessness and interferes with alveolar–capillary gas exchange, leading to hypoxaemia. Initially, dyspnoea occurs on exercise or lying flat (orthopnoea and paroxysmal nocturnal dyspnoea) but later occurs at rest.

Right heart failure (Figure 6) results in congestion in the systemic venous system, leading to raised jugular venous pressure, hepatomegaly, ascites, and dependent subcutaneous pitting oedema.

In congestive cardiac failure, the features of both pulmonary and systemic venous congestion are present.

Clinical features of left heart failure

Symptoms
- Anxiety
- Dyspnoea
- Tachypnoea
- Orthopnoea
- Paroxysmal nocturnal dyspnoea
- Reduced exercise tolerance

Signs
- Tachycardia
- Pulmonary crepitations
- Wheeze (cardiac asthma)
- Cough productive of pink frothy sputum
- Cyanosis
- Third heart sound (gallop rhythm)
- Displaced apex beat
- Pulsus alternans

5

Clinical features of right heart failure

Symptoms
- Breathlessness
- Fatigue
- Confusion

Signs
- Elevated jugular venous pressure
- Dependent pitting oedema
- Tender and smooth enlargement of liver
- Ascites
- Right ventricular heave

6

Investigations

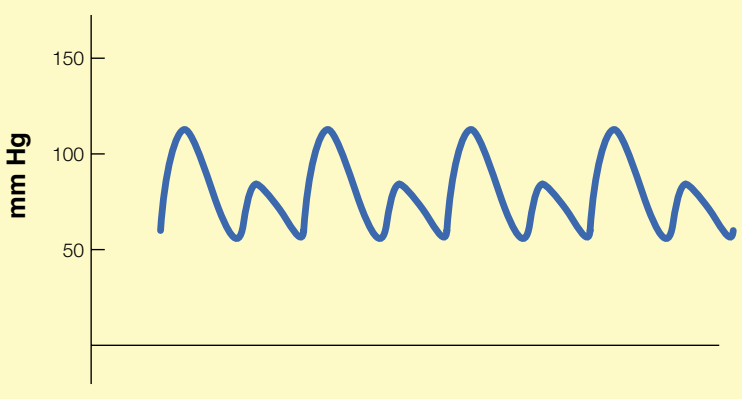
Blood tests: a full blood count should be carried out to identify anaemia. Urea and electrolytes, magnesium and phosphate should be measured. This is especially important in patients taking diuretics and angiotensin-converting enzyme (ACE) inhibitors, which may affect potassium and magnesium handling. Hypophosphataemia can aggravate heart failure. The cardiac enzymes should be assessed. The myocardial-bound isoenzyme fraction of creatine kinase and troponin I or T are specific for myocardial damage. Thyroid function tests should be carried out to identify hypo- and hyperthyroidism.

12-lead ECG is invaluable to detect either full-thickness or subendocardial infarction, left ventricular hypertrophy and dysrhythmias. In myocardial ischaemia, the ECG may be normal between attacks.

Chest radiography: the initial findings include upper lobe blood diversion, perihilar haze and peribronchial cuffing. Later, septal lines (Kerley A and B lines), bat's wing perihilar shadowing and pleural effusions occur. Depending on the cause, the heart size may be normal (acute failure) or enlarged (chronic). Although pulmonary oedema is usually a manifestation of left-sided heart disease, it can be caused by other pathology in critically ill patients (e.g. over-vigorous fluid replacement or pulmonary endothelial damage for example in the acute respiratory distress syndrome (ARDS) or acute lung injury (ALI).

Arterial waveform: in severe heart failure, pulsus alternans, characterized by alternately strong and weak beats in the presence of a regular rhythm may occur (Figure 7). There is absence of bigeminy on the ECG monitor. This is due to the prolonged recovery time of damaged myocardium and indicates a poor prognosis.

Pulsus alternans



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Central venous pressure (CVP) and PCWP monitoring: measurement of the CVP provides an assessment of right artial pressure and is used as an indirect estimate of right ventricular end diastolic pressure. However, factors such as intravascular volume, intrathoracic pressure and venous tone also affect CVP. Elevated left atrial pressure is a common finding in left heart failure and can be estimated by measuring PCWP using a pulmonary artery catheter. This may be useful in differentiating cardiogenic (high PCWP) from non-cardiogenic pulmonary oedema (e.g. ARDS) and also permits rational use of vasoactive drugs and intravenous fluids. As with CVP monitoring, responses to treatment and trends are more important than absolute values, which are often influenced by intermittent positive-pressure ventilation (IPPV), positive end-expiratory pressure (PEEP), pulmonary disease and myocardial ischaemia.

Echocardiography: transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) may provide useful information regarding valvular or other cardiac abnormalities (e.g. ventricular aneurysm, pericardial effusion), regional wall motion and ventricular ejection fraction. An estimation of the ejection fraction in a patient on inotropes, lying in bed doing very little does not provide a true picture of the actual state of the failing heart. However, TTE may not provide adequate views of the aorta and atria and may be unsuitable in patients with COPD or in the obese. TOE is useful in the diagnosis of endocarditis, left atrial pathology (e.g. thrombus), aortic dissection and in patients with mechanical valves.

Oesophageal Doppler monitoring provides flow-based rather than pressure-based monitoring by measuring blood flow in the descending thoracic aorta. It provides good correlation with other estimates of cardiac output and allows assessment of left ventricular filling (preload), contractility and afterload. Changes in waveform provide beat-by-beat visualization of trends and the effects of dynamic challenges to the circulation with fluids, vasodilators or inotropes. It requires repositioning from time to time and is not practical in the non-sedated patient.

Coronary angiography provides a diagnostic tool and allows therapeutic intervention.

Management of acute heart failure

Severe heart failure is a medical emergency, and effective management requires an assessment of the underlying cause, improvement of the haemodynamic status, relief of pulmonary congestion and improvement in tissue oxygenation.

Underlying aetiology
When the diagnosis of heart failure is made, treatment should be directed at the underlying aetiology. For instance, coronary ischaemia should be identified and revascularization considered using percutaneous coronary angioplasty or coronary artery bypass grafting because revascularization may improve ventricular function. Other life-saving treatments include mitral valve surgery for acute mitral regurgitation or closure of a ventricular septal defect caused by myocardial infarct.

Aggravating factors
Regardless of the cause, any aggravating factors should be identified and treated. For example, supraventicular tachyarrhythmias (e.g. atrial fibrillation), should be controlled using appropriate antidysrhythmic drugs.

General measures
The patient will be most comfortable in the sitting position because this encourages blood pooling in dependent parts. Hypoxaemia should be treated initially using high-concentration oxygen (> 60%) by face mask. Unless there are contraindications, subcutaneous low molecular weight heparin (e.g. dalteparin 2500 units) should be administered daily.

Drugs
The drugs used in the treatment of heart failure may be considered in terms of their effects on factors that influence cardiac output (preload, contractility, afterload and heart rate). In severe heart failure, drugs may be best administered intravenously because gut oedema may reduce the absorption of orally administered drugs.

Opioids: morphine, 2 mg i.v. bolus, acts by relieving the distress of dyspnoea and reducing preload by vasodilatation.

Loop diuretics: drugs such as furosemide (frusemide), 40 mg, and bumetanide, 1 mg, act by reducing preload and as potent loop diuretics. Loop diuretics are most effective when the pulmonary oedema is a component of congestive cardiac failure and if the volume of the extracellular fluid compartment is generally increased. When left ventricular failure is acute, pulmonary oedema is a result of fluid shift from the systemic circulation and there is minimal fluid retention. Overzealous use of diuretics in this situation risks hypovolaemia and hypotension.

Nitrates: glyceryl trinitrate and isosorbide dinitrate (infusion rates of up to 12 mg/hour) are useful in the treatment of acute left ventricular failure because they reduce venous return and left ventricular work. Being potent coronary vasodilators they are also useful in myocardial ischaemia. Tolerance rapidly develops with continuous high-dose infusion but reducing the dose for 4 to 8 hours each day usually maintains effectiveness.

Phosphodiesterase inhibitors: enoximone and milrinone are potent inodilators that do not act via adrenergic receptors. Consequently, they may be effective when catecholamines have failed. Their main use is the short-term treatment of severe congestive heart failure, especially in patients with diastolic dysfunction. Phosphodiesterase inhibitors increase cardiac output by 30–70% in patients with heart failure without increasing heart rate significantly because they reduce systemic vascular resistance and pulmonary vascular resistance.

Inotropes: inotropic support with agents such as dopamine and dobutamine (both 5–20 μg/kg/minute) may be required in patients with heart failure or cardiogenic shock. At lower doses (2.5 μg/kg/minute) dopamine may have additional direct renal effects but these have been challenged as being secondary to improvements in cardiac output. Both drugs have inotropic and chronotropic actions via β_1-adrenergic receptors, though at higher doses, dopamine may also stimulate receptors causing increased systemic vascular resistance. Dobutamine reduces preload and afterload, which may reduce blood pressure. Dopamine also depresses prolactin, luteinizing hormone, growth hormone and thyroid function, thereby obtundingthe body's endocrine response to stress. It may alter immuno-logical function, causing humoral and cell-mediated immunosuppression.

Ventilatory support
If hypoxaemia is resistant to high-concentration oxygen delivered by simple face mask, or hypercapnia develops, non-invasive positive-pressure ventilation such as continuous positive airway pressure or bilevel positive airway pressure may be required. These may obviate the need for tracheal intubation and IPPV. Positive-pressure ventilation improves arterial oxygenation, increases functional residual capacity and lung compliance, reduces the work of breathing, and improves V/Q matching. It also improves cardiac function by reducing left ventricular afterload and decreasing myocardial oxygen consumption. In severe pulmonary oedema, with copious pink frothy sputum, repeated bronchial aspirations are required, but removal of PEEP during aspiration should be of limited duration.

Other measures
Venesection still has a role to play in acute pulmonary oedema resistant to other therapies. Continuous veno-venous haemofiltration may be useful in the presence of oliguric renal failure resistant to diuretic. Circulatory assist devices such as intra-aortic balloon pump and left ventricular assist devices can be useful in certain patients with cardiogenic shock resistant to vasoactive therapy. Indications include peri-partum cardiomyopathy, myocarditis or as a bridge to corrective valve surgery, coronary artery bypass surgery or heart transplantation.

Management of chronic heart failure

Once acute heart failure has been stabilized, management is directed at improving prognosis and reducing hospital admissions. Despite the large number of drugs used in the treatment of heart failure, only the ACE inhibitors (e.g. captopril) and β-blockers improve survival. Recently, low-dose spironolactone, 25 mg/day, has also been shown to improve survival in patients with severe congestive cardiac failure (ejection fraction < 35%), when combined with loop diuretics and ACE inhibitors.

Cardiopulmonary Resuscitation

Jerry Nolan

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Successful resuscitation from cardiac arrest requires the prompt application of a sequence of interventions known as the 'chain of survival'. The chances of survival are highest for patients in ventricular fibrillation (VF) for whom defibrillation is required as rapidly as possible. After the onset of cardiac arrest, the chances of successful defibrillation decline by about 10% per minute. For this reason, the focus is on rapid defibrillation. The first 'link' in this chain is activation of the emergency services. Out of hospital this implies a telephone call to emergency medical services; inside hospital, the cardiac arrest team should be alerted. The second link, basic life support (BLS) is required unless defibrillation (the third link) can be attempted immediately. The fourth link in the chain, early advanced life support (ALS), maximizes the opportunity for long-term survival.

Resuscitation guidelines

Cardiac arrest teams work more efficiently if all members follow standardized protocols. Following an extensive evaluation exercise, the science supporting the first internationally accepted cardiopulmonary resuscitation (CPR) guidelines was published in August 2000.

Basic life support

The purpose of BLS is to maintain adequate circulation and ventilation until the underlying cause of the cardiorespiratory arrest can be reversed. Failure of the circulation for 3–4 minutes (less if the patient is hypoxaemic initially) will lead to irreversible cerebral damage, and any delay in starting BLS will reduce the chances of a successful outcome.

Classically, BLS implies that no equipment is employed. However, in a health care environment, the professional rescuer will have access to additional personnel and equipment. In particular, adjuncts to airway management are normally available. Nevertheless, the health care professional may have to perform CPR away from a health care environment and therefore should be competent in BLS with no additional equipment.

Mechanism for the production of blood flow during BLS: chest compressions produce forward blood flow by a combination of two mechanisms:
- direct compression of the heart (cardiac pump)
- a generalized increase in intrathoracic pressure (thoracic pump); venous collapse at the thoracic inlet prevents backflow of blood. Even when performed optimally, chest compressions achieve less than 30% of the normal cerebral perfusion.

BLS sequence of actions: brief outlines of the sequence of BLS actions for the lay person are given in Figures 1 and 2.

Basic life support

1 Ensure safety of rescuer and patient

2 Check to see if the patient responds to gentle shaking of the shoulders (shake and shout)

3 If he does not respond:
- Shout for assistance
- Open his airway (head tilt and chin lift manoeuvre). If there is any possibility of a cervical spine injury, avoid head tilt
- Check for breathing for up to 10 seconds

4 If he is breathing:
- Turn him into the recovery position

5 If he is not breathing:
- Send someone for assistance or, if you are on your own, leave the patient and go for assistance yourself
- Give two effective rescue breaths
  Ensure head tilt and chin lift, and pinch the patient's nose
  Blow steadily into his mouth over about 1.5–2 seconds, watching for clear chest rise

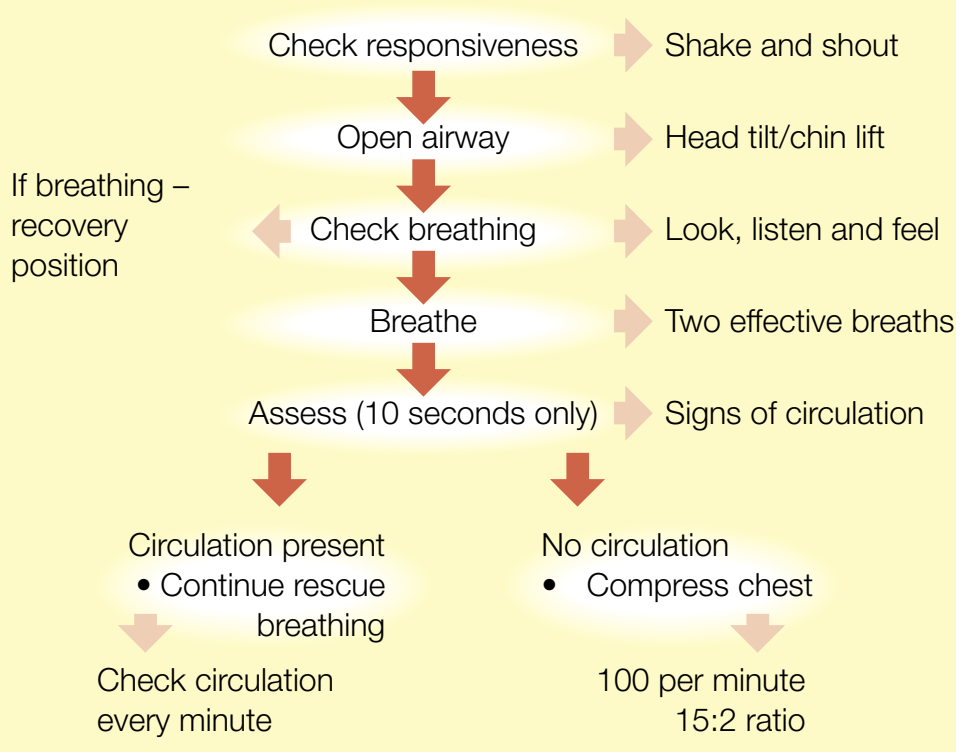
6 Assess the patient for signs of a circulation (taking no more than 10 seconds):
- Look for any movement
- Check the carotid pulse (if adequately trained to do so)

7 If you are confident that you can detect signs of a circulation:
- Continue rescue breathing, until the patient starts breathing on his own
- About every minute recheck for signs of a circulation

8 If there are no signs of a circulation:
- Start chest compressions using the heel of your hand placed over the middle of the lower half of the sternum
- Interlock the fingers of both hands and ensure that pressure is not applied over the patient's ribs
- Compress the sternum by 4–5 cm
- Release the pressure, then repeat at a rate of about 100 times a minute. Compression and release should take an equal amount of time
- Continue compressions and breaths in a ratio of 15:2

1

Basic life support algorithm



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When to go for assistance: it is vital for rescuers to get assistance as quickly as possible. When more than one rescuer is available, one should start resuscitation while another goes for assistance. Advice on how the lone rescuer should proceed depends on the likelihood of the casualty being in VF.
- In trauma, drowning, or if the patient is a child, the rescuer should perform resuscitation for about 1 minute before going for assistance, because the arrest rhythm is less likely to be VF.
- If the patient is an adult, and the cause of unconsciousness is not trauma or drowning, the rescuer should seek assistance once it has been established that the patient is apnoeic.

No ventilation CPR: the standard method of performing basic CPR is difficult for the lay person to learn and there is evidence that skill retention is poor. During the first few minutes of cardiac arrest, the use of chest compressions alone may be as effective as chest compressions combined with mouth-to-mouth ventilation. In the presence of a patent airway, it likely that chest compressions result in some alveolar ventilation; this may be supplemented by the patient's spontaneous gasps.

BLS in hospital: following cardiac arrest within the hospital, it is likely that more than one health care professional will be available, making it possible to undertake several actions simultaneously. A defibrillator should be close at hand; in the pulseless patient the priority is to bring this to the patient. If the patient has a pulse, urgent medical assessment will be required. In the intervening period, the patient should be monitored, oxygen administered and intravenous access secured.

Airway management and ventilation should be undertaken with the most appropriate equipment immediately at hand. The level of staff training will influence the choice of equipment. A pocket mask, which may be supplemented with an oral airway and oxygen, a laryngeal mask airway and bag–valve apparatus, or a bag–valve–mask device are all suitable.

BLS with defibrillation: traditionally, defibrillation has been viewed as an ALS intervention. However, the increasing availability of simple automated external defibrillators (AEDs) has moved defibrillation into the domain of BLS. Health care personnel and lay people can use AEDs safely and effectively after a short training programme (typically about 4 hours). It is no longer acceptable for nursing staff to have to await the arrival of a cardiac arrest team before attempting defibrillation of a patient in VF, because any delay reduces the chance of survival.

Advanced life support

Treatment algorithm: cardiac arrest rhythms can be divided into two main groups:
- ventricular fibrillation/pulseless ventricular tachycardia (VF/VT)
- other rhythms – asystole, pulseless electrical activity (PEA).

The only difference in the management of these groups is the need for defibrillation in patients who are in VF/VT. Maintenance of BLS, airway management, venous access, the administration of adrenaline (epinephrine) and the identification and correction of contributing factors are common to both groups. The algorithm for the management of cardiac arrest (Figure 3) is used in conjunction with either manual or automated defibrillators.

VF/VT: in adults, the most common rhythm at the onset of cardiac arrest is VF. This may be preceded by a period of pulseless VT. Most long-term survivors of cardiac arrest fall into this group. In order to achieve success, patients must be defibrillated promptly.

BLS should be started if there is any delay in obtaining a defibrillator, but it must not delay defibrillation. If the arrest was monitored, a single precordial thump may be appropriate. If delivered early enough, this may provide enough kinetic energy to convert a fibrillating myocardium to sinus rhythm.

Defibrillation – the initial three shocks are given with energies of 200 J, 200 J and 360 J (or their equivalent – see below). The aim should be to administer all three shocks (if required) in less than 1 minute. After delivery of a shock, there is a delay of a few seconds before an ECG display of diagnostic quality is obtained. Even when a rhythm normally compatible with a cardiac output is obtained, there is often a period of temporary impairment in cardiac contractility, resulting in a pulse that is too weak to palpate. For this reason, if the rhythm following a shock is asystole or PEA, only 1 minute of CPR is given before reassessing the rhythm.

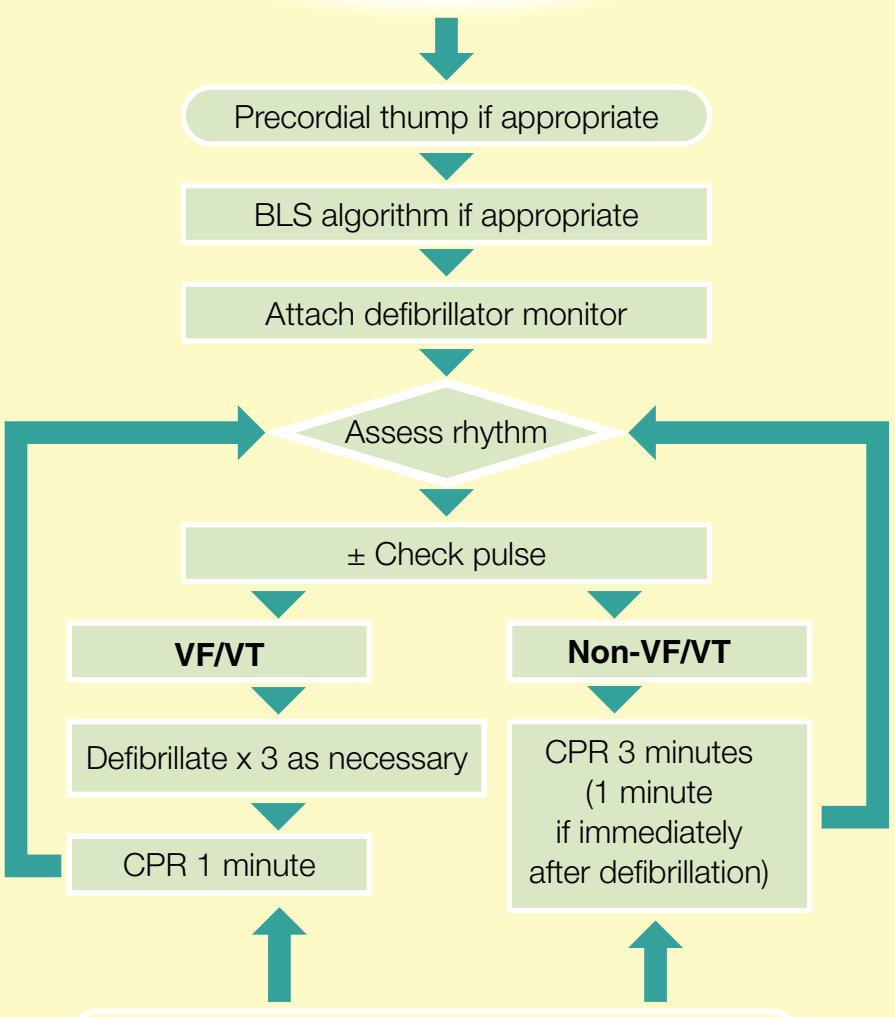
For defibrillators using a conventional damped sinusoidal waveform, the rationale for starting defibrillation at 200 J is that it will cause little myocardial injury and, in most recoverable situations, is adequate to defibrillate the patient successfully. The second shock should also be at 200 J, because the first shock lowers the chest impedance, thereby increasing the current reaching the heart. Third and subsequent shocks are given at 360 J. A number of new defibrillators deliver shocks with biphasic waveforms (polarity is reversed midway through shock delivery). These appear to be more effective than conventional sinusoidal waveform defibrillators; defibrillation is more successful at a lower energy (typically 150 J). Many defibrillators also incorporate impedance compensation (i.e. the shock waveform is adjusted according to the impedance of the patient's chest). The optimal energy level and waveform for biphasic defibrillation remains to be determined.

Airway and ventilation management – if VF persists after three shocks, 1 minute of BLS at a compression:ventilation ratio of 15:2 is undertaken in an attempt to preserve cerebral and myocardial viability. In expert hands, tracheal intubation provides the most secure airway. Attempted intubation by unskilled personnel will delay more important interventions such as chest compressions and further shocks. Furthermore, there is a significant possibility of unrecognized oesophageal intubation. In the absence of a skilled intubator, a laryngeal mask airway or a Combitube are useful alternatives; these devices are less likely to cause gastric inflation and regurgitation than a face mask. The highest possible concentration of oxygen, preferably 100%, should be delivered to the patient's lungs. Once the patient has been intubated, chest compressions should continue throughout ventilation. It takes at least 1 minute for chest compressions to generate the maximal coronary perfusion; this optimal perfusion pressure has to be re-established each time that chest compressions are interrupted.

Drugs – intravenous access should be established as soon as possible. The chosen route will depend on the skills and equipment available. Adrenaline (epinephrine), 1 mg i.v., should be given every 3 minutes. Alternatively, adrenaline, 2–3 mg diluted in 10 ml, can be given via the tracheal tube. Although used universally, the evidence that adrenaline improves outcome following cardiac arrest is weak. There are preliminary data supporting the use of a single dose of vasopressin, 40 units, instead of repeated doses of adrenaline, but long-term outcome data are awaited.

If the patient remains in VF after 1 minute of CPR, three further shocks of 360 J are given. The left-hand loop of the algorithm (Figure 3) is continued with each sequence of three shocks followed by 1 minute of CPR. Potentially reversible causes ('4 Hs and 4 Ts' – see Figure 3) must be excluded, because each can impair the ability to defibrillate VF successfully.

Universal algorithm for the management of cardiac arrest



If VF persists, the use of an antiarrhythmic drug should be considered. Historically, despite the lack of robust data, lidocaine (lignocaine) has been recommended after 12 unsuccessful shocks. Compared with placebo, amiodarone produces an improvement in short-term survival from refractory VF. In the International Guidelines 2000, amiodarone replaces lidocaine as the antiarrhythmic of choice in refractory VF. The use of bicarbonate during cardiac arrest remains controversial. A dose of 50 mmol can be considered if the arterial pH is < 7.1, but there is no good evidence to support this. The generation of carbon dioxide may cause a temporary intracellular acidosis.

Non-VF/VT: the outcome from non-VF/VT is poor unless a reversible cause can be found and treated effectively. With time, VF will degenerate to PEA and asystole.

Asystole – the possibility of a misdiagnosis must be considered; lead disconnection, incorrect gain setting, or equipment failure will give the appearance of asystole despite underlying VF. If there is any doubt, the patient should be treated as for VF. Otherwise, BLS is commenced (or restarted) for 3 minutes, the airway is secured and the patient's lungs are ventilated. Adrenaline, 1 mg, is given every 3 minutes. Although atropine, 3 mg i.v., or 6 mg via the tracheal tube, is traditionally given to block vagal activity, there is no proof that it alters outcome.

Whenever a diagnosis of asystole is made, the ECG should be checked carefully for the presence of P waves or slow ventricular activity. These may respond to cardiac pacing, either external or transvenous. Reversible factors should be identified and treated promptly. The use of high-dose adrenaline is no longer recommended.

PEA is cardiac arrest in the presence of a rhythm normally associated with a cardiac output. The patient's best chance of survival is prompt identification and treatment of any underlying cause (4 Hs and 4 Ts). CPR is started immediately, and a patent airway, ventilation and venous access are secured. Adrenaline, 1 mg i.v., is administered every 3 minutes.

Post-resuscitation care

Patients resuscitated after a short period of cardiac arrest and who have adequate spontaneous ventilation may be managed in a coronary care unit. After more than a few minutes of circulatory arrest, followed by restoration of spontaneous circulation, the patient is likely to require a period of ventilatory and cardiovascular support on an ICU. The duration and level of ventilatory support should be tailored to the requirements of the individual patient.

Outcome

Despite developments in the emergency services, the outcome from prehospital cardiac arrest remains poor, with a survival to hospital discharge rate of about 5%. After cardiac arrest within the hospital, the survival to hospital discharge after VF is as high as 40%. After an initial rhythm of asystole or PEA, this figure is just 6%.

At least two-thirds of in-patients sustaining a cardiac arrest display signs of significant deterioration (e.g. hypoxia, tachypnoea, hypotension) before they arrest. If medical and nursing staff are trained to recognize and treat these physiological abnormalities at an earlier stage, cardiac arrest may be prevented. This strategy is infinitely more sensible than waiting to call a cardiac arrest team after the patient has effectively died.

FURTHER READING

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Chronic Obstructive Pulmonary Disease and Chronic Respiratory Failure

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Chronic obstructive pulmonary disease (COPD) describes a spectrum of diseases that are characterized by airflow limitation due to intrinsic airways disease (e.g. chronic bronchitis), bronchospasm (e.g. asthma) and/or parenchyma destruction with associated loss of elastic recoil (e.g. emphysema). Airflow limitation is generally progressive, may be accompanied by airway hyperactivity and may be at least partially reversible. Risk factors for COPD include cigarette smoking and α_1-antitrypsin deficiency (AAT). Most patients with COPD have a combination of the three conditions described below.

Chronic bronchitis is defined as the presence of a chronic cough with sputum production that occurs most days of the week, at least 3 months of the year, for more than two consecutive years in the absence of other specific causes (e.g. asthma, cystic fibrosis, bronchiectasis). Most patients with chronic bronchitis do not have any significant airflow limitation and should not be classified as having COPD. There is mucosal and submucosal oedema and inflammation, with an increase in the number and size of the submucosal mucous glands.

Asthma is an inflammatory disease of the airways that results in reversible airflow limitation. Unlike the minority of asthmatics with poorly reversible airflow limitation, most patients respond well to therapy and therefore do not have COPD.

Emphysema is defined pathologically as a permanent, abnormal air-space enlargement that occurs distal to the terminal bronchiole and includes destruction of alveolar septa.

Diagnosis

COPD is primarily a clinical diagnosis. However, severe emphysema and lung hyperinflation can be diagnosed on a chest radiograph. The lung fields are enlarged and hyperlucent, the diaphragms flattened and the cardiac shadow is narrow. On the lateral film the volume of retrosternal air space is enlarged.

Measurement of the forced expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 to forced vital capacity (FVC) is critical to assess the severity of the disease, to predict prognosis and to follow progression. An FEV_1/FVC ratio of less than 70% is diagnostic of airways obstruction. It falls progressively as the severity of COPD increases.

As patients with COPD deteriorate, respiratory failure (a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) greater than 6.7 kPa or a partial pressure of oxygen in arterial blood (PaO_2) less than 8 kPa breathing air at sea level) often ensues and is frequently chronic and progressive. Hypercapnia is not usually seen until FEV_1 falls below 1 litre. Polycythaemia is seldom seen until PaO_2 is less than 7.2 kPa.

Long-term treatment

As COPD is an irreversible and progressive process, treatment is symptomatic and cannot alter the underlying pathology or improve survival.

Stopping smoking

Smokers with COPD have an accelerated fall in FEV_1. Stopping smoking reduces the rate of decline of FEV_1 at any stage of the disease.

Medications

Bronchodilators provide the mainstay of therapy for most patients. They act by reducing bronchomotor tone and the level of pulmonary hyperinflation. Inhaled agents are as effective as oral agents.

Short-acting β_2-agonists (e.g. salbutamol) have a rapid onset of action and are either used regularly or as required. They activate specific β_2-adrenergic receptors on smooth muscle cell surfaces, which leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) and smooth muscle relaxation. β_2-agonists are available as liquids for nebulization, in aerosol form delivered by pressurized metered-dose inhalers and as dry powders that can be inhaled via special self-actuated devices. Pressurized metered-dose inhalers are the most widely used, but dry powder delivery methods are likely to increase because they do not use chlorofluorocarbon (CFC) propellants.

Anticholinergic agents compete with acetylcholine at postganglionic muscarinic receptors, thereby decreasing cholinergically mediated bronchomotor tone and leading to bronchodilatation. Although muscarinic receptors are more numerous in the larger airways, anticholinergic bronchodilatation occurs at all levels of the bronchial tree. Anticholinergic agents also block vagally mediated reflex arcs that cause bronchoconstriction thereby inhibiting airway reactivity. Anticholinergics have a slower onset of action than β_2-agonists and are best given regularly. Anticholinergics and β_2-agonists may act synergistically.

Theophyllines have been widely used since the early 1900s but their use has diminished owing to their narrow therapeutic range and toxicity. In COPD, theophyllines are only modest bronchodilators with a variable effect on exercise tolerance and symptoms. They are metabolized in the liver but the extent varies between patients because metabolic enzymes are affected by other drugs and disease states (Figure 1).

Theophyllines were thought to produce bronchodilatation by increasing intracellular cAMP, but the precise mechanism is unknown and may involve increased intracellular calcium transport, adenosine antagonism or prostaglandin E_2 inhibition. Theophyllines also appear to increase mucociliary clearance, reduce pulmonary vascular resistance and may improve diaphragm and cardiac muscle contractility. Side-effects include nausea, vomiting, tremor, nystagmus, seizures, gastro-oesophageal reflux and arrhythmias. Plasma theophylline levels should be monitored and maintained in the therapeutic range.

Factors that affect theophylline dose

Need to increase dose

- Cigarettes
- Hyperthyroidism
- Marijuana
- Barbiturates
- Phenytoin
- Rifampicin
- Carbamazepine

Need to decrease dose

- Congestive heart failure
- Liver dysfunction
- Viral/acute illness
- Age > 60 years
- PaO_2 < 6 kPa
- Allopurinol
- Cimetidine
- Ciprofloxacin
- Erythromycin
- Propranolol
- Oral contraceptives
- Verapamil

Corticosteroids: the presence of inflammatory changes in the airways of patients with COPD provides a rationale for the use of corticosteroids. However, the relationship between inflammatory changes, pulmonary function and therapeutic response is not clearly established. Long-term oral corticosteroid therapy may slow the decline of FEV_1 but is not recommended because of the side-effects. On present evidence, inhaled corticosteroids (e.g. beclomethasone, up to 800 µg/day, budesonide, 1600 µg/day, or fluticasone, 2 mg/day) should be given to patients with an objective response to corticosteroids.

Other agents: there is no evidence to support the use of prophylactic antibiotics, other anti-inflammatory drugs (e.g. sodium cromoglycate, nedocromil, antihistamines) pulmonary vasodilators or mucolytics in COPD.

Management of acute exacerbation of COPD

Infections, cardiac failure and pulmonary embolism are the most common factors to precipitate acute respiratory failure in patients with COPD. Signs and symptoms include increasing dyspnoea, increased sputum production (often purulent) and wheeze. Worsening gas exchange is the initial presentation. Stable COPD patients usually have altered ventilation–perfusion (V/Q) matching that worsens when acute respiratory failure develops. For instance, increased airways resistance reduces ventilation in some areas of the lung, thereby increasing low V/Q units; additionally, hyperinflation reduces blood flow in distended alveoli which increases high V/Q units. These alterations are the main reason for the increase in $PaCO_2$ that occurs in COPD despite maintenance of minute ventilation. Worsening of V/Q mismatch is limited by hypoxic pulmonary vasoconstriction but high concentration oxygen may abolish this reflex, causing a deterioration in V/Q mismatch and a further increase in $PaCO_2$.

Presenting history: consider the following:

- previous exercise tolerance (how independent is the patient under normal circumstances and during exacerbation?)
- assess current treatments (use of nebulizers and long-term oxygen therapy)
- time course of current exacerbation
- current symptoms (sputum volume and purulence, dyspnoea, wheeze, chest tightness)
- previous admissions over the last 5 years (any to ICU?)
- smoking history
- social circumstances and quality of life.

Examination: look for the following:

- signs of infection (e.g. pyrexia, purulent sputum)
- signs of airway obstruction (tachypnoea, use of accessory muscles, pursed-lip breathing, audible wheeze)
- peripheral oedema, cyanosis or confusion.

Investigations: the following investigations may be helpful.

- Arterial blood gas analysis and inspired oxygen concentration – hypoxaemia may be severe (less than 4 kPa). The extent of hypercarbia depends on the severity of the condition but $PaCO_2$ levels greater than 10.6 kPa are uncommon. Arterial pH is usually well maintained because bicarbonate is chronically retained. A respiratory acidosis suggests a recent exacerbation and a pH below 7.26 predicts a poor outcome.
- Chest radiograph, preferably a posteroanterior view to check for pneumonia and pneumothorax.
- Full blood count – polycythaemia and leucocytosis occur in severe disease.
- Urea and electrolytes – hypokalaemia is common due to β_2-antagonist, corticosteroids and diuretic therapy.
- ECG – right heart hypertrophy and strain suggest cor pulmonale.
- Initial FEV_1 and peak flow should be assessed.
- Microbial culture of purulent sputum and blood is required.

Treatment

Oxygen therapy – all critically ill patients require 100% oxygen in the emergency situation while the initial assessment is made and therapy commenced. Subsequently many patients with an acute exacerbation of COPD will continue to benefit from high flow oxygen and the aim of oxygen therapy is a PaO_2 of at least 8 kPa. However, when given high inspired oxygen concentrations, a few patients may increase their $PaCO_2$ through complex mechanisms involving altered V/Q mismatch, the Haldane effect and decreased minute ventilation. This acute rise in $PaCO_2$ may cause 'carbonarcosis' with agitation, drowsiness or coma. Monitoring by serial arterial blood gas measurements is essential and when the pH is less than 7.26 the inspired oxygen concentration should be titrated to relieve severe hypoxaemia while maintaining a level of consciousness that retains the patient's ability to cough and cooperate. The level of carbon dioxide is not of prime importance. Once stable, the patient can be monitored using pulse oximetry, but repeat arterial blood gases should be performed at any time if the patient's clinical condition deteriorates.

Some patients with COPD are chronically hypoxaemic and develop counter-regulatory mechanisms such as increased haematocrit and increased oxygen extraction from the tissues. These patients can tolerate acute hypoxaemia better than others.

Bronchodilators – nebulized bronchodilators should be given at least every 4–6 hours. For moderate exacerbations either a β_2-agonist (e.g. salbutamol, 2.5–5 mg) or an anticholinergic (e.g. ipratropium, 0.25–0.5 mg) is appropriate, but for severe exacerbations both should be given because they have a synergistic effect. Although some practitioners power nebulizers using the wall-mounted oxygen supply, the use of compressed air may be preferable in COPD patients with hypercapnia or a respiratory acidosis. Oxygen can be given by nasal prongs at 1–2 litres/minute during nebulization.

Intravenous bronchodilators can be used if the patient fails to respond to nebulizers. There is no place for intravenous β_2-agonists but aminophylline, 0.5 mg/kg/hour, is proven to be of benefit.

Antibiotics – infection often worsens COPD and antibiotics should be administered to any patient with acute-on-chronic respiratory failure (pH < 7.35) and two or more of the following:

- increased breathlessness
- increased sputum volume
- purulent sputum.

Likely pathogens include *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis*. Atypical pathogens are seldom a problem though *Chlamydia pneumoniae* may be found. Some infections are viral. For moderate exacerbations, oral antibiotics (amoxicillin (amoxycillin) or tetracycline) should be used but in severe exacerbations, an intravenous broad-spectrum cephalosporin with the addition of a macrolide, if necessary, will be required.

Corticosteroids – it is unclear if systemic corticosteroids alter the course of an acute exacerbation of COPD, but it is common practice to use a 7–14 day course of prednisolone, 0.5 mg/kg/day, or hydrocortisone, 200 mg/day, especially if:

- the patient usually takes corticosteroids
- there has been a previous response to corticosteroids
- the airflow obstruction is resistant to bronchodilators
- this is the first presentation of airways obstruction.

Diuretics should be given if there is peripheral oedema or a raised jugular venous pressure.

Respiratory stimulants – hypercapnia during COPD exacerbations may be due to respiratory muscle fatigue or a blunted ventilatory drive. Doxapram may be used if the respiratory rate is less than 15/minute and acts centrally to increase respiratory drive and respiratory muscle activity. Its effect is significant for only 24–48 hours; the main factor limiting its use is side-effects that can lead to agitation. It should not be used if non-invasive ventilation is being considered.

Anticoagulants – pulmonary emboli are probably more common than previously recognized in severe COPD but full anticoagulation treatment is not currently recommended. Nevertheless, prophylactic subcutaneous heparin must be prescribed for all patients with acute-on-chronic respiratory failure.

Nutrition – many patients with COPD have an increased resting metabolic rate and nearly 50% of those admitted to hospital with acute respiratory failure have some degree of protein calorie malnutrition. Feeds high in carbohydrate should be avoided because they increase carbon dioxide production and oxygen consumption.

Physiotherapy – there are few data to suggest that chest physiotherapy reduces sputum retention in acute exacerbations of COPD and so it cannot be recommended routinely. However, it seems appropriate to provide physiotherapy in those patients who have large volumes of retained sputum in the acute phase.

Managing respiratory failure with mechanical ventilation

Ventilatory support, either as non-invasive ventilation or intermittent positive-pressure ventilation (IPPV) via a tracheal tube, may be necessary for patients who fail to respond to supportive treatment and controlled oxygen therapy. The main goal of mechanical ventilation is the support of gas exchange and fatigued respiratory muscles while the precipitating cause of acute respiratory failure is treated. A trial of non-invasive ventilation should be performed in all patients with respiratory failure and intubation should be reserved for non-responders and those unable to cooperate.

Non-invasive positive-pressure ventilation (NIPPV)

NIPPV avoids the morbidity and mortality associated with IPPV (e.g. sedative drugs, nosocomial chest infections, ventilator dependence) and may reduce intubation rates, mortality, and length of hospital stay. It can be applied intermittently, avoids the need for sedation, and allows the patient to eat, talk and drink. It can also be used outside the ICU, thereby reducing the demand for ICU beds. NIPPV is most beneficial when used early and it has been suggested that all COPD patients with a respiratory acidosis (pH < 7.35) after initial treatment are offered NIPPV.

NIPPV uses two ventilatory techniques – continuous positive airway pressure and inspiratory assist (pressure support) (see page 343). On non-invasive ventilators these pressures are set as expiratory positive airways pressure (EPAP) and inspiratory positive airways pressure (IPAP). The pressure support delivered is IPAP–EPAP.

Patient selection for NIPPV is important. Confused patients and those with a large volume of secretions are less likely to respond well. The prerequisites for success are:

- patient cooperation
- patient can maintain airway and expectorate secretions
- adequate cough reflex
- patient can breathe unaided for several minutes
- functioning gastrointestinal tract
- haemodynamic stability.

Negative non-invasive ventilation

The application of intermittent subatmospheric pressure to the chest wall generates the same gradient of pressure between the peripheral and central veins as a spontaneous breath. Various devices have been used including tank ventilators, cuirasses and jacket ventilators. These techniques are used, mainly to provide long-term support for patients with limited respiratory reserve and nocturnal hypoventilation due to restrictive disorders such as kyphoscoliosis, thoracoplasty, and residual paralysis from poliomyelitis. More recently, non-invasive high-frequency oscillation has been shown to increase carbon dioxide elimination. Consequently the Hayek oscillator has been developed. It consists of a cuirass that surrounds the chest and which maintains subatmospheric pressure with superimposed oscillations.

IPPV

In certain situations NIPPV is unsuccessful and IPPV should be considered (Figure 2). Many medical and ethical issues surround the use of IPPV for COPD patients including the patient's wishes, the likelihood that the patient will survive to leave hospital with a good quality of life and the availability of resources. The provision of IPPV may also cause unnecessary distress to the patient and their relatives. NIPPV can be useful in supporting the patient until the appropriateness of tracheal intubation and mechanical ventilation can be determined. Senior medical staff must be involved in this discussion.

Indications for tracheal intubation and ventilatory support are:

- severe respiratory distress
- failure to cough
- decreasing level of consciousness
- agitated, confused patient.

Determining when to use intermittent positive pressure ventilation (IPPV)

Factors to encourage use of IPPV

- Reversible reason for current decline
- First episode of respiratory failure
- Good quality of life

Factors to discourage use of IPPV

- Previously documented severe chronic obstructive pulmonary disease found to be unresponsive to relevant therapy
- Poor quality of life
- Severe co-morbidity (e.g. congestive heart failure, cancer)

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Management as the patient recovers

As the patient's condition improves (less dyspnoea, better peak expiratory flow rate (PEFR), improved oxygen saturation in arterial blood) the nebulized bronchodilator can be changed to the patient's usual inhaler. Antibiotics and corticosteroids can usually be stopped after 1 week. PEFR should be recorded twice daily until clinically stable and both FEV_1 and arterial blood gases (on air) should be recorded before hospital discharge. Before discharge the patient's inhaler technique should be assessed and advice given on the treatment regimen and on how to stop smoking.

FURTHER READING

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CNS Infections in Intensive Care

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Many CNS infections can be treated in a general ward, but prolonged seizures, coma, septic shock or airway compromise are indications for ICU admission for treatment and supportive care. In the UK, severe CNS infections fall into three categories: meningitis, encephalitis and cerebral abscess.

Acute bacterial meningitis

This pyogenic infection of the subarachnoid space and cerebral ventricles is the most common intracranial infection in the UK (incidence 3–5/100,000). The usual causative organisms are:

- *Streptococcus pneumoniae* (40%)
- *Neisseria meningitidis*
- *Haemophilus influenzae*
- *Staphylococcus aureus.*

In post-transplant, alcoholic, diabetic, immunosuppressed or HIV-positive patients, the organism may be atypical (e.g. *Listeria monocytogenes*).

Pathophysiology – bacteria colonize the bloodstream via the nasal or oropharyngeal mucosa, and cross the blood–brain barrier. Direct spread from trauma, sinusitis or mastoiditis, or haematogenous spread from distant infection also occurs. Lipopolysaccharide and teichoic acid produced by Gram-negative and Gram-positive bacteria, respectively, induce meningeal inflammation and cause leucocyte chemoattraction and vascular endothelial damage. This results in cerebral oedema and ischaemia, disruption of the blood–brain barrier and failure of cerebral autoregulation. Blockage of CSF flow may cause hydrocephalus.

Clinical features include:

- a prodromal period of malaise, myalgia, upper respiratory tract symptoms, joint pains and fever
- severe headache
- vomiting
- photophobia
- neck stiffness
- decreased conscious level
- rash: petechial or purpuric (meningococcal infections); maculopapular (staphylococcal or pneumococcal infections)
- cranial nerve lesions
- seizures
- papilloedema
- septic shock (meningococcal and pneumococcal disease).

Signs in the very young and old may be more subtle. The differential diagnosis of acute bacterial meningitis includes viral meningitis, encephalitis, subarachnoid haemorrhage, subdural empyema, brain abscess and legionnaires' disease.

Investigations – the diagnosis is primarily clinical when a rash is present; otherwise it rests on detecting organisms from blood culture or CSF. Lumbar puncture is contraindicated in the presence of focal neurological signs, papilloedema or depressed conscious level unless raised intracranial pressure (ICP) has been excluded by CT scan. Early lumbar puncture (i.e. within 2 hours of antibiotic treatment) may yield diagnostic information from a Gram stain, culture, polymerase chain reaction (PCR) or latex agglutination test. CSF is characteristically turbid, with over 1000 neutrophils/mm^3, low glucose and raised protein levels. Viral meningitis may also cause a neutrophil leucocytosis early in the illness, though it normally leads to a lymphocytosis.

There may be a coagulopathy, peripheral neutrophilia and renal impairment, the latter especially if shock is present.

Management – recommended antibiotics are cefotaxime, 2 g 4–6 hourly i.v., or ceftriaxone, 2 g 12 hourly i.v. Vancomycin, 1 g 12 hourly adjusted according to levels, should be considered in areas with a high prevalence of resistant pneumococci, or if the infection arises after neurosurgery. Different therapy is required in the immunosuppressed, elderly or neonates. Close contacts of patients should receive prophylactic rifampicin, 600 mg 12 hourly for 2 days (10 mg/kg 12 hourly for children). Corticosteroids are beneficial in children with *Haemophilus* meningitis. Early treatment with dexamethasone, 10 mg continued 6 hourly for 4 days, has been shown to improve outcomes in adults with acute bacterial meningitis. If *Listeria* meningitis is considered a possible diagnosis, ampicillin, 1–2 g 6 hourly i.v., should be added.

Intensive care management focuses on supportive care and prevention of secondary brain injury due to ischaemia and hypoxia. Specific guidance includes:

- intubation and ventilation for patients with a Glasgow Coma Score of 8 or less, loss of airway protection or persistent seizures
- avoid factors that increase ICP
- adjust ventilation to maintain a $PaCO_2$ of 4.0–4.5
- nurse the patient in a head-up position
- tape, rather than tie, tracheal tubes
- maintain a normal plasma sodium and euglycaemia
- there should be a low threshold for repeating a CT scan
- if hydrocephalus is present, ventricular drainage may be required
- enteral nutrition should be commenced early
- fever should be treated (active cooling and/or paracetamol)
- treat syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and diabetes insipidus.

Raised ICP should be treated with mannitol, furosemide (frusemide) or hypertonic saline. The cerebral perfusion pressure (mean arterial pressure (MAP) – ICP) should be kept above 70 mm Hg with fluid and vasopressors (e.g. noradrenaline (norepinephrine)). Fluid resuscitation should be guided by arterial blood pressure, central venous pressure and, where appropriate, pulmonary artery pressure monitoring. If cerebral oedema is severe, a thiopental (thiopentone) infusion may decrease cerebral oxygen demands and ICP.

Complications – status epilepticus should be treated with phenytoin, loading dose of 15 mg/kg given over 30–60 minutes, if benzodiazepines fail. If it is persistent, thiopental (thiopentone) or propofol infusion may be required. Continuous full or processed EEG monitoring may be required to detect subclinical status epilepticus or to optimize the thiopental (thiopentone) infusion rate to achieve burst suppression. Neurological deterioration may indicate worsening cerebral oedema or the development of hydrocephalus, subdural empyema or sagittal sinus thrombosis. Long-term complications include cranial nerve palsies, hemiparesis and deafness. Skin loss and digital or limb ischaemia are complications of meningococcal sepsis.

Outcome – mortality is about 25%. It is worse in children and the elderly, in those with a delayed diagnosis, comatose on admission or with raised ICP.

Viral encephalitis

Encephalitis is inflammation of the brain parenchyma, often with meningeal involvement (meningo-encephalitis). It is caused by:

- herpes simplex virus (HSV) I (the most common cause in Europe; annual incidence 1/250,000) 30% of cases are associated with herpes labialis or genitalis
- HSV II (neonates, immunosuppressed patients)
- other viruses (measles, mumps, rubella, varicella zoster, polio, HIV, cytomegalovirus, rabies and Epstein–Barr viruses).

Pathophysiology – virus reaching the brain via the nasal mucosa, or from respiratory or enteral infections causes direct cerebral cytotoxicity by lysis, and excites an inflammatory response leading to cerebral oedema, vascular obstruction, cerebral ischaemia, infarction and atrophy.

Clinical features and diagnosis – in herpes encephalitis, a 7–10-day prodrome of fever, malaise, headache, upper respiratory tract infection, myalgia and personality change leads to focal seizures, confusion, irritability and focal neurological deficits. In severe cases, coma ensues. The differential diagnoses include:

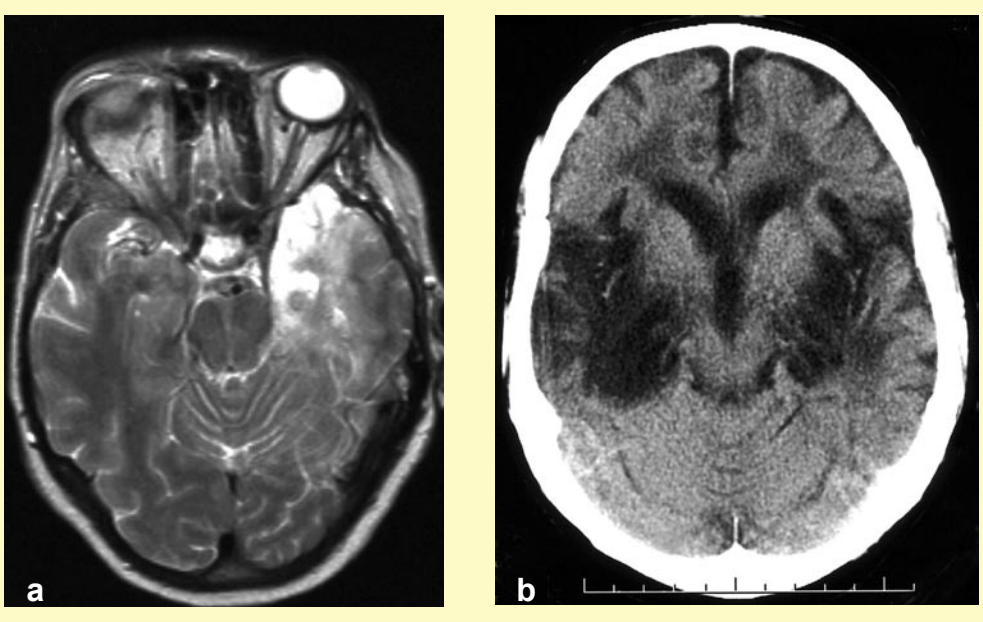
- infectious encephalitides of non-viral origin (e.g. Lyme disease)
- viral meningitis
- acute bacterial meningitis
- sagittal sinus thrombosis
- metabolic and toxic encephalopathies (cocaine and chemotherapeutic agents)
- carcinomatous meningitis
- cerebrovascular accident
- cerebral abscess
- connective tissue disease causing cerebral vasculitis
- cerebral malaria.

In immunosuppressed patients, progressive multifocal leucoencephalopathy, *Toxoplasma*, cryptococcal meningitis, tertiary syphilis, CNS lymphoma, or tuberculous meningitis are alternative diagnoses.

Investigations include:

- a full travel history
- blood culture
- blood for viral and fungal serology; blood films for malaria parasites
- EEG (bilateral periodic lateralized epileptiform discharges are pathognomonic of HSV encephalitis)
- CSF examination, if lumbar puncture is not contraindicated (lymphocytic pleocytosis 50–1500/mm^3, low or normal glucose and a mildly elevated protein)
- CT or MRI if there are focal neurological signs or a decreased conscious level (Figure 1). MRI is more sensitive in detecting the changes of HSV encephalitis
- PCR for HSV and cytomegalovirus (sensitivity > 95%).

Brain biopsy may be required if there is deterioration despite aciclovir, if CT suggests an alternative diagnosis, or in the immunosuppressed. Viruses are detected by immunohistochemical staining of brain tissue.



a Acute herpes encephalitis. T2 axial MRI of the brain showing hyperintensity and swelling of the grey and white matter of the pole of the left temporal lobe (arrowed). **b** Post-herpetic atrophy. CT scan showing marked atrophy and gliosis of both temporal lobes (arrowed) following herpetic infection. Herpes encephalitis is more often bilateral than unilateral. *Scans courtesy of Dr D Collie, Western General Hospital, Edinburgh.*

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Intensive care management is similar to that for acute bacterial meningitis, although if HSV encephalitis is suspected, aciclovir, 10 mg/kg/over 1 hour i.v. then 8 hourly for 10 days (adjusted in renal failure), should be started. Cytomegalovirus encephalitis is treated with ganciclovir, 5 mg/kg 12 hourly i.v. for 14–21 days. If treatment for retinitis has already been given, add foscarnet, 90 mg/kg 12 hourly. There is no specific treatment for other viral encephalitides; supportive care is indicated.

Complications – worsening cerebral oedema and necrosis may occur, especially in HSV encephalitis. Repeat CT scan may show hydrocephalus or severe oedema; craniotomy with decompressive temporal lobectomy may be life-saving. However, if the swelling is in the dominant hemisphere, residual disability is severe. CSF drainage may relieve hydrocephalus. Bilateral brain swelling with failed response to ICP treatment leads to tentorial herniation and brain death. Such patients are unsuitable as organ donors owing to viraemia.

Outcome in HSV encephalitis is worse in patients over 30 years of age, if treatment with aciclovir is delayed beyond 4 days from onset, and if coma and cerebral oedema are present. Sequelae include amnesia, cognitive deficits, personality change and epilepsy. Secondary brain injury due to hypoxia and infarction may cause physical disability. The mortality is 10–30%, and 60% of survivors who present in coma have neurological sequelae.

Parasitic intracranial infection

Epidemiologically, the most important parasitic infection is cerebral malaria caused by *Plasmodium falciparum.* In the UK, there are up to 2000 cases of malaria every year (usually in the pyrexial traveller or immigrant).

Cerebral malaria: obstruction of cerebral blood vessels by parasitized erythrocytes causes decreased cerebral blood flow, tissue hypoxia and inflammation. The clinical features include:

- coma
- seizures
- hypertonia
- extensor posturing
- hypoglycaemia
- haemolytic anaemia
- coagulopathy
- dysconjugate gaze
- raised ICP
- brainstem herniation.

A mortality of 15–25% can be reduced to 5% with intensive care. Investigations include:

- peripheral blood smears show malarial parasites
- antigen detection with the ParaSight F test
- lumbar puncture may yield parasites in the CSF.

Treatment should be started if clinical suspicion is high, even if tests are negative. Treatment involves quinine, 20 mg/kg over 4 hours i.v. then 10 mg/kg over 4 hours repeated 8 hourly thereafter. Supportive intensive care and ICP management may be required. Exchange transfusion is indicated if parasitaemia reaches 5–10%.

Cerebral abscess and subdural empyema

A localized suppurative infection of the brain parenchyma may arise by direct spread (e.g. sinusitis, mastoiditis, penetrating head trauma, meningitis) or by haematogenous spread (e.g. endocarditis, skin or soft tissue infections, pneumonia, dental abscesses, otitis media). Infecting organisms are often a mixture of aerobic and anaerobic, including streptococci, staphylococci, *Bacteroides*, and less commonly *Klebsiella* and *Pseudomonas*. In the immunocompromised patient, causal organisms may be atypical.

Pathophysiology – a localized area of cerebritis undergoes necrosis and liquefaction. A fibrous capsule with surrounding vasogenic oedema develops. Subdural empyema is the result of spread of infection from sinuses, or following trauma or neurosurgery. Abscess formation may cause rapid deterioration with fever, mass effect, cerebral oedema and tentorial herniation.

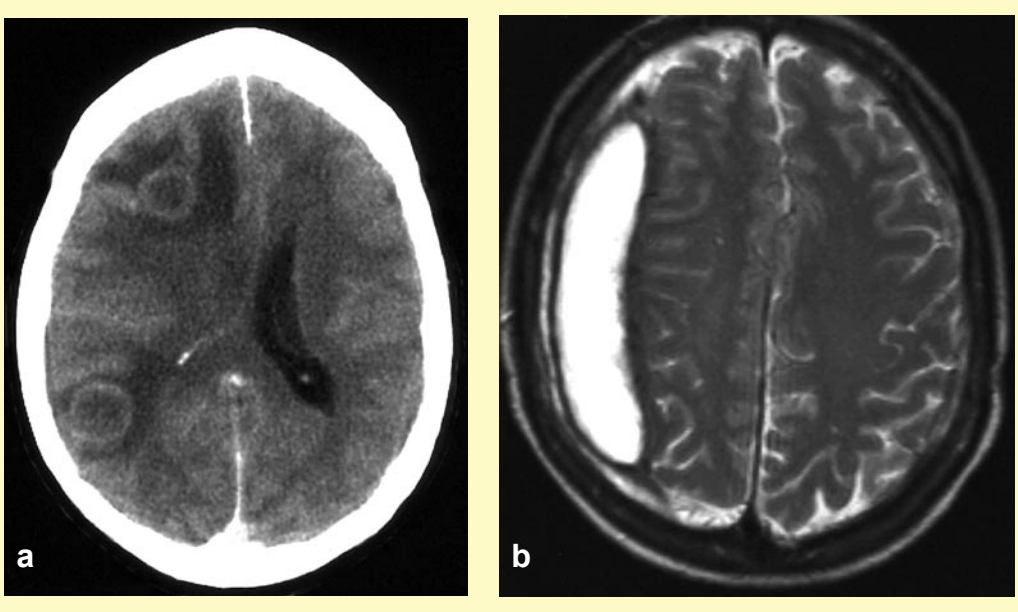
Clinical features and diagnosis – clinical features include:

- headache
- fever (50%)
- focal neurological deficits
- behavioural changes
- decreased conscious level (50%)
- seizures (30%).

Rapid onset and deterioration may indicate rupture into the ventricles. Multiple abscesses carry a higher risk of severe cerebral oedema. Brainstem abscesses may cause cranial nerve palsies, nystagmus, ataxia, swallowing difficulties, abnormal breathing patterns and airway compromise. The differential diagnoses include:

- any cerebral space-occupying lesion
- meningitis
- encephalitis
- cerebrovascular accident
- multiple sclerosis
- cerebral sarcoid.

Investigations – white cell count and ESR are raised. Blood, urine and sputum cultures should be sent for viral, fungal and *Toxoplasma* serology. CT or MRI with contrast should be carried out (MRI is more sensitive for detecting multiple small abscesses and cerebritis; enhancement with contrast favours *Toxoplasma* or cerebral lymphoma, Figure 2). Lumbar puncture is contraindicated in the presence of a space-occupying lesion.



a Cerebral abscesses. Contrast-enhanced CT scan showing multiple thin-walled ring-enhancing lesions (arrowed) in the right cerebral hemisphere with surrounding oedema, and mass-effect with effacement of the right lateral ventricle. Radiologically it may be impossible to distinguish cerebral abscesses from multiple cerebral metastases. **b** Subdural empyema. MRI scan showing a large subdural empyema in the right parietal region (arrowed) causing mass-effect and midline shift, with thickened and inflamed dura mater. Scans courtesy of Dr D Collie, Western General Hospital, Edinburgh.

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Management – for early, small, multiple, inaccessible, brainstem and some multilocular abscesses, medical treatment with antibiotics is first-line therapy (ceftazidime, 2 g 8 hourly i.v., and metronidazole, 500 mg 8 hourly i.v., the latter to cover anaerobes). Vancomycin, 1 g 12 hourly i.v. adjusted according to levels, is given in the case of post-surgical infection, staphylococcal infection or cephalosporin allergy. Serial CT scans can monitor the size of the abscess to determine the need for drainage. Antibiotics should be continued for 6–8 weeks.

Aspiration is indicated for abscesses over 2.5 cm in diameter, deterioration due to cerebral oedema, diagnostic culture or failure of medical treatment. Abscesses should be drained stereotactically under general anaesthesia. Rapid increase in size with worsening neurological function may necessitate urgent craniotomy and excision. General intensive care management follows the principles of neurointensive care outlined above. Dexamethasone, 10 mg bolus followed by 4 mg 6 hourly, is indicated for worsening cerebral oedema.

Outcome – complications include seizures, hydrocephalus and ventriculitis. Mortality is 15–25%, worse in the elderly and immunosuppressed, those with multiple abscesses and those with rapid deterioration. Brainstem abscesses are associated with a good outcome and resolution of deficits.

Post-surgical infections

Neurosurgical patients in ICU are at risk of infection via ventriculostomy catheters and ICP monitoring devices. Meticulous attention to asepsis during insertion and dressing of such devices must be observed. CSF should be sampled regularly for surveillance culture, or if the temperature or white cell count are raised.

Shunt infections require high dose antibiotics, removal of the shunt and later replacement in a separate location. Common organisms are staphylococci and Gram-negative organisms. Antibiotics may be administered directly into the CSF if the infection proves persistent. Patients with a CSF leak are susceptible to meningitis; there should be a low threshold for CSF examination and antibiotic treatment. ◆

DIC and other Coagulopathies in the ICU

Colin Green

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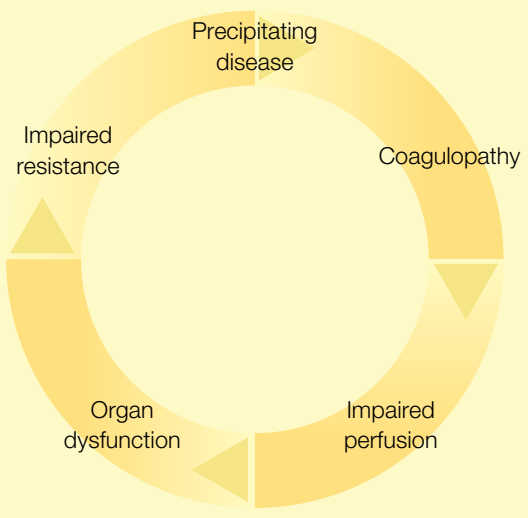
Disseminated intravascular coagulation (DIC) and other disorders of the clotting mechanisms are common in the ICU. They are usually the manifestation of a diffuse disease state, which must be treated in conjunction with the clotting defect to break the cycle (Figure 1).

Cessation of bleeding following trauma to blood vessels depends on:
- contraction of the vessel wall
- formation of a platelet plug at the break
- formation of a fibrin clot.

The relative importance of these elements varies with the site and size of the vessels involved.

Consequences of coagulopathy



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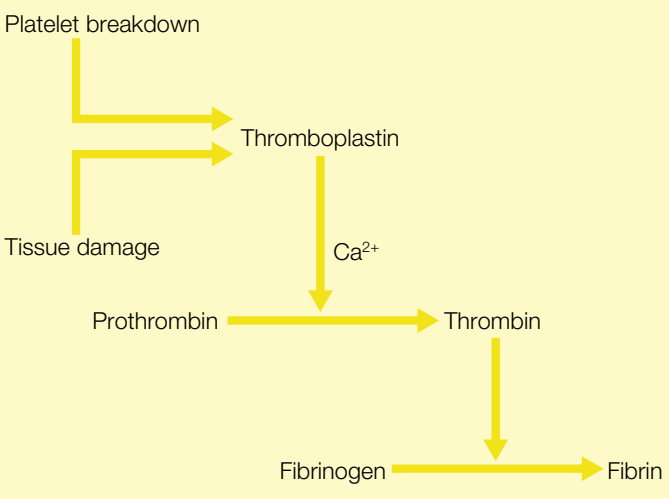
Platelet breakdown or tissue damage produces thromboplastin, which, in the presence of calcium ions, results in the formation of thrombin from prothrombin. As a continuation of the clotting cascade, fibrinogen is converted to fibrin, which forms a clot (Figure 2). The coagulation cascade creates a stable fibrin clot. This cascade is an integrated sequence of enzyme reactions, which amplifies a small stimulus into a large response. If this amplification is inappropriate to the clinical requirements, the cycle described in Figure 1 may be set in motion. The sequence begins when factor VII is exposed to tissue factor released at the injured endothelium. A complex forms, which acts on factors IX and X to produce thrombin. Thrombin causes formation of fibrin, which becomes cross-linked, forming a clot. The sequence is nominally divided into intrinsic and extrinsic components (Figure 3). Thrombin also interacts with thrombomodulin, producing a protein conformation that activates protein C. This is an anticoagulant protein involved in the control of the coagulation response to injury. It is a vitamin K-dependent plasma protein, which is synthesized in the liver and circulates as a pro-enzyme. Activated protein C reduces fibrin production and platelet activation, and has a negative feedback effect on thrombin generation. It also prevents activation of factors Va and VIIIa.

Plasmin is an enzyme that breaks down fibrin and clot, thus re-establishing circulation in small vessels. It is present in the plasma as a precursor (plasminogen). Streptokinase is a therapeutic activator of plasminogen.

Clotting cascade



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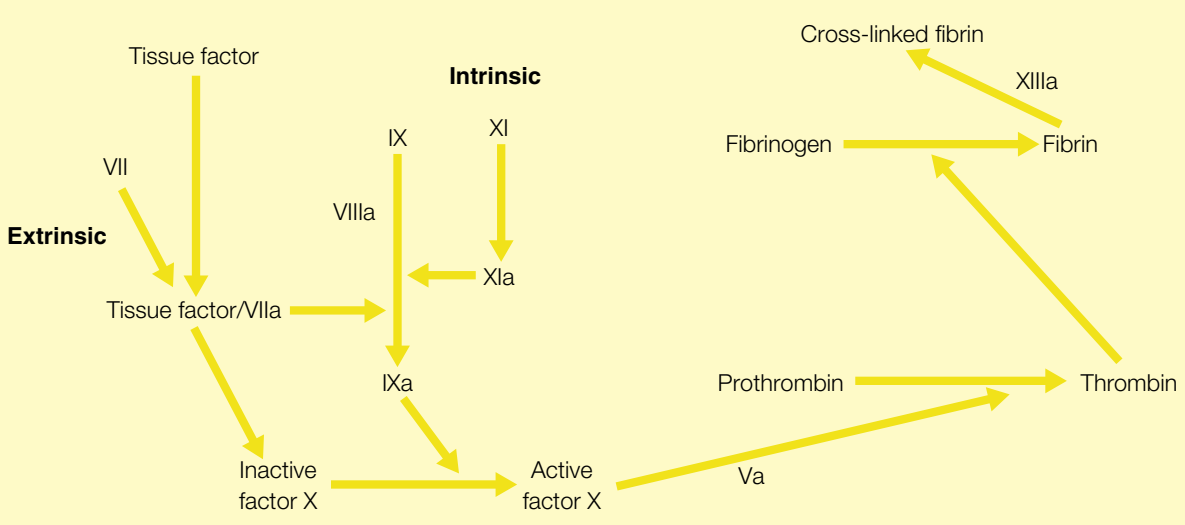
Coagulation cascade



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DIC

DIC is the most common coagulopathy in the ICU. It is a patho-logical phenomenon involving pan-activation of haemostasis and intravascular formation of fibrin. Sepsis (particularly if caused by Gram-negative organisms) is the most common stimulus but others include:
- trauma (surgery, burns, crush injury, fat embolism)
- obstetric causes (abruptio placentae, amniotic fluid embolus, pre-eclampsia)
- shock (hypovolaemia)
- liver disease (cirrhosis, cholestasis)
- malignancy
- immunological disease (ABO incompatible transfusions).
  Activation may be via:
- the extrinsic pathway by tissue factor released from damaged endothelium or leucocytes
- the intrinsic pathway
- a pathway bypassing normal activation
- direct effects on endothelium or platelets.

Complement activation and cytokine release may amplify the effects. These activities usually produce DIC in its acute or fulminant form, however, it is possible for DIC to appear in a subacute or chronic form. The result is excessive release of thrombin and the deposition of fibrin in the microvasculature. This prothrombic state leads to organ dysfunction and failure. At the same time, excessive plasmin levels lead to clot lysis (fibrinolysis) and the patient presents with haemorrhage, either spontaneously from mucosal surfaces or provoked by intravascular cannulation. Therefore, DIC depends on a balance between thrombosis and fibrinolysis and these opposing elements are represented by the extremes of DIC. The clinical diagnosis of DIC may be inferred by overt haemorrhage or by organ dysfunction, particularly in the presence of one of the common stimuli.

Investigations should include:
- platelet count (decreased)
- prothrombin time (prolonged)
- activated partial thromboplastin time (prolonged)
- fibrin degradation products (elevated); however, this measures only plasmin-cleaved fibrinogen or fibrin (if positive it does not indicate thrombin formation)
- fibrinogen levels (depressed).

The pattern of changes in these tests is often variable. D-dimer assay of plasma samples may be more useful. This is an antigen formed when plasmin breaks down the cross-linked fibrin. It distinguishes between fibrinolysis and fibrinogenolysis. A positive test indicates the presence of thrombin and plasmin.

Treatment is often difficult and controversial. The first step is elimination of the stimulus. Secondary treatment involves replacing deficient clotting factors, though some believe that this exacerbates the situation. Also, it is often argued that plasma protease inhibitors are always present in sufficient concentrations to halt increased coagulation caused by enriched component concentrations. Correction of coagulopathy involves:
- platelet transfusions if there is thrombocytopenia
- fresh frozen plasma to replace clotting factor deficiencies
- cryoprecipitate infusions to maintain fibrinogen levels at 100–150 mg/dl.

Tertiary treatment may involve heparin, but this is potentially dangerous and should be undertaken only after seeking haematological advice. Heparin potentiates antithrombin and therefore inhibits thrombin, factor Xa and other coagulation factors. In the presence of adequate levels of antithrombin, it may inhibit thrombin formation. Heparin is advisable if there are obvious signs of thrombosis or if there is protein C or protein S deficiency. In these circumstances, heparin is usually started as an infusion without a loading dose and its rate of infusion is adjusted according to the level of coagulation component measured (e.g. fibrin degradation products, D-dimer or fibrinogen).

Outcome: DIC is associated with a high mortality rate, mainly due to the underlying cause, rather than to DIC itself. The morbidity associated with DIC is largely related to thrombotic events and the resultant organ dysfunction, although catastrophic haemorrhage is certainly possible.

Other coagulopathies occurring in critical care

Platelet dysfunction

Coagulopathy caused by platelet defects occurs because of a decrease in the absolute number of platelets in circulation or a reduction in their ability to function properly.

Platelet adhesion and aggregation are primary events in normal coagulation. Platelets are first activated by adenosine diphosphate (ADP) (released by damaged endothelial cells), collagen (exposed by endothelial damage) and thrombin. The platelet surface is then modified, binding plasma fibrinogen with extracellular calcium to form an aggregate. The platelets then provide a phospholipid platform, which allows further plasma factor activation. Some inherited conditions affect the absolute number of platelets (e.g. idiopathic autoimmune thrombocytopenia), their adhesion (e.g. Bernard–Soulier syndrome) or their reactivity to collagen or abnormalities in prostaglandin pathways. These are rare and unlikely to be the cause of haemorrhage in most critical care settings. Abnormalities in platelet numbers or activity induced by disease processes or drugs are more common.

Many of the precipitants of DIC result in consumption of large numbers of platelets, rendering the patient thrombocytopenic. This fuels the haemorrhagic element of DIC. Treatment in these cases is aimed at eliminating the cause of DIC and increasing platelet numbers by transfusion.

Iatrogenic platelet dysfunction is common in the ICU. Massive transfusion without platelet transfusion decreases platelet numbers by dilution. Aspirin is the most common drug causing platelet dysfunction. It inhibits cyclo-oxidase and thus inhibits the ability of the platelets to adhere to subendothelial components and aggregate. Long-term aspirin therapy in high doses or self-inflicted overdose thus interferes with clotting.

Heparin is commonly used in extracorporeal circuits (e.g. cardiopulmonary bypass or haemofiltration circuits) to prevent thrombin formation. However, it does not prevent sequestration of platelets. For this reason, low-molecular-weight heparins are commonly used in extracorporeal circuits because they have less effect on platelets. Cardiopulmonary bypass circuits reduce platelet numbers by sequestration and may be a common cause of postoperative haemorrhage in cardiac ICUs. The induced hypothermia which accompanies cardiopulmonary bypass depresses thromboxane A2 synthesis and causes platelet dysfunction.

Platelet dysfunction is also seen in renal failure, due to the effect of urea. The defect lies in the interaction between platelets and the vessel wall.

Liver disease

Liver dysfunction is common in the ICU because of diffuse disease (e.g. septicaemia) or as a primary presentation (e.g. alcoholic cirrhosis, paracetamol overdose). Coagulation factors II, VIII, IX and X are produced by the liver; all except factor IX are involved in the extrinsic system. The synthesis of these factors relies on a vitamin K-dependent carboxylase which causes partial carboxylation and lowered activity. Deficiency is detected by prolongation of the prothrombin time. Vitamin K is poorly absorbed if there is intestinal malabsorption (common in many systemic illnesses), biliary obstruction or an enteric fistula, because bile salts are required for vitamin K absorption. Vitamin K is antagonized by coumarins (e.g. warfarin).

Fresh frozen plasma is used to treat coagulopathy due to liver disease.

Inherited disorders

Other specific, inherited disorders of clotting are uncommon and require haematological advice. ◆

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Ethical Issues in Resuscitation and Intensive Care Medicine

Gary Smith

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An ethic is a moral principle or a set of principles considered by an individual, group or society to be correct. All areas of healthcare raise moral and ethical dilemmas, but those concerning resuscitation and intensive care medicine (Figure 1) often appear more acute. There are several reasons for this.

- Patients are often unconscious, making it impossible for them to give consent or provide opinions regarding whether treatment should be administered.
- Patient's relatives are more often directly involved in decision-making on behalf of the patient than in other areas of healthcare.
- Intensive care resources are limited and rationing inevitably occurs.
- Ethical issues often involve life and death decisions. Open and honest discussion of difficult ethical matters by patients (where possible), their relatives and healthcare workers usually permits their resolution, however, very rarely, this leads to conflict. This article describes the principles of ethical decision-making and considers some areas that provide dilemmas for intensive care staff. The rights of children and of the unborn child are not considered here.

Examples of ethical issues in resuscitation and intensive care medicine

- Informed consent
- Blood transfusion and Jehovah's Witnesses
- The unconscious patient
- Withholding or withdrawal of treatment
- Research into resuscitation and intensive care medicine
- Decisions not to attempt resuscitation
- Brain death, organ donation and transplantation
- Quality of life
- Cost–benefit
- Patient confidentiality
- Advance statements
- Human immunodeficiency virus infection testing

1

Principles of ethics

It is generally accepted that there are at least four, equally weighted, principles to consider when making ethical decisions.

Respect for autonomy: this is the right of a fully informed individual to choose a certain course of action for him/herself. It encompasses decisions regarding the acceptance or refusal of treatment. The traditional paternalistic approach to healthcare delivery, in which doctors and nurses 'know best' and are the sole decision-makers, is increasingly seen as inappropriate. Consequently, a model of partnership between healthcare professionals and patients is now recommended. In general, provided a patient is competent, and the decision is rational, there is an obligation for healthcare professionals to respect the patient's voluntary decision, even if they disagree (e.g. respecting the decision of a Jehovah's Witness to refuse blood transfusions). Ethically, such an obligation is deemed to be binding, unless it is overridden or outweighed by competing moral obligations. If competent patients make irrational decisions, this may impact on the autonomy of other patients or healthcare workers. However, the courts have ruled that doctors are not obliged to provide treatment contrary to their clinical judgement.

Beneficence is the obligation to do good and is the basis for all medical and nursing care. The end point of beneficence has traditionally been interpreted as 'preserving life'. However, in situations where life is of such poor quality (e.g. because of pain or severe disability) that it is considered less beneficial for the patient than death, the principle of beneficence may include palliation and ensuring a 'good death'.

Non-maleficence is the obligation to avoid doing harm (*primum non nocere*). Conflicts may arise if beneficial medical interventions also cause harm. The potential for the 'double effect' of treatment is well recognized when morphine is administered for palliation, but inadvertently causes respiratory depression or even death.

Justice is the right of a patient to receive an equal share of the distribution of healthcare. Healthcare should not be distributed on the basis of arbitrary criteria (e.g. age, gender, race, sexual orientation) but should be apportioned fairly. Therefore, the principle of justice implies equity (fairness) and equality, and is manifest in arguments over the rationing of healthcare. Discussions about the principle of justice inevitably include the concepts of 'utilitarianism' – bringing about the greatest good to the greatest number of patients – and 'deontology', which relates to the duty of healthcare workers to individual patients.

Dilemmas

Some examples of dilemmas in intensive care and resuscitation are discussed below.

Patient consent

Informed consent is required prior to medical or surgical intervention (e.g. clinical examination, surgical operation, teaching session, entry into a research trial, medical photography) on a competent adult. Although there is generally no legal obligation to obtain written consent, it is regarded as good practice. Nevertheless, verbal or implied consent (i.e. acquiescence to the intervention in full knowledge of what the intervention entails) may suffice. Failure to obtain consent may result in charges of assault; inadequate counselling may result in charges of negligence. Informed consent demands that the patient understands the nature and purpose of the intervention, receives a full explanation of the benefits and risks of the procedure and is provided with a similar description of the alternative measures available. Consequently, the doctor obtaining consent (usually the person undertaking the procedure) must have a thorough knowledge of these matters, otherwise truly 'informed' consent cannot be obtained. For informed consent to be valid, the patient must consent voluntarily and freely.

In intensive care and during resuscitation, it may be impossible to obtain the patient's consent if they are unconscious. Doctors must then act 'in good faith' by providing care that is required to save life or prevent significant clinical deterioration. However, if there is evidence (e.g. a legally binding advanced directive) that a previously competent adult would wish to refuse all or some forms of treatment, this should be respected. In England, Wales and Northern Ireland, no one (not even a relative with enduring power of attorney) may consent legally on behalf of another adult, even though there is an increasing tendency for family members to believe that they have this authority. Consequently, the relatives of an unconscious adult cannot give consent for an operation or any other intervention. It is, however, good practice to discuss the intention to operate with them to establish that they understand the actions about to be taken and the reasoning behind them. This is termed 'informed assent' and is done, in part, to diminish risks of subsequent litigation by relatives who claim that procedures were undertaken without their knowledge. Informed assent has no legal status and has the risk of conflicting with the patient's right to confidentiality.

Consent for human immunodeficiency virus (HIV) infection testing: informed consent must be obtained from any competent patient in whom an HIV test is contemplated. This applies even when the test is being considered because a healthcare worker feels at risk of disease transmission following a needle-stick injury from a potentially HIV-infected patient. If a patient is unconscious, an HIV test may be undertaken without consent, if the test result confers a specific benefit to the patient (e.g. helps to make a diagnosis). If a healthcare worker has a needle-stick injury from an untested, unconscious patient, and the patient is unlikely to regain consciousness within 48 hours, patient testing may be justified but should be discussed with the Trust's Occupational Health Service. If a healthcare worker has a needle-stick injury from a patient who subsequently dies, and there is good reason to suspect that the patient was HIV-positive, it is advised that the dead patient's blood is tested.

Advance statements

Competent persons may state in advance their choices for treatment in the event of becoming incapacitated. This legally binding opinion is known as an advance statement or 'living will'. Such statements may include clear instructions regarding the refusal of certain therapies (advanced directive), may describe the degree of irreversible deterioration beyond which no life-sustaining support should be given and may nominate another person who should be consulted at the time that such decisions must be made. Advanced statements may be written or in the form of a witnessed oral statement.

Withholding and withdrawal of treatment

Modern medicine brings both benefits and dilemmas. In the ICU, the availability of technology does not imply that it is correct for it to be used for all patients. Unfortunately, it may have limited efficacy in some patients and may merely prolong the dying process rather than prolonging life. For instance, physiological stability may be easily obtained using vasoactive drugs and intermittent positive-pressure ventilation, but this does not guarantee hospital survival. In such circumstances, decisions may be made to withhold or limit the extent of treatment offered, or to withdraw that already being provided. Generally, treatment is withdrawn when it has ceased or failed to achieve the benefits for which it was used.

Occasionally, even a treatment that might produce short-term benefit may be withheld or withdrawn if the patient is suffering from a terminal illness. Factors usually taken into account in the decision to withhold or withdraw treatment include the diagnosis, severity of disease, co-existing illnesses, prognosis, response to current treatment, physiological reserve, anticipated quality of life and the patient's wishes, if known.

There is an important distinction between withdrawing or withholding treatment in patients in whom no clinical benefit can be obtained and a deliberate act to end a patient's life (e.g. euthanasia or murder). Withholding or withdrawal of treatment raises several ethical dilemmas, including:

- the wishes of the (often unconscious) patient
- the validity and legality of opinions or decisions made by a surrogate
- the diversion of limited resources from patients with a good chance of survival to those who are unlikely to benefit, if treatment is not withheld or withdrawn
- the definition of futility and who defines it
- the nature of medical treatment (legally, the use of artificial nutrition and hydration constitutes a medical treatment, thus, the principles that cover the withdrawal of any other artificial organ support equally apply to artificial nutrition and hydration)
- withdrawal involves a physical act (e.g. turning off a vasoactive drug) that often brings about the rapid demise of the patient; some healthcare workers find this psychologically unacceptable.

Decisions not to attempt resuscitation

A specific area in which treatment may be withheld is cardiopulmonary resuscitation (CPR). CPR may be attempted whenever cardiac or respiratory function ceases. However, as cardiopulmonary failure is an inevitable part of dying, healthcare workers should identify patients for whom it is a terminal event in their illness and for whom a prior 'do not attempt resuscitation' (DNAR) decision may be appropriate. Guidance on DNAR decisions has been published recently in a combined statement by the British Medical Association, Resuscitation Council (UK) and the Royal College of Nursing. In addition, the Department of Health has mandated that NHS Trusts must have an agreed resuscitation policy that gives respect to patient's wishes. Trusts must also identify a Non-Executive Director to be responsible for overseeing implementation of the policy and its audit.

DNAR decisions cannot be generalized and should always be made on an individual basis, ideally as part of an overall care plan for the patient and in advance of cardiopulmonary arrest. Discussions with the patient, and their family, are potentially distressing and must be handled sensitively; senior, experienced members of the medical team should undertake these. The overall responsibility for DNAR decisions rests with the consultant in charge of the patient's care. Any discussions about whether to attempt CPR should be documented, signed and dated in the patient's record. If the clinical decision is challenged and agreement cannot be reached, legal assistance may help to clarify the appropriate course of action.

Overall survival to hospital discharge following cardiac arrest is about 15%, but may be considerably lower for certain patients (e.g. those with sepsis or cancer). Inappropriate use of CPR makes death undignified and may have ethical implications for others. For instance, repeated attempts that provide only short-term clinical success can be emotionally draining for the patient's family and may mean that resources are diverted from patients with a potentially better outcome. Additionally, failed CPR can lower the morale and enthusiasm of the healthcare team.

The public often has the misconception that a DNAR decision is analogous with a decision not to treat. In fact, a decision not to perform CPR is entirely consistent with the full provision of medical and nursing care up to that point. Consequently, patients and their families should be reassured that all other treatment and care (e.g. analgesia, antibiotics, physiotherapy) may continue to be offered. Finally, decisions about resuscitation must be reviewed regularly and in the light of changes in the patient's condition and wishes.

Research in intensive care patients
Research performed on intensive care patients or those under-going CPR poses several ethical difficulties. For instance, the heterogeneity of patients in ICUs limits the generality of research outcomes. Additionally, the ability to obtain a patient's consent is limited by disease-induced coma or pharmacological sedation. If a patient is unable to give consent to entry into a trial, it is customary to obtain informed assent from the patient's next-of-kin, although deferred consent (consent after patient recovery) is an alternative approach for some studies. Particular problems arise for research into areas of CPR where consent cannot be obtained from the patient and there is insufficient time to obtain informed assent from relatives. Finally, the ethical principles of beneficence and non-maleficence are important here because patients entering into trials do not necessarily benefit from doing so, and may actually be harmed by it. In general, it is advisable to discuss all research into areas of resuscitation or intensive care with the Local or Regional Research Ethics Committees.

Human Rights Act 1998

The Human Rights Act 1998 came into force in October 2000, bringing into UK law many of the rights set out in the European Convention on Human Rights. The Act includes numerous Articles, some of which have implications for healthcare (especially, Articles 2, 3, 5, 6, 8, 9, 10, 12 and 14). For instance, Article 2, which covers the right to life, has implications for withholding or withdrawing treatment. This Article does not mean that healthcare workers must always strive to save life. Rather, it implies that the medical decision-making process must consider the patient's right to life and that the NHS must act 'reasonably' in its decision-making. Withholding or withdrawing treatment does not breach Article 2 if non-treatment is in the patient's best interest (e.g. withdrawing nutrition in a patient with persistent vegetative state). Other Articles of the Act that may have implications for critical care include Article 3 (treatment without consent), Article 8 (the right to be provided with sufficient information to give valid, informed consent) and Article 9 (the right to refuse life-prolonging therapy).

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Fever in ICU Patients

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Fever is one of the most common physical signs in critically ill patients. The Society of Critical Care Medicine defines body temperature over 38.3◦C as clinically significant fever. This figure is a conversion of 101◦F to centigrade, and in general a temperature over 38◦C is considered significant.

Fever may indicate infective or non-infective inflammatory processes. Both are common in ICUs and attempts to correlate different processes with temperature ranges and timing have limited clinical value. Prolonged fever is associated with a higher mortality. The causes of fever vary, but ventilator-associated pneumonia, catheter-related sepsis, urinary tract infection and acute myocardial infarction are ubiquitous. Surgical patients have additional potential causes of fever.

Infection is the most common cause of death in critically ill patients, therefore fever should always be taken seriously. Rigorous efforts should be made to identify the sources of sepsis at an early stage. Critically ill patients often have complex underlying illness, therefore it is essential that a detailed history is obtained and that there is access to hospital records. Physical examination should be thorough and include all sites of potential infection. Because of the increasing risk of developing multiple-resistant infection, antibiotic therapy should be based on microbiological cultures; empirical therapy is occasionally necessary. A diagnosis of non-infectious fever should be made only in the appropriate circumstances and in the absence of clinical evidence of sepsis.

Pathophysiology: fever occurs when thermoregulatory mechanisms produce and sustain an elevated body temperature. Exogenous pyrogens (microorganisms, immunological mediators, toxic agents) trigger cytokine release (interleukins 1 and 6 and tumour necrosis factor-α) from monocytes, lymphocytes, macrophages and endothelial cells. These bind with receptors in the preoptic anterior hypothalamus, releasing prostaglandins (PGs), predominantly PGE_2 causing local cyclic-AMP release. This decreases the activity of local warm-sensitive neurons, increasing heat production, activating heat conservation and modifying the thermoregulatory ‘set point’ of the hypothalamus.

Hypermetabolic states (e.g. malignant hyperpyrexia) cause fever by increased heat production.

Fever patterns: a reliable diagnosis cannot be made from the pattern of fever. Most patients have remittent or intermittent fever with or without rigors that usually follow diurnal variation when due to infection.
- Sustained fevers may occur in patients with infectious or non-infectious causes.
- Patients with severe sepsis may be afebrile or hypothermic.
- Septic afebrile patients have a higher mortality.
- The cooling effect of continuous veno-venous haemofiltration may mask ‘latent’ fever.

Aetiology

Non-infectious: in non-infectious fever the temperature is usually less than 38.9◦C. Drug or transfusion reactions may cause higher temperatures (Figure 1). Postoperative patients who develop fever in the first few days may have no infective source.
- General anaesthesia affects anterior hypothalamic thermoregulation (similar patients receiving regional or local anaesthesia remain apyrexial).
- Cytokine release from tissue injury or blood transfusion may be implicated.
- Acute adrenal insufficiency may present as fever.
- Malignant hyperthermia (see later), is usually detected intraoperatively, but its onset may be delayed.

Non-infectious causes of fever

- Acute respiratory distress syndrome (ARDS)
- Adrenal insufficiency
- Alcohol/drug withdrawal
- Aspiration pneumonitis
- Bowel ischaemia
- Deep venous thrombo-phlebitis
- Dissecting aortic aneurysm
- Giant cell arteritis
- Gout and pseudogout
- Haemorrhage into CNS, lung, retroperitoneum, adrenals
- Heat stroke
- Henoch–Schoenlein purpura
- HIV-related non-infective fever
- Hypersensitivity reactions
- Hyperthyroidism
- Myocardial infarction
- Neoplastic fevers
- Pancreatitis
- Pulmonary atelectasis
- Pulmonary/fat embolism
- Post surgical (first 2 days)
- Reaction to blood products
- Reaction to drugs
- Rheumatoid arthritis
- Seizures
- Systemic lupus erythematosus
- Transplant rejection

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Drug-induced fever (e.g. by antibiotics, anticholinergics, streptokinase) is easily overlooked, little reported and its incidence unknown. High spiking temperatures, chills, leukocytosis and eosinophilia are characteristic. Relative bradycardia is rare.

Fever occurring in a patient receiving blood or blood products may signify a transfusion reaction. Platelet reactions are most common. Fever may be a sign of clinically unsuspected acute myocardial infarction.

The combination of prolonged fever, leukocytosis and pulmonary infiltrates is often inappropriately diagnosed as nosocomial or ventilator-associated pneumonia. Diagnosis may be improved by semiquantitative culture of non-bronchoscopic lavage specimens. Fever may be a feature of the chronic fibroproliferative stages of acute respiratory distress syndrome (ARDS).

Infectious: a temperature over 38.9◦C for more than 2 days usually indicates infection (Figure 2). Critically ill patients are vulnerable to nosocomial infections owing to prolonged hospitalization, antibiotic therapy, invasive devices, co-morbidity and debility. There are particular concerns in surgical patients.
- Delayed resolution of fever despite definitive intervention and antibiotic therapy (e.g. appendix abscess, peritonitis, ascending cholangitis) does not necessarily imply continuing sepsis.
- Fever following trauma may indicate bacterial contamination of wounds, joints or bone; tetanus should also be considered.
- Clostridial myonecrosis or streptococcal cellulitis may cause fever within 72 hours of elective surgery.
- Fever and pain may be presenting symptoms of necrotizing fasciitis in susceptible patients (e.g. the obese, those with diabetes).

Infectious causes of fever in intensive care

Respiratory
- Sinusitis
- Lung abscess
- Empyema
- Pneumonia
- Tracheobronchitis

Invasive devices
- Intravenous/arterial lines (phlebitis, bacteraemia, fungaemia)
- Cardiac valve prosthesis or pacemaker
- Urinary catheter (pyelonephritis, prostatitis, prostatic abscess, urinary infection)

Gastrointestinal
- Antibiotic-associated colitis
- Cholecystitis/cholangitis, acalculous cholecystitis
- Infections due to transfusion (hepatitis B and C, cytomegalovirus)
- Diverticulitis

Surgical
- Wound infection
- Peritonitis
- Deep infection/abscess

Neurological
- Meningitis/encephalitis
- Cerebral/epidural abscess
- Tetanus, poliomyelitis

Cardiovascular
- Endocarditis
- Infected arterial graft
- Viral myocarditis

Skin, soft tissue and bone
- Cellulitis
- Decubitus ulcer
- Necrotizing fasciitis
- Septic arthritis/osteomyelitis

2

Common infective causes

Catheter-related sepsis: about 25% of central venous catheters become colonized; 5% of patients with a central venous catheter develop catheter-related sepsis. The incidence is related to:
- technique of catheter insertion
- length of time *in situ*
- number of ports
- quality of sterile precautions during handling.

Common causal organisms include *Staphylococcus aureus* and coagulase-negative staphylococci, enterococci, Gram-negative bacteria and *Candida* spp. The incidence of catheter-related sepsis can be reduced by strict aseptic precautions during insertion and handling and the use of antimicrobial-bonded catheters.

Ventilator-associated pneumonia is said to occur in 25% of ventilated patients, but is probably overdiagnosed. Focused antibiotic policies guided by non-bronchoscopic lung lavage investigation may improve the outcome of suspected ventilator-assisted pneumonia.

Nosocomial sinusitis is an important, often unrecognized source of infection. It is:
- associated with use of nasogastric/nasotracheal tube (incidence lower with oral tubes)
- diagnosed on clinical or radiological suspicion or transnasal puncture
- treated by removing nasal tubes, sinus drainage and antibiotics. Radiological abnormalities of sinuses do not necessarily imply infection.

Urinary tract infection: urinary tract colonization is common, but clinically significant urinary tract sepsis is rare in patients with normal urine flow. Obstruction or other abnormalities of the urinary tract increase the risk. Urine may yield positive bacterial cultures until the catheter is removed. The use of unnecessary antibiotics risks inducing multiple-resistant bacteria.

Treatment
- Thorough clinical examination is essential.
- The cause (e.g. abscess drainage, potentially infected lines) should be removed or treated.
- Investigations and microbiological surveillance should be performed and repeated as required.
- The diagnosis of non-infectious fever is one of exclusion.

Antipyretics are generally best avoided because fever is an important component of the host response. The response to treatment is more difficult to assess in patients taking antipyretics and temperature enhances the host defences and increases pathogen susceptibility. However, high temperatures are symptomatically unpleasant and other effects (e.g. increased cardiac output, oxygen consumption, carbon dioxide production and energy expenditure) may be deleterious. Antipyretics may be appropriate for some patients, for example those with limited cardio-respiratory reserve or neurological injury. If the body temperature is over 41◦C it is important to prevent further escalation because of the increased risk of cerebral injury.

Cooling methods: the use of sponging, fans and hypothermia blankets is controversial and may be no more effective than antipyretics. Core cooling methods, such as intravenous cooling cannulae, body cavity irrigation or extracorporeal methods are probably more effective. Muscle relaxants may be beneficial to prevent shivering. Large temperature fluctuations, hypermetabolism, increased oxygen consumption and rebound hyperthermia may occur after cooling.

Specific indications for fever reduction: moderate fever may offer physiological advantage, but there is no evidence that very high temperatures (over 40.5◦C) are beneficial. The risk of thermal cerebral injury increases with duration as temperature exceeds 41◦C. Seizures induced by hyperpyrexia and hypoglycaemia multiply this risk and further increase heat production. Fever reduction is therefore indicated in conditions in which hyperpyrexia occurs, including malignant hyperpyrexia, heat stroke, neurolept-malignant syndrome and viral encephalitis. The role of induced hypothermia following traumatic head injury remains unconfirmed, but because persistent pyrexia is associated with a worse outcome, antipyretics and active cooling may be indicated.

Relative indications for fever reduction
Septicaemia/septic shock – in patients with severe sepsis and hyperpyrexia, continuous veno-venous haemofiltration may improve haemodynamic stability and reduce vasopressor requirements although the benefits remain unproven. Whether the effect is secondary to cytokine removal, cooling or both is unknown.

Postcardiac arrest – induced hypothermia may improve outcome and antipyretics or active cooling may be beneficial.

'Febrile' fits in children – cooling to normothermia may reduce the seizure threshold, but antipyretics should be reserved for children with severe discomfort or high fever.

Patients with critical oxygenation – in patients with refractory hypoxaemia, reducing the oxygen demand is logical, though not evidence-based. ◆

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Fluid and Electrolyte Balance in Intensive Care Patients

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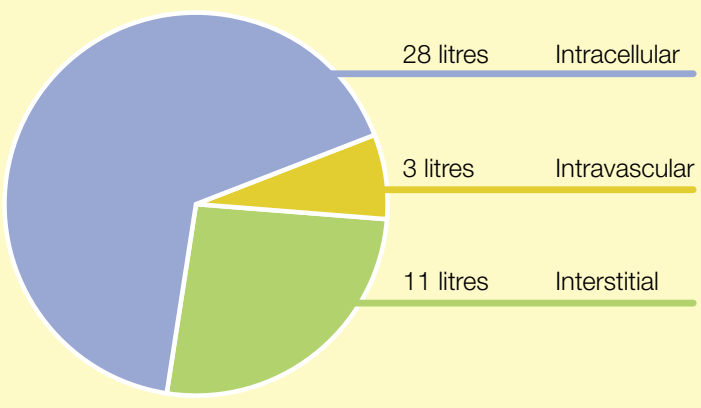
Fluid and electrolyte balance is one of the basic principles of management of the critically ill patient. Attaining this balance can be achieved only with a good working knowledge of the underlying physiology of body fluid compartments coupled with practical management strategies including accurate record keeping and appropriate interpretation.

Body fluid compartments

In a 70 kg man about 60% of body weight is made up of water (42 litres), for women the value is 55% and declines with age. The total body water is not distributed evenly throughout the body. It is divided into two major components: the intracellular fluid (ICF) and extracellular fluid (ECF), which contain about 28 and 14 litres, respectively. The extracellular space is divided into intravascular and interstitial compartments (see *Anaesthesia and Intensive Care Medicine* **2:2:** 69). The intravascular fluid is the plasma volume, which constitutes about 3 litres, and the interstitium holds the remaining 11 litres (Figure 1). Each compartment contains different concentrations of electrolytes and proteins (Figure 2).

Distribution of body water in the three major body fluid compartments



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Distribution of electrolytes, water and protein between body fluid compartments

	Intravascular (mmol/litre)	Interstitial (mmol/litre)	Intracellular (mmol/litre)	Typical plasma (mmol/litre)	Daily requirements (mmol/kg/day)
Sodium	140	145	10	135–150	1–1.5
Potassium	3.7	3.8	155	3.5–5.0	1–1.5
Chloride	102	115	3	98–107	1–1.5
Calcium	1.2	1.2	0.01	2.2–2.6	0.07–0.14
Magnesium	0.8	0.8	10	0.7–1.0	0.14–0.17
Phosphate	1.1	1	105	0.8–1.4	0.28–0.56
Bicarbonate	28	30	10	22–30	
Water	3	11	28		2–2.4 litres/day

2

Physical principles

Several physical principles govern the distribution of fluid and electrolytes between body fluid compartments.

Diffusion

Electrolytes move from a region of high concentration to a region of lower concentration in an attempt to achieve equilibrium by diffusion. If diffusion occurs across a membrane then the permeability of that membrane to the electrolyte influences the rate of diffusion. Diffusion is commonly accompanied by bulk flow through biological membranes (when the concentration difference is high) with ordered flow of particles rather than the unordered movement of diffusion alone.

Osmosis

Osmosis is the diffusion of water through a semipermeable membrane from a region of low osmolality to a region of higher osmolality. It leads to the movement of water through all body fluid compartments. The osmotic pressure generated by particles (electrolytes and proteins) is proportional to their number and not their mass.

Active transport

Active transport is an energy requiring process that regulates sodium and potassium exchange at the cell membrane. This gives rise to electrochemical imbalance across the membrane and helps to maintain the resting membrane potential and cell volume.

Colloid osmotic pressure

Any particle (electrolyte or protein) can exert an osmotic pressure, but the free diffusion of electrolytes across the capillary wall negates their osmotic effect. Passage of proteins across the capillary wall is impeded in the normal state. For this reason they exert an osmotic effect within the capillary, commonly referred to as the colloid osmotic pressure or oncotic pressure. The osmotic effect of these proteins is about 50% greater than would be expected for the proteins alone. The reason for this is that most proteins are negatively charged, attracting positively charged ions such as sodium (the Gibbs–Donnan effect). These positively charged ions are osmotically active and therefore increase the effective osmotic pressure.

Starling equation

In health, the movement of fluid across the capillary wall can be described by the Starling equation:

$$J_v = K_{fc}[(P_c - P_i) - \sigma(\pi_p - \pi_i)]$$

where: J_v, solvent flux; K_{fc}, filtration coefficient; P_c, capillary hydrostatic pressure; P_i, interstitial hydrostatic pressure; σ, reflection coefficient; π_p, protein osmotic pressure (oncotic) of plasma; π_i, protein osmotic pressure (oncotic) of interstial fluid.

The reflection coefficient is 0 if the capillary is freely permeable to the protein or colloid in question and 1 if it is impermeable.

In most capillaries the Starling equation is positive, indicating some net movement of fluid to the interstitium. This fluid is normally absorbed by the lymphatic system and returned to the intravascular space. In disease, the permeability of the capillary often increases and more protein and fluid is lost to the interstitium. This decreases the plasma oncotic pressure and, despite an up-regulation of the absorptive capacity of the lymphatic system, interstitial oedema results when interstitial fluid is formed faster than it can be removed by lymphatics. It is for this reason that colloids are given to restore the plasma oncotic pressure and retain fluid within the intravascular space. However, oncotic pressure is dependent on the number of osmotically active particles and not their size or mass. The ideal choice of colloid is therefore a compromise between intravascular retention (dependent on the size of the colloid particles and the rate of their metabolism) and osmotic pressure potential. The lower molecular weight succinylated gelatins are suitable for intravascular expansion if there is a low suspicion of capillary leak. The medium molecular weight hydroxyethyl starches are more suitable for conditions such as sepsis where there is a greater degree of capillary leak.

Crystalloids distribute according to their predominant electrolyte or particle. Fluids such as 5% glucose distribute evenly through all three compartments because the glucose is rapidly metabolized to water. 0.9% saline distributes evenly between the intravascular and interstitial spaces (ECF) because the capillary endothelium is freely permeable to sodium, hence their similar sodium content. There will be some entry of sodium into the cell but this is returned to the interstitial space by the sodium–potassium pump to regulate cell volume and electrochemical balance.

Water and electrolyte balance

The principal electrolytes are sodium, potassium, chloride, calcium, magnesium and phosphate. Many of these electrolytes and minerals are integral constituents of enteral and parenteral feeds and can be adjusted easily for individual patients. However, deficiencies and excesses are common in critical care. It is routine to measure the plasma concentrations of these electrolytes, though they are poorly reflective of total body stores. Excessively high or low values may induce deleterious effects and should be corrected on an as-required basis. All deficiencies or excesses of electrolytes are the result of an imbalance in supply and loss, redistribution and disordered regulation. Where possible, it is important to identify the cause of the abnormality in order to correct the problem. Patients in ICU are subjected to a wide range of noxious stimuli and exhibit an up-regulation in their neuroendocrine response. This results in a tendency to retain water and sodium.

Water

Water and sodium balance are difficult to separate because of their linked regulation mechanisms. The average daily water requirement is 2–2.4 litres/day, generally achieved via parenteral or enteral feeding and drug carriage volume. If these volumes are not achieved they can be supplemented with a crystalloid. The daily fluid loss varies depending on the patient's condition, and it is usual for electrolytes to be lost in proportion to water. However, conditions such as excess sweating, hyperthyroidism, fever, diabetes insipidus and hypercalcaemia cause more water than electrolytes to be lost. 5% glucose may be used to supply intravenous water. In general, there is a further insensible loss of 500 ml/day from the lungs and skin, which must be taken into account in fluid balance calculations.

Sodium

The normal concentration of sodium in plasma is 135–150 mmol/litre. Its principal route of excretion is via the kidney and is mainly regulated by the renin-angiotensin-aldosterone system. The distribution of water and sodium throughout the extravascular space means that they are inextricably linked when considering maintenance and replacement. For the most part, 1–1.5 mmol/kg/day of sodium is required and is usually met from the maintenance fluid or administered feed. Hyper- and hyponatraemia are common and it is important to establish the cause before embarking on treatment. Oedematous patients generally have high body sodium stores but may have relative water deficiency. It should be established if body sodium stores are high, normal or low and whether body water is normal or low. The rate and degree of correction also differs in hyper- and hyponatraemia depending on whether the aetiology is acute or chronic.

Potassium

Potassium is predominantly an intracellular ion, the excretion of which is mainly via the kidney. The normal plasma concentration is 3.5–5.0 mmol/litre. Potassium is exchanged in the kidney for sodium and hydrogen ions and redistributed across cell membranes depending on the acid–base status of the plasma. It is important to maintain potassium because of its effects on membrane stabilization.

Hypokalaemia is a potent stimulus for arrhythmias and promotes muscular weakness. Potassium supplementation is commonly required and should not exceed 40 mmol/hour because the rate of change of potassium is also a potent arrythmogenic stimulus.

Hyperkalaemia can cause life-threatening dysrhythmias and is common in patients with renal impairment. Treatment options include ion exchange resins, glucose and insulin infusions, intravenous bicarbonate, calcium chloride and dialysis.

Magnesium

Magnesium is primarily an intracellular ion and is involved in energy production, utilization and membrane stabilization most often as an enzyme cofactor. It is regulated mainly by the influence of parathyroid hormone (PTH) and aldosterone on the kidney. The normal plasma concentration is 0.7–1.0 mmol/litre. Deficiency is common and a potent source of arrhythmias. It should be corrected with 20–40 mmol infused over 1–2 hours.

Calcium

Calcium is widely distributed with normal plasma concentrations of 2.2–2.6 mmol/litre. PTH and calcitriol regulate its concentration. Only the ionized fraction is active and when it is less than 0.8 mmol/litre may cause tetany, convulsions and a prolonged QT interval. If symptomatic, 5–10 ml of 10% calcium chloride can be administered over 5 minutes.

Phosphate

Phosphate and calcium regulation are linked but calcitriol predominantly regulates phosphate. Severe hypophosphataemia, especially when below 0.3 mmol/litre, can limit ATP formation. Symptoms and signs include muscle weakness, myocardial depression and platelet dysfunction. Supplementation, although empirical, can be achieved with a maximum rate of infusion of 9 mmol over 12 hours.

Fluid management strategies

Maintenance

In general, most maintenance requirements are met from enteral or parenteral feeding and drug carriage fluid. These may be supplemented with a crystalloid. For those who are not fed and/or receiving colloid solutions, a salt containing crystalloid (e.g. lactated Ringer's solution or 0.9% saline) may be required at about 80–100 ml/hour.

Replacement

In general, replacement of fluid should be like for like. Most of the solutions lost from the body contain salt and should be replaced as such. However, it is important to take into account the type of fluid being lost when considering its replacement (e.g. blood, large or small bowel fluid, ascitic fluid, pleural fluid) because they have differing water and electrolyte concentrations. Blood is generally given in a reactionary fashion to maintain haemoglobin at 8–10 g/dl, though a liberal transfusion practice has recently been questioned.

In critical care patients, the correction of hypovolaemia is important to maintain oxygen delivery to the tissues and for removal of waste products.

It is difficult to gain information on the adequacy of resuscitation of the interstitial and intracellular compartments. Many 'soft' endpoints, such as thirst, tissue turgor and fluid balance charts offer at best empirical estimates. The intravascular compartment has in comparison 'harder' end points such as heart rate, central venous pressure, stroke volume, blood pressure and pulmonary artery wedge pressure which, when challenged dynamically, allow an assessment of the adequacy of resuscitation of the circulating volume. Static pressure measurements are a poor guide to the adequacy of intravascular volume replacement. The most efficient way to achieve adequate circulating volume is to use a fluid challenge approach with a colloid. There is controversy as to whether a colloid or crystalloid is most suitable for resuscitation. Colloids are retained in the intravascular space long enough for adequate change in the haemodynamic end points to be assessed and exert a persisting colloid osmotic pressure. Crystalloids do not exhibit this effect, making colloids the logical choice. Fluid may be administered as boluses of 100–200 ml and their effect on haemodynamic end points such as central venous pressure or stroke volume must be observed. Fluid challenges should be repeated until there is no rise in stroke volume or there is a rise in central venous pressure greater than 3 mm Hg. The distribution of the administered fluid is then largely predictable according to its properties and the nature of the underlying illness.

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Gastrointestinal Tract Haemorrhage and Ulcer Prophylaxis in ICU

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Gastrointestinal tract haemorrhage is classified as upper or lower depending on the source of bleeding (about 20% are lower). Acute gastrointestinal bleeding is a common cause of hospital and ICU admission and has a mortality of about 10%. Risk factors that increase the likelihood of death include old age, co-morbidity, coagulopathy and the magnitude of bleeding. Ulcers involving arteries, such as those close to the left gastric artery on the lesser gastric curve, or on the posterior duodenal wall, are particularly problematic. Figure 1 lists the common causes of bleeding.

Common causes of gastrointestinal haemorrhage

Upper gastrointestinal haemorrhage	**Percentage (%)**
Duodenal ulcer	40
Gastric ulcer	17
Acute erosions (gastritis, oesophagitis, duodenitis)	12
Varices	10
Mallory–Weiss tear	5
Cancer	3
Other	13
Lower gastrointestinal haemorrhage	
Colon	74
• Diverticular disease	16
• Angiodysplasia	30
• Carcinoma of the colon	11
Rectal lesion	4
Upper gastrointestinal tract	11
Small bowel	9
• Inflammatory bowel disease	
• Meckel's diverticulum	
• Arteriovenous malformation	

1

Clinical features
Upper gastrointestinal bleeding is characterized by haemat-emesis and the passage of melaena (stools blackened by altered blood). Bleeding ulcers are often painless, especially in the elderly. Signs of massive blood loss are hypovolaemia, pallor, tachycardia, sweating, cyanosis, altered mental sensorium and oliguria. A more occult presentation is possible with pallor, fatigue and the development of anaemia. A history of vomiting before haematemesis suggests a Mallory–Weiss tear.

Lower gastrointestinal bleeding arises from a distal source and is characterized by the passage of fresh blood per rectum (haematochezia). However, bleeding from the small bowel or right colon may manifest as melaena. Abdominal pain suggests ischaemia or inflammatory bowel disease, whereas painless lesions include diverticulosis, angiodysplasia and Meckel's diverticulum. Haemorrhoids (which become swollen in portal hypertension) can be a profound source of bleeding. An occult presentation with anaemia is more likely with lower than with upper gastrointestinal bleeding.

Investigations may include combinations of:
- blood (urgent to include full blood count, coagulation screen, urea and electrolytes, cross-match)
- endoscopy
- angiography
- radiolabelled red cell scan.

Investigations and management are often concurrent, depending on the severity of the case. Blood tests and endoscopy are essential. Barium studies have been superseded by endoscopy. Angiography and radionuclide tests are useful only in lesions that are bleeding briskly at the time. These lesions are usually best managed with surgery, but these techniques may be considered in surgically high-risk patients.

Management

Non-variceal upper gastrointestinal bleeding

Resuscitation – severe hypovolaemia leads to a depressed conscious level and is therefore a potential risk to airway patency, especially when associated with vomiting. The patient should be resuscitated using clear fluids, colloids and blood, guided by regular monitoring of vital signs (including postural blood pressure, conscious level and urine output) and repeat blood investigations. This is best achieved in a high dependency nursing area where invasive monitoring can be instituted; particularly for elderly patients in whom co-morbidity and existing drug therapies make resuscitation more difficult.

Assessment and management – patients who require early intervention (endoscopy or surgery) include those at high risk and those with evidence of significant bleeding (e.g. presence of postural hypotension, cardiovascular instability and blood loss requiring 4 or more units of red cells to be transfused in 12 hours). Rockall devised a scoring system (Figure 2) to stratify the risk of re-bleeding and death following gastrointestinal haemorrhage. This system can help to identify at-risk patients, possibly triggering management decisions at a certain score (e.g. 3, central venous pressure monitoring; 5, surgical referral).

The Rockall score for stratifying risk of re-bleeding and death following upper gastrointestinal haemorrhage

Contributor	**Score**			
	0	**1**	**2**	**3**
Age (years)	< 60	60–80	> 80	
Shock	None	Pulse > 100 Blood pressure > 100	Blood pressure < 100	
Co-morbidity	None		Ischaemic heart disease, congestive heart failure	Renal/liver failure, disseminated malignancy
Diagnosis	None, Mallory–Weiss tear	All others	Upper gastrointestinal tract malignancy	
Endoscopic findings	None		Blood in upper gastro-intestinal tract, adherent clot, visible vessel	

2

Pharmacological intervention includes the early use of proton-pump inhibitors to aid ulcer healing. These can be given intravenously in the first instance. Bleeding due to coagulopathy should be managed with the administration of blood products (as guided by investigations) and antifibrinolytic agents (e.g. tranexamic acid).

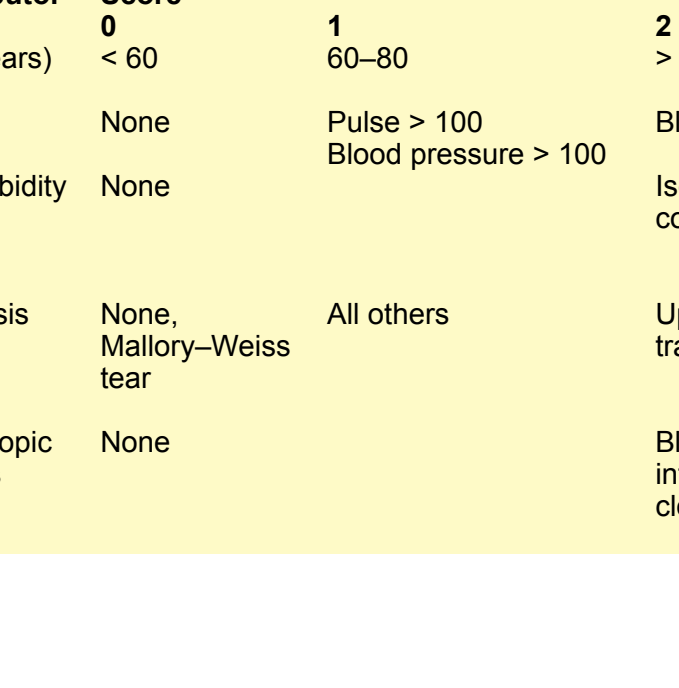
Endoscopic therapy can stop haemorrhage from some sources of upper gastrointestinal bleeding (see below). Endoscopic techniques include adrenaline (epinephrine) injection, electro-coagulation, thermal probes and laser photocoagulation. The initial haemorrhage is usually stopped in over 90% of cases; but 90% of arterial bleeds re-bleed. Endoscopic treatment is more effective than medical treatment alone at reducing the rate of re-bleeding and subsequent transfusion requirements.

Surgery is the definitive treatment for upper gastrointestinal bleeding, but the mortality is 15–20%. Procedures include under-running of bleeding ulcers to secure haemostasis, vagotomy or partial gastrectomy. Results are better when surgery is performed early; therefore, there must be close liaison between senior members of the medical, intensive care and surgical teams.

Variceal bleeding

Acute variceal bleeding is a complication of portal hypertension and has a high mortality. Management includes fluid resuscitation concurrent with medical, endoscopic and/or surgical intervention. Guidelines for management are shown in Figure 3.

Guidelines for management of variceal bleeding



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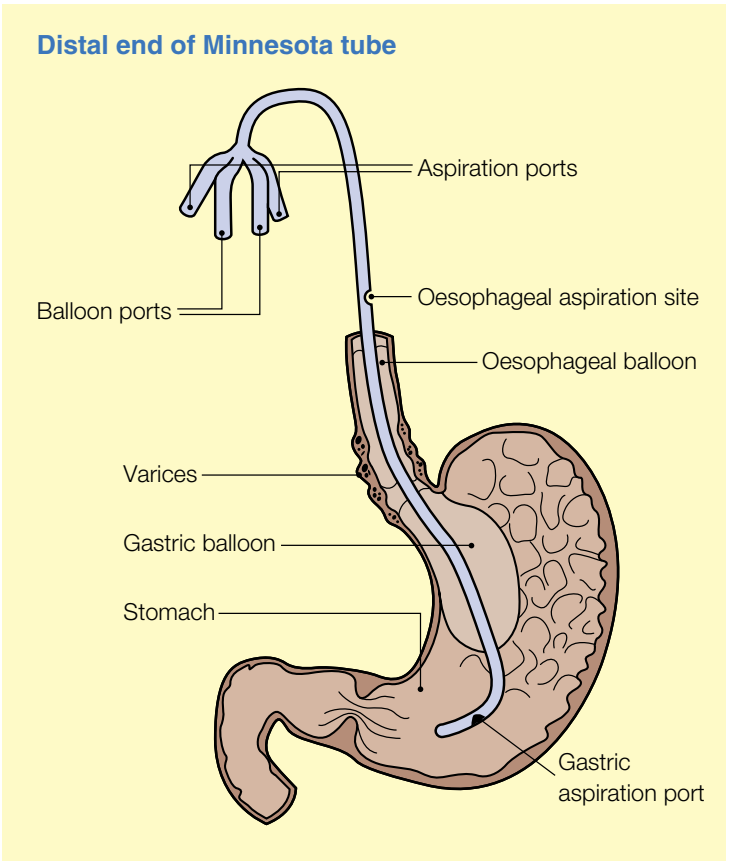
Resuscitation – gastrointestinal haemorrhage with a background of liver disease can precipitate an encephalopathy; therefore attention to airway, breathing and circulation is required. Bleeding can be torrential, but care must be taken not to over-transfuse because rebound portal hypertension risks re-bleeding.

Medical management – the reversal of coagulopathy using blood products is paramount. Antidiuretic hormone (ADH) analogues (vasopressin, terlipressin) are used to lower portal pressure, but can cause cardiac ischaemia and coagulopathy. Somatostatin analogues given as an infusion (e.g. octreotide) are safer but reports of efficacy are varied. Long-term non-selective β-adrenergic receptor blocking agents can decrease portal hypertension and re-bleeding.

Endoscopic therapy – endoscopic injection of a sclerosing agent into varices causes venous thrombosis and tissue fibrosis allowing about 85% of bleeds to be controlled. Complications (ulceration, chest pain, mediastinitis) are common. Gastric lesions are more difficult to inject and control than oesophageal varices. The use of rubber bands to ligate varices is as effective as injection sclerotherapy with fewer complications.

Balloon tamponade – using a balloon to exert direct pressure on the bleeding point can control variceal bleeding. The Sengstaken–Blakemore tube has been replaced by the Minnesota (oesophageal and gastric balloons and aspiration ports) (Figure 4) and Linton (gastric balloon with oesophageal and gastric ports) tubes. Pressure on the gastric veins feeding the varices seems to be more important than direct pressure on the oesophageal varices. Limiting the duration of inflation and pressure is likely to be important in preventing pressure necrosis of the oesophageal mucosa, but definitive advice regarding the precise time to initiate balloon tamponade and the duration of placement is difficult to find. Complications of balloon tamponade include:
- incorrect placement
- aspiration pneumonia
- airway obstruction
- oesophago-gastric rupture
- tissue pressure necrosis.

Tamponade is successful in about 85% of cases, but re-bleeding occurs in about 45% following balloon deflation. Successful tamponade should be followed by re-endoscopy and further intervention as required.



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Transjugular intrahepatic portosystemic shunt (TIPSS) – using a catheter placed via the jugular vein into the hepatic vein under radiological guidance, a stent can be introduced to create an intrahepatic portosystemic shunt. This reduces portal blood pressure and the risk of bleeding. Complications of TIPSS include intra-abdominal haemorrhage, stent occlusion and hepatic encephalopathy. TIPSS has little impact on long-term survival.

Surgery – the control of bleeding can be achieved by staple transection of the oesophagus or by forming a portocaval shunt. However, long-term survival is not improved.

Lower gastrointestinal bleeding

Lower gastrointestinal bleeds are seldom immediately life-threatening. However, careful resuscitation and monitoring are required.

Endoscopy – electrocoagulation and heater probes can stop bleeding vascular points. Bleeding polyps can be removed.

Angiography – injecting embolizing agents into the vessel identified at angiography can stop vascular bleeding points.

Surgery – surgical removal of bleeding diverticular lesions or vascular abnormalities is indicated when other measures have been unsuccessful. Surgery may also be indicated if the source of bleeding is not identified.

Acute stress ulceration in ICU patients

Patients may present with peptic ulceration caused by pre-existing disease, as part of their critical illness, or secondary to drug therapy (e.g. steroids or non-steroidal anti-inflammatory drugs). In each case, an imbalance between mucosal protection and acid production results. ICU patients are prone to acute stress ulceration, especially those with sepsis, shock, burns, multiple trauma, head injury, spinal injury, respiratory failure, renal failure or hepatic failure.

The incidence of acute stress ulceration has decreased but remains about 20%. Presentation may be occult or overt, with lesions most commonly found in the gastric fundus. Potential sequelae include:

- cardiovascular collapse
- anaemia (requiring blood transfusion)
- increased urea load in the gut
- aspiration of regurgitated or vomited gastric contents.

Prophylaxis and treatment

Significant bleeding should be managed as above. The incidence of stress ulceration is lowered by prophylactic therapy aimed at alkalinizing the gastric contents (gastric pH > 3.5). However, ulceration can occur despite these measures and there is no guarantee of reduced mortality. Alkalinization of the stomach contents may cause overgrowth of gastric bacteria with the potential to lead to nosocomial pneumonia.

Supportive treatment includes optimizing oxygenation and perfusion.

Enteral feeding may reduce ulceration by improving local tissue perfusion and maintaining local protective mechanisms.

Antacids (e.g. magnesium, aluminium) have to be given often to alkalinize the gastric contents effectively. They can lead to ileus or diarrhoea and are seldom used.

H_2-receptor antagonists (e.g. cimetidine, ranitidine, famotidine) act by blocking acid production by the gastric parietal cells. Ranitidine is the most commonly used agent; it can be given intravenously or via a nasogastric tube. The dose should be decreased for patients with renal impairment.

Mucosal strengtheners – sucralfate is a basic aluminium salt of sucrose octasulphate that protects the gastric mucosa against acidity by adhering to the gastric mucosal surface and increasing mucus production. It does not alter gastric acidity and therefore causes no disruption to the normal gastric flora. Problems with its use include constipation, aluminium toxicity and the formation of bezoar when mixed with nasogastric feeds. Bismuth chelate may act in a similar way to sucralfate. It also helps to eradicate *Helicobacter pylori*.

Proton-pump inhibitors (e.g. omeprazole, lanzoprazole) irreversibly inhibit the H^+/K^+-ATPase (proton pump) enzyme to reduce the amount of H^+ transported to the gastric lumen by the parietal cells.

Other drugs – antibiotics may be used to eradicate *H. pylori*. Misoprostol, a prostaglandin E_1 analogue, helps to decrease acid production and improve healing but causes diarrhoea and can only be given orally. ◆

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Generalized Convulsive Status Epilepticus

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Generalized convulsive status epilepticus (GCSE) is the most common form of status epilepticus and affects about 14,000 people annually in the UK. It is a medical emergency and failure to recognize and treat it effectively results in major morbidity and mortality. It is traditionally defined as continuous seizure activity lasting 30 minutes or intermittent seizure activity lasting 30 minutes during which consciousness is not regained.

Clinical features: GCSE is usually diagnosed easily by observation alone and is characterized by unconsciousness, tonic-clonic muscle activity, tongue biting and urinary incontinence. However, as the duration of seizure activity increases, clinical signs of abnormal muscular activity may become subtle (e.g. restricted to minor twitching of the fingers or eyelids). There is seldom doubt about the diagnosis, but other conditions that should be considered include rigors due to sepsis, myoclonic jerking, generalized dystonia and pseudostatus epilepticus.

Aetiology: determining the aetiology of GCSE is of fundamental importance and may be divided into acute and chronic processes (Figure 1). In 50% of cases of GCSE presenting to non-specialized centres, status epilepticus is the first manifestation of epilepsy. The aetiology also affects the prognosis of GCSE.

Aetiological factors of GCSE

Acute processes
- Electrolyte disturbance (e.g. sodium, calcium imbalance)
- CNS infection (e.g. encephalitis, meningitis)
- Cerebral trauma
- Cerebrovascular accident
- Drug toxicity (e.g. alcohol, cocaine)
- Hypoxic cerebral damage
- Generalized sepsis
- Renal failure

Chronic processes
- Pre-existing epilepsy
- Poor anti-epileptic drug compliance
- Alcoholism (especially withdrawal)
- Cerebral space-occupying lesion

1

Pathophysiology: two distinct phases with specific neurophysiological changes occur during the progression of GCSE. In phase I, the increased metabolic requirements of abnormally discharging neurons are adequately met. The increased cerebral activity results in a coupled increase in cerebral blood flow and an increase in autonomic activity. The latter results in tachycardia, hypertension and an increase in blood glucose levels. After about 30 minutes of seizure activity, the compensatory mechanisms that have maintained adequate cerebral perfusion begin to fail. This stage (phase II) is characterized by a failure of cerebral autoregulation, a rise in intracranial pressure, systemic hypotension, hypoglycaemia and a rise in systemic and intracranial lactate levels. When this occurs, cerebral oxygen requirements exceed supply and electromechanical dissociation occurs in which cerebral seizure activity may be accompanied by minimal visible muscular twitching.

The disruption of normal cerebral physiology is further compounded by many of the systemic derangements that are seen during GCSE. These include CNS pathology (cerebral anoxia, haemorrhage, oedema, hippocampal damage, cerebral venous thrombosis), respiratory system pathology (respiratory failure, pneumonia, pulmonary hypertension, pulmonary oedema, pulmonary embolus), cardiovascular system pathology (arrhythmias, hyper/hypotension, myocardial infarction, cardiac arrest), metabolic disorders (electrolyte imbalance, metabolic acidosis, hyperpyrexia, renal and hepatic failure, acute pancreatitis) and other complications (rhabdomyolysis, fractures, sepsis syndromes, disseminated intravascular coagulation).

Management

GCSE requires decisive and rapid treatment. The longer GCSE continues, the greater the likelihood of neuronal damage, systemic complications, unresponsiveness to treatment and the development of chronic epilepsy. The mortality of GCSE is also related to its duration. Management falls into three categories that need to be instituted simultaneously:
- emergency medical management
- identification and investigation of aetiological factors that have precipitated status epilepticus
- drug treatment of the seizures.

Emergency medical management

Monitoring of ECG, blood pressure and pulse oximetry should be started immediately. Generally, patients in GCSE require early tracheal intubation and mechanical ventilation to protect the airway from aspiration of gastric contents and to ensure adequate ventilation and oxygenation while seizures are being controlled. A rapid sequence induction of anaesthesia should be performed using thiopental (thiopentone) or propofol followed by suxamethonium. Before induction, intravenous access is often required to allow fluid resuscitation. The administration of fluids is often all that is needed to restore normotension, but patients who have experienced prolonged status epilepticus may also require inotropic therapy. Blood pressure should be maintained at normal or supranormal levels to ensure an adequate cerebral perfusion pressure. Following intubation, the use of long-acting non-depolarizing neuromuscular blocking drugs is seldom necessary and obscures the clinical manifestations of continuing seizure activity.

Blood should be taken for determination of electrolytes, full blood count, blood glucose, toxicology screen, liver function tests and arterial blood gas analysis. Patients with pre-existing epilepsy should have their anti-epileptic drug levels measured.

A bedside test for glucose should be performed immediately and, if hypoglycaemia is present, 50% glucose, 50 ml, should be given. The theoretical danger of exacerbating cerebral ischaemia by an increased blood glucose level is outweighed by the correction of hypoglycaemia. If there is evidence of alcoholism or malnutrition, intravenous thiamine, 100 mg, should be given before administration of glucose to avoid precipitating Wernicke's encephalopathy.

Metabolic acidosis is common during uncontrolled status epilepticus, but acid–base balance is usually restored with control of seizures and with adequate resuscitation. There is experimental evidence that acidosis in GCSE may be neuroprotective.

High temperatures may occur in status epilepticus due to the increased muscle activity and may exacerbate or prolong seizure activity. Where possible, normal body temperature should be maintained using surface cooling and antipyretic agents.

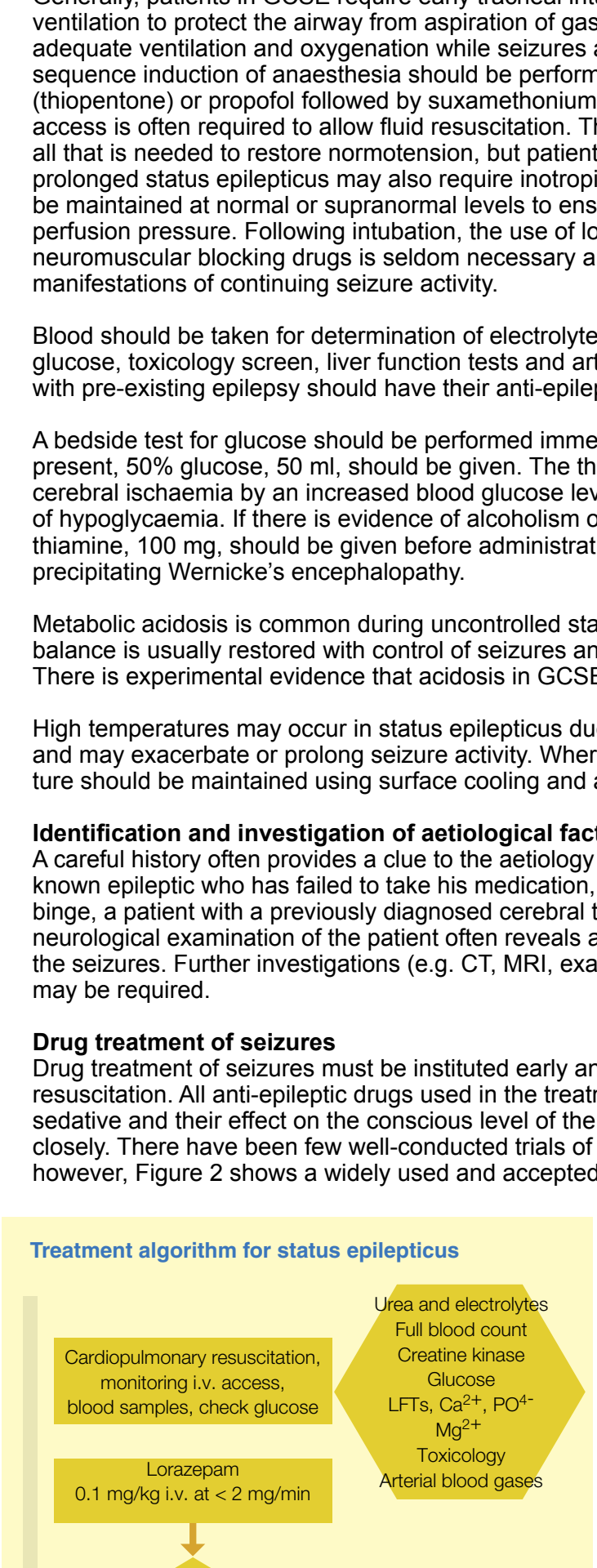
Identification and investigation of aetiological factors

A careful history often provides a clue to the aetiology of the status epilepticus (e.g. a known epileptic who has failed to take his medication, an alcoholic who has been on a binge, a patient with a previously diagnosed cerebral tumour). Similarly, a general and neurological examination of the patient often reveals a systemic or neurological cause of the seizures. Further investigations (e.g. CT, MRI, examination of CSF, blood cultures) may be required.

Drug treatment of seizures

Drug treatment of seizures must be instituted early and should proceed during resuscitation. All anti-epileptic drugs used in the treatment of status epilepticus are sedative and their effect on the conscious level of the patient needs to be monitored closely. There have been few well-conducted trials of the optimum treatment for GCSE, however, Figure 2 shows a widely used and accepted regimen.

Treatment algorithm for status epilepticus



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Benzodiazepines act by enhancing γ-aminobutyric acid (GABA)-mediated inhibition in the CNS by increasing chloride conductance at the post-synaptic ligand-gated $GABA_A$ receptor. Lorazepam, 0.1 mg/kg i.v., is the benzodiazepine of choice in GCSE. Although it is less lipophilic than diazepam, it terminates seizures as rapidly as the latter. Its main advantage is its long duration of action (over 12 hours) and it is often effective as the sole agent in terminating GCSE. In contrast, diazepam has a short duration of action due to rapid redistribution to body fat stores and is less effective than lorazepam.

Hydantoins (phenytoin and fosphenytoin): if seizures continue following administration of lorazepam, phenytoin, 20 mg/kg i.v., is the drug of choice as a second-line treatment. It acts by blocking neuronal sodium channels and inhibiting repetitive firing of neurons. The range of normal therapeutic plasma levels is 40–80 µg/litre.

Phenytoin should be given only via a large vein, because of its high alkalinity. It should be made up in saline and concurrent administration of other drugs should be avoided because of the risk of precipitation. The maximum rate of infusion is 50 mg/minute, but even lower rates carry the risk of hypotension and arrhythmias. Meticulous monitoring of ECG and blood pressure is mandatory.

Fosphenytoin is a recently introduced water-soluble prodrug of phenytoin and its dose is expressed in 'phenytoin equivalence' (75 mg of fosphenytoin is labelled '50 mg phenytoin equivalent'). Its main advantage over phenytoin is that it can be administered more rapidly. However, serious cardiovascular sequelae may occur and careful monitoring during and after administration is vital.

Phenobarbital (phenobarbitone): if seizures persist despite adequate plasma levels of phenytoin, phenobarbital (phenobarbitone), 10–20 mg/kg i.v., should be given. This barbiturate acts on a receptor site associated with $GABA_A$ chloride channels. Its main side-effects include excessive sedation, respiratory depression and hypotension.

General anaesthesia: refractory status epilepticus that has not responded to hydantoins and/or phenobarbitone requires general anaesthesia using either thiopental (thiopentone) or propofol. This should be carried out in a specialist unit where the anaesthetic agents can be titrated against continuous EEG monitoring. Most authorities aim for a burst suppression pattern on EEG though evidence that outcome is improved is sparse. Optimum levels of phenytoin and phenobarbital (phenobarbitone) should be maintained during this period. Patients are intermittently woken while being monitored for evidence of clinical or electroencephalographic seizures.

Prognosis

Adult GCSE carries an overall mortality of about 25%. Over 85% of those who die do so as a result of the aetiology of the status epilepticus; only about 2% of deaths are due to the GCSE itself. The aetiology also determines outcome; 90% of patients with status epilepticus secondary to drug withdrawal have a good outcome compared with only 30% of patients with status epilepticus due to stroke. Duration of seizures is also an important factor; GCSE lasting over 1 hour has a mortality of 35% while seizures lasting less than 30 minutes have a mortality of 3.7%. ◆

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Immune Dysfunction, Immunodeficiency and Immunotherapy

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Critical illness produces multiple defects in immune function with impairment of all components of the immune response. The most common cause of death in patients who have been in the ICU more than 7 days is sepsis. Particular care is required in patients who are immunosuppressed; the emphasis should be on prevention, early detection and aggressive treatment of infection. Although these patients have a worse prognosis than immunocompetent patients, it is not hopeless. However, those who require prolonged intubation and ventilation without return of immune function almost invariably die.

Immune dysfunction due to critical illness

Intravascular catheters and tracheal tubes bypass the normal barriers to infection. Mucosal barrier function may be reduced by ischaemia, trauma or ulceration. Sedation, recumbency, acid suppression and antibiotic use contribute to pooling of secretions, bacterial overgrowth and selection of resistant organisms.

Immune function, particularly cell-mediated immunity and neutrophil function, is depressed following shock or trauma and may persist for days or weeks. Causes include poor nutrition, direct effects of the inflammatory response on immune function, drugs, and metabolic and endocrine effects, particularly uraemia and hyperglycaemia.

Specific immunodeficiencies

Most immunodeficient patients in ICU have acquired rather than congenital disease. The most important clinical groups are neutropenia, T cell deficits (including HIV), and broad-spectrum immunodeficiency related to haematological or other malignancy, chemotherapy and the post-transplant patient. Less important (but significant) are hypogammaglobulinaemias, splenectomy and complement deficiencies. Patients may have more than one immune defect (e.g. lymphoma causing T cell dysfunction and cytotoxic-induced neutropenia).

Neutropenia occurs following decreased production, increased use or decreased survival of neutrophils. It is considered mild if the total neutrophil count is 1–1.8 x 10^9/litre, moderate if 0.5–1.0 and severe below 0.5.

Acquired neutropenia is usually caused by viral infections or drugs but severe bacterial sepsis is an important cause (Figure 1). Automated blood analysers may occasionally read falsely low neutrophil counts and unless neutropenia is an expected part of the patient's illness, a blood film should be checked to confirm the count.

Causes of acquired neutropenia

Infection
- Viruses (influenza)
- Severe sepsis (damage to myeloid precursors and adherence of neutrophils to endothelium)
- Chronic infections (splenic sequestration, brucella, kala-azar, malaria, tuberculosis)

Drugs
Direct toxicity
- Dose related (cytotoxic drugs)
- Idiosyncratic (chloramphenicol, carbimazole, phenothiazines work by enzyme blockade; usually presents within 1–2 weeks and resolves over similar period)

Immunogenic
- Antibody to complex between drug neutrophil surface proteins (phenytoin, chlorpropamide, levamisole, clozepam; reversible within 2 weeks of stopping drug)

Marrow infiltration/obliteration
- Tumour infiltration, radiation damage, myelofibrosis, osteosclerosis

Nutritional defects
- Protein malnutrition, B_{12} or folate deficiency, copper or zinc deficiency

Auto-immune
- Idiopathic or associated with other autoimmune disease
- Neutrophil autoantibodies
- Rheumatoid arthritis, systemic lupus erythematosus, Felty's syndrome

Splenomegaly
- Sequestration (chronic infections (as above), Gaucher's disease, sarcoidosis, lymphoma; usually associated with low haemoglobin and platelet count)

Haemodialysis
- Lung sequestration

Functional disorders
- Chronic granulomatous disease
- Decreased phagocytic function (many systemic diseases e.g. diabetes mellitus, uraemia, malnutrition, alcohol abuse, steroids)

1

Qualitative or quantitative defects in neutrophil function lead to impaired bacterial and fungal killing. Bacterial infections predominate initially. Traditionally, Gram-negative infections have been the most common and remain the most lethal. 50% of neutropenic patients with *Pseudomonas* bacteraemia die within 24 hours unless treated. With increasing use of long-term intravascular cannulae and prophylactic antibiotics, Gram-positive organisms are more common and account for over 50% of isolates in febrile neutropenia. With increasing duration of neutropenia, fungal infections become more common.

Prevention of infection – scrupulous attention to hygiene and isolation in side-rooms with positive pressure and, preferably, high efficiency particulate air (hepa) filtration are important. Cross-infection rates increase as the staff:patient ratio falls, particularly when infectious and immunosuppressed patients are being cared for by the same personnel. As antibiotic resistance increases, these precautions become more vital.

Diagnosis – the symptoms and signs of sepsis may be subtle or absent. Fever may be the sole indicator of infection. However, absence of fever or hypothermia does not rule it out.

Consider why the patient is neutropenic and for how long. What symptoms are there to suggest a source of infection? Was the infection acquired in the community or in hospital? Has the patient had previous infections? Are there any relevant, contributory drugs?

Examination is often unrewarding but should be thorough with particular attention to head and neck, pharynx, ears, optic fundi, chest, abdomen, skin and perineum.

Investigations should include full blood count and film, routine biochemistry (including liver function), cultures of blood, urine, stool if there is diarrhoea and aspirates from vesicles or pustules. Sputum is unreliable; bronchoscopic lavage should be performed if respiratory infection is likely (or blind broncho-alveolar lavage if the patient is intubated). Any suggestion of intracranial pathology should prompt a CT of the brain followed by lumbar puncture. Chest radiographs should be performed routinely. Consider sinus radiographs (but CT is better). CT of chest, abdomen and pelvis may be required if there are no obvious clinical clues.

Treatment – if the neutrophil count is less than 0.5 x 10^9/litre or there is haemodynamic compromise or organ dysfunction, empirical treatment should be started with broad-spectrum antibiotics. If the neutrophil count is more than 0.5 x 10^9/litre and the patient is well, relevant cultures should be performed and the patient observed closely. Antibiotics should be directed primarily at Gram-negative organisms (especially *Pseudomonas*) but the choice of antibiotic should be discussed, at the time, with the microbiology service, unless there is a unit protocol. Treatment for Gram-positive organisms can usually be delayed pending culture results unless the patient is unwell or there is high clinical suspicion. Meropenem or *Tazocin* ± an aminoglycoside often suffices. Metronidazole should be added if there is severe mucositis, necrosing gingivitis, perianal tenderness or abdominal pain.

If fever persists and cultures are negative, re-evaluation is required. The empirical addition of vancomycin or teicoplanin is required to cover Gram-positive infections, many of which are due to cell-wall-deficient organisms, which do not survive conventional culture techniques. With appropriate antimicrobial treatment, the mean time to defervescence is 5 days. Empirical antifungal treatment should be considered in patients who remain febrile after this.

It is common to continue antibiotics until the neutrophil count recovers (often 14 days) but this increases the risk of fungal and resistant bacterial infections. It may be safe and produce fewer complications if antibiotics are stopped 3–5 days after defervescence, provided the patient is monitored closely.

Fungal infections – about 30% of patients who fail to respond to antibiotics have *Candida* or *Aspergillus* infection. Fluconazole has few side-effects and is active against *Candida albicans* and *Cryptococcus* spp. but is ineffective against some other *Candida* species and *Aspergillus*. Amphotericin B has been the mainstay of treatment for these latter organisms but its side-effects include fever, rigors, hypotension and, especially, nephrotoxicity. Lipid-based preparations are less toxic but more expensive. Caspofungin and *Voriconazole*, new antifungals with a broad spectrum of activity and apparently a better safety profile, are promising.

Viruses – herpes simplex, zoster, cytomegalovirus (CMV) and adenovirus infections are common in neutropenia, especially if there is co-existent depression of cell-mediated immunity. Treatment is described below.

Deficiency of cell-mediated immunity: worldwide, the most common cause of T cell deficiency is HIV infection, although in the UK, antiretroviral drugs have reduced its impact. Immunosuppressive treatments (e.g. corticosteroids, ciclosporin (cyclosporin)) are also important causes. Infections are most common with intracellular pathogens (*Mycobacteria* spp., *Listeria*), viral infections, fungi and parasites.

Mycobacteria – *Mycobacterium tuberculosis* usually occurs due to re-activation of old infection. It is common in myelodysplasia, chronic lymphocytic leukaemia and hairy cell leukaemia. Presentation is often atypical, progress rapid and extrapulmonary and disseminated infections are common. Non-tuberculous mycobacteria (especially *Mycobacterium avium-intracellulare* and *kansasii*) are more common in HIV.

Viral infections are common, particularly herpes simplex, zoster, CMV and adenoviruses. Hepatitis B, Epstein–Barr virus and papillomavirus may cause problems. Measles can cause life-threatening infections, especially in children. Herpes simplex and zoster are usually responsive to aciclovir but some simplex isolates are now resistant. Foscarnet is usually effective, but is toxic (renal impairment in 50%). Ganciclovir remains first-line treatment for CMV; some resistance is emerging and foscarnet is an alternative treatment for CMV retinitis in AIDS. Mortality remains high, especially in CMV pneumonitis. Susceptible patients exposed to measles or herpes zoster should receive passive protection with human normal immunoglobulin or varicella-zoster immunoglobulin, respectively. Live-attenuated vaccines should not be used (nor should live-attenuated polio vaccine be given to siblings of susceptible patients because of the risk of intrafamilial transmission).

Fungi – superficial fungal infections are uncommon (except oropharyngeal candidiasis in HIV) but deep-seated or disseminated infections occur due to organisms such as *Histoplasma capsulatum*. Cryptococcal infections are uncommon except in HIV or in patients on high-dose corticosteroids.

Parasitic infections include pneumocystis, toxoplasma and cryptosporidiosis. More rarely, re-activation of malaria, strongyloidiasis or babesiosis may occur.

Pneumocystis pneumonia (PCP) usually presents as progressive respiratory failure with characteristic widespread pulmonary crackles and alveolar shadowing on a chest radiograph. First-line treatment is high-dose co-trimoxazole, 120 mg/kg/day. Steroids are beneficial if pneumonia is severe. Toxoplasmosis often presents as a CNS infection with multiple space-occupying lesions; pyrimethamine/sulphadiazine is usually effective.

Cryptosporidiosis presents as non-resolving diarrhoea. The organism is naturally resistant to most antibiotics and treatment is mainly symptomatic.

The diagnostic approach, initial cultures and imaging are similar to those for neutropenia but the search for infection must be more extensive. As well as routine surveillance cultures, CSF, bone marrow and tests for specific parasites (e.g. strongyloidiasis) should be considered if past exposure is possible.

Other causes of immunodeficiency

Hypogammaglobulinaemia occurs in common variable immunodeficiency (congenital, but mainly presents in the third decade). Functional hypogammaglobulinaemia may occur in multiple myeloma and chronic parasitic infections (e.g. trypanosomiasis). Patients present with recurrent respiratory and gastrointestinal infections.

Complement deficiency leads to recurrent pyogenic infections. Recurrent meningococcal or overwhelming pneumococcal infections may occur. Systemic lupus erythematosus is the most common cause of acquired complement deficiency.

Splenectomy is followed by an annual risk of serious sepsis of 0.5–1%. The risk diminishes over time, but is never eliminated. Functional asplenia (e.g. sickle cell disease) carries similar risks. *Streptococcus pneumoniae* is the most common organism (66% of cases). *Haemophilus influenzae* and *Escherichia coli* are also important, as is malaria, which may be fulminant. Patients should receive long-term antibiotic prophylaxis and immunization against *S. pneumoniae* and *H. influenzae*.

Infections in transplant patients – these patients are at particular risk, not only do they have the underlying disease that made transplantation necessary, those who have had solid organ transplantation have suffered a major surgical insult followed by powerful immune suppression. Bone marrow transplant patients have a particularly intense immunosuppression: before transplantation they undergo ablative treatment leading to absent immune function. However, provided they survive the acute period, the transplanted marrow gradually recovers and much of its immune function is regained.

Organ support in immunodeficiency – management of organ failures in immunosuppressed patients is no different from that in patients with preserved immune function.

Immunotherapy

Attempts to modulate the immune response in critically ill patients have been disappointing. Broad-spectrum immunosuppression with corticosteroids at various doses has produced no convincing benefit (and possible harm at high doses). Specific treatments of individual components of the inflammatory response using monoclonal antibodies have failed to show benefit. The exception is activated protein C, primarily an antithrombotic agent with anti-inflammatory properties which appears to produce an absolute reduction in mortality in severe sepsis.

Other forms of immunotherapy, including intravenous immunoglobulin and, to a lesser extent, plasma exchange have been effective in a limited number of conditions such as Guillain–Barré syndrome and thrombotic thrombocytopenic purpura, respectively. Colony-stimulating factors have been shown to reduce the duration of neutropenia in non-critically ill, haematology patients but have not been shown to produce a clear reduction in mortality. There is no evidence that they are effective in the critically ill. ◆

The Intensive Care Management of Acute Severe Asthma

Kathleen Nolan

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In Western industrial countries, asthma affects about 5% of adults and 10–15% of children. Its prevalence, severity, and mortality are rising, due to a redefinition of diagnostic criteria and increased exposure to allergens and atmospheric pollutants.

Asthma is characterized by partially reversible airway obstruction, airway inflammation and airway hyperresponsiveness.

The diagnosis is often made clinically on a history of episodes of reversible airflow obstruction, often precipitated by factors such as environmental allergens, viral respiratory infections, irritants, drugs or food additives, exercise and cold air.

Pathophysiology

The primary defect in asthma is airflow obstruction with resultant lung hyperinflation and increased work of breathing and oxygen consumption. Eventually, hyperinflation cannot be maintained and there is a reduced total lung capacity, airway closure, alveolar hypoventilation and deteriorating gas exchange.

Bronchial obstruction causes a low ventilation:perfusion (V/Q) ratio, while alveolar overdistension raises the ratio; these lead to hypoxaemia and an increase in dead space.

Pulmonary artery pressure rises owing to hypoxic pulmonary vasoconstriction and the pressure of overdistended alveoli on pulmonary vasculature. High pulmonary artery pressures may impair right ventricular performance and cause leftward displacement of the interventricular septum and impaired left ventricular function. Pulmonary oedema may occur, due to left ventricular dysfunction, or the high negative intrathoracic pressures generated to overcome severe airway obstruction.

Signs and symptoms

The typical signs and symptoms of an acute asthma attack are listed in Figure 1. Risk factors for death include a long history of the disease in young to middle-aged patients, previous life-threatening attacks or hospitalizations, delay in obtaining medical aid, and sudden onset with a rapidly progressive course.

Criteria for admission to ICU include:

- deteriorating peak flow, worsening or persisting hypoxia, or hypercapnia
- exhaustion, feeble respiration, confusion, or drowsiness
- coma or respiratory arrest.

On physical examination, there is hyperinflation, accessory muscle use (in inspiration and expiration) and widespread wheeze. Patients with acute asthma usually have a combination of hypoxaemia, hypocapnia and respiratory alkalosis on arterial blood gas analysis. A normal or increased partial pressure of carbon dioxide in arterial blood ($PaCO_2$) is a danger sign, although observing the trend in $PaCO_2$ is more useful. Monitoring should include continuous ECG and oximetry, frequent estimations of respiratory rate, level of consciousness, blood pressure, temperature and peak expiratory flow rate measurements. Regular examinations of the chest should evaluate air entry, accessory muscle use and evidence of subcutaneous emphysema.

Indicators of a severe asthma attack[1]

Potentially life-threatening features

- Unable to complete sentences in one breath
- Respiratory rate ≥ 25 breaths/minute
- Heart rate ≥ 110 beats/minute
- Peak expiratory flow rate ≤ 50% of predicted normal or if best normal if known
- Peak expiratory flow rate < 200 litre/minute if best normal not known

Immediately life-threatening features

- Peak expiratory flow rate < 33% of predicted normal or best normal if known
- Silent chest, cyanosis, or feeble respiratory effort
- Bradycardia or hypotension
- Exhaustion, confusion, or coma

[1] Statement by the British Thoracic Society, 1997.

Treatment

Initial treatment is directed at the relief of bronchospasm and airway inflammation, using oxygen, β_2-adrenergic agonists, corticosteroids and other agents (Figure 2).

Oxygen – almost all patients have hypoxaemia during acute exacerbations of asthma. Humidified oxygen is administered in high concentrations as determined by pulse oximetry (SpO_2) or arterial blood gas analysis.

β-sympathomimetic agents – the inhaled β_2-adrenergic agonists (salbutamol, terbutaline) have a rapid onset of action and are the first-line treatment for the relief of bronchoconstriction. Salbutamol has more side-effects including hyperglycaemia, hypokalaemia and lactic acidosis. One empirical approach is to start nebulized β_2-agonists as first-line treatment and then to use the intravenous form if the response is poor or the patient is moribund.

Corticosteroids are the most effective treatment for chronic inflammation of asthma. The peak response occurs 6–12 hours after an intravenous dose. Intravenous corticosteroids should be given early and continued until the life-threatening phase is over; oral and inhaled corticosteroids are then appropriate.

Anticholinergic agents block muscarinic receptors, inhibit vagal tone and promote bronchodilatation. They are medium potency bronchodilators and produce substantively less bronchodilatation than sympathomimetics. Nebulized ipratropium is indicated when asthma is severe on presentation, or when β_2-adrenergic agonist therapy fails.

Intravenous aminophylline is regarded as a second-line drug because of its narrow therapeutic range and high incidence of side-effects (cardiac arrhythmias and seizures). Its mechanism of action is unclear, because at therapeutic concentrations phosphodiesterase inhibition is minimal and bronchodilatation is weak There are wide variations in the elimination of aminophylline and plasma concentrations should be checked regularly. The dose is reduced in the elderly and those with hepatic or cardiac disease.

Medical therapy for life-threatening acute asthma[1]

Oxygen

Use the highest concentration available and set a high flow rate

High-dose inhaled β_2-agonists

Salbutamol, 5 mg, or terbutaline, 10 mg, nebulized with oxygen or with a metered dose
inhaler into a large spacer devise (two puffs 10–20 times)

High-dose systemic corticosteroids

Prednisolone, 30–60 mg orally, or hydrocortisone, 200 mg i.v., or both, immediately

If life-threatening features are present

Add ipratropium, 0.5 mg, to the nebulized β_2-agonist

Give aminophylline, 250 mg i.v. over 20 minutes, or salbutamol, 250 µg i.v. over 10 minutes. Continue with infusion. Do not give bolus aminophylline to patients already taking oral theophyllines

[1] Statement by the British Thoracic Society, 1993.

Mechanical ventilation

1–3% of patients admitted to hospital with acute asthma require intermittent positive-pressure ventilation (IPPV). It is indicated in asthmatic patients who exhibit:

- decreasing or decreased level of consciousness
- decreasing PaO_2
- increasing $PaCO_2$
- increasing arterial paradox (fall in systolic blood pressure on inspiration)
- increasing heart rate
- increasing respiratory rate
- decreasing peak expiratory flow rate
- decreasing ability to speak.

Even patients presenting with gross hypercarbia may be managed without IPPV, if medical therapy produces rapid improvement. In contrast, a patient with a low but rising $PaCO_2$ may require IPPV. Other indicators of the severity of an attack will aid decision making (Figure 1).

At the time of intubation, patients with severe asthma are often tachycardic, tachypnoeic, hypoxic, hypercarbic, acidotic, hypovolaemic and hypokalaemic. Unless a difficult intubation is anticipated, rapid sequence induction is appropriate. For potentially difficult intubations, inhalation induction (sevoflurane in oxygen), or an awake blind nasal or fibre-optic intubation with topical anaesthesia may be used. Following intubation, the patient should be given sedatives and, if necessary, muscle relaxants; control mode ventilation is preferable. The chosen ventilatory mode should achieve adequate oxygenation and ventilation at the lowest possible airway pressures, thereby minimizing the risk of barotrauma. This involves the delivery of low tidal volumes (6–8 ml/kg) at a slow rate (< 10 cycles/minute), aiming to keep peak airway pressures below 35 cm H_2O. A prolonged expiratory phase is preferred (I:E 1:2–1:4). Hypercapnia is tolerated ($PaCO_2$ up to 15 kPa) in the belief that it is less harmful than barotrauma. Severe ventilation–perfusion mismatch may be improved using bronchial lavage to remove mucous plugs and, more controversially, positive end expiratory pressure.

Complications of IPPV in asthma are related to barotrauma (e.g. pneumothorax, pneumomediastinum, subcutaneous emphysema) or cardiac depression (e.g. hypotension).

Additional bronchodilators

Inhalation anaesthetics – treatment of ventilated asthmatics with volatile inhalational agents often reduces peak airway pressures and improves arterial blood gases. Halothane (0.5–3.0%) has a low therapeutic ratio in the acidotic, hypovolaemic patient and its prolonged use is associated with bromide toxicity. Isoflurane (0.5–3.0%) is safer and probably as effective. Adequate gas scavenging facilities must be available in the ICU.

Intravenous anaesthetics – ketamine, infusion 10–40 µg/kg/minute, is a potent bronchodilator. It increases catecholamine levels and directly relaxes bronchial smooth muscle, however, it is not licensed for use as a sedative or bronchodilator.

Magnesium sulphate – anecdotal evidence suggests that magnesium sulphate provides useful bronchodilatation, however, this is not confirmed by controlled studies.

Helium-oxygen mixtures – the inclusion of helium, a low density gas, in inhaled gas mixtures lowers airway resistance and decreases respiratory work.

Nitric oxide is a short-acting, endogenous vasodilator and bronchodilator. Its bronchodilatory may be useful.

Weaning: the duration of IPPV in acute severe asthma varies considerably. Complications of mechanical ventilation, such as barotrauma and infection, tend to prolong the duration of ventilation and may be associated with reduced survival. Reversal of bronchospasm is indicated by the absence of wheeze, and a fall in peak inflation pressures, dynamic compliance or the alveolar to arterial oxygen difference.

Mortality in asthma patients undergoing IPPV: reported rates are as high as 38%, but include cases of brain injury from cardiorespiratory arrest prior to ventilatory support. In over 10,000 children with acute asthma, 27 (0.3%) needed IPPV. The single death associated with asthma and IPPV represents 4% of ventilated cases. Death in asthmatics receiving IPPV usually results from barotrauma, hypotension, cardiac arrhythmias or sepsis.

Extracorporeal support

There are several reports of extracorporeal lung assist (ECLA) in severe asthma. With modern ICU management, acute severe asthma has such a low mortality that the additional survival afforded by ECLA is probably marginal.

Outcome

An increase in the mortality rate from asthma has been observed despite improvements in pathophysiological findings and the introduction of new effective therapeutic agents. Patients who have previously required ICU admission and IPPV are at significant risk during subsequent exacerbations of asthma.

Intensive Care Management of Pulmonary Embolism

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Incidence and natural history

Pulmonary embolism is not an isolated disease of the chest but a complication of venous thrombosis. Determining the true incidence of pulmonary emboli is problematic because the presentation is often silent or clinically ambiguous, the diagnosis is difficult, and the intensity of post-mortem examination for pulmonary embolism varies.

The incidence in the USA is estimated to be at least 500,000 per year with a mortality rate of 10%. The incidence is highest in those undergoing emergency surgery following trauma (e.g. hip fractures) and pelvic surgery. Following total hip replacement, 5% of elderly patients develop a pulmonary embolism; nearly half of these cases are fatal. Clinical presentation ranges from the haemodynamically stable patient with pleuritic chest pain to the patient presenting with no cardiac output. The fatality rate is less than 5% in treated patients who are haemodynamically stable at presentation but about 20% in those with persistent hypotension. The mortality from massive pulmonary embolism is high and many patients die before treatment can be initiated. Greater emphasis on prophylaxis is needed if mortality and morbidity are to be reduced in those presenting with cardiorespiratory arrest or severe hypotension.

Pathogenesis

Pulmonary emboli occur as a result of thrombi at a distal site, therefore it is important to consider the whole disease process. Most thrombi form at the site of venous valves in the calf and most of them resolve spontaneously (80%). The other 20% of calf thrombi extend proximally to the ilio-femoral veins. Thrombi that remain confined to the calf pose little risk of embolization, while thrombi in the ilio-femoral systems pose a 50% risk of embolization.

Over 90% of pulmonary emboli originate from the lower extremities. Less common causes of embolization include, axillosubclavian thrombosis, which may occur spontaneously or be related to indwelling central venous catheters. Septic emboli may develop from infected peripheral thrombi; common in intravenous drug abusers.

Pathophysiology

When venous thrombi become dislodged from their site of formation they travel proximally to the heart and lodge in the pulmonary arterial tree. A large embolus will settle at the bifurcation of the pulmonary artery, forming a saddle embolus, which is invariably fatal. The effects of an embolus depend on:

- the extent of pulmonary vascular obstruction
- the pre-existing function of the cardiopulmonary system
- the time over which the obstruction accumulates.

If an embolus obstructs less than 50% of the pulmonary circulation, it may cause no symptoms in a previously fit patient, but cause compromise in a patient with pre-existing cardiopulmonary disease. When more than 50% of the pulmonary circulation is suddenly occluded the patient presents with haemodynamic instability ranging from hypotension to cardiorespiratory arrest.

Obstruction of the pulmonary vascular bed acutely increases right ventricular afterload. The thin-walled right ventricle is designed to work against a low resistance pulmonary circulation and hence functions poorly against a sudden increase in pulmonary vascular resistance. As the right ventricle dilates it pushes the interventricular septum to the left, impeding filling of the left ventricle compounding the fall in cardiac output. The fall in aortic pressure and the rise in right ventricular pressure may cause ischaemia of the right ventricle due to coronary hypoperfusion. The cardinal pulmonary effect is altered gas exchange. The main causes are:

- ventilation–perfusion mismatch – normal parts of the lung become overperfused but have inadequate ventilation to oxygenate the extra blood flow fully
- low mixed venous oxygen saturation caused by decreased cardiac output

accentuates hypoxaemia because there is insufficient time for the desaturated blood to become oxygenated as it passes through the over-perfused part of the lung. Carbon dioxide elimination is nearly always normal because there is a compensatory increase in minute ventilation.

Clinical manifestations

The clinical features of acute life-threatening pulmonary embolism can be explained in terms of the pathophysiological changes. The patient presenting to the ICU team will often have severe cardiorespiratory compromise. Patients will be acutely distressed with dyspnoea and tachypnoea. The physical signs are those of reduced cardiac output, namely, sinus tachycardia, hypotension, cool clammy peripheries, and confusion. There will be both central and peripheral cyanosis and signs of acute right heart strain: a raised central venous pressure, a palpable right ventricular heave, and a gallop rhythm. Finally, patients may present in atrial fibrillation due to a dilated right heart.

The symptoms and signs described above are not specific to pulmonary embolism; they are often the manifestation of any critical illness.

Investigations

Non-imaging diagnostic methods

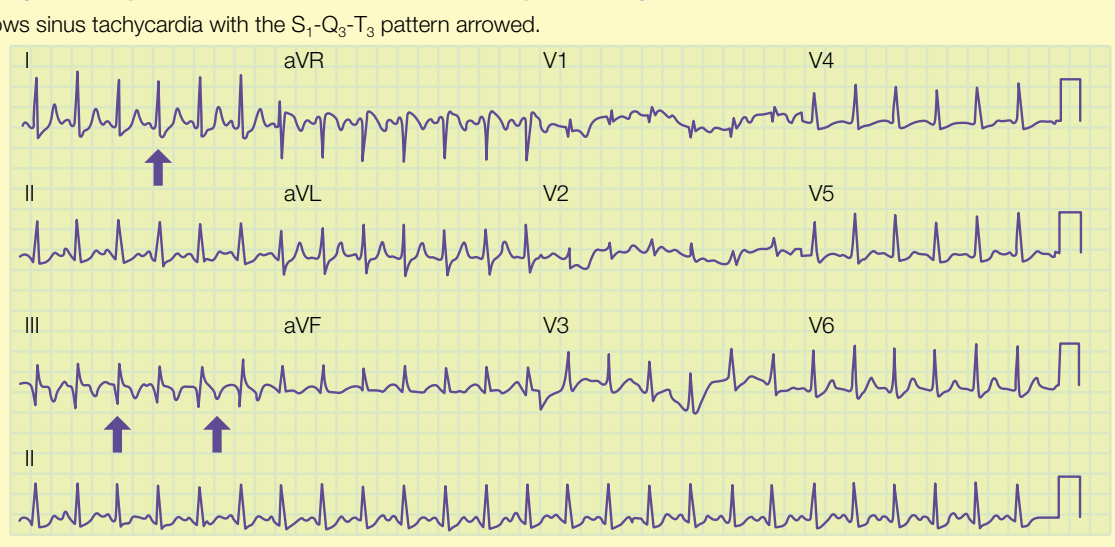
ECG – the ECG is abnormal in over 70% of patients with pulmonary embolism but these changes are nonspecific. Common findings are sinus tachycardia and ST segment abnormalities. In massive pulmonary embolism, evidence of right heart strain may be seen (right axis deviation, T wave inversion in V1–3). The classic S_1-Q_3-T_3 pattern seldom occurs (Figure 1). The ECG is useful in excluding other conditions such as myocardial infarction.

Arterial blood gases – the characteristic changes are a reduced partial pressure of oxygen in arterial blood (PaO_2) and a normal or low partial pressure of carbon dioxide. An abnormal PaO_2 is nonspecific.

Plasma D-dimer enzyme-linked immunosorbent assay (ELISA) relies on the principle that endogenous fibrinolysis is occurring in an effort to break down thrombus to fibrin degradation products (D-dimers). Although elevated levels of D-dimers are sensitive for the presence of pulmonary embolism they are not specific. A variety of clinical conditions encountered in the ICU can result in accelerated fibrinolysis (e.g. recent surgery, myocardial infarction, sepsis).

ECG of a 28-year-old patient who died from a massive pulmonary embolism

The ECG shows sinus tachycardia with the S_1-Q_3-T_3 pattern arrowed.



1

Imaging diagnostic methods

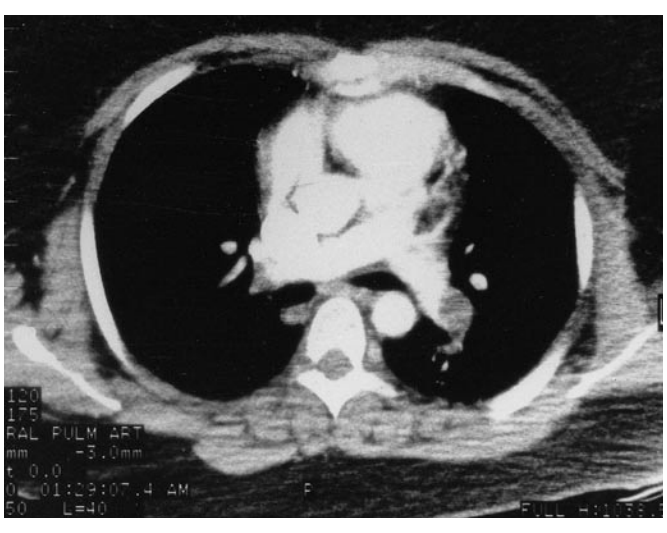
Chest radiography – most patients with a pulmonary embolism have an abnormal chest radiograph. In massive embolism a plump pulmonary artery shadow can be seen in the presence of oligaemia in those parts of the lung affected by emboli. There may be signs of pulmonary infarction; a wedge-shaped area along the pleural surface.

Echocardiography – transthoracic echocardiography can detect right ventricular dilatation and may reveal thrombus floating in the right ventricle or atrium. Transoesophageal echocardiography is particularly useful in the ICU because the patient is often too unstable for transportation. It allows detection of emboli involving the main trunk and the right and left pulmonary arteries.

Pulmonary angiography remains the diagnostic gold standard. It is expensive, invasive, and carries a 0.3% risk of mortality. Angiographic interpretation relies heavily on image quality and the observer's experience. Risks include vasodilatation due to contrast and the possibility of pushing clot in the right heart into the lungs.

Contrast-enhanced spiral CT is emerging as a first-line investigation. The technique is faster, less complex, and less operator dependent than angiography. The procedure has over 90% specificity and sensitivity in diagnosing pulmonary embolism in the main, lobar and segmental pulmonary arteries (Figure 2).

Ventilation–perfusion scanning is the most common imaging method used in the diagnosis of pulmonary embolism, but it cannot be performed in intubated patients.



2 Spiral CT scan of the same patient as in Figure 1. There is a filling defect in the left main pulmonary artery consistent with a large pulmonary embolism.

Management

Diagnostic uncertainty is often accentuated in the critical care setting where the complexity of safe transport often becomes a major determining factor in the diagnostic approach. Subsequently, management decisions are often based on incomplete clinical data.

Resuscitation

Oxygen therapy – oxygen should be administered in high concentration by mask. Patients with a decreased level of consciousness and/or severe respiratory distress require ventilation. Attention should be paid to full monitoring of resuscitation efforts in the form of ECG, invasive blood pressure, and central venous pressure monitoring. Arterial blood gas values can be used to assess the degree of hypoxaemia and indicate the presence of a metabolic acidosis due to hypoperfusion.

Haemodynamic support – the aim of treatment is to restore tissue perfusion to maintain end organ perfusion. It is imperative to maintain right heart filling pressures. The central venous pressure is raised in patients with pulmonary embolism; often as high as 20 mm Hg, this should not prevent fluid administration. A pulmonary artery catheter is not essential but may be useful in monitoring the response of fluid challenges. If hypotension exists after fluid-loading, inotropes should be started (e.g. adrenaline (epinephrine), 0.3–1.5 μg/kg/minute), and the dose titrated to blood pressure.

Definitive treatment

Heparin remains the mainstay of therapy for pulmonary embolism. A loading dose of 10,000 units i.v. or 100–150 units/kg followed by an infusion of 15–25 units/kg/hour is administered as soon as possible. The activated partial thromboplastin time (APTT) ratio should be checked every 6 hours and the infusion adjusted to maintain an APTT ratio of 2–2.5 normal.

Warfarin can be started early because it takes 5 days to achieve its full effect. Heparin should be continued for at least 5 days or until the international normalized ratio (INR) is 2–3. Warfarin without intravenous heparin depresses protein S and C activity at the onset, thus creating a thrombogenic potential.

Thrombolysis – the use of thrombolytic agents in acute pulmonary embolism remains controversial. Trials have failed to show any benefit over conventional treatment. Thrombolytics can increase the rate of thrombolysis in the first 24 hours but there is no convincing evidence that it decreases morbidity or mortality. There is a substantial risk of bleeding including intracranial haemorrhage (0.5–2%).

On this basis, thrombolytic agents should be reserved for those in whom accelerated thrombolysis may be considered lifesaving. Tissue plasminogen activator (tPA), 100 mg as an intravenous infusion over 2 hours is the thrombolytic of choice (less allogenic). It can be administered peripherally or into a pulmonary artery catheter. Heparin infusion is started after thrombolysis to maintain the APTT ratio at 2–2.5.

Pulmonary embolectomy is limited to centres with cardiothoracic surgeons. It has a high mortality rate and should be considered only in particular circumstances, for example in those in whom thrombolysis is contraindicated or who fail to respond.

Other therapies: low molecular weight heparin (LMWH) is licensed for the treatment of pulmonary embolism. It has little use in the compromised patient because subcutaneous LMWH takes 2–4 hours to reach therapeutic effect. Balloon-tipped catheters under fluoroscopy have been used to extract emboli; further investigation is required before their use becomes widespread.

Nitric oxide has been used as an adjunct to critical care management. It is a selective pulmonary vasodilator used to increase oxygenation by improving ventilation–perfusion matching. There are case reports advocating its use because it allows life-threatening hypoxaemia to be improved while instituting definitive therapy.

Intensive Care Myopathy and Neuropathy

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The effects of the systemic inflammatory response syndrome (SIRS) on the main organs are widely known, but the effects on peripheral nerve and muscle in the critically ill have only recently begun to be recognized and understood.

Definitions
Recovery from critical illness may be followed by critical illness neuropathy and/or critical illness myopathy. Critical illness neuropathy is an acute axonal neuropathy developing in critically ill patients which remits spontaneously when the critical illness has passed. Critical illness myopathy is an acute myopathy developing during a critical illness. The incidence of myopathy and polyneuropathy varies among studies, but it is estimated that 70–80% of patients with severe sepsis or multiple organ failure develop some form of critical illness neuropathy or myopathy. Various neuropathies and myopathies have been described.

Neuropathies
Critical illness polyneuropathy (CIP) is a common, diffuse, axonal motor and sensory neuropathy, which develops while patients are critically ill in the ICU and, generally, remits spontaneously as the patient recovers from their underlying critical illness. There is a primary axonal degeneration of peripheral motor and sensory fibres, but no evidence of inflammation. Muscle shows scattered atrophic fibres with occasional necrotic fibres.

Acute motor neuropathy is a variant of CIP associated in some cases with the administration of competitive neuromuscular blocking agents (e.g. pancuronium bromide, vecuronium) given for more than 48 hours. There is severe primary axonal degeneration of predominantly motor fibres, demonstrable with nerve conduction studies and electromyography (EMG). Muscle biopsies are non-specific and may show denervation, and atrophic and necrotic changes. Electrophysiological testing may show defects in neuromuscular transmission consistent with a postsynaptic defect.

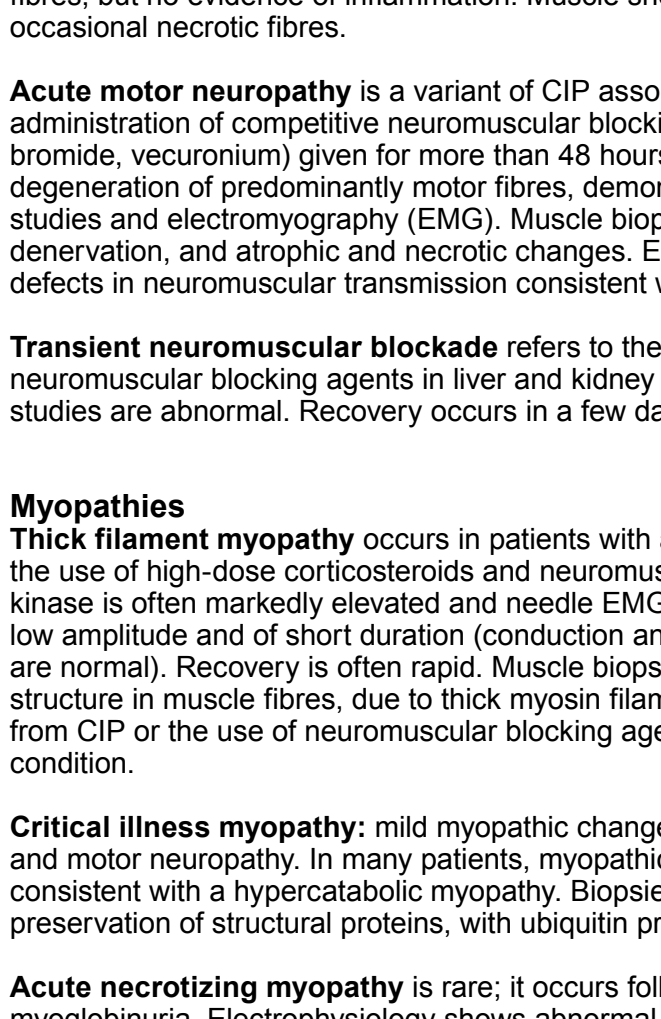
Transient neuromuscular blockade refers to the prolonged effect of competitive neuromuscular blocking agents in liver and kidney failure. Repetitive nerve stimulation studies are abnormal. Recovery occurs in a few days following cessation of the drugs.

Myopathies
Thick filament myopathy occurs in patients with acute asthma and is associated with the use of high-dose corticosteroids and neuromuscular blocking agents. Creatine kinase is often markedly elevated and needle EMG motor unit potentials are polyphasic, low amplitude and of short duration (conduction and repetitive nerve stimulation studies are normal). Recovery is often rapid. Muscle biopsy shows characteristic loss of central structure in muscle fibres, due to thick myosin filament destruction. Muscle denervation from CIP or the use of neuromuscular blocking agents predisposes patients to this condition.

Critical illness myopathy: mild myopathic changes are often seen in patients with CIP and motor neuropathy. In many patients, myopathic changes are more pronounced, consistent with a hypercatabolic myopathy. Biopsies show loss of myosin but relative preservation of structural proteins, with ubiquitin proteolysis.

Acute necrotizing myopathy is rare; it occurs following insults that cause myoglobinuria. Electrophysiology shows abnormal spontaneous activity, highly elevated creatine and myoglobinuria. Muscle biopsy shows widespread necrosis. Recovery is variable.

Pathophysiology
The pathophysiology of critical illness neuropathy and myo-pathy is poorly understood. There is often a marked discrepancy between the results of electrophysiological and histological studies. Early in critical illness, there is often marked atrophy of type I and II muscle fibres, with necrosis being rare; at this stage electrophysiological investigations are normal. Electron microscopy shows early loss of myosin but retention of structural proteins (Figure 1). However, when critical illness neuropathy and myopathy become clinically apparent later during illness, histological examination of peripheral nerves is often normal, despite abnormal EMG and nerve conduction studies as seen in CIP.



Electron micrograph of skeletal muscle taken from **a** normal muscle and **b** a patient with multiple organ failure. Between the Z lines, where the actin is attached there is almost complete loss of the double-ended myosin filaments (arrowed) that form the characteristic central A band.

1

It has been speculated that axonal degeneration is a consequence of the circulating mediators of SIRS, resulting in a common endothelial and vascular pathology that leads to nerve and muscle damage. In this theory, blood vessels supplying peripheral nerves are susceptible to disruption of the microcirculation in critical illness. The resulting increase in vascular permeability and oedema may result in hypoxic neural damage, not manifesting histologically until severe energy deficits occur. In these circumstances, neuromuscular drugs could also have a direct toxic effect on axons. Studies have failed to show any convincing evidence for nutritional deficiencies, medication, Guillain–Barré syndrome, or types of primary illness or injury as primary causes of critical illness myopathy or neuropathy. Severe CIP is asssociated with prolonged ICU stay, hyperglycaemia and hypoalbuminaemia.

History and examination
These patients appear to be recovering from sepsis and multiple organ failure, often following prolonged ventilation, but have difficulty weaning from the ventilator and have limb weakness. Lung or cardiac causes of respiratory insufficiency need to be excluded before considering the diagnosis of neuropathy or myopathy.

Aside from weakness and muscle wasting, neurological signs of neuropathy or myopathy may not always be present. In particular, tendon reflexes may be normal instead of decreased in some patients, and even exaggerated if the patient has a co-existing CNS disorder. A useful sign is that deep painful stimulation of limbs may show weak movements but strong facial grimacing.

Differential diagnosis
It is important to exclude conditions that would have begun before admission to the ICU, such as acute infective, traumatic or neoplastic spinal cord compression, Guillain–Barré syndrome, myasthenia gravis or muscular dystrophy. Usually these conditions are obvious before admission, but deterioration is often so rapid that diagnosis before ICU admission is impossible.

Investigations
Depending on the clinical variables, involvement of the high cervical spinal cord, peripheral nerves, neuromuscular junctions and muscles should be investigated. Patients with weakness following trauma should be investigated for spinal cord trauma before investigations for critical illness neuropathy or myopathy. EMG is the most useful initial investigation. EMG evidence of denervation activity consistent with axonal degeneration is diagnostic of CIP in the absence of other more plausible causes. If performed, nerve conduction studies in CIP show normal speed of impulse conduction but decreased compound motor and sensory nerve action potential amplitudes. Nerve conduction studies may be useful in diagnosing acute motor neuropathy, evidenced by markedly reduced compound motor but normal sensory nerve action potential amplitudes. Repetitive nerve stimulation studies are helpful in establishing the diagnosis of transient neuromuscular blockade. Serum creatine kinase is often elevated in thick filament and necrotizing myopathy but may be normal. Muscle biopsy is the investigation of choice for suspected myopathy and should be performed on all critically ill patients with new onset of weakness and the absence of electrodiagnostic findings suggestive of CIP or transient neuromuscular blockade.

Management
There is no specific therapy for critical illness neuropathy and myopathy. However, it is important to limit or prevent them because of their variable prognosis. The severity of critical illness neuropathy correlates with prolonged sepsis and catabolism, therefore sepsis must be treated aggressively, with attention to adequate nutrition. Evidence also suggests that tight glycaemic control reduces the incidence of CIP. Muscle relaxants and corticosteroids should be used sparingly, especially in acute asthma and in the presence of renal or liver failure. Prolonged physio-therapy and rehabilitation therapy is the mainstay of treatment for established conditions. Careful positioning of the patient is essential to avoid further nerve damage due to pressure areas.

Prognosis
The degree of recovery from critical illness neuropathy and myopathy is related to the severity of the condition. Milder cases of neuropathy are associated with recovery in weeks whereas more severe forms may take months to recover. Some patients with severe neuropathy, especially with evidence of slowing of nerve conduction may not recover. Generally, there is a rapid recovery following thick filament myopathy, but the prognosis may be poorer for some cases of necrotizing myopathy. ◆

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Management of the Poisoned Patient

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Poisoning is a common cause of hospital attendance, but seldom requires admission to the ICU. In many cases the poison is known and the patient requires only supportive care. Occasionally, the history is unclear or unobtainable; in such cases, the recognition of certain toxicological syndromes or toxidromes (Figure 1) and the selective use of investigations may help. The management of all poisoned patients is summarized in Figure 2.

Recognizable clinical toxidromes

Toxidrome	Features	Causative agents
Anticholinergic	• Agitation, hallucinations, coma • Tachycardia • Large pupils • Dry skin • Urinary retention • Warm, flushed peripheries	• Antihistamines (diphenhydramine) • Anticholinergic plants such as Atropa belladonna (deadly nightshade) • Tricyclic antidepressants • Atropine • Antiparkinsonian agents
Cholinergic	• Lacrimation • Salivation • Bradycardia • Increased respiratory tract secretions • Diaphoresis • Vomiting • Diarrhoea and urinary incontinence • Fasciculations	• Organophosphate carbamate insectides
Opiate	• Respiratory depression • Depressed conscious level • Small pupils	• Heroin and other opiates
Sedative-hypnotic	• Depressed conscious level • Mild respiratory depression • Hypotension in large ingestions	• Benzodiazepines • Some sedative hypnotics
Serotonergic	• Confusion, agitation, restlessness • Myoclonus, hyperreflexia • Diaphoresis • Tremor, rigidity • Hyperthermia	• Serotonergic antidepressants especially in combination (e.g. serotonin reuptake inhibitors, monoamine oxidase inhibitors and tricyclic antidepressants)
Sympathomimetic	• Tachycardia • Hypertension • Hyperthermia • Agitated delirium • Large pupils • Diaphoresis	• Cocaine • Amphetamines, methylenedioxymethamphetamine (MDMA; ecstasy) • Alcohol or sedative hypnotic withdrawal

1

Management sequence for the poisoned patient

Primary survey
A
- Oxygen
- Manual airway opening manoeuvres
- Simple airway adjuncts
- Rapid sequence intubation for airway protection

B
- Assist ventilation as required

C
- Intravenous access 12-lead ECG
- Correct arrhythmias and hypotension
- Monitor urine output

D
- Glasgow Coma Score, pupils, cranial nerves, lateralizing signs (CT scan), blood glucose

E
- Exclude hypothermia
- Fully expose

Monitoring
- Respiratory rate, ECG, non-invasive blood pressure, pulse oximetry

Secondary survey
- Track marks, pressure areas, co-existing injuries, characteristic odour, recognizable toxidrome

History

Investigations
Radiographic
- Chest radiograph for evidence of pulmonary aspiration or non-cardiogenic pulmonary oedema (opiates, salicylates)
- Abdominal radiograph for ingested metals (e.g. iron, lead, zinc)

Laboratory
- Full blood count, urea and electrolytes, arterial blood gases
- Anion gap, plasma osmolality
- Urinalysis: blood, glucose, ketones, urine osmolality
- Advice: Toxbase on-line
- Levels: paracetamol; others as indicated (salicylate, iron, lithium)

Gastric decontamination
- Activated charcoal
- Whole bowel irrigation

Antidote
- Diagnostic – naloxone
- Treatment – N-acetylcysteine

Increased elimination
- Multiple dose activated charcoal
- Haemofiltration or haemodialysis

Supportive

Follow-up/referral

2

Primary survey and resuscitation

Airway and breathing: many drugs taken in overdose cause a variable depression of conscious level that leads to airway obstruction, depressed airway reflexes and reduced ventilatory drive. Patients are at risk of aspiration of gastric contents, hypoxaemia, hypercapnia, and aspiration of vomit. Indications for tracheal intubation include: the inability to maintain a patent airway; a Glasgow Coma Score of 8/15 or less; agitation or combative behaviour that risks harm to the patient; hypoxaemia; and hypoventilation. Careful thought should also be given to the anticipated clinical course of the patient. For example, patients with a fluctuating conscious level, those requiring interhospital transfer and those in whom future deterioration can be predicted should be intubated electively.

A rapid sequence induction technique minimizes the adverse consequences of airway manipulation and intubation, such as pulmonary aspiration, arrhythmias and raised intracranial pressure. The temptation to intubate a comatose patient without providing anaesthesia must be resisted, because this could exacerbate the arrhythmogenic effects of certain poisons. The presence or absence of a gag reflex does not correlate with conscious level or true airway protective ability and should not influence the decision to intubate.

Circulation: some poisons have direct negatively chronotropic or inotropic effects (e.g. β-blockers, calcium antagonists), while others (e.g. tricyclic antidepressants) cause severe tachydysrhythmias that reduce contractility indirectly or precipitate cardiac arrest. CNS depression or drugs with an effect on the peripheral circulation (e.g. α-blockers) may also cause hypotension, whereas sympathomimetics (e.g. amphetamines) may result in tachycardia and severe life-threatening hypertension.

Hypotension will sometimes respond to intravenous crystalloid alone, but a failure to reverse hypotension or oliguria may necessitate central venous or pulmonary artery catheterization to guide volume therapy and vasoactive support.

Arrhythmias should be corrected, though standard advanced life-support guidelines may require modification, because tachyarrhythmias are likely to be refractory to anti-arrhythmic agents or cardioversion. Initial attention must be paid to correcting hypoxaemia, hypercapnia, and electrolyte and acid–base disturbances. For instance, the use of deliberate hyperventilation or intravenous sodium bicarbonate (1–2 mmol/kg body weight) to produce alkalaemia appears to reduce the risk of dysrhythmias, and possibly seizures, in tricyclic antidepressant poisoning.

Disability (neurological assessment): some agents (e.g. insulin, alcohol, hypoglycaemic agents) lower blood glucose and, thus, conscious level; therefore blood glucose measurement should form part of the neurological examination. The presence of lateralizing signs such as hemiparesis may indicate coexisting pathology. Ataxia, nystagmus and seizures may provide clues to toxin ingested.

Exposure and full examination (secondary survey) of the skin may reveal track marks suggesting intravenous drug abuse. Patients who remain unconscious for many hours before being found may develop hypothermia, skin blistering, peripheral neuropathy and rhabdomyolysis.

History

Where possible, the amount and type of poison ingested, as well as the exact time of exposure, should be identified. Co-morbid conditions and the patient's usual medications may influence the progress of the poisoning or the patient's recovery. In patients who have no apparent cause for their condition, consideration should be given to the possibility of body packing or stuffing, in which large quantities of illegal drugs are hidden within body cavities. Such suspicion necessitates rectal and vaginal examination, abdominal radiology and enteroscopy.

Investigations

Blood: routine blood count and urea and electrolyte tests are important to assess the impact of poisoning on electrolyte homeostasis and renal function. An elevated serum creatine phosphokinase may suggest rhabdomyolysis due either to pressure-induced myonecrosis or from a direct toxic effect on myocytes. Arterial blood gas analysis permits assessment of ventilation and identifies acid–base disturbances. Modern blood-gas analysers also provide quantitative evidence of carbon monoxide or abnormal haemoglobin complexes. Other useful investigations include calculation of any anion or osmolar gap. If the anion gap exceeds 16 $\pm$ 4 mmol/litre, it may support the diagnosis of poisoning by salicylates, iron or toxic alcohols. An osmolar gap (the difference in measured and calculated serum osmolality) indicates the presence of unmeasured osmotically active substances (e.g. ethylene glycol).

Urine: the presence of pigment in the urine (haemoglobin or myoglobin), in the absence of RBCs on urine microscopy, suggests myoglobinuria and diagnosis of rhabdomyolysis.

Toxicological investigations: there is seldom an indication for a blanket toxicology screen, because they are expensive, often unavailable during the patient's hospitalization and seldom alter the clinical management. Nevertheless, paracetamol levels should be requested, since the demonstration of toxicity necessitates the administration of *N*-acetylcysteine to prevent hepatocellular injury. Further advice on specific poisons can be obtained:
- on-line at www.spib.axl.co.uk
- by telephone in the UK from the National Poisons Information Service on 0870 600 6266.

Gastrointestinal decontamination

There are several ways to prevent the further uptake of poison present in the gastrointestinal tract, including emesis, lavage and activated charcoal, but few have sound evidence for their use. In particular, the role of gastric lavage is now reserved for patients with life-threatening poisoning presenting to hospital within 1 hour of ingestion.

Specific antidote therapy

Most patients improve with supportive care alone, though some require the administration of specific antagonists or antidotes. The response to the administration of the opiate antagonist naloxone (0.4–0.8 mg i.v. or 0.8 mg i.m. or s.c.) can assist in the diagnosis of opiate overdose. However, the benzodiazepine antagonist, flumazenil, should not be used empirically, because it can induce an acute withdrawal reaction in chronic benzodiazepine users, and may induce seizures if the toxic effects of a tricyclic antidepressant overdose are being masked by concomitant benzodiazepine ingestion.

Enhanced elimination
Activated charcoal, 1 g/kg every 4 hours, may increase elimination of poisons that have an enterohepatic circulation. In addition, the gut wall acts as a semipermeable membrane and assists removal of the drug by an 'intestinal dialysis'.

Forced alkaline or acid diuresis: now seldom used, these methods involve the manipulation of urine pH in order to maintain weak acids (e.g. salicylates, phenobarbitone) or weak bases (e.g. amphetamine, phencyclidine) in their ionized, lipid-insoluble form to limit renal tubular reabsorption. Careful monitoring of acid–base status, electrolytes, and fluid balance is required.

Dialytic techniques: haemodialysis is effective at removing toxins that are poorly protein bound, and have a molecular weight less than 500 Da. Drugs with a high volume of distribution such as tricyclic antidepressants are not cleared effectively. Continuous haemofiltration methods can remove larger molecules than haemodialysis, and continuous methods may be more suitable for drugs with a high volume of distribution (e.g. lithium). In charcoal haemoperfusion, blood is passed via an extracorporeal circuit over a cartridge of activated charcoal. This method is more suitable than haemodialysis for the removal of large or protein-bound molecules. However, it can result in thrombocytopenia, coagulopathy, hypothermia and hypocalcaemia, and in many cases provides no greater clearance of poison than multiple doses of activated charcoal.

Follow-up
Many poisoned patients are young, otherwise fit, adults who often have treatable underlying psychiatric illness. Referral for psychiatric assessment should always be undertaken when they have recovered from acute poisoning.

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Nosocomial Bacterial Infections

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Nosocomial infections are those acquired in or associated with hospitals. Any infection can, in theory, occur in hospital, but there are many factors in the hospital environment that lead to a particular spectrum of infective problems (Figure 1). Nosocomial infections are common, and may be serious or fatal. Some are unavoidable, but doctors must remember that their duty of care to their patients extends to fundamental matters such as basic hygiene and avoidance of unnecessary antibiotics, which may prevent patients becoming infected.

Typical hospital organisms

	Usual location	Risk factors for acquisition	Typical infections	Comments
Methicillin-resistant *Staphylococcus aureus*	Nasal or cutaneous	Antibiotic use Skin lesions Overcrowding, poor infection control	Skin/wound Orthopaedic Intravenous devices Bacteraemia Endocarditis Respiratory tract Prosthetic devices	Occasional case reports of isolates developing resistance to glycopeptides, which are the agents of choice for invasive infections
Enterococci and vancomycin-resistant enterococci	Gut Hospital environment	Antibiotics – particularly cephalosporins, glycopeptides	Low virulence Typically, vulnerable ICU patients, or renal patients in whom glycopeptide antibiotics are commonly used	Vancomycin-resistant enterococci are more correctly, but rarely, termed 'glycopeptide-resistant enterococci' Heat and disinfectant tolerant, so survive well in hospital environment
Clostridium difficile	Gut Hospital environment	Antibiotics Chemotherapy Lack of hygiene Elderly care wards	Antibiotic-associated diarrhoea/ pseudomembranous colitis	Large outbreaks with fatal cases reported Predisposed by loss of native bowel flora, hence a number of suggested 'alternative'remedies based on the principle of replacing this flora (e.g. live yoghurt, donor faeces)
Multi-resistant Gram-negatives	Gut Hospital environment	Antibiotics Lack of hygiene High-dependency units	Intra-abdominal, respiratory and bloodstream infections in vulnerable patients	Various species (e.g. *Acinetobacter, Klebsiella, Enterobacter, Stenotrophomonas)* Many are indolent opportunists, but some (e.g. *Klebsiella*, *Pseudomonas aeruginosa*) can cause aggressive, virulent infections

NB: Most nosocomial infections are caused by the patient's own flora or by cross-infection with more sensitive organisms not listed above

Background

It is reasonable to expect medical and nursing care to be safe, but hospitals have always been hazardous places – until the 20th century, they were avoided by those who had the option of being treated elsewhere. Paradoxically, with the advent of modern medicine and large urban hospitals in the 19th century, overcrowding, squalor and ignorance increased the danger to patients, and there was a significant risk of death from nosocomial infection following many procedures, from childbirth to amputation.

The current situation is much improved, but hospital-acquired infections still cause considerable illness and some mortality. It has been estimated that, at any one time, 9% of in-patients in the UK have a nosocomial infection; the incidence is highest in surgical wards and ICUs, and lowest in medical units. Apart from the obvious ethical significance of harm resulting from medical or nursing care, nosocomial infections cause a financial burden to hospitals, patients and society. A recent estimate of the cost in the UK was up to £1000 million/year. This figure does not include costs of litigation and compensation; courts increasingly tend to assume that hospital staff are at fault in cases of nosocomial infection.

Predisposing factors for nosocomial bacterial infection

Underlying patient factors (Figure 2) – many patients are intrinsically vulnerable to infection; they are at the extremes of age, are debilitated, or have an underlying illness causing immunodeficiency (e.g. HIV). Neurological illness may lead to aspiration pneumonia; immobility and dehydration may encourage urinary tract infection (UTI). Skin disease and bedsores allow organisms to enter subcutaneous tissue. In addition, and importantly, the normal flora of all patients includes potential pathogens such as *Escherichia coli* in the gut and *Staphylococcus aureus* in the nose.

Predisposing factors in nosocomial infection

Patient factors
- Debility
- Extremes of age
- Impaired gag reflex (e.g. cerebrovascular accident)
- Trauma
- Immunosuppressive illness (e.g. HIV)
- Normal flora – potential pathogens

Medical and surgical interventions
- Surgical incisions
- Intravascular devices
- Urinary catheters
- Prostheses
- Antibiotic use
- Immunosuppression
- Anaesthesia and ventilation

Hospital environment
- Other patients' organisms
- Cross-infection – transient staff carriage
- Environmental organisms
- Lack of hygiene
- Overcrowding
- Understaffing
- Hospital pathogens

Medical and surgical interventions – surgical incisions and intravascular devices provide means of entry for pathogens. Urinary catheterization often causes UTIs. Prosthetic joints and heart valves provide a protected niche for bacterial growth, which usually results in loss of the prosthesis. Immunosuppressive therapy allows even low-virulence organisms to assume a dangerously pathogenic role.

Less obvious ways in which medical therapy can facilitate infection include anaesthesia and ventilation (may lead to nosocomial pneumonia) and antibiotics (alter normal flora, reducing resistance to colonization by hospital organisms). Inadequate disinfection of endoscopes can transmit pathogens such as *Mycobacterium tuberculosis* and *Salmonella*.

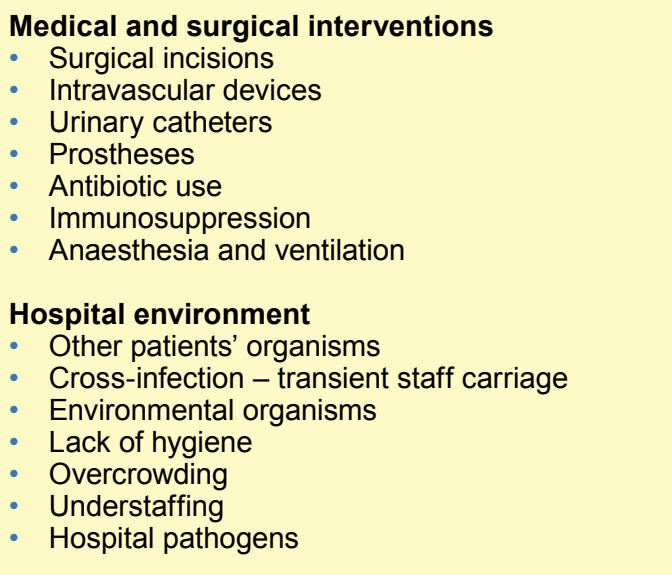
Hospital environment – patients may become infected with new organisms, usually from other patients, or more rarely from staff or the inanimate environment. Transient hand carriage by medical or nursing staff is thought to be the main route of spread, but occasionally other routes are involved, such as the airborne route for respiratory pathogens. Overcrowding, understaffing and lack of hygiene, particularly lack of handwashing, increase the risk of cross-infection.

Antibiotic use in hospital has selected resistant organisms, which readily colonize and infect patients. Many (e.g. coagulase-negative staphylococci, enterococci) are of relatively low virulence, but can cause severe illness in compromised patients; some (e.g. methicillin-resistant *Staph. areus*, MRSA) can be as virulent as their more sensitive counterparts.

Common syndromes and problems of nosocomial bacterial infection

Most nosocomial infections fall into a small number of common categories (Figure 3). Specialist units (e.g. burns, transplant, neurosurgery) see different infections, in addition to the following syndromes. The importance of nosocomial viral and fungal infections should not be overlooked.

Foci of nosocomial bacterial infections



Line-associated infections and bacteraemia: one-third of cases of nosocomial bacteraemia are associated with an intravenous device, 25% are from an unknown source, and the remainder have various sources, including the urinary tract, the gut and ventilator-associated pneumonia. Almost 50% of isolates are staphylococci (MRSA proportion increasing), and these are most likely to be line-associated. The remainder are mostly Gram-negative (*E. coli*, *Klebsiella*, *Enterobacter*, *Proteus* and *Pseudomonas*), with small numbers of enterococci and *Candida* (not bacteria, but generally included in reviews of 'bacteraemia'). Gram-negatives may be line-associated, but are more likely to have a urinary source, or to arise from the gut in patients with intra-abdominal pathology or neutropenia.

Intravenous lines provide both a break in the skin, allowing entry of organisms, and a protected site for bacterial growth shielded from immune defences by a biofilm of platelets, fibrin and bacterial slime. The risk is greater with increasing age of the line, central and multi-lumen lines, and poor insertion technique or line care, leading to infection of the insertion site or hub. Pre-existing skin disease and colonization with pathogens such as MRSA, also increase the risk of infection. The heavy normal flora of the groin means that femoral lines are often infected, despite careful insertion technique.

Presentation and diagnosis – line infections present with septicaemia or obvious infection of the exit site or tunnel, or are silent. Other sequelae (which may manifest only after line removal) include endocarditis and disseminated abscesses (e.g. spinal, ophthalmic). Blood cultures and culture of the line tip, or exit site if clinically infected, are the usual means of diagnosis. There has been interest in diagnostic methods that avoid line removal (e.g. line brushings, quantitative line blood cultures), but these have yet to gain wide acceptance.

Management – line infections (except some caused by coagulase-negative staphylococci) are almost never eradicated by antibiotics without line removal. Infected lines are sometimes left *in situ*, particularly when intravenous access is difficult, but this increases the risk of septicaemic complications.

Nosocomial chest infections: pneumonia is responsible for about 25% of all nosocomial infections, but the precise diagnosis is often uncertain; in severely ill patients, there may be other explanations for fever, hypoxia and pulmonary infiltrates on radiography (e.g. pulmonary oedema, shock lung, segmental collapse). Furthermore, the respiratory tract of hospitalized patients is often colonized with various organisms, and it is difficult to distinguish colonization from genuine pneumonia, even when deep sample collection techniques (e.g. broncholaveolar lavage) are used. The approach must therefore be pragmatic. Microbiology of respiratory samples should guide treatment in those with clinical and radiological evidence of lung sepsis, but the possibility of under-treatment and over-treatment should be acknowledged.

Most studies implicate a variety of Gram-negative organisms as the predominant causative agents, with doubts over the significance of culture results as described above. *Staph. aureus*, particularly MRSA, is the only commonly implicated Gram-positive organism; pneumococci are seldom isolated, but may be under-diagnosed. Thus, empirical treatment guide-lines for nosocomial pneumonia assume Gram-negatives to be the likely cause, and generally recommend agents with Gram-negative activity (e.g. broad-spectrum cephalosporins).

Hospital-acquired tuberculosis and legionnaire's disease are rare, but important because of their severity and because of the possibility of outbreaks. Any smear-positive TB patient who is not adequately isolated may spread the organism to other patients; unrecognized multidrug-resistant TB poses the greatest risk, because these patients are likely to remain infectious for longer. All non-immune contacts are theoretically at risk, but the greatest risk of progression to disease is in HIV-positive and other severely immunosuppressed contacts.

Legionella infection is acquired from the environment; transmission between patients does not occur. The organism normally inhabits water, preferably at 20–40˚C, and is spread to patients via airborne droplets. Sources within hospitals include water-cooled ventilation systems (formerly the cause of large outbreaks), shower heads and tap water. Patients most at risk include the elderly, those with chronic respiratory disease, and the immunosuppressed, particularly recent transplant recipients. The infection presents as severe pneumonia; the organism grows poorly, so diagnosis usually depends on serology or urinary antigen detection.

Surgical site infections: despite asepsis and antibiotic pro-phylaxis, surgical site infections remain common. It is believed that infection usually arises from the patient's own skin flora, inoculated into the wound during surgery; hair follicles and sweat glands cannot be completely sterilized during skin preparation, so no surgical field is completely sterile. Other possible sources include theatre staff (who inevitably shed skin flakes and respiratory droplets during the procedure), perforated gut and contaminated traumatic wounds. These infections usually manifest soon after surgery.

The incidence of infection varies between hospitals and types of surgery. In a recent large English survey, the lowest rates (2–3.5%) were in orthopaedic procedures, and the highest (10–15%) in amputations and abdominal surgery. Severe underlying illness and lengthy operations increase the risk – more than 35% of severely ill patients undergoing prolonged large bowel surgery develop infection. Staphylococci (mostly *Staph. aureus*, 50% of which are MRSA) cause almost 50% of infections; most of the remainder are caused by Gram-negatives, including *E. coli* and *Pseudomonas*.

Most infections are superficial and easily treatable. Deeper infections are rarer, and may be catastrophic, particularly when surgery involves bone, brain, a prosthesis, a vascular graft or a transplant. Group A *Streptococcus* can cause rapidly spreading, often fatal necrotic infections (necrotizing fasciitis).

Urinary tract infections (UTIs): urinary cathers are used routinely in the care of acutely and chronically ill patients, and are responsible for most cases of nosocomial UTI. It is said that bacteriuria develops in 5% of catheterized patients per day; unhygienic insertion technique probably increases the risk, and also increases the risk of cross-infection with other patients' organisms. Greater age, debility and dehydration also increase the risk of UTI. It is important to distinguish asymptomatic bacteriuria from symptomatic infection; the latter occurs in only a minority.

It is reasonable to treat symptomatic infection with anti-biotics, but unless the catheter is removed, the urinary tract will not be sterilized, and may become colonized with antibiotic-resistant organisms. For this reason, it is not recommended to investigate urinary samples from asymptomatic chronically catheterized patients. ◆

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www.cdc.gov/ncidod/hip/default.htm (CDC Hospital Infection Program; US government website dealing with all aspects of hospital infections.)

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Nutrition in Critical Illness

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Patient nutrition is an often neglected aspect of the overall management of patients, but 50% of surgical patients suffer protein energy malnutrition. Sepsis, injury and starvation are the main contributors to postoperative morbidity and mortality. Following the initial resuscitation of the critically ill patient, the nutritional status should be assessed and a plan of nutritional management made. It is best to use the enteral route if possible, however adequate calorie intake is often difficult to achieve. The currently available intravenous feeding regimens present a confusing array of mixtures of fat, carbohydrate, amino acids, vitamins and minerals and there are several steps to follow to initiate treatment safely. Many hospitals have a nutrition team, which assists with the management of enteral feed or total parenteral nutrition and helps with monitoring during treatment, but the clinician should have a working knowledge of patient nutrition to initiate a good management plan.

Nutritional requirements

The average 70 kg man requires about 2000 kcal/day. Without food, the body uses glycogen stores and then muscle protein, to provide energy. In the healthy person, the metabolic rate is reduced and stores are conserved. In illness or after surgery, burns or trauma, the following sequence occurs.

- Energy requirements are increased by up to 30%.
- Metabolism is affected by altered levels of catecholamines and cortisol.
- Blood sugar control becomes deranged as patients develop an apparent increased resistance to insulin.
- There are major fluid and electrolyte losses from diarrhoea, vomiting or nasogastric losses, excessive sweating, stoma losses and surgical drains.
- Fluid shifts, caused by leaky membranes or fluid moving into the third space, create difficulties in assessing fluid balance.

Assessing nutritional status

The following identify patients at risk of protein energy malnutrition:

- clinical history (e.g. nausea, vomiting, diarrhoea, abdominal distension, previous surgery, weight fluctuations)
- dietary history (types and amounts of food taken, dysphagia)
- physical examination (weight: height, body mass index (BMI), general appearance).

The following tests can be used to establish the severity of protein energy malnutrition and the response to nutritional intervention:

- anthropometric (skin fold thickness)
- biochemical (albumin, transferrin and pre-albumin)
- immunological (lymphocyte count).

However, they are unspecific, and similar abnormalities may be found in other conditions. In particular, albumin can fall rapidly with sepsis.

Enteral feeding

If the patient has any functional bowel, the enteral route should be used if possible. The best nutrition comes from a balanced diet that is chewed, swallowed and digested. Gut motility is influenced by hormones released during mastication. Stomach emptying controls the delivery of food to the jejunum to maximize absorption. The gut mucosa is more likely to retain its normal function if it is bathed in the correct nutrients. The large bowel requires an adequate amount of fibre to ensure regular soft bowel actions. As soon as any of these aspects of feeding are defective, the absorption of nutrients is affected. Factors that reduce the chances of successful enteral feeding are shown in Figure 1. Problems associated with enteral feeding are listed in Figure 2.

Factors that reduce the chances of successful enteral feeding

Inadequate swallow due to:

- Sedation
- Intubation/tracheostomy
- Pharyngeal dysfunction
- Oesophageal disease
- Surgery

Reduced gastric emptying and/or gut motility

- Opioids
- Pain/anxiety
- Postoperative gastric stasis
- Pyloric swelling

Suture lines – perceived risk of anastomotic leak

Paralytic ileus

1

Problems associated with enteral feeding

Problem	Management
• Large gastric aspirates	Use prokinetics (e.g. metoclopramide, erythromycin)
• Diarrhoea	Give fibre feed, examine stool specimen for *Clostridium difficile*, check for faecal impaction and overflow
• Patient can't or won't have a nasogastric tube	Use gastrostomy
• Distended abdomen	Check for constipation, paralytic ileus
• Aspiration/regurgitation of feed causing lung contamination	Monitor gastric residual 4-hourly Limit volume of feed used or use parenteral route
• Failure to deliver target volume	Follow local unit protocol, avoid stopping feed unless absolutely necessary

2

Routes of enteral feeding

Nasogastric feeding is the most commonly used route, but it relies on adequate gastric emptying. Sometimes it is impossible to pass the nasogastric tube or maintain its position. Feed is usually started at about 30 ml/hour via a continuous infusion pump and increased slowly, provided the gastric residue after 4 hours does not exceed 200 ml. Regimens aim for a maximum calorie intake that is dependent on weight and general condition.

Nasojejunal feeding avoids the pylorus and is used in patients with gastric stasis. Nasojejunal tubes are more difficult to pass and often require insertion under direct fibre-optic observation. Feeds are started at about 30 ml/hour. Absorption is assessed by checking for abdominal discomfort and distension.

Percutaneous gastric feeding – using an endoscopic technique, a tube is passed percutaneously into the stomach to avoid the discomfort of a nasogastric tube. These can be used for continuous or bolus feeds. They are commonly used in patients requiring long-term enteral feeding, such as those with cerebral palsy, after head injury and following major maxillo-facial surgery.

Percutaneous jejunal feeding – the percutaneously placed tube passes from the stomach into the jejunum. This route is sometimes used for postoperative feeding if gastric stasis is likely and a nasojejunal tube cannot be passed.

Type of enteral feed

Most enteral feeds are a mixture of fat, carbohydrate, protein, water, electrolytes, minerals and fibre (Figure 3). Standard feeds have about 1 kcal/ml, but more concentrated versions are available with about 1.5 kcal/ml. Energy is delivered as fat and carbohydrate.

Approximate combinations of nutrients in enteral feeds

	Elderly/Frail	Normal	Sepsis
Protein (nitrogen)	8–10 g	10–16 g	16–20 g
Carbohydrate	700 cal	1000 cal	1200 cal
Fat	700 cal	1000 cal	1200 cal
Total calories (non-nitrogen)	1400 cal	2000 cal	2400 cal
Total volume	2.5 litres	2.5 litres	3.0 litres

3

Some specialist feeds (e.g. *Pulmocare*) provide a greater percentage of calories as fat (by providing fewer calories derived from carbohydrate, the amount of carbon dioxide produced is reduced, thereby assisting ventilatory weaning in some patients). Other specialized feeds (e.g. elemental solutions of amino acids or peptides) are available for patients with short-bowel syndrome, malabsorption or severe inflammatory bowel disease. Extra food supplements can also be used to provide extra fat or carbohydrate.

Weaning off enteral feed

Many patients return to general wards on established enteral feed. Weaning back to a normal diet can be best achieved by its introduction during the day and continuing with enteral feed at night, reducing the night feeds as the daytime feed increases. The normal daytime diet can be supplemented by sip feeds comprising sachets of easy-to-digest, milk-based, flavoured feed. Ward nursing staff should be encouraged to keep a clear record of nutritional intake, remembering that nutrition stops for surgery and investigations. Intake is also affected if patients do not like the food offered, are unable to open the packaging or incapable of feeding without assistance. Ward dietitians have an important role in advising on nutritional requirements and can be helpful in finding suitable food supplements to suit an individual patient's needs.

Parenteral feeding

When the bowel is not functioning, unable to be used or all attempts at feeding using this route have failed, parenteral nutrition is indicated. A multidisciplinary nutrition team including doctors, nurses, pharmacists and dietitians can improve the efficacy of total parenteral nutrition (TPN). Insertion of a feeding line is usually undertaken by doctors and cared for by nurses; the dietitian can advise on nutritional requirements and the pharmacist can recommend nutritional preparations and additives. The whole team has a role to play in the continuing care of the feeding line, monitoring of response to therapy and audit of complications.

Patient selection

Common reasons for requiring TPN are:

- post surgery – if bowel function is likely to be disturbed
- short-bowel syndrome
- gastrointestinal fistulae
- prolonged paralytic ileus
- inflammatory bowel disease
- preoperatively – in malnourished patients with ineffective bowel function.

Sepsis, severe burns and pancreatitis were also considered reasons for using the parenteral route, but enteral nutrition is now recognized as more appropriate. In some cases, a combination of parenteral nutrition and enteral feed may be used.

Venous access

Ideally, TPN should be given via a tunnelled subclavian vein central line. The incidence of catheter-associated infection can be reduced by meticulous care during insertion, using a full aseptic technique. A post-insertion, chest radiograph should be taken to exclude a pneumothorax and to check that the catheter tip lies in the inferior vena cava (such positioning reduces the risk of thrombosis). To reduce the risk of catheter-related sepsis, the feeding line should be used for TPN only, and no other drugs or fluids should be given through the catheter nor should the line be used for blood sampling. Some mixtures of TPN are specially formulated to be given peripherally for short-term treatment, but intravenous lines used for such a purpose generally have a short life.

Choice of mixture

TPN solutions should contain a balanced mix of protein, carbohydrate and lipid, together with water, vitamins, electrolytes and minerals. Generally TPN is produced in large bags containing all the requirements for 24 hours. Protein is provided as a balanced solution of essential (40%) and non-essential (60%) amino acids.

Lipid emulsions are used because it is possible to supply a large amount of energy in a small volume (9 kcal/g), which is non-irritant to veins. Glucose (4 kcal/g) is used as the main source of carbohydrate, but requires close control of blood sugar. Feeds with a high proportion of glucose may delay weaning from ventilation in some patients, because they sometimes cause excess carbon dioxide production. Other micronutrients must be added to mixtures to avoid deficiency after a few days. These include vitamins and trace elements, which are usually added to the bags in the pharmacy. Electrolytes can be added if required. Phosphate supplements may be required in considerable amounts in patients with malnutrition.

Monitoring

when the intravenous route is chosen for feeding, it is important that the correct nutrients are given in the correct proportions to avoid serious derangement of electrolytes, blood sugar and fat metabolism. Figure 4 lists the routine investigations that should be undertaken.

Monitoring for patients being given parenteral feeding

Investigation	Frequency	Comment
Blood sugar	4 hourly until stable 6–12 hourly when stable	Patients may require insulin therapy – good glycaemic control is important in critical illness
White cell count	Daily	Rising white count may be first sign of developing sepsis
Electrolytes	Daily	May need additional potassium in daily bag
Urea/creatinine	Daily	Initially to ensure renal function, longer term to guide nitrogen requirements
Calcium/phosphate	Twice weekly	Phosphate can fall dramatically at start of treatment. Hypocalcaemia is common in pancreatitis and sepsis
Plasma lipidaemia	Twice weekly	Liver may not clear lipid infusions
Liver function tests	Twice weekly	Albumin may indicate efficacy of treatment, total parenteral nutrition can cause fatty liver and raised liver enzymes
Plasma transferrin and pre-albumin	Weekly	Assessment of efficacy of treatment
Urinary urea	Alternate weeks	To aid assessment of nitrogen balance
Trace elements (e.g. zinc, copper, iron, selenium)	Alternate weeks	These may become deficient after several weeks' treatment

Recent advances

The constituents of TPN have been modified and simplified over the past few years. The use of a single bag every 24 hours reduces the infection risk by reducing the need to handle the line connections. Several companies have special bags that allow mixing of the constituents immediately before use without the risk of contamination, this increases the shelf-life of the product and enables the pharmacy to supply TPN almost on demand. The vitamins and minerals required are available in single-day vials for addition immediately before use.

Recent research on immunotherapy suggests that the addition of substances such as glutamine, arginine and the omega-3 fatty acids, may enhance the immune response during critical illness. Recent work suggests that blood sugar control in a tight range reduces mortality in critical care patients. ◆

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Organ Donation and Maintenance of the Multiple Organ Donor

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The first reported human-to-human transplant involved corneal grafting and was carried out in Czechoslovakia in 1905. Today, corneas can be stored in an eye bank for up to 30 days, enabling over 2000 transplants to take place in the UK every year. The first successful kidney transplant was performed between two identical twins in the USA in 1954. Improvements in surgery and anti-rejection therapy have led to 75% 5-year functional survival for transplanted kidneys. In 1983, the first combined heart and lung transplant was performed at Harefield Hospital, UK. Today, there are nine UK heart and lung transplant centres and seven UK liver transplant centres. There is a shortage of all human organs for transplantation, partly because of reduced death rates from road-traffic accidents and the loss of public confidence following 'scandals' regarding organ removal. Consequently, it is vital that when suitable organs become available, they are maintained and used appropriately.

Criteria for donation

Living donors (usually first-degree relatives) can donate one kidney, a lung or liver lobe without adverse clinical effect. Corneas, heart valves, bone and skin can be donated up to 24 hours after asystole. The need to maintain structural and functional integrity in other organs dictates that they are usually removed from 'beating heart' donors (i.e. those with brainstem death whose breathing is maintained on a ventilator), though kidneys are occasionally removed in asystole. General criteria for donation are:

- the donor should be 0–75 years (age ranges change regularly)
- diagnosis of brainstem death must have been made according to current criteria
- respiratory support is being maintained (not always necessary for kidney donation)
- no evidence of malignancy (except certain primary brain tumours)
- no evidence of transmittable infection (Figure 1)
- no objection by the Coroner or, in Scotland, the Procurator Fiscal.

If the potential donor fulfils the above criteria, an adequately trained and informed member of staff should approach the family for 'informed assent' to remove organs. The family may decline the offer or stipulate which organs can be removed. Tissues for research may be taken only if this has been agreed by the family or the deceased. Most major religious and cultural groups support transplantation, but some have specific objections. The involvement of a religious leader may be helpful. Once assent has been obtained, the transplant co-ordinator begins the process of organizing the donation process.

Contraindications to organ donation

Infections
- HIV/AIDS
- Hepatitis
- CJD
- Malaria
- Syphilis
- Tuberculosis
- Rabies
- Major systemic sepsis
- CNS disease of unknown aetiology

Malignancies
- Leukaemia
- Lymphoma
- Myeloma
- Any tumour affecting the organ to be transplanted

1

Donation process

Potential contraindications to donation must be identified at an early stage. This often involves detailed, sensitive and explicit questioning of the potential donor's family to exclude the possibility of communicable diseases and to identify possible risk factors (Figures 1 and 2). A full medical and social history should be obtained and a range of supporting laboratory tests undertaken:

- tissue typing
- virology (hepatitis B and C, HIV infection, cytomegalovirus)
- haematology (blood group, cross-match, full blood count, coagulation screen)
- biochemistry (urea and electrolytes, creatinine, liver function tests)
- arterial blood gas analysis
- 12-lead ECG
- chest radiograph
- microbiology (culture and sensitivity results).

Risk factors for communicable disease

People at risk include those:
- who have ever injected themselves with drugs
- who have ever worked as prostitutes
- men who have ever had sex with another man
- who have ever had sex with anyone living in Africa
- who have been treated for haemophilia
- who received human growth hormone before 1985
- who have a family history of CJD
- who have had malaria, rabies or tuberculosis
- who have ever had a neurological disorder of unknown origin
- who have ever had sex with anyone from the above list

2

Organ removal occurs in the referring hospital; the operating theatre co-ordinator should be informed. The transplant co-ordinator organizes the arrival of the retrieval team(s). The donation process may take 12–18 hours, therefore the family may require considerable psychological support.

Physiological changes following brainstem death

Following brainstem death, there is loss of autonomic and endocrine homeostasis. If left untreated, these eventually lead to asystole, usually within 72 hours.

Cardiovascular instability – ischaemia of the brainstem causes an increase in sympathetic outflow to maintain cerebral perfusion. This 'sympathetic storm' may cause arrhythmias, myocardial ischaemia or infarction. Brainstem death results in a loss of sympathetic tone and progressive hypotension. Hypovolaemia due to use of diuretics, mannitol or diabetes insipidus may compound this problem. Arrhythmias due to previous infarction, electrolyte imbalance or hypothermia are common.

Pulmonary effects – the sympathetic storm may cause pulmonary capillary damage; pulmonary oedema occurs in up to half of brainstem-dead patients. Progressive hypoxaemia due to aspiration or infection is also common.

Endocrine failure – there is dysfunction of the hypothalamic–pituitary axis, leading to a fall in circulating cortisol, insulin and free triiodothyronine. This causes electrolyte imbalance, abnormal cellular metabolism, hyperglycaemia and myocardial depression. Diabetes insipidus, due to loss of posterior pituitary function, occurs in about 65% of brainstem-dead patients and results in hypovolaemia and electrolyte abnormalities.

Temperature regulation – the thermoregulatory centre is situated in the hypothalamus; brainstem death causes poikilothermia. Hypothermia results from loss of heat by conduction, convection and radiation, combined with lack of muscular activity, a low metabolic rate and loss of vasomotor tone.

Clinical management of the organ donor

Once brainstem death is diagnosed, the management of the 'donor' is directed to maintaining optimal organ perfusion and oxygenation with a normal fluid, electrolyte and acid–base balance.

Cardiovascular and electrolyte management – particular attention is required if diabetes insipidus occurs, because incorrect replacement of hypotonic urine with salt-containing isotonic solutions causes hypernatraemia. Care should be taken with the choice of site for vascular cannulae. Where possible the arterial cannula is best situated in the left arm and the central venous catheter in the right internal jugular vein. The use of adrenaline (epinephrine) may result in organ ischaemia and preferably is avoided. Dopamine, dobutamine or noradrenaline (norepinephrine) may be used in low doses; suggested goals are:

- mean arterial pressure over 60 mm Hg
- central venous pressure 6–12 mm Hg
- urine output 1–2 ml/kg/hour
- potassium greater than 4.5 mmol/litre.

Respiratory support – the lowest possible fraction of inspired oxygen (FiO_2) should be used. Positive end-expiratory pressure (PEEP) of 5 cm H_2O or over improves oxygenation, prevents airway collapse and limits pulmonary oedema. Carbon dioxide production falls after brainstem death, therefore a reduction in delivered minute volume may be appropriate (best achieved by reducing rate, rather than tidal volume, to prevent airway collapse). Strict asepsis should be maintained when undertaking tracheal toilet, and sputum samples should be sent for microbiological surveillance. Suitable targets are:

- partial pressure of oxygen in arterial blood (PaO_2) over 10 kPa
- $PaCO_2$ 4.5–5.5 kPa
- PEEP 5–7.5 cm H_2O
- FiO_2 less than 40%.

Endocrine replacement improves haemodynamic instability, reduces inotrope requirements and delays asystole. Suggested regimens for adults include:

- antidiuretic hormone (ADH) (vasopressin): bolus 1 unit, infusion 1.5–4 units/hour
- triiodothyronine (T3): bolus 4 μg, infusion 3 μg/hour
- hydrocortisone, 5 mg/kg, or methylprednisolone, 30 mg/kg
- insulin to maintain blood glucose at 4–6 mmol/litre.

Other management issues – the donor's temperature should be maintained using warmed fluids, warmed humidified gases and forced air, and warming blankets. Up to one-third of patients may develop disseminated intravascular coagulation owing to the release of plasminogen activators from dead brain tissue. Coagulopathies may require corrective treatment with blood products; the haematocrit should be maintained at 30%.

Anaesthetic considerations – brainstem-dead patients do not require analgesia or sedation, but may have intact spinal reflexes that cause hypertension or muscular contractions during surgery. Neuromuscular blocking agents and anaesthetic agents or opiates should be used to prevent reflex contractions and perioperative hypertension, respectively. Temperature may fall rapidly following skin incision, predisposing to ventricular fibrillation. Blood loss may be considerable and this should be replaced until circulatory arrest occurs.

Follow-up – the final care of the donor should be identical to that of any other patient who has died. The time of death is recorded as the time of completion of the first set of brainstem death tests. The transplant co-ordinator usually writes to the donor's family within 2 weeks of donation to thank them and inform them of the outcome of the recipient operations. ◆

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Organization of and Admission Criteria for High Dependency and Intensive Care Units

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The term 'critical care' is increasingly used to encompass both intensive and high dependency care, but there are important differences between them in terms of organization, patients and treatments.

- Intensive care is 'a service for patients with potentially reversible conditions who can benefit from more detailed observation and invasive treatment than can safely be provided in general wards or high dependency areas'.
- High dependency units (HDUs) provide a level of care intermediate between an ordinary ward and an ICU.

In some hospitals, one area may fulfil both roles: this may be appropriate when separate units would be small and lack flexibility.

Organization

Intensive care
ICUs require a nurse:patient ratio of 1:1, a resident doctor without other duties and consultant cover throughout 24 hours. Few consultants are full-time intensivists, but they should not have other duties while covering the ICU. Most ICUs are 'general', though some support a specific specialty. In the UK, a typical unit contains six beds; this is small in comparison with those in other European countries and the USA. Larger UK units may have greater flexibility to cope with fluctuating demand, but do not necessarily have better outcomes or lower costs. An ICU where care is provided by a team of intensivists, supported by other clinicians when requested, is described as a 'closed' unit. A unit in which patient care is delivered by more than one group of doctors is termed an 'open' unit. In the UK, the latter is more common, though the former may be associated with better outcomes.

High dependency care
For most hospitals, HDUs are a recent development. Many are specialty, usually surgically, based though general units are preferable. HDUs provide greater monitoring and nursing input than is given on general wards, may provide support for single-organ failure (but not ventilation) and can act as a 'step down' area for patients between the ICU and the general ward. The nurse:patient ratio on an HDU is 1:2. There is seldom a resident doctor. Patients are admitted and cared for by their referring team, the members of which will have duties elsewhere. The ICU staff may be involved in aspects of management, but will not be the principal caring team.

Admission criteria

Admission criteria must be practical and ethical. The precise indications for admission depend on the particular unit and the other acute care facilities available. The decision about admission to ICU is a clinical one for the ICU consultant. It is based on the patient's present condition, the treatment possible, the likely response, co-morbidities and the patient's wishes. Scoring systems used for ICU audit (e.g. APACHE, SAPS or MPM, see page 94) cannot be used for individual patient prognostication or admission decisions. Chronological age influences survival after intensive care, but should not be the sole arbiter for ICU admission. Indeed, limited physiological reserve means that elderly patients may require admission to the ICU or HDU in cases where younger patients would not. Similar considerations apply to patients with chronic disease, but patients with irreversible progression of chronic disease should not be admitted.

When to admit
In principle, patients should be referred early and by a consultant. The working arrangements of many hospitals make this difficult to achieve. Many patients are referred late in their illness, after potentially avoidable deterioration, which may include cardiac arrest. To overcome this, some hospitals have developed an emergency team that accepts calls from nursing or medical staff in an attempt to ensure early referral. Typical criteria for referral are given in Figure 1. Late admission may be partly the result of a lack of ICU beds, but staff attitudes are also important. Doctors outside the ICU may fail to appreciate what an ICU can offer or may see ICU referral as an admission of failure. Doctors within the ICU may give the impression that they are too busy to be bothered with patients who are not 'really sick'.

Specific criteria for ICU referral

Airway
- Actual or threatened airway obstruction
- Impaired ability to protect airway

Breathing
- Respiratory rate < 8 or > 30
- Respiratory arrest
- Oxygen saturation < 90% on 50% oxygen
- Worsening respiratory acidosis

Circulation
- Pulse < 40 or > 140
- Systolic blood pressure < 90 mm Hg
- Cardiac arrest
- Metabolic acidosis [H^+] > 62 nmol/litre
- Urine output < 0.5 ml/kg/hour

Neurological
- Repeated or prolonged seizures
- Decreasing conscious level

General
- Patient causing concern to medical, nursing, physiotherapy staff

Note
Much depends on whether there is an identified and easily remediable cause. It is the start of an adverse trend despite treatment that is important

Source: McQuillan *et al. BMJ* 1998; **316**: 1853–8.

1

Who to admit and where
Patients who require tracheal intubation and ventilation should be admitted to an ICU, as should patients who require support for two or more organ systems (Figure 2), even if they do not require ventilation (Figure 3). Patients who require close monitoring rather than organ support can usually be managed in an HDU, as can many with single-organ failure (except those who require ventilation).

Classification of organ system monitoring and support

Advanced respiratory support
- Mechanical ventilatory support (excluding mask continuous positive airway pressure or non-invasive ventilation)
- Possibility of sudden, precipitous deterioration in respiratory function requiring immediate tracheal intubation and mechanical ventilation

Basic respiratory monitoring and support
- Need for more than 40% oxygen via a fixed performance mask
- Possibility of progressive deterioration to the point of needing advanced respiratory support
- Need for physiotherapy to clear secretions at least 2-hourly
- Patients recently extubated after prolonged intubation and ventilation
- Need for mask, continuous positive airway pressure or non-invasive ventilation
- Patients intubated to protect the airway but not requiring ventilation

Circulatory support
- Need for vasoactive drugs to support arterial pressure or cardiac output
- Support for circulatory instability due to hypovolaemia from any cause which is unresponsive to modest volume replacement
- Patients resuscitated after cardiac arrest where intensive or high dependency care is considered clinically appropriate

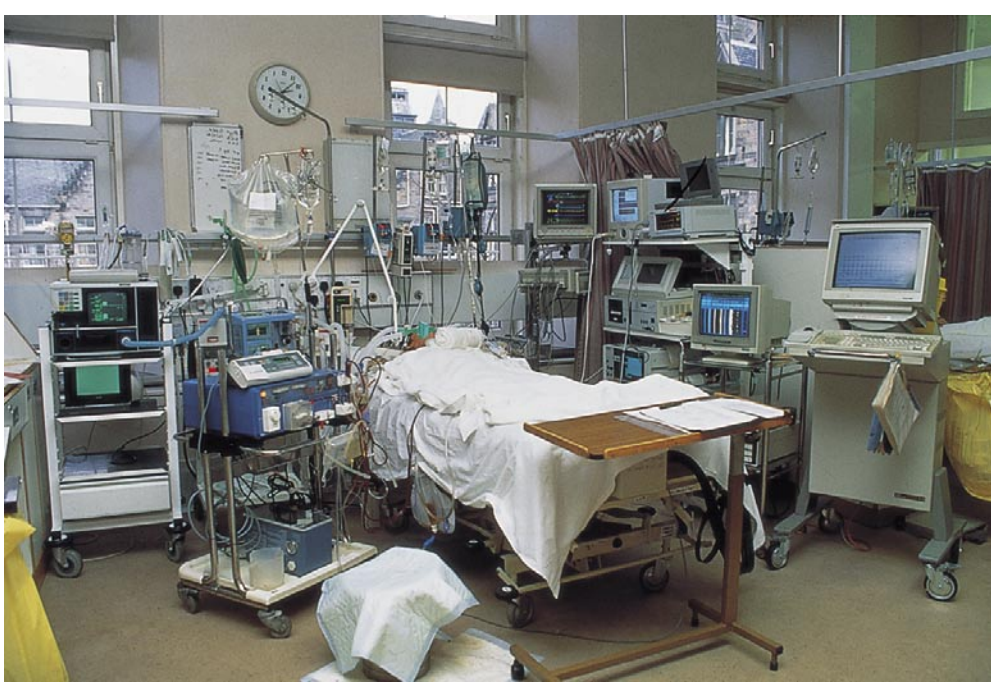
Neurological monitoring and support
- CNS depression, from whatever cause, sufficient to prejudice the airway and protective reflexes
- Invasive neurological monitoring

Renal support
- Need for acute renal replacement therapy

Notes
- Patients requiring advanced respiratory support should be admitted to ICU
- Patients requiring support of two or more organ systems should be admitted to ICU
- Patients requiring single-organ support may be suitable for high dependency rather than intensive care

Source: DoH. *Guidelines on Admission to and Discharge from Intensive Care and High Dependency Units*. London: HMSO, 1996.

2



3 Intensive care treatment of a patient with multiple organ failure.

Respiratory: patients may be referred with hypoxaemia or ventilatory failure. The decision to ventilate a patient may be based on blood gas results, but is usually made on clinical criteria. Patients who are clearly exhausted (e.g. confused, unable to talk, using accessory muscles) and not responding to treatment should be ventilated before respiratory arrest ensues, irrespective of their blood gases. Some patients with hypoxaemia and dyspnoea may respond well to continuous positive airway pressure in the HDU.

Cardiovascular: patients with deteriorating tissue perfusion (e.g. cool peripheries, peripheral cyanosis, reduced skin turgor, slow capillary refill, oliguria, reduced conscious level and metabolic acidosis) should be referred to ICU. Metabolic acidosis is often overlooked when interpreting blood gas or biochemistry results. Patients in shock may have surprisingly normal blood pressure. Although oxygen and fluids are almost invariably required, the underlying cause of shock must be diagnosed and treated. Patients requiring large-volume fluid replacement, central venous pressure monitoring or vasoactive drugs should be admitted to an HDU or ICU.

Neurological: many patients with impaired consciousness caused by head injuries, intracranial haemorrhage, meningitis, encephalitis, drug overdose, hepatic encephalopathy, hypoxia or other causes require admission to the ICU or HDU. Airway obstruction, absent airway reflexes, hypoxaemia, and hypoventilation are all indications for intubation and controlled ventilation. Patients with severe head injuries require ventilation with intracranial pressure monitoring.

Intravenous anaesthetic agents may be used to control recurrent seizures, but they should be administered in an ICU.

Patients with neuromuscular diseases (e.g. Guillain–Barré, myasthenia gravis) may require ventilatory support if airway reflexes are impaired or vital capacity is reduced (< 1000 ml).

High-risk surgery: the perioperative risk of major non-cardiac surgery is high, as is the risk of more modest surgery in patients with significant cardiorespiratory disease. Surgery produces a predictable, but temporary, physiological stress, and such patients can benefit greatly from admission to HDU or ICU postoperatively. Some advocate admission before surgery for 'pre-optimization', aiming for a cardiac index of 4.5 litre/minute/m^2 and oxygen delivery of 600 ml/minute/m^2. Although pre-optimization remains controversial, the value of good perioperative care is established.

Who not to admit

Patients should not be admitted to the ICU if they are too well, if they refuse or if they are too ill to benefit. Admitting patients who are too well wastes resources and exposes the individuals to potential complications.

Patients have the same right to refuse intensive care as they do any other treatment. If they are unable to express a view (e.g. because of coma), discussion with the relatives may be helpful in ascertaining the patient's wishes. Any advance directive should be respected, but, in practice, these are uncommon and may be ambiguous.

Patients should not be admitted if further treatment is futile, whether this is because of co-morbidity or the acute illness. This is often difficult to judge and may be best resolved by a trial of therapy. There is increasing concern that patients may survive but have a poor quality of life. However, doctors should be careful not to make decisions based on their own opinion of another individual's existing or future quality of life.

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Oxygen Delivery and Uptake

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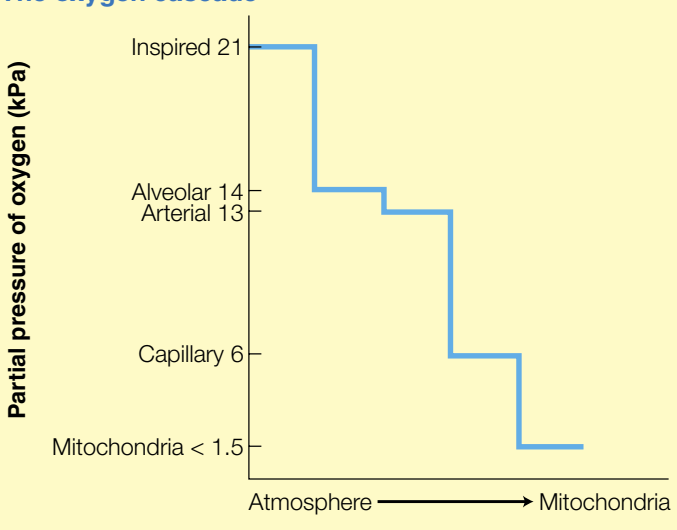
Oxygen is transported from the atmosphere to the tissues where it is used in the mitochondria to produce high-energy phosphate bonds. The declining partial pressure of oxygen as it is transported from the atmosphere to the mitochondria is described by the oxygen cascade (Figure 1).

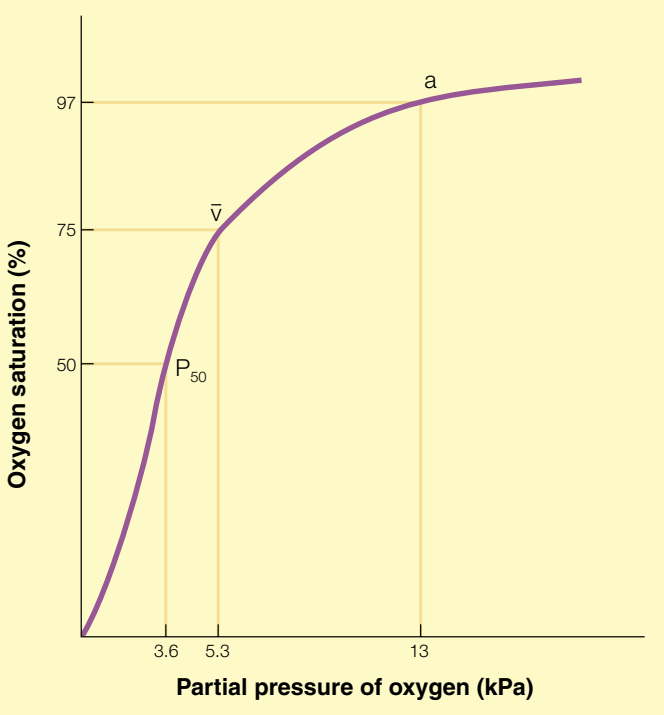
The oxygen cascade



Oxygen carriage in blood

Oxygen in the alveolus diffuses across the pulmonary capillary membranes; in the capillaries it is bound to haemoglobin and dissolved in plasma. The amount of oxygen dissolved in plasma is proportional to its partial pressure (Henry's law) and represents 0.023 ml/100 ml blood/kPa. Oxygen is transported more efficiently when bound to haemoglobin (an iron-porphyrin compound of four polypeptide chains bound to a protein – globin), forming a readily reversible compound known as oxyhaemoglobin. The degree of binding depends on the number of polypeptide chains bound to oxygen. Increased oxygen binding leads to the sigmoid shape of the oxygen dissociation curve (Figure 2). Oxygen loading and unloading differs according to the shape of this curve. Oxygen delivery to the tissues is facilitated by a right shift of P_{50} (the partial pressure of oxygen at which 50% of haemoglobin is saturated) caused by acidosis, raised partial pressure of carbon dioxide in arterial blood ($PaCO_2$), increased temperature and elevated levels of RBC 2,3-diphosphoglycerate.

Oxygen dissociation curve



P_{50}, partial pressure of oxygen at which 50% of haemoglobin is saturated; $\bar{v}$, partial pressure/oxygen saturation of mixed venous blood; a, partial pressure/oxygen saturation of arterial blood.

Oxygen delivery
Oxygen delivery (DO_2) = blood flow x arterial oxygen content of blood (CaO_2)

$$CaO_2 = (Hb \times O_2 \text{ saturation}/100 \times 1.39) + 0.023\ PaO_2$$

where: Hb is haemoglobin concentration in g/dl (theoretically 1 g of pure Hb can combine with 1.39 ml of oxygen); PaO_2, partial pressure of oxygen in arterial blood measured in kPa (0.023 PaO_2 is the amount of dissolved oxygen in 100 ml blood where $PaO_2$is measured in kPa).

A worked example concerning oxygen delivery to the body as a whole is given below.

DO_2 = cardiac output x blood oxygen content
Assume Hb = 15 g/dl
Assume blood to be 100% saturated and the partial pressure of oxygen to be 13 kPa
Assume cardiac output to be 5 litre/minute (i.e. 50 dl/minute)
$DO_2 = 50 \times [(1.39 \times 1 \times 15) + 0.023 \times 13]$ ml/minute
$DO_2 = 50 \times (20.85 + 0.3) = 1056$ ml/minute
Therefore DO_2 is about 1000 ml/minute
Note that the value for dissolved oxygen under normal conditions is so small (0.3 ml/100 ml of blood) that in most clinical situations it may be discounted

Factors affecting oxygen delivery
The oxygen flux equation shows that the factors affecting oxygen delivery to the tissues are:

- cardiac output or regional blood flow
- haemoglobin concentration and abnormal haemoglobin (e.g. carboxyhaemoglobin, methaemoglobin)
- oxygen saturation (related to the partial pressure of oxygen by the dissociation curve).

Manipulating these factors may alter oxygen delivery. For instance, cardiac output may be increased by the use of fluids, inotropes or peripheral vasodilators. Haemoglobin concentration may be increased by the use of RBC transfusion, though transfusion may cause a drop in cardiac output and may not increase overall oxygen delivery. The optimum level of haemoglobin varies depending on the clinical circumstance and remains the subject of great debate. Under normal conditions, blood in the pulmonary capillaries is almost 100% saturated and therefore increasing the concentration of inspired oxygen has little effect on global oxygen delivery. However, if the alveolar/capillary membrane is diseased (e.g. by pneumonia, aspiration) increasing the inspired oxygen concentration may be beneficial. Manipulation of the above factors may be important because the outcome of some high-risk surgical patients has been linked to augmentation of oxygen delivery.

Oxygen uptake

The equation that quantifies single-organ or whole-body oxygen uptake is based on the Fick principle. Using this formula, the saturation of mixed venous blood (SvO_2) reflects the overall degree of oxygen consumption. A worked example, assuming that the saturation of mixed venous blood is 75% and that its partial pressure of oxygen is 5.3 kPa, is provided below.

Oxygen uptake (VO_2) = cardiac output x (arterial O_2 content – mixed venous O_2 content)
$VO_2 = 50 \times \{[(1.39 \times 1 \times 15) + 0.023 \times 13] – [(1.39 \times 0.75 \times 15) + 0.023 \times 5.3]\}$ ml/minute
$VO_2 = 50 \times (21.15 – 15.76) = 269.5$ ml/minute
Therefore global oxygen uptake is about 250 ml/minute

VO_2, calculated using SvO_2, represents the adequacy of whole- body oxygen consumption. SvO_2 is the 'flow-weighted' average of the venous drainage from various tissues. Therefore SvO_2 may be little changed despite severe hypoxia in a tissue receiving little blood flow. SvO_2 also remains relatively normal if cells are unable to utilize the oxygen delivered to them. A clinical example is cyanide poisoning. As cardiac output falls, oxygen is more avidly extracted by tissues and therefore mixed venous oxygen saturation falls.

Relationship between oxygen delivery and uptake

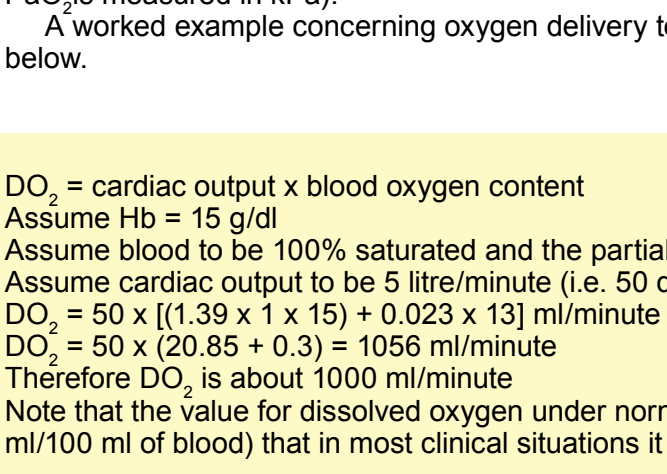
Oxygen delivery is considerably greater than uptake, providing a large margin of safety. To meet metabolic demands, oxygen utilization may need to rise 12-fold. In normal subjects, cardiac output is able to increase only six- or seven-fold, therefore the oxygen extraction ratio (O_2ER) must also be increased if metabolic demands are to be met.

$$O_2ER = VO_2/DO_2$$

VO_2 seldom exceeds DO_2, though it may in a hypermetabolic disease (e.g. sepsis). Usually DO_2 decreases as a result of myocardial failure or haemorrhage and VO_2 is maintained by increasing O_2ER until DO_2crit is reached. DO_2crit is the critical value of oxygen delivery at which oxygen consumption becomes supply dependent (i.e. the point of inflexion in Figure 3). At this point, oxygen extraction is maximal. The amount of oxygen that can be taken up by the tissues is then dependent on the amount of oxygen delivered.

Many studies have examined the relationship between oxygen delivery and uptake. Unfortunately many of them are flawed because they calculate both oxygen delivery and uptake from shared variables with the potential for artefactual results, termed mathematical coupling. Ideally, studies should use independent methods of measuring oxygen uptake and delivery. Further work is needed to clarify the relationship between oxygen delivery and uptake in humans in a clinical setting, before these measurements can be used to guide treatments aimed at improving clinical outcome.

Relationship between oxygen delivery and uptake



As oxygen delivery (DO_2) decreases, oxygen uptake (VO_2) is maintained at the required level by increasing oxygen extraction. VO_2 is independent of delivery over this portion of the curve. When oxygen extraction is maximal (DO_2crit), uptake becomes dependent on supply as demonstrated by the sloping portion of the curve.

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Archie J P. Mathematical Coupling of Data – A Common Source of Error. *Ann Surg* 1981; **193:** 296–303.
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The Postoperative Patient in the ICU

Martin Street

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The major reasons for admitting patients to an ICU in the postoperative period are the extent of surgery and the presence of significant co-morbidity. This period presents particular physiological challenges, but with the application of resources available in the ICU (Figure 1) patient outcome is improved.

Regardless of the surgical procedure, the clinical management of patients in the ICU has common therapeutic goals.

Resources available in the ICU

- Increased nursing staff levels
- Increased medical staff levels
- Availability of invasive monitoring
- Availability of respiratory support
- Comprehensive understanding of the complex pathophysiology in the postoperative period
- Early warning of complications
- Higher levels of physiotherapy support
- Reduction in perioperative morbidity

Maintenance of tissue perfusion

Multiple organ dysfunction syndrome (MODS) is a leading cause of death in non-cardiac ICUs, with a mortality of more than 50%. Treatment of MODS is largely supportive, therefore its prevention is vital. Current thoughts regarding its generation involve the 'two-hit' theory – an initial insult primes the host response and a second insult leads to a massive release of stress hormones, causing profound cardiovascular and pulmonary changes, and the activation of endothelium complement and clotting pathways. The initial insult can be multifactorial, including infection, trauma, pancreatitis and prolonged shock. Second insults include reperfusion injury, hypoxia and infection. The maintenance of tissue perfusion into the postoperative period is therefore crucial.

It is not clinically possible to measure tissue perfusion at a microvascular level, therefore there is reliance on whole-body estimations of cardiac output, oxygen delivery, mixed venous saturation and blood lactate. In the absence of peripheral vascular disease, estimating the temperature gradient along the limb may give a rough guide to limb perfusion, but more sophisticated estimations may be made by invasive monitoring. Careful monitoring of cardiac filling pressures (central venous or pulmonary capillary wedge pressures) together with cardiac output enables precise titration of fluids and inotropic drugs.

Renal circulation: adequate urine output (> 0.5 ml/kg/hour) has traditionally been seen as a marker for adequate renal vascular perfusion. However, previous administration of loop diuretics may give false reassurance that the patient is adequately hydrated, while coexisting cardiac failure and oliguria may coincide with water overload. The routine use of low-dose dopamine has not been shown to prevent renal failure.

Splanchnic circulation: the introduction of gastric tonometry to assess the pH of the intramucosal cells lining the stomach is believed by some to indicate adequacy of splanchnic perfusion and is used as a basis for fluid resuscitation. Others have found this less reliable as an end-point for cardiovascular management and trial evidence does not support its routine use.

Maintenance of oxygenation

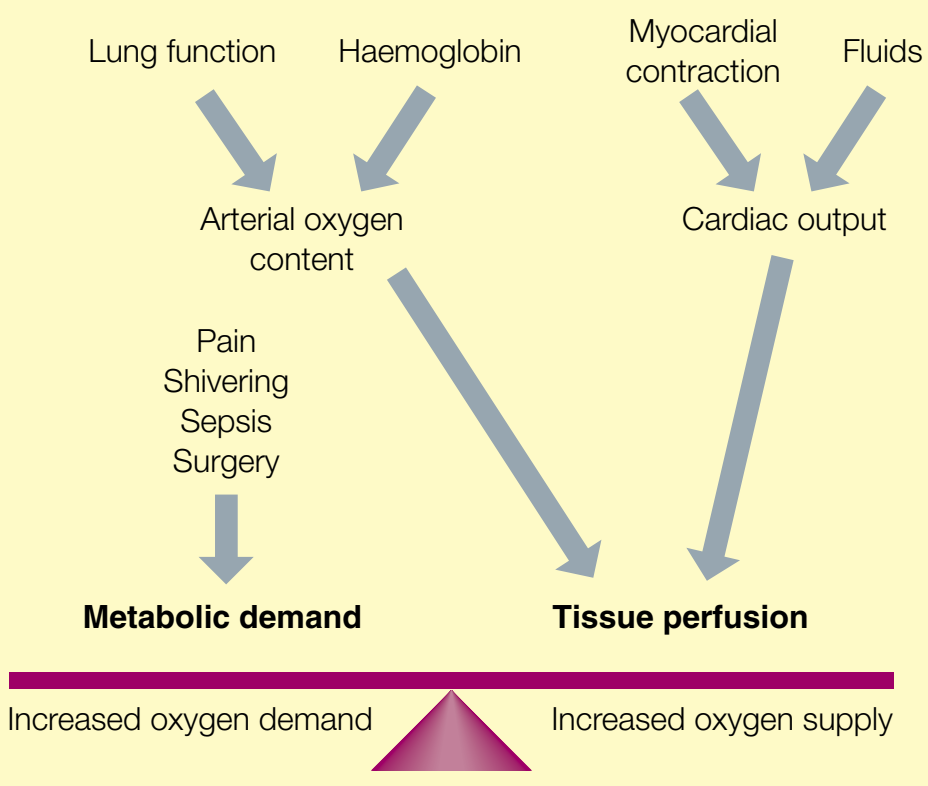
In the immediate postoperative phase, the elimination of nitrous oxide results in falls in arterial saturation. Increased intrapulmonary shunting and ventilation/perfusion mismatch should be treated with supplemental oxygen. Patients whose ventilation is based entirely on hypoxic drive seldom present for elective surgery, but they should be monitored carefully for hypoventilation and rises in arterial carbon dioxide ($Paco_2$).

In clinical practice it is difficult to improve arterial oxygenation significantly because few patients have a haemoglobin saturation below 95% preoperatively. Clinical management should be directed towards halting any decline in pulmonary function. The pain associated with large abdominal incisions has a deleterious effect on respiratory function, causing a reduction in tidal volume and functional residual capacity. The sudden cessation of smoking postoperatively increases secretion production and small airways plugging. This, together with the inhibition of coughing, results in alveolar instability and a tendency to alveolar collapse. Radiographic evidence of basal or plate-like atelectasis often precedes a further reduction in lower lung zone or lobar (usually the left lower lobe) aeration. Respiratory physiotherapy promotes the clearance of secretions and enhances alveolar recruitment in areas of atelectasis.

The combination of poor airway secretion clearance and alveolar instability increases the risk of nosocomial infection. Gram-negative pathogens usually predominate; however, the prolonged use of antibiotics perioperatively risks the selection of more resistant organisms such as *Pseudomonas aeruginosa*.

Postoperative ventilation: elective ventilation is commonly employed following major surgical procedures. This reduces both the metabolic demand associated with the work of breathing and voluntary muscular activity. It allows better matching of oxygen demand to supply until the effects of fluid shifts and blood loss are overcome (Figure 2).

Balance of tissue perfusion and metabolic demand



Analgesia and sedation

Adequate analgesia and sedation maintains patient comfort, ameliorates the metabolic response to surgery and trauma and halts the postoperative decline in lung function. It may be achieved by continuous or patient-controlled opiate infusions. However, local anaesthetic epidural infusions provide better analgesia and improve ability to cough.

Sedation for postoperative ventilation is best achieved with short-acting drugs (e.g. benzodiazepines, propofol) administered by infusion. Their hypotensive side-effects can usually be ameliorated by fluid or inotropic support.

Simple clinical end-points (Figure 3) can be used to guide successful weaning from ventilatory support in the postoperative period.

Clinical management of postoperative ventilation

• Warm peripheries	Achieve by producing adequate cardiac output with the administration of fluids and inotropes to ensure adequate peripheral perfusion
• Wake	Reduce sedation
• Wean	Gradually reduce respiratory support

Maintenance of homeostasis

Haemostasis

Bleeding is a common event in the postoperative phase and results from a variety of causes:

- ligature failure
- relaxation of vessel wall spasm
- hypothermia
- coagulation disorder
- thrombocytopenia.

Patients requiring transfusions exceeding 1 unit/hour over a 4-hour period should be assessed, if necessary by laparotomy, to exclude surgical causes. Haemorrhage may be caused by a combination of 'surgical bleeding' (e.g. slipped surgical ties) and a coagulopathy in the same patient; these may require simultaneous correction.

Haemoglobin

It has been accepted practice to transfuse patients to a haemoglobin of 10 g/dl both pre- and post-surgery. Recent studies have called this arbitrary practice into question and emphasized the disadvantages of supporting a higher haemoglobin in critically ill patients (Figure 4). Further trials are required to elucidate the risk:benefit ratios of these two competing strategies. The use of haemopoietic drugs such as erythropoietin, which offer the benefit of a high haemoglobin without the side-effects of transfusion, may prove useful. However, they are not currently recommended, primarily on cost grounds.

Relative merits of competing transfusion strategies

Advantages of higher haemoglobin

- Improved arterial carriage of oxygen
- Decreased risk of coronary ischaemia
- Margin of safety for further blood loss

Advantages of fewer transfusions and lower haemoglobin

- Improved microcirculatory blood flow and oxygen delivery
- Decreased cardiac work from decreased blood viscosity
- Decreased immunosuppression

Nutrition

In healthy individuals, the intestinal mucosa is an efficient barrier to the entry of bacteria and bacterial products into the portal circulation. Atrophy of the mucosa occurs rapidly after surgery and injury, and is also quantitatively associated with its severity.

Total parenteral nutrition has also been associated with mucosal atrophy and increased bacterial translocation. The introduction of the amino acid glutamine into total parenteral nutrition solutions and the establishment of early enteral nutrition have been shown to inhibit these mucosal changes and to be associated with increased patient survival. The addition of omega-3 fatty acids, arginine and nucleotides to the enteral feed may confer additional benefits.

The placement of enteral feed directly into the jejunum, using percutaneous or endoscopically placed tubes, may be safely instituted in conditions such as pancreatitis that historically have been managed with intravenous feeding.

Pain Relief in Intensive Care

Sue Smith

Sue Smith is Consultant in Anaesthesia and Intensive Care. Her interests include pharmacology, nutrition and steroid metabolism in the critically ill.

For patients in the ICU, many aspects of their illness and treatment may lead to discomfort and pain. However, pain is difficult to assess in ICU patients because of communication difficulties and because the usual clinical signs of pain (sweating, tachycardia, hypertension) may be caused by sepsis, stress or catecholamine administration. Nevertheless, there are opportunities to use analgesic techniques that would be unsuitable for other hospital patients.

Opiate analgesics

Opiates provide the mainstay for analgesia in critically ill patients. Their systemic effects (Figure 1) predominantly result from their actions on μ receptors.

Systemic effects of opiates

Cardiovascular system
- Decrease systemic vascular resistance
- Decrease blood pressure, partly due to histamine release
- Bradycardia in high doses

Respiratory system
- Respiratory depression
- Decreased ventilatory response to hypoxia and hypercapnia
- Antitussive
- 'Wooden chest' syndrome

CNS
- Potent analgesic
- Causes drowsiness
- Relieves anxiety
- Produces euphoria
- Miosis is produced by direct stimulation of the Edinger–Westphal nucleus
- Muscle rigidity

Renal system
- Increased tone in the ureters, bladder detrusor muscle and sphincter
- Urinary retention

Gastrointestinal system
- Nausea, vomiting
- Constipation due to decreased gastrointestinal motility
- Decreased gastric acid, biliary and pancreatic secretions

Metabolic
- Increased secretion of antidiuretic hormone leading to impaired water excretion, hyponatraemia

Other
- Mild diaphoresis and pruritus due to histamine release

Side-effects
- Hallucinations
- Dependence

1

Morphine
Morphine is a phenanthrene derivative. It is both a μ and κ receptor agonist. It can be administered orally, intramuscularly, intravenously (single dose, infusion or via a patient-controlled analgesia device), intrathecally or into the epidural space**.** Age and disease, especially liver and renal failure, alter its pharmacokinetics.

Morphine is well absorbed when administered orally but is susceptible to first-pass metabolism. The bioavailability by this route is only 15–50%. It is 20–40% protein bound and equilibrates slowly with the CSF. There is no correlation between plasma drug levels and the degree of analgesia.

Morphine is metabolized in the liver by conjugation to morphine-3-glucuronide, morphine-6-glucuronide and nor-morphine. The glucuronides are potent analgesics in their own right and have longer elimination half-lives than morphine.

Excretion of morphine occurs predominantly via the urine, but 7–10% appears in the faeces. The clearance of morphine is 1–23 ml/minute/kg and its elimination half-life is 1.7–4.5 hours. The elimination half-lives of the glucuronides vary from 4.5 to over 100 hours with declining renal function.

Morphine metabolites are water soluble, renally excreted and are not removed efficiently by haemodialysis/haemodiafiltration.

Alfentanil
Alfentanil is a highly selective, synthetic, anilinoperidine derivative with μ agonist activity. It produces a bradycardia of vagal origin with hypotension, but cardiac output, systemic vascular resistance and pulmonary capillary wedge pressure are unaffected.

Chest wall rigidity may result from μ receptor stimulation of GABA-ergic interneurons. Alfentanil causes minimal histamine release; bronchospasm is not a feature. The stress response is reduced.

Alfentanil is 10–20 times more potent than morphine, but does not produce hypnosis or sedation. It is 85–92% protein bound and is predominantly metabolized by the hepatic cytochrome P450 enzyme group by N-dealkylation to noralfentanil. The remainder is metabolized using other reactions, including hydroxylation, O-demethylation, and amide hydrolysis followed by acetylation. The major phase II pathway is by glucuronidation. There is evidence for genetic polymorphism in its metabolism and several pathways are saturable. At low doses (< 2 mg/hour in adults), the drug exhibits first-order kinetics, but in liver failure, septic shock or when higher dosing regimens are used, zero-order kinetics operate, thus explaining the long recovery time from termination of the infusion. Its elimination half-life for first-order kinetics is 100 minutes but increases exponentially when saturation occurs. Likewise, the half-life is greatly increased in liver disease and in the elderly. Erythromycin, cimetidine and ranitidine significantly inhibit its metabolism.

Studies suggest that the higher costs of alfentanil (in com-bination with propofol) are outweighed by shorter weaning times, shorter stays in ICU, and a lowered incidence of withdrawal syndromes compared with morphine and midazolam.

Remifentanil
Remifentanil seems to be an ideal analgesic agent for critically ill patients because of its cardiovascular stability and organ- independent pharmacokinetics. It undergoes rapid ester hydrolysis by non-specific esterases to a carboxylic acid derivative, which is much less potent and is excreted by the liver.

Remifentanil is unlicensed, but undergoing trials for ICU use. It does not possess sedative actions and causes significant nausea and vomiting. ‘Board-like’ rigidity, due to GABA-receptor activation in the chest wall can make respiration and ventilation difficult. Consequently, care must be taken in the flushing of intravenous lines in which remifentanil has been administered.

Pethidine
Pethidine is of limited use in critically ill patients because its metabolite (norpethidine) accumulates in renal failure and is excitatory and epileptogenic.

Codeine phosphate
Codeine has a low affinity for opioid receptors. It is less potent than morphine and is traditionally used for analgesia in patients with head injuries, because of the alleged reduced risk of respiratory depression.

If the drug is given intravenously or in overdose, cardio-vascular collapse may occur. Therefore, its use is limited to the treatment of diarrhoea (reduced gastrointestinal motility) and in managing mild-to-moderate pain. The dose should be reduced in patients with renal failure.

Non-opioid analgesics

Paracetamol
Paracetamol is an acetanilide derivative that can be administered orally, enterally or rectally. It is a potent prostaglandin synthesis inhibitor within the CNS; this explains its antipyretic action (inhibition of pyrogen-induced, prostaglandin synthesis by the anterior pituitary). It acts peripherally as an analgesic by blocking bradykinin-sensitive nociceptors. The drug is rapidly absorbed from the stomach, therefore plasma levels can be used as a measure of gastric emptying. Bioavailability is 70–90% owing to first-pass metabolism in the liver. 80% is metabolized to glucuronide and sulphate derivatives, and 10% is metabolized via the cytochrome P450 group to a highly reactive metabolite, which is immediately inactivated by conjugation with glutathione.

Non-steroidal anti-inflammatory drugs (NSAIDs)
NSAIDs are useful for the relief of musculoskeletal pain, as an adjuvant to paracetamol and for reducing opiate dose. However, all NSAIDs, even the highly selective COX-2 inhibitors, have significant side-effects (Figure 2), especially in critically ill patients. NSAIDs exert their anti-inflammatory, analgesic and antipyretic actions by reversibly blocking the conversion of arachidonic acid to PGG_2 – a reaction catalysed by cyclo-oxygenase.

NSAIDs are extensively protein bound and a given dose has a greater effect if hypoproteinaemia exists. NSAIDs increase the anticoagulant effect of concurrently administered warfarin by displacement from plasma proteins.

Side-effects of non-steroidal anti-inflammatory drugs

Cardiovascular system
- Hypertension
- Sodium and water retention
- Peripheral oedema
- Closure of ductus arteriosus

Gastrointestinal system
- Gastritis
- Gastric ulceration and haemorrhage
- Small bowel villous atrophy
- Diarrhoea
- Reversible hepatic dysfunction

Renal system
- Interstitial nephritis
- Renal vasoconstriction
- Cortical blood flow diversion
- Acute renal failure with hypovolaemia and ACE inhibitors

Blood
- Inhibition of platelet aggregation
- Prolongation of the bleeding time
- Decreased killer T cell activity

2

Entonox
The combination of inhaled *Entonox* (50% oxygen; 50% nitrous oxide) may be of benefit during physiotherapy or if regular dressing changes are required (e.g. burns, necrotizing fasciitis).

Antidepressants
Antidepressants have mood-altering properties and permit rapid eye movement (REM) sleep patterns to be established. Tricyclic antidepressants have analgesic properties and also block the reuptake of noradrenaline at the postsynaptic nerve terminals. Noradrenaline is a potent analgesic in the CNS and both pain relief and mood alteration occur within 3–7 days.

The high incidence of anticholinergic side-effects and drug interactions may limit the use of antidepressants.

Epidural blockade

Epidural analgesia is increasing in the ICU because it provides superior pain relief without sedation. The combination of a dilute local anaesthetic solution with a preservative-free opioid produces superior analgesia. The use of epidural analgesia in patients with severe chest injuries has reduced mortality and morbidity by avoiding the need for intubation and ventilation. Epidurals preserve the cough reflex, allow deep breathing, preserve functional residual capacity, facilitate chest physiotherapy and permit early mobilization.

Concerns have been raised about the possible link between epidural anaesthesia and anastomotic breakdown following bowel surgery. One possible cause is that hypotension and reduced cardiac output following the epidural may decrease splanchnic blood flow.

Epidural anaesthesia is useful in reducing the incidence of post-amputation phantom limb pain, especially if the autonomic blockade is established before amputation.

Regional blockade

The ability to leave a catheter in the femoral nerve sheath makes local anaesthetic, femoral nerve blocks useful for relieving pain after femoral fractures or mid-thigh amputations.

Similarly, catheters may be placed in the axillary or brachial plexus sheaths to provide analgesia for fractures and vasodilatation when extensive reconstructive surgery has been undertaken. It may also protect against reflex autonomic dystrophies.

For analgesia to be satisfactory with an intercostal nerve block (e.g. for fractured ribs), it must be repeatedly performed, with the risk of a pneumothorax. This complication is avoided by the placement of an intrapleural catheter and the use of a local anaesthetic infusion.

Stellate ganglion blocks may be used in certain situations, such as quinine overdose, methanol toxicity and inadvertent drug extravasation into the upper limb tissues.

Other therapies

Attention to pressure areas, mobilization, nutrition, mood, prevention of sleep deprivation and communication will relieve the discomfort of immobility. The pleasure of touch and massage may also promote well-being. Transcutaneous electrical nerve stimulation (TENS) machines may also help. Occasionally, other assistance may be required, such as the specialist advice of neurologists, chronic pain specialists or the palliative care team.

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The Role of Tracheostomy in ICU

Andrew R Bodenham
Ben N Barry

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Historically the main indication for tracheostomy has been to bypass an upper airway obstruction, for example that caused by diphtheria. Modern open surgical tracheostomy techniques were standardized in 1909 by Chevalier-Jackson. In the early days of intensive care, including the Scandinavian poliomyelitis epidemics of the 1950s, tracheostomy became the accepted means of airway management for provision of longer-term assisted ventilation (Figure 1). Tracheostomy provides protection against aspiration of pharyngeal secretions and access for suctioning pulmonary secretions. In the following decades, patients requiring intensive care were more commonly managed initially by translaryngeal intubation with tracheostomy only after 2–3 weeks. The recent development of percutaneous tracheostomy techniques has reawakened interest in the place of tracheostomy in the ICU.

1 Adolescent in the early days of the Tetanus Unit at Leeds General Infirmary. Manual ventilation via a red rubber tracheostomy tube with carbon dioxide absorption in a Waters' canister. The patient made a full recovery. Photograph kindly provided by Professor J Norman.

Indications for tracheostomy in the ICU

The most common indication for tracheostomy in ICU patients is prolonged airway care, though there are often coexisting problems that favour early tracheostomy in preference to prolonged translaryngeal intubation (Figure 2). Survivors of prolonged intensive care are often profoundly weak (e.g. from critical illness neuropathy or myopathy) and are therefore unable to clear pulmonary secretions unaided until their condition improves. Acute upper airway obstruction is usually managed initially by translaryngeal intubation but tracheostomy may be used to secure the airway in patients undergoing head and neck surgery, for example for obstructing tumours and after laryngectomy. Patients with laryngeal incompetence, brain injury, cerebrovascular or neuromuscular disease, may require long-term tracheostomy to reduce the risk of aspiration and facilitate removal of pulmonary secretions.

Indications for tracheostomy in ICU

- Prolonged weaning from assisted ventilation
- Acute and chronic neuromuscular conditions
- Poor cardiorespiratory reserve
- Bulbar dysfunction
- Brain injury
- Upper airway obstruction

2

Benefits of tracheostomy

Tracheostomy offers the patient significant advantages over prolonged translaryngeal intubation. The patient is generally more comfortable, allowing a reduction in sedative, analgesic and muscle-relaxant drugs; clearance of airway secretions, general nursing care and enteral nutrition are all facilitated. There is a reduced incidence of accidental extubation and endobronchial intubation. Verbal communication may be possible as the patient awakens and regains laryngeal competence. A fenestrated (speaking) tracheostomy tube may be inserted, or the tube cuff may be deflated to allow phonation. Airway res-istance and anatomical dead space are reduced, reducing the work of breathing and improving the chances of weaning from assisted ventilation. Tracheostomy may allow earlier discharge from the ICU to the high-dependency unit or a general ward.

Timing of tracheostomy

The decision when to convert translaryngeal intubation to tracheostomy remains controversial. An assessment of the risks and benefits for performing a tracheostomy should be carried out daily. Tracheostomy is associated with serious complications (see below). Conversely, the incidence of laryngeal injury and subglottic stenosis increases significantly over time with prolonged translaryngeal intubation.

It is desirable to minimize the risks of both means of airway maintenance. The present consensus is that translaryngeal intubation should be converted to tracheostomy at 7–14 days, unless rapid improvement is likely. If it is apparent earlier that the patient will require prolonged respiratory support (e.g. Guillain–Barré syndrome, cervical cord injury or traumatic brain injury) then earlier tracheostomy may be appropriate. If there is uncertainty about the patient's ability to maintain airway and respiratory function unaided, a trial of extubation is often performed to ascertain the need for prolonged airway instrumentation.

In children and adolescents, the relative risks of tracheostomy are higher than in adults, therefore it is usual not to perform tracheostomy unless it is likely to become a long-term or permanent requirement.

Complications of tracheostomy

The complications of tracheostomy are common to all insertion techniques (Figure 3). The distinction between early and late complications is somewhat artificial because many problems on initial insertion or re-insertion may develop into late complications. The changing indications, less frequent use of open insertion techniques, use of less traumatic tubes and better aftercare should reduce the incidence of complications. However, the overall number of complications is likely to increase as the number of tracheostomies performed in intensive care patients increases.

Complications of tracheostomy

Early

- Haemorrhage
- Obstruction by blood clot or mucous plugs
- Misplacement
- Dislodgement
- Subcutaneous emphysema
- Pneumothorax
- Injury to adjacent structures

Late

- Stomal infection
- Tracheal stenosis
- Tracheo-oesophageal fistula
- Tracheo-innominate artery fistula
- Tracheomalacia
- Obstruction by mucous plugs

3

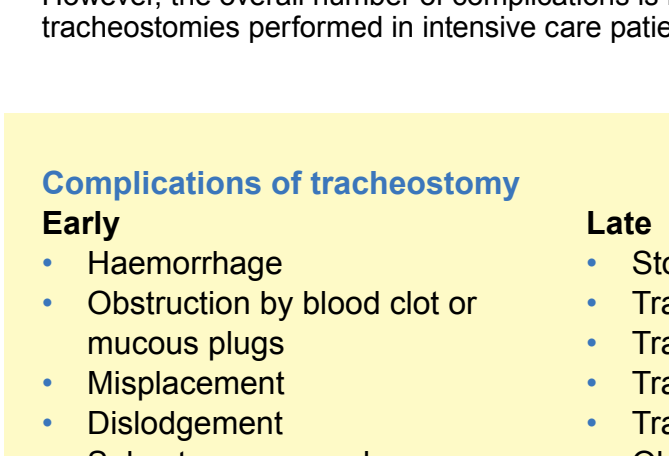
Tracheostomy techniques

Open tracheostomy

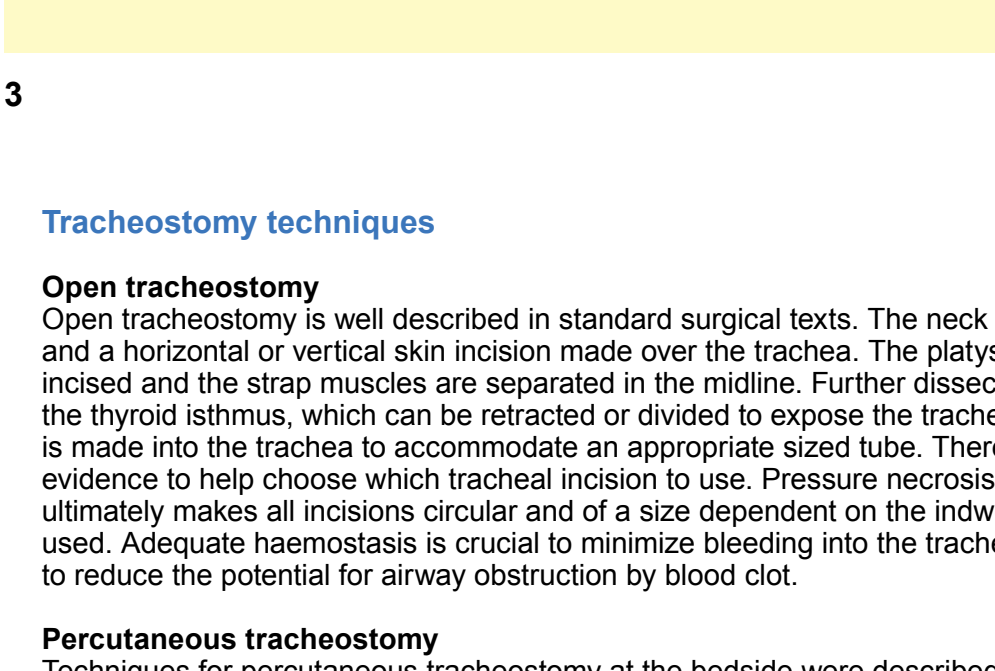
Open tracheostomy is well described in standard surgical texts. The neck is extended and a horizontal or vertical skin incision made over the trachea. The platysma muscle is incised and the strap muscles are separated in the midline. Further dissection exposes the thyroid isthmus, which can be retracted or divided to expose the trachea. An incision is made into the trachea to accommodate an appropriate sized tube. There is little evidence to help choose which tracheal incision to use. Pressure necrosis from the tube ultimately makes all incisions circular and of a size dependent on the indwelling tube used. Adequate haemostasis is crucial to minimize bleeding into the trachea, and thus to reduce the potential for airway obstruction by blood clot.

Percutaneous tracheostomy

Techniques for percutaneous tracheostomy at the bedside were described in the 1960s but medical museums contain much earlier instruments for rapid tracheostomy (Figure 4). New techniques based on the Seldinger needle-guidewire method and better materials have allowed safer percutaneous airway access. Common to all dilatational techniques are: a superficial skin incision, localization of the trachea by needle with free aspiration of air, insertion of a guidewire, formation of a tract with blunt dilators and subsequent insertion of a tracheostomy tube. The technique of dilatation varies between different kits using one or more serial dilators, or specially designed forceps (Figure 5).



4 Tracheostomy set from the 19th century. Note fenestrated silver tube with inner liner. Scalpel and sharp introducing forceps. Kit kindly lent for photography from Thackray Medical Museum, Leeds.



5 Percutaneous tracheostomy kits. **a** Cook Ciaglia serial dilators,12 FG to 36 FG (Portex tube mounted on 24 FG dilator); **b** Cook Blue Rhino single dilator; **c** Portex kit – dilating forceps, cannula over needle, guidewire and dilator; **d** indentations on Portex dilating forceps marking top of groove through which guidewire runs to allow insertion of forceps in closed position.

In ICU, procedures are performed at the bedside with the patient in the conventional position for tracheostomy. Procedures should be performed or supervised by senior staff in daylight hours when surgical and theatre assistance is readily available if required. Anaesthesia should be provided as for a conventional surgical tracheostomy and by a separate anaesthetist. The authors currently use a total intravenous technique with propofol and alfentanil infusions; a muscle relaxant is not essential but makes the procedure easier. The procedure can be performed under local anaesthesia alone, but this is likely to be unpleasant for the patient. The patient is usually already intubated and ventilated prior to the procedure; a laryngeal mask airway provides an alternative means of airway control. The anaesthetist withdraws the tracheal tube under direct laryngoscopy until the cuff is seen to lie within the larynx, avoiding the risk of transfixion of the tube or cuff with the needle and guidewire.

After preparation with sterilizing solution and the application of drapes to maintain a sterile field, the area of incision is infiltrated with local anaesthetic (e.g. 1% lidocaine (lignocaine) with adrenaline (epinephrine) 1:200,000). A superficial 1.5–2 cm horizontal skin incision is made over the space between the second and third or third and fourth tracheal rings. The subcut-aneous and pretracheal fascial layers are opened by blunt dissection with forceps; on occasion, large anterior jugular veins are identified and may require ligation. The trachea is palpated through the incision to improve orientation and confirm anatomy. The thyroid isthmus need not be identified or specifically avoided. The trachea is entered with a cannula over needle, confirmed by the free aspiration of air into a partially fluid-filled syringe. A guidewire is passed into the trachea and the tract dilated to accept an 8 or 9 mm internal diameter tracheostomy tube.

Bronchoscopy using a fibre-optic scope passed through the tracheal tube may be used routinely to guide correct placement of needle, guidewire and tube or may be reserved for teaching or difficult cases only. The presence of a fibre-optic scope may hinder ventilation with consequent risk of hypoxia or elevation in partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and intracranial pressure. It is also easy to cause expensive damage to the bronchoscope by needle puncture.

Open versus percutaneous techniques

Studies have tended to favour percutaneous techniques in ICU patients, but operator experience and aftercare are likely to be as important as individual insertion technique or reported device malfunction. In many units, dilatational techniques have almost completely replaced conventional techniques in adult patients. Percutaneous techniques have the following advantages:

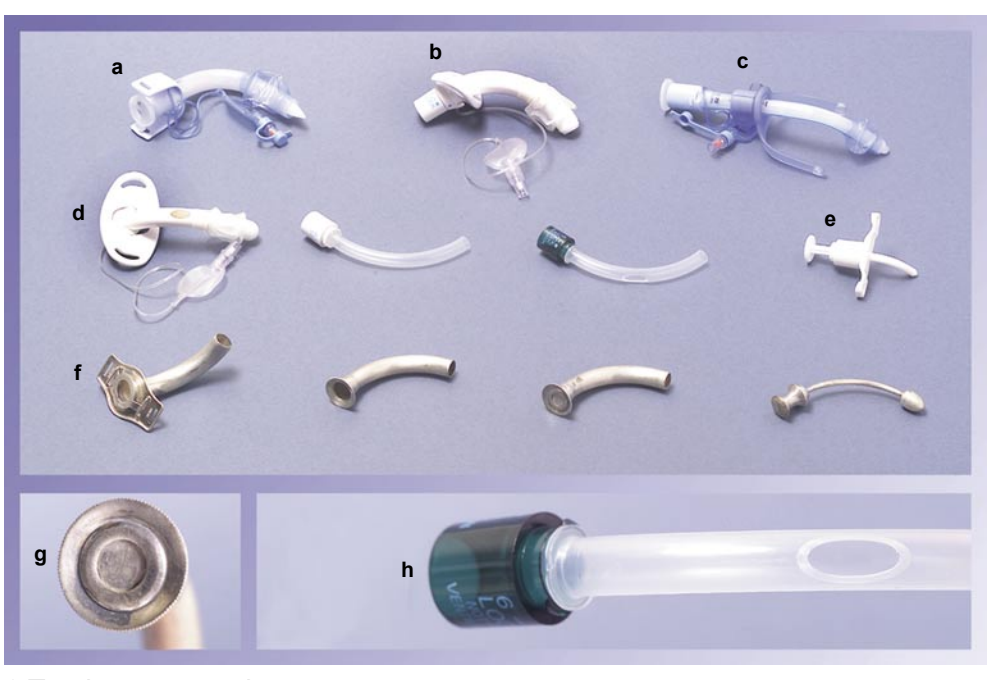
- quicker and easier to perform at the bedside
- less risk of early bleeding
- reduced risk of stomal infection
- better cosmetic result by virtue of the smaller incision.

However, there is a higher risk of tracheal damage and other complications related to insertion.

With experience, percutanous techniques can be successfully performed in more difficult patients including those with abnormal coagulation, chronic lung disease, morbid obesity, previous tracheostomy or thyroidectomy, halo-traction and critical oxygen dependency. Relative contraindications to dilatational techniques include a large goitre, malignant infiltration or other anatomical abnormalities. Worldwide, many centres routinely use open techniques because of the cost of percutaneous devices, lack of experience in such techniques and conservatism in medical practice.

Choice of tracheostomy tube

A large number of different tubes and materials are commercially available (Figure 6) and some manufacturers provide custom-made tubes. In an adult, 7–9 mm internal diameter tubes are typically used. In the patient with an increased distance between skin and trachea (e.g. obesity, tumour, haematoma) a long-shanked adjustable flange tracheostomy tube should be used. Tubes are available with fenestrations to allow speech, removable inner liners for ease in cleaning, plus various other features to aid communication and suction of secretions.



6 Tracheostomy tubes.
a Portex 9.0 mm profile cuff tube; **b** Shiley size 8 low pressure cuff tube; **c** Portex 7.0 mm adjustable flange tube; **d** Shiley size 6 fenestrated tube with plain and fenestrated inner tubes; **e** Shiley 3.0 neonatal tube; **f** silver 34 FG tube with plain and speaking valve inner tubes and trocar; **g** silver tube speaking valve; **h** Shiley fenestrated inner tube.

Role of cricothyroidotomy

The larynx lies superficially at the level of the cricothyroid membrane and so this procedure may be performed rapidly in an emergency to relieve airway obstruction. Kits are available for rapid insertion of 4–6 mm tubes using a modified Seldinger technique or a traditional surgical cut-down may be performed. Cricothyroidotomy in the non-emergency setting is commonly referred to as ‘minitracheostomy’; it has been used for patients with sputum retention and atelectasis not requiring protection against pulmonary aspiration or assisted ventilation. The widespread use of percutaneous tracheostomy has made the use of minitracheostomy for such patients less common.

Aftercare and decannulation

Obstruction is a recurrent problem with all types of tracheostomy tube. Humidification, tracheal suction and physiotherapy are all essential to avoid accumulation of respiratory secretions with crusting and subsequent tube blockage. If left untreated, the patient will suffer respiratory distress, hypoxia and hypercapnoea, proceeding to cardiorespiratory arrest.

The risk may be reduced by adequate frequency of suction and removal of the inner tube for cleaning, or changing the tube, as applicable. In the short term, a spontaneously breathing patient will manage to breathe adequately through a formed stoma. Never be afraid to remove a tracheostomy tube if there is doubt regarding its patency and the adequacy of the airway. The stoma will usually be established by 7 days and there should be little difficulty in replacing the tube: alternatively the patient may be reintubated by the oral route.

In the patient who is recovering following intensive care, there is a general tendency to leave the tracheostomy tube in place for too long. Once the patient is able to cough to clear secretions and protect the airway, consideration should be given to removing the tube, because its presence limits generation of an effective cough and may promote a tracheitis. There is no ideal way to assess when the patient is ready for decannulation, though a multidisciplinary approach, in consultation with physiotherapists and nurses is prudent. The risks associated with a failed decannulation are likely to be minimized if decannulation is carried out during daylight hours because the patient requires a period of close observation and may require tube reinsertion. After successful decannulation, stomas are usually left to granulate and close spontaneously. Recently closed wounds may be re-opened by blunt dissection if needed. A few patients require late surgery to release a tethered wound or excise a persistent sinus.

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Secondary Transport of the Critically Ill

Saxon Ridley

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Transport of patients may be divided into primary and secondary. Primary transport refers to the movement of patients from the scene of an accident or the onset of illness to hospital where their presenting problems can be assessed, stabilized and treated. Secondary transport refers to the movement of the patient after initial assessment and may be to specialized diagnostic or therapeutic facilities within the same hospital (intra-hospital) or another hospital (inter-hospital).

In the UK, the secondary transfer of critically ill patients started under the auspices of the Clinical Shock Study Group in Glasgow. This specialized transfer team has been responsible for most of the inter-hospital transfers in the West of Scotland for almost 30 years. Early publications from this group outlined the physiological changes that could be expected during transfer of critically ill patients and these principles form the basis of the clinical management of such patients. In the UK, just over 10,000 critically ill patients require secondary transfer each year. Despite the logistic advantages and improved patient outcome when transfers are undertaken by specialist teams, there are few such teams and most transfers are undertaken by the staff of the referring hospital who do not regularly perform such tasks.

In the UK, where intensive care facilities are relatively sparse, the concept of ICUs working together as a web to provide a geographical or regional service is being considered to maximize the use of resources. The recent introduction of the National Intensive Care Bed Register and biannual census of ICU beds emphasizes the political interest in this area.

Reasons for transfer

Patients may require transfer to an alternative ICU for several reasons.

Upgrade in care: specialist services may not be available at the base hospital. Examples include regional centres for cardiac and neurosurgery, burns and renal failure management. Occasionally, transfer is required because the referring clinician believes that the patient may benefit from the greater expertise and experience available at a larger centre.

Special investigations such as MRI under general anaesthesia are available only at certain large hospitals.

Inadequate facilities at the referring hospital may require the patient to be transferred to an ICU.

Social: moving a critically ill patient to an ICU nearer home to facilitate family support and minimize disruption to family life may be advantageous.

Principles

The principles underpinning transfer of the critically ill may be broadly divided into organizational and clinical. Attention to both is vital if transfer is to be effective and safe.

Organization
Good communication between the referring and receiving hospitals is essential. Communication is usually on a regional or geographical pattern. Senior medical staff should make all transfer decisions.

Nominated consultant: in each hospital a consultant should be responsible for the transfer of all critically ill patients. The consultant should develop local protocols for a safe and efficient transfer service that can be maintained on a 24-hour basis. The consultant should also be responsible for auditing care during transfer and ensuring that the accompanying staff are adequately trained.

Accompanying personnel: working in the confined space of an ambulance is difficult and should not be delegated to inexperienced staff because clinical signs are not easy to recognize and the work is unsupervised. Training of the accompanying staff is vital to ensure patient safety.

Transfer teams: ideally, movement of critically ill patients should be conducted as a regionally or geographically based service; however, this would require significant additional funds and may not be feasible in the short term. Regional teams are probably best for the semi-elective transfer of patients requiring an upgrade of care or special investigations. For potentially unstable patients requiring urgent surgery, the regional team's response time may be too long and the patient may require a more expeditious transfer.

Clinical principles
The overriding clinical principle is that the intensive care environment should be moved with the critically ill patient, though active intervention is almost impossible *en route*.

Preparation and stabilization: anything that may have to be done *en route* should be carried out before departure. Resuscitation, stabilization and preparation are mandatory before departure from the referring hospital. Monitoring is essential to ensure stability or to detect any adverse physiological changes that may occur during transfer. The systolic arterial blood pressure must be measured with an intra-arterial cannula because vibration and movement artefacts make non-invasive methods unreliable. Manipulation of the cardiac filling pressures may be needed to stabilize the patient before transfer. Patients must be hypervolaemic and if fluids alone are inadequate to render the patient hyperdynamic, then inotropes should be added. Modern portable transfer monitors have at least two pressure channels and so should allow simultaneous measurement of arterial and central venous blood pressure.

Stabilization of the respiratory system usually involves tracheal intubation and mechanical ventilation. The effectiveness of mechanical ventilation should be checked by blood gas analysis before departure and capnography *en route*. A high inspired oxygen fraction is required because of changes in ventilation/perfusion mismatch associated with acceleration and deceleration forces during transfer.

Sedation is vital so that the adrenergic response to transfer is minimized. An uncontrolled adrenergic response confuses the physiological trends associated with transfer.

Speed of transfer: a stable ICU patient should be moved at normal speed in an unhurried fashion. Normalization of physiological parameters before transfer offers some scope for deterioration as a result of the normal forces experienced during travel. Speed is required only for specific, initial life-saving interventions such as extradural haematoma evacuation and aortic aneurysm rupture repair. Relevant case notes, radiographs, a referral letter and investigation reports should be transferred with the patient. A record of the patient's physiological parameters and interventions undertaken *en route* should also be left at the receiving centre.

Personnel

Medical staff: all medical staff involved in transferring critically ill patients should be competent in intensive care medicine and be familiar with the equipment used in the care of these patients. Before taking responsibility for a transfer, staff should receive training and accompany transfers as an observer. Resources are required to achieve this and to ensure safe transfer systems throughout the UK. At least two personnel should accompany a patient during transfer; often the second member of the team is a nurse who should be experienced in the care of the critically ill and specifically in patient transfer.

Insurance cover: adequate insurance to cover the death or disability of staff accompanying patients as a result of road traffic accidents is required. In the UK, such personal accident insurance is one of the benefits of membership of specialist societies such as the Intensive Care Society and the Association of Anaesthetists.

Equipment

The equipment required during a transfer may be divided into four broad categories (Figure 1). The first category is the equipment needed for basic care such as the ICU bed or cot, laundry, sources of warmth and comfort. Life support equipment such as the ventilator and other respiratory support, including oxygen supply may be considered as the second category. The third category includes monitoring devices and the fourth includes equipment required to treat the patient. Two types of treatment equipment are required: that needed for continuing intensive therapy and that required for emergencies arising because of physiological deterioration or equipment failure (e.g. blocked tracheal tube, loss of oxygen, power failure, avulsed intravenous infusion lines).Equipment required for intra-hospital transfer is similar to that needed for inter-hospital transfer; to avoid duplication of equipment and to maximize staff familiarity with one standard apparatus inventory, institutions may elect to use their inter-hospital mobile ICU for intra-hospital transfers.

Categories of equipment for transfer

Basic care
- ICU bed or cot, warmth, comfort

Life support equipment
Airway
- Laryngoscopes, spare batteries and bulbs
- Sterile cuffed tracheal tubes (various sizes)
- Sterile cuffed tracheotomy tubes (various sizes)
- Tracheal tube introducers (metal and gum elastic)
- Airways, oral and nasal (various sizes)
- Suction catheters and suction device
- Catheter mounts
- Disposable humidifiers
- Fixed-performance oxygen masks and piping
- Lubricating jelly
- Artery forceps
- Tape and adhesive dressing
- Magill forceps

Breathing
- Portable ventilators (ideally capable of volume-controlled ventilation, positive end expiratory pressure generation, variable inspired oxygen fraction, lightweight, simple, gas driven, robust and reliable)
- Oxygen cylinder with appropriate pressure-reducing valves for ventilator and fresh gas flow to face mask
- Disposable (or autoclavable) ventilator tubing
- Self-inflating resuscitation bag with anaesthetic masks (various sizes)

Circulation
- Intravenous cannulae (various sizes)
- Cannulae appropriate for intra-arterial pressure monitoring
- Intravenous fluids and administration sets
- Central venous catheters (various lengths and diameters)
- Sutures and dressings
- Infusion pumps with appropriate syringes
- Three-way Luer lock taps and intravenous line extensions

Monitoring equipment
- Central venous and pulmonary occlusion pressures, direct measurement
- Arterial oxygen saturation
- Temperature
- Blood pressure (direct intra-arterial and non-invasive)
- ECG
- End tidal carbon dioxide tension

Treatment
Continuing ICU management
- Drugs and intravenous fluids

Emergency treatment needed during transfer
- Nasogastric tubes (various sizes)
- Scissors and razors
- Syringes and needles
- Sterile, plain and alcohol-soaked swabs
- Gloves and aprons
- Defibrillator

Children
During the development of paediatric intensive care services, the importance of regional retrieval teams was appreciated and now most regional paediatric ICUs support such teams. Adverse events are more common if paediatric retrieval is not carried out expertly. For example, a study in Birmingham, UK, reported that 75% of transfers were complicated by an adverse physiological event, equipment failure, or inadequate documentation of vital signs. In 1995, an American study of 180 paediatric transfers reported adverse physiology changes occurring in 72% and major equipment mishaps in 10%. Major interventions were required in 40% of these transfers. In a subsequent phase, the introduction of a specialist paediatric transfer team resulted in no adverse events. In another study, it was found that only 4% of 51 critically ill children suffered preventable physiological deterioration when accompanied by a specialist transfer team. The patient's severity of illness, as judged by the PRISM (Pediatric Risk of Mortality) score, decreased during transfer, reflecting an improved clinical state as a result of the pre-transfer and intra-transfer resuscitation.

Neurosurgical
Emergency neurosurgical patients requiring further management at the regional neurosurgical centre represent a dilemma. The effects of secondary brain damage, mainly resulting from hypoxia and hypotension, must be minimized. These complications are best treated by experienced staff who are familiar with the problems that occur during transfer. However, the response time of any regional transfer team may limit their effectiveness under such circumstances and staff from the referring hospital must move the patient. This is best managed if protocols and guidelines developed in conjunction with the regional neurosurgical centre are followed (Figure 2).

Guidelines used for transfer of patients requiring further neurosurgical management

Indications for intubation and ventilation before transfer

- Coma (Glasgow Coma Score – GCS ≤ 8)
- Loss of airway reflexes
- Ventilatory insufficiency
  ($Pa_{O_2} \leq 9$ kPa on air or ≤ 13 kPa on O_2)
  ($Pa_{CO_2} \leq 6$ kPa)
- Respiratory arrhythmia
- Spontaneous hyperventilation with $Pa_{CO_2} \leq 3.5$ kPa

Additional indications for intubation

- Deteriorating consciousness (decrease in GCS by ≥ 2)
- Fractured mandible
- Bleeding into the upper airway
- Patient fitting

Aeromedical
Road transfer is satisfactory for most critically ill patients. It has the advantages of low-cost, rapid mobilization, less weather dependency and easier patient monitoring.

Air transfer should be considered for longer journeys (over 50 miles or 2 hours). Its apparent speed must be balanced against organizational delays and intervehicle transfer at either end of the flight. Helicopters are recommended for journeys of 50–150 miles or where access is difficult, but they provide a less comfortable environment than road ambulance or fixed- wing aircraft. Helicopters are expensive and have a poorer safety record than fixed-wing aircraft. Fixed-wing aircraft, preferably pressurized, should be selected for transfer distances over 150 miles.

The problems associated with aeromedical transfers are altitude, temperature control, noise, vibration, visibility and unfamiliar environments. Changes in barometric pressure are hazardous, because a small pneumothorax expands by 20% with an increase in altitude of 6000 ft.

Quality and audit

Transfer forms are vital to record physiological changes and therapy before and during transfer. Regular audit of transfers is necessary to maintain and improve standards. The responsible consultant should review all transfers in and out of the hospital and a similar process should be established at regional and national level. The referring hospital, the receiving hospital, the ambulance service and any external auditing system should retain copies of the transfer documentation.

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Sedation and Neuromuscular Paralysis in the ICU

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Patients receiving mechanical ventilation usually require sedation and/or analgesia. The patient's underlying disease state and the indications for mechanical ventilation should be considered before selecting and administering sedative agents. The risk of prolonged sedation after discontinuation of drug therapy can be reduced with careful selection of agents and their dosing regimen. There must be a clear reason for using muscle relaxants, because there are disadvantages to their use.

Sedation

During intensive care, sedation is required to relieve the discomfort and anxiety caused by procedures such as tracheal suction, physiotherapy and manual handling, and to facilitate the tolerance of tracheal tubes and intermittent positive-pressure ventilation (IPPV). It may also be useful in managing other aspects of intensive care, such as insomnia, hallucinations and agitation. However, the use of sedation should not be excessive and, in general, the aim should be to create a cooperative, calm and pain-free patient who will tolerate the necessary interventions of intensive care and permit clinically useful assessments to be undertaken.

Inappropriately deep sedation should be avoided, because it has several potential adverse effects including hypotension, prolonged recovery time, delayed weaning from IPPV, ileus, the development of drug tolerance or a 'chronic' confusional state. Occasionally, deep sedation is appropriate, for example in the management of patients with refractory hypoxaemia or raised intracranial pressure, or in those for whom neuromuscular paralysis is appropriate (see below). It may also be used to reduce oxygen consumption and metabolism.

Although pharmacological methods of managing anxiety and discomfort in the ICU are the mainstay of therapy, other approaches may be useful:

- good communication between ICU staff and the patient
- control of the environment (e.g. noise, temperature, humidity)
- management of thirst, hunger, constipation
- attention to ventilation (hypercapnia increases sedative requirements)
- aromatherapy and massage
- adequate analgesia (may include regional techniques).

Pharmacological methods of sedation

The ideal sedative agent possesses the following qualities:

- an easily controllable level of sedation
- no effect on major organ functions
- a short onset and offset of action
- metabolic pathways independent of hepatic or renal function
- no accumulation
- inactive metabolites
- inexpensive
- no interactions with other ICU drugs.

Drugs used for sedation include opiates, benzodiazepines, propofol, barbiturates, butyrophenones and other antipsychotic agents, central-acting α_2-agonists, and the volatile anaesthetic isoflurane. Newer rapidly titratable drugs are also available including alfentanil and remifentanil (Figure 1).

Sedative drugs may be administered by bolus or by continuous infusion. In general, sedation is best maintained using an infusion technique, with additional boluses 'as required'. Bolus administration alone leads to fluctuating sedation levels. The clearance of most commonly administered drugs relies on metabolism and excretion by the liver or kidney or both; their duration is prolonged in hepatic or renal failure. Drugs metabolized at least in part by other mechanisms include propofol and remifentanil.

Opioids are traditionally given to treat pain, but they possess sedative properties by virtue of their central action on opioid receptors. In the UK, morphine, fentanyl and alfentanil are the most commonly used, though others (e.g. remifentanil) are being considered. The specific features of opiates are listed inFigure 2. The adverse effects of opioids include:

- respiratory depression
- cardiovascular depression (hypotension and bradycardia are common, secondary to a decrease in sympathetic tone)
- depression of intestinal motility
- pruritus.

Benzodiazepines used in the ICU include midazolam, diazepam and lorazepam. They all exhibit anxiolytic, hypnotic, muscle relaxant and anticonvulsant effects, and synergy with opioids. Rapid intravenous injection in an unstable patient may produce airway compromise and cardiovascular depression. Diazepam, and to a lesser extent midazolam, have active metabolites that can accumulate over days of use and extend their duration of action. Lorazepam does not accumulate in lipid stores or have an active metabolite, but its elimination half-life is more than 10 hours. Overdose or accumulation of benzodiazepines can be reversed by flumazenil. This benzodiazepine-receptor antagonist has a shorter half-life than agonist benzodiazepines and may need to be given by infusion.

Propofol (2,6-diisopropylphenol) is a lipid-soluble agent with a rapid onset and short duration of action. Recovery from sedation usually occurs within 10 minutes and is not significantly lengthened by prolonged drug administration. However, some accumulation may occur in obese patients, because the drug is lipid soluble. Propofol is rapidly metabolized by hepatic and extrahepatic mechanisms. When compared with midazolam for ICU sedation, propofol has shorter arousal times, but there is no difference in the quality of sedation. Propofol is a potent vasodilator, and can cause significant hypotension, especially in the hypovolaemic or septic patient. Prolonged infusions lead to increased serum triglyceride and cholesterol concentrations. In fluid-restricted patients, the large volume of infusion may pose problems. Propofol is not licensed for sedation in children because several deaths have been reported following its use in very young children. Patients receiving propofol infusions may develop green or reddish-brown urine.

Ketamine – in subanaesthetic concentrations ketamine has analgesic and sedative properties, but it should not be used as monotherapy because of its excitatory and hallucinogenic side-effects. These can be avoided if ketamine is administered in combination with a benzodiazepine or propofol. Ketamine acts at the N-methyl-D-aspartate (NMDA) receptor. Its catecholamine-releasing properties may have advantages or disadvantages, depending on the circumstances. It is expensive.

Barbiturates are unsuitable for therapeutic sedation, because they are cardiovascular depressants and accumulate following prolonged use. Thiopental (thiopentone) may be useful in managing status epilepticus or raised intracranial pressure.

Etomidate is not used by infusion on the ICU, because an excess mortality has been associated with its use, secondary to adrenal suppression.

Butyrophenones and phenothiazines – haloperidol and other antipsychotic agents (e.g. chlorpromazine) have greater antipsychotic than sedative effects at lower doses, and decrease hallucinations, paranoia and motor activity. They can be used for promoting calmness and clarity in critically ill patients with delerium or delerium tremens. Haloperidol may be the preferred agent, because it exhibits less α-adrenoceptor-blocking tendency, but any of these agents may cause vasodilatation, hypotension, a prolonged QT interval, extrapyramidal symptoms or neuroleptic malignant syndrome.

Clonidine – α_2-adrenoceptor agonists (e.g. clonidine) inhibit catecholamine release, and exert synergistic interactions with opioids and other sedatives. Administration of α_2-adrenoceptor agonists results in functional central sympatheticolysis, which may be useful in withdrawal syndrome from chronic alcohol abuse, during the weaning from long-term mechanical ventilation and in patients with tetanus. Clonidine doses are usually 0.9–1.5 mg/day, but may range up to 15 mg/day. Contraindications include hypovolaemia (risk of refractory hypotension) and severe arrhythmias.

Isoflurane delivered into the ventilator circuit in concentrations of 0.25–0.50% has been used to provide sedation of ICU patients. Problems include vasodilatation and the need for expired vapour scavenging.

Chloral hydrate is used in paediatric intensive care practice as an adjunct to intravenous sedation, particularly during weaning from ventilation. It is metabolized in the liver to the active compound trichloroethanol. The acetate and glucuronide metabolites accumulate in renal dysfunction

Pharmacology and dose of sedative drugs

	Plasma half-life (hours)	Elimination/ metabolism	Recovery time after prolonged sedation	Active metabolites (half-life hours)	Loading dose (mg/kg)	Infusion rate (mg/kg/ hour)
Morphine	2–4	Liver >> kidney	Days	Morphine-6-glucuronide (2–10)	0.05–0.15	0.02–0.1
Fentanyl	1.5–6	Liver	Hours–days	None	0.0001–0.0004	0.001–0.004
Alfentanil	1–2	Liver	Minutes–hours	None	0.004–0.014	0.01–0.1
Remifentanil	0.7–1.2	Blood/tissue Esterases	Unchanged	None	0.0005–0.001	0.0001–0.0005
Midazolam	1.0–12.3[1]	Liver	Hours–days[1]	None	0.025–0.35	0.025–0.2
Diazepam	20–50	Liver	Days	Desmethyldiazepam (30–200) + others	0.1–0.2	0.007–0.15
Lorazepam	10–20	Liver	Days	None	0.02–0.04	0.002–0.05
Propofol	< 1	Liver/extra-hepatic	Minutes–hours	None	0.5–3[2]	0.5–8

[1] May accumulate, especially after 48 hours, in the elderly and in obese patients, exacerbated by liver or renal failure. Initial short half-life results from redistribution into fat, not elimination.

[2] Slow intravenous titration until loss of consciousness occurs, because it may cause significant hypotension, especially if the patient is hypovolaemic or shocked.

1

Specific features of opiates in the ICU

Morphine

- Cheap, 'gold-standard'
- Long-acting, slow to reach steady state
- Renally excreted, metabolite (morphine-6-glucuronide) accumulates in renal failure
- May cause histamine release, risking hypotension

Fentanyl

- Initial rapid redistribution, but lipid stores are soon saturated
- No additional accumulation in renal failure
- Minimal cardiovascular effects

Alfentanil

- Relative lack of lipid solubility and short half-life minimize accumulation, except in severe hepatic failure
- Minimal cardiovascular effects
- Relatively expensive

Remifentanil

- Metabolized by nonspecific blood and tissue esterases, hence short duration of action unaffected by organ dysfunction
- Expensive

Pethidine

- Metabolite (norpethidine) accumulates during infusion and may cause convulsions

2

Monitoring sedation levels

Clinical – several sedation scores have been advocated, but none has undergone rigorous testing or gained widespread clinical acceptance. Ideally, a sedation score for regular use in a busy ICU must be valid and simple. Most objective sedation scores based on a single continuum (e.g. the Ramsay scale; Figure 3) are simple to use, but lack the detail to document the patient's mental state accurately. They do not contain a separate assessment for pain, and fail to distinguish between level of consciousness and abnormal mental states. In October 1999, the Intensive Care Society published national guidelines on sedation, concentrating on the principles of management, applicable to any drug.

Electrophysiological – most sedation scores are useless for patients receiving neuromuscular relaxants in whom an accurate physiological monitor is required. Possibilities include:

- bispectral index, a form of EEG processing
- auditory-evoked potentials
- oesophageal contractility.

The first two techniques appear reliable at discriminating consciousness from unconsciousness in the anaesthetized patient, but their role in the ICU has yet to be established.

Neuromuscular paralysis

The use of muscle relaxants fell from about 90% in the early 1980s to less than 10% in the 1990s. During this period, ICU practice changed from the use of deep to rousable sedation. Indications for muscle relaxants in the ICU include:

- refractory hypoxaemia (may decrease oxygen consumption)
- to allow inverse ratio or prone ventilation
- raised intracranial pressure
- status epilepticus
- tetanus
- during patient transport.

Ramsay scale for clinical endpoints for sedation

Level	Description
1	Anxious, agitated or restless
2	Cooperative, oriented, and tranquil
3	Responds to commands only
4	Asleep, but brisk response to glabellar tap or loud auditory stimuli
5	Asleep, but sluggish response to glabellar tap or loud auditory stimuli
6	No response

3

Neuromuscular blockers – the ultra-short acting depolarizing agent suxamethonium (succinylcholine) is predominantly used to facilitate emergency tracheal intubation. It is unsuitable for prolonged or frequently repeated use in the ICU. Figure 4 shows the features of commonly used non-depolarizing agents.

Monitoring neuromuscular blockade in intensive care is required to avoid overdose. The degree of neuromuscular blockade can be assessed by stopping the infusion, by witholding further doses, or by regular measurement of neuromuscular transmission using a peripheral nerve stimulator (e.g. train-of-four count).

Problems with muscle relaxants

- The patient may receive inadequate sedation.
- Accumulation of the parent compound or active metabolite may occur with the aminosteroidal muscle relaxants, especially during hepatic or renal impairment.
- Prolonged neuromuscular paralysis may occur after discontinuing relaxant therapy, as a result of drug accumulation or, in some cases, a myopathy. Myopathy is more likely in the presence of severe sepsis, or high-dose corticosteroid therapy.
- The protective reflexes may be lost.
- Hypokalaemia, hyperkalaemia, hypophosphataemia and many drugs (e.g. aminoglycoside antibiotics) may enhance paralysis.

Features of common non-depolarizing agents

Vecuronium

- Chemical analogue of the aminosteroid pancuronium
- Intubating dose 0.1 mg/kg, duration 35–45 minutes
- Infusion dose 1–2 μg/kg/minute
- Cardiovascularly stable
- Short duration of action makes it suitable for administration by infusion
- May accumulate when renal function is impaired

Pancuronium

- Long-acting (0.1 mg/kg lasts 90–100 minutes)
- Possesses vagolytic effects
- May accumulate if given by infusion

Rocuronium

- Aminosteroid agent, similar to vecuronium but with a slightly longer duration of action
- After a bolus dose of 0.6–1.2 mg/kg, onset time is almost as rapid as suxamethonium. Satisfactory intubating conditions occur after about 75 seconds (or less with higher dose)

Atracurium

- Benzylisoquinolinium derivative with a duration of action similar to vecuronium; can be given by continuous infusion
- Intubating dose, 0.4–0.5 mg/kg; infusion, 4–12 μg/kg/minute
- Organ-independent metabolism; little tendency to accumulate
- Histamine release common if given too rapidly
- A metabolite (laudanosine) accumulates in profound hepatic failure; it causes convulsions in animals, but not in humans

Cisatracurium

- Potent stereoisomer of atracurium; lower doses required, resulting in less generation of laudanosine
- No histamine release in clinical doses
- May be the agent of choice on the ICU, for its cardiovascular stability, and organ-independent metabolism
- Intubating dose, 0.1 mg/kg; infusion dose, 1–2 μg/kg/minute

4

Sepsis

Jonathan M Fielden

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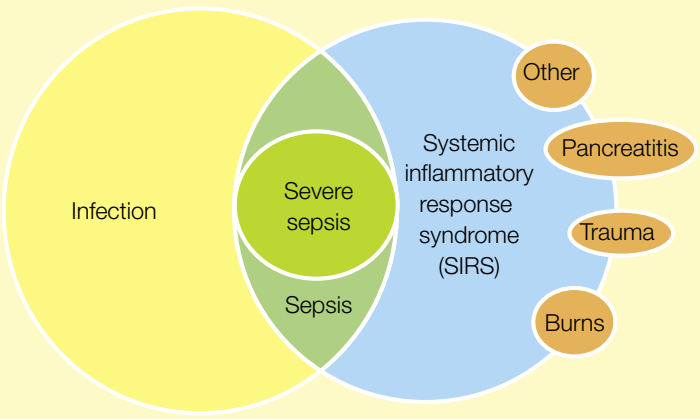
Sepsis remains a significant challenge to intensive care medicine. It is the cause of 27.7% of UK adult general ICU admissions. These 23,000 cases represent an estimated incidence of 0.5/1000 population; mortality is about 45%. In the USA, sepsis is the thirteenth leading cause of death and is a significant economic burden. Sepsis kills as many people as acute myocardial infarction. Early recognition and removal of the source of infection are key factors in management. Until recently, treatment has been largely supportive but understanding of the sepsis process has allowed the development of novel interventions that are improving survival.

Definition

Sepsis is part of the body's response to infection (Figure 1). Early investigations into treatment for sepsis were hampered by a lack of knowledge about the mechanisms driving sepsis. Bone *et al.* clarified this and produced the agreed consensus definitions (Figure 2). Sepsis is characterized by a systemic inflammatory response (SIRS) to an infective insult and key abnormalities of the homeostasis of coagulation and endothelial function. However, only 60% of cases are likely to be confirmed microbiologically and there is no correlation between severity of sepsis and documented infection. Bone *et al.* also categorized the stages of the body's response to sepsis (Figure 3). Recent research has revealed the key aspects of the pathophysiological derangement and allowed targeted research.

Spectrum of response



1

ACCP/SCCM consensus conference definitions[1]

Systemic inflammatory response syndrome (SIRS)
Response to a wide variety of severe clinical insults manifest by two or more of the following:
- temperature > 38 °C or < 36 °C
- heart rate > 90 beats/minute
- respiratory rate > 20 breaths/minute or partial pressure of carbon dioxide in arterial blood ($PaCO_2$) < 4.2 kPa (32 mm Hg)
- WCC > 12 x 10^9/litre or < 4 x 10^9/litre, or > 10% immature forms

Sepsis
Two SIRS criteria plus (signs of) infection

Severe sepsis/SIRS
Sepsis/SIRS associated with organ dysfunction, hypoperfusion of hypotension

Sepsis-induced hypotension
Systolic blood pressure < 90 mm Hg or reduction > 40 mm Hg from baseline in absence of other causes

Septic shock/SIRS shock
Severe sepsis/SIRS with hypotension despite adequate fluid resuscitation with perfusion abnormalities including those requiring inotropes

Multiple organ dysfunction syndrome (MODS)
Presence of organ dysfunction in an acutely ill patient such that homeostasis cannot be maintained without intervention

[1]ACCP, American College of Chest Physicians; SCCM, Society of Critical Care Medicine.

2

Reaction to sepsis

Infectious insult
Host factors
- Epithelial barrier
- Local defence (e.g. pH)
- Immune status
- Genetic factors

Immunity
- T and B cell response

Infecting agent factors
- Bacteria (link to epithelium, biofilms)
- Gram-negative endotoxaemia
- Gram-positive exotoxins
- Fungi

Preliminary systemic response
Febrile reaction
Cytokines
- Tumour necrosis factor-α
- Interleukin-1
- Interleukin-6
- Interleukin-8
- Interferon-γ

Overwhelming systemic response
Endothelial cell dysfunction
- Shift of phenotype to thrombotic state
- Increased permeability
- Vasodilatation

Organ dysfunction

Compensatory anti-inflammatory reaction
- Interleukin-4
- Interleukin-10
- Transforming growth factor-β

Immunomodulatory failure

3

Mechanism of sepsis-induced multiple organ failure

The SIRS response in sepsis results in systemic vasodilatation, increased cardiac output, falling blood pressure and reduced oxygen extraction from the tissues. The circulatory abnormalities of SIRS and sepsis lead to global tissue hypoxia. The key advancement in understanding the link between sepsis and multiple organ failure was the definition of the disturbance of homeostasis of coagulation and fibrinolysis. The initial insult (infection in sepsis) alters endothelial function with the release of tissue factors. There is also release of a variety of cytokines (the proinflammatory agents: tumour necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6; the excess anti-inflammatory cytokines IL-4, IL-10, IL1-receptor antagonist and soluble TNF receptor I and II) and upregulation of circulating monocytes. This leads to activation of the extrinsic system of coagulation and formation of thrombin, further amplifying the thrombotic response via the intrinsic coagulation cascade. The subsequent microvascular clotting leads to organ dysfunction and failure. There is also a reduction in some of the natural inhibitors of clotting (e.g. activated protein C) from increased consumption and endothelial injury. The normal homeostatic balance of fibrinolysis in the face of thrombosis is also disrupted in sepsis by increased inhibition from cytokine-induced increases in plasminogen activator inhibitor type 1 and plasmin–antiplasmin complexes.

The combination of increased thrombosis and reduced fibrinolysis creates microthrombi, which lead to multiple organ dysfunction and organ failure. The clinical manifestations are seen as the development of, for example, acute respiratory distress syndrome, disseminated intravascular coagulation or renal failure.

Management of the septic patient

The first step in the treatment of sepsis is recognition of the critically ill patient. The signs are often missed, and delay in referral to ICU and poor management of critically ill patients is all too common. Maintaining a high index of suspicion, monitoring the vital signs for the hallmarks of SIRS and identifying the possible sources of infection are vital. One of the most sensitive markers of deterioration in critically ill patients is an increase in respiratory rate, a sign often poorly recorded unless emphasized with the use of Medical Early Warning Scores or a similar system. Careful history and examination identify possible sources of infection and guide initial therapy.

Initial therapy

Immediate resuscitation based on the 'ABDCE' system is important to stabilize the patient. At this stage, exact diagnosis is unimportant and treating immediate life-threatening problems is the goal. Once the patient is stabilized, possible sites of infection should be examined, including:
- all body surfaces and cavities
- blood
- sputum or bronchoalveolar lavage fluid
- aspirated lesions/collections
- urine
- faeces
- CSF should be cultured if there is suspicion of intracerebral infection (provided raised intracranial pressure can be confidently excluded).

Intra-abdominal signs should prompt early surgical review and operative intervention unless good reason suggests otherwise. Blood should be taken for blood count, urea and electrolytes, calcium, magnesium, liver function tests, coagulation tests (prothrombin time, activated partial thromboplastin time, fibrinogen) and arterial blood gases including assessment of lactate. Some advocate assessment of other biochemical markers of infection (e.g. procalcitonin, C-reactive protein, von Willebrand factor) but this has yet to receive universal acceptance.

Indwelling intravascular catheters should be assessed for signs of phlebitis or infection. If not required, they should be removed and cultures taken from the insertion site and per lumen. Chest radiography and imaging of other sites should be arranged. If invasive monitoring or inotropic support is required, admission to a high dependency unit is indicated. Patients requiring respiratory support or monitoring beyond the capabilities of this unit should be admitted to ICU.

Antibiotic therapy

Initial therapy should be guided by a clinical impression of the probable site of infection, together with guidance from microbiologists on empirical therapy and specific agents, once microbiological sensitivities are known. Early accurate treatment is important and should be guided by local knowledge and agreed guidelines to prevent overuse of broad-spectrum antibiotics and further development of microbiological resistance. As a guide, use the right drug, at the right dose, at the right time, treat the patient and not the figures, and avoid toxicity.

Supportive management

Early management to return physiological parameters towards the normal range for that patient shows promise in improving outcome. Rivers *et al.* have recently shown a reduction in hospital mortality for early (i.e. Emergency Department) goal-directed therapy using a protocol to drive up central venous pressure to 8–12 mm Hg, by maintaining mean arterial pressure (MAP) at 65–90 mm Hg and keeping central venous blood oxygen saturation above 70%, using fluids, inotropes and vasopressors. This contradicts some earlier studies of goal-directed therapy in ICU, but Rivers and his colleagues argue that early intervention prevents the augmentation of the SIRS response driven by tissue hypoxia in the uncorrected septic patient. Furthermore, they were not aiming for supranormal values, which may have been a problem with earlier studies. The principle of early detection and correction of reduced tissue perfusion seems logical.

First-line treatment involves fluid resuscitation, aiming for a MAP of 65–90 mm Hg. Central venous pressure can be used as a guide for 'over filling' but aiming for a specific value, particularly when the patient is ventilated, is difficult. The place of pulmonary artery catheters is under debate and subject to a multicentre trial. Several studies promote their use, particularly before high risk surgery but others doubt the benefit. Initially, the use of the Rivers criteria for central venous pressure, MAP and urine output (> 0.5 ml/kg/hour) are reasonable aims. This can be supplemented by using lactate measurements and measurement of oxygen delivery and use.

There is no evidence that the use of any particular inotrope is best in sepsis. Noradrenaline (norepinephrine) is probably the first vasopressor of choice when aiming to reverse the vasodilatation and reduced systemic vascular resistance often seen in sepsis. When increased inotropy and chronotropy are required, dobutamine is often used. Adrenaline (epinephrine) has the benefit of α and β sympathetic activity and is often advocated if simplicity is required (e.g. initial resuscitation, theatre); there is evidence of detriment from increased hepatic lactate production. There are advocates for other inotropes (e.g. dopexamine) but the use of dopamine is diminishing because of significant evidence against its use.

Many patients require ventilation to maximize oxygenation and minimize the work of breathing. Following work in acute respiratory distress syndrome, most advocate the use of a protective lung ventilation strategy with tidal volumes limited to 6–8 ml/kg, mean airway pressures less than 35 cm H_2O, relatively high positive end-expiratory pressure (PEEP) of 5–15 cm H_2O, and a limitation of fraction of oxygen in inspired air (FiO_2) to a maximum of 0.6.

Early aggressive (high volume 30–50 ml/kg) continuous veno-venous haemofiltration (CVVHF) is advocated in sepsis. It is thought that the removal of inflammatory mediators aids resolution of the SIRS response. Whether short-term or prolonged CVVHF is best is unproven. However, the development of renal failure is common and continued CVVHF is often required. Continuous treatment is more beneficial than intermittent.

As part of aiming to return physiological parameters to normal, aggressive management of blood sugar (4.4–6.1 mmol/litre) levels with insulin is beneficial. In addition, treatment of the relative adrenal insufficiency often found in sepsis with replacement doses of hydrocortisone, 300 mg/24 hours, often reduces inotropic requirements.

Novel therapies

Vasopressin – the profound vasodilatation seen in sepsis can become refractory to catecholamine support. Treatment with vasopressin or vasopressin analogues (e.g. terlipressin) improves MAP and reduces the need for other vasopressors. This matches the research evidence of the basis of vasodilatory shock in sepsis and SIRS. The mechanism is thought to be related to the relative naivety of the vasopressin receptors to stimulus during sepsis, unlike the down-regulated catecholamine receptors.

Methylene blue is known to be an antioxidant. Infusion of methylene blue improves vascular responsiveness to inotropes in the septic patient.

Activated protein C is one of the most recent treatments available in sepsis. It has a physiological role in maintaining the coagulation and fibrinolytic balance as well as in reducing inflammation through inhibiting thrombin-mediated inflammatory activities and leucocyte attachment to the endothelium. It is reduced during sepsis and levels correlate to poor outcome. The PROWESS study showed that activated protein C could significantly reduce (28 day) mortality in sepsis (absolute risk reduction 6.1%), a goal not achieved by any other inflammatory/coagulation mediator study. Although awaiting long-term outcome data, and despite its high cost, this seems to be a significant and cost-effective advance.

Prevention

Close attention to hand washing and skin decontamination with alcohol reduce nosocomial spread. Efforts to limit antibiotic resistance through careful policies and surveillance are important. Simple measures to reduce ventilation-associated pneumonia such as semi-recumbent positioning also have a role, as does careful insertion and management of indwelling intravenous and urinary catheters. Adequate and appropriate nutrition, ideally via the enteral route, should be administered.

Outcome

Sepsis carries a high mortality (45%). Until the recent PROWESS trial, most research showed a mortality of 30–60%. It increases by 15–20% for each additional organ failure, and non-survivors tend to consume significant health resources. There is hope that early normalization of physiology and the appropriate use of agents that reduce the SIRS response (e.g. activated protein C) will reduce mortality. ◆

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Severity of Illness Scoring Systems

John Pappachan

John Pappachan is Consultant in Intensive Care Medicine at Southampton University Hospitals Trust, UK. He trained in Newcastle, London and Wessex. His research interests include the epidemiology of intensive care, renal replacement strategies in sepsis, and the genetic predisposition to sepsis.

This contribution describes systems used to predict the hospital outcome of patients admitted to an ICU. An acute physiology score is usually derived using values obtained in the first 24 hours following ICU admission. Hospital outcome is then predicted using a logistic regression equation. Development and validation, a brief description of the most popular systems, their applicability in the UK and the standardized mortality ratio (SMR) are described.

Scoring systems

Data collection on the ICU is necessary to facilitate research, quality assurance and resource management. Severity of illness scoring systems aid the case-mix adjusted collection of such data. However, none is perfect and their use to triage individual patients and to compare the quality of care in different ICUs is severely limited. An appreciation of their limitations and the statistical methods of assessing their goodness of fit are vital if the information that they provide is to be used appropriately.

Potential uses for scoring systems include:

- case-mix adjustment for entry into randomized controlled trials
- audit and comparison of ICU performance
- a mechanism to decide resource allocation.

Scoring systems use a logistic regression equation based, variably, on disease severity, age and diagnosis to derive the probability of hospital death (on a scale of 0 to 1, where 0 = survival and 1 = death). The SMR describes the ratio of expected to observed deaths. Case-mix variation and the need to derive binary (live or die) data from a probability estimate, limit the use of such systems to evaluate ICU performance.

System development and validation

Patient variables and the coefficients used to describe their influence on survival are selected either by clinical consensus or more robust statistical analysis. Typically, systems are developed from information collected on a cohort of patients admitted to a group of ICUs over a given period. The predictive equation is then validated on a subsequent cohort of patients admitted to the same or other units.

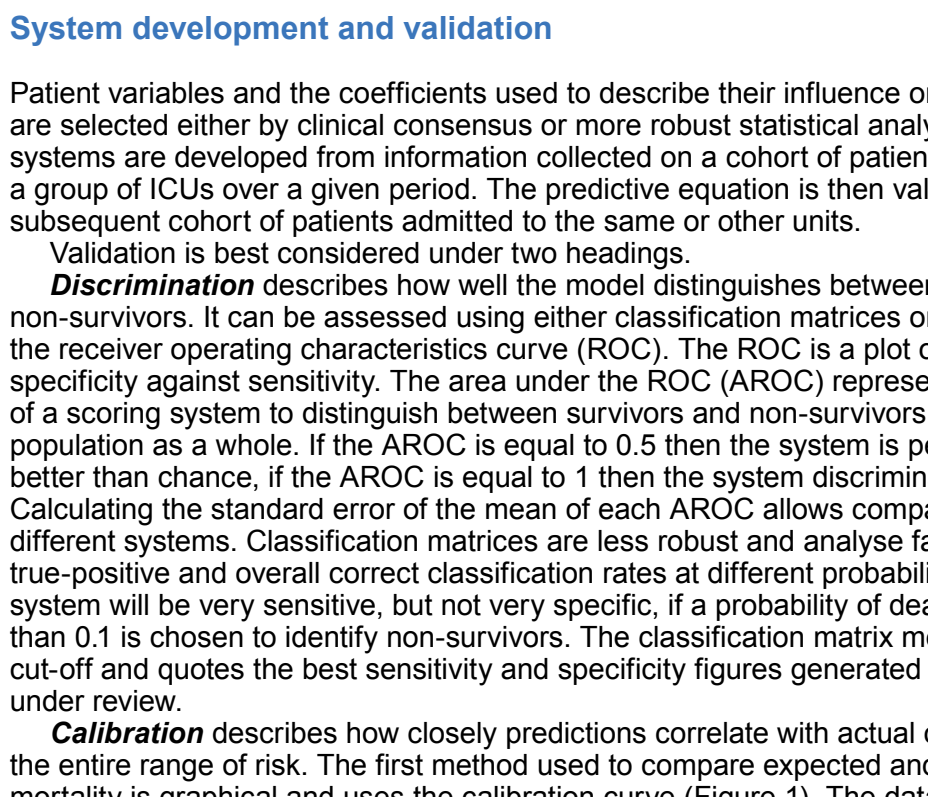
Validation is best considered under two headings.

Discrimination describes how well the model distinguishes between survivors and non-survivors. It can be assessed using either classification matrices or the area under the receiver operating characteristics curve (ROC). The ROC is a plot of derivatives of specificity against sensitivity. The area under the ROC (AROC) represents the ability of a scoring system to distinguish between survivors and non-survivors in the patient population as a whole. If the AROC is equal to 0.5 then the system is performing no better than chance, if the AROC is equal to 1 then the system discriminates perfectly. Calculating the standard error of the mean of each AROC allows comparison between different systems. Classification matrices are less robust and analyse false-negative, true-positive and overall correct classification rates at different probability cut offs. A system will be very sensitive, but not very specific, if a probability of death of greater than 0.1 is chosen to identify non-survivors. The classification matrix method varies the cut-off and quotes the best sensitivity and specificity figures generated by the system under review.

Calibration describes how closely predictions correlate with actual outcome across the entire range of risk. The first method used to compare expected and observed mortality is graphical and uses the calibration curve (Figure 1). The data generated when APACHE III (see below) was applied to ICU patients in the UK demonstrated the trend for observed mortality to increase as the predicted risk of hospital death increases. However, there was a significant overestimation of mortality in the lower-risk bands, which represented most of the sample population. This implies either that the system does not fit the data, or that the ICUs examined were performing poorly.

In an attempt to answer this question, a statistically more robust method of assessing calibration is used. The Hosmer–Lemeshow C and H cumulative χ^2 statistics compare the actual and expected mortality rates across 10 defined bands of mortality risk (H^2) and 10 deciles, which include equal numbers of patients (C^2). A significant result ($p < 0.05$) suggests poor system calibration. The only published assessment of APACHE III in UK patients suggests poor 'goodness of fit'. That for the APACHE II system (see below) in a selected group of ICUs suggests better, but still imperfect, calibration. To date, no system has been both developed and validated in UK patients. Thus it is not possible accurately to assign an observed difference between predicted and observed outcome to poor ICU performance or poor system fit.

Calibration curve describing the relationship between observed and expected mortality using APACHE III in the ICU (UK)



1

APACHE II and other systems

APACHE II used a theoretical approach to the selection and weighting of variables used in its predictive equation. This was based on consensus opinion and the findings of previous studies. Other scoring systems, for example the Mortality Prediction Model (MPM), were developed using a combination of univariate and multivariate logistic regression techniques. Neither approach has been proven to be superior in terms of the resulting goodness of fit of the system to target populations.

APACHE II was developed in 1985 from a database of 5815 intensive care admissions to 13 ICUs in the USA. The severity of illness of patients is assessed using the worst values of 12 physiological variables in the first 24 hours following admission to the ICU. These values generate an acute physiology score (APS) by following the weighting system described in Figure 2. Adding the weightings for chronic disease and age to the APS generates the final APACHE II score. The probability of hospital mortality is generated using the logistic regression equation shown in Figure 2. This equation adds the diagnostic category weight.

APACHE III, the direct successor of APACHE II, uses 17 physiological variables, comorbidity and age to produce an acute physiology score. In addition, it uses the diagnostic code and a weighting for source before ICU admission to predict outcome, length of stay, and the likely intensity of nursing required. It presently represents the largest published ICU database and has been promoted for use as a management tool for use in the allocation and evaluation of ICU resources. However, its predictive equation is not in the public domain, its claimed correction for lead-time bias (the effect of treatment before ICU admission) is unproven, and it has been shown to fit a UK database poorly.

There are a variety of simplified, more physiologically based systems available, such as the MPM and the Simplified Acute Physiology Score (SAPS).

The APACHE II weights for physiological variables

Physiological variable	High abnormal range					Low abnormal range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature – rectal (°C)	≥ 41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤ 29.9
Mean arterial pressure	≥ 160	130–159	110–129		70–109		50–69		≤ 49
Heart rate (ventricular)	≥ 180	140–179	110–139		70–109		55–69	40–54	≤ 39
Respiratory rate (non-ventilated or ventilated)	≥ 50	35–49		25–34	12–24	10–11	6–9		≤ 5
Oxygenation: A-aDO_2 or PaO_2 (mm Hg) A: $F_IO_2 \geq 0.5$ record A-aDO_2	≥ 500	350–499	200–349		< 200				
B: $F_IO_2 \leq 0.5$ record only PaO_2					> 70	61–70		55–60	< 55
Arterial pH	≥ 7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	< 7.15
Serum sodium (mmol/litre)	≥ 180	160–179	155–159	150–154	130–149		120–129	111–119	≤ 110
Serum potassium (mmol/litre)	≥ 7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		< 2.5
Serum creatinine (mg/100 ml) – double point score for acute renal failure	≥ 3.5	2–3.4	1.5–1.9		0.6–1.4		< 0.6		
Haematocrit (%)	≥ 60		50–59.9	46–49.9	30–45.9		20–29.9		< 20
WBC (total/mm^3; 1000s)	≥ 40		20–39.9	15–19.9	3–14.9		1–2.9		< 1

Glasgow coma score (GCS). Score = 15 minus actual GCS
Total acute physiology score (APS) = sum of the 12 individual variable points.
The APS is summed with age points and chronic health points according to APACHE II definitions.
The probability of hospital death (R) is then calculated from the equation:
ln (R/1 – R) = –3.517+ (APACHE II score x 0.146) + (0.603, only if post-emergency surgery) + (diagnostic category weight).

Source: Knaus W A, Draper E A, Wagner D P, Zimmerman J E. *Crit Care Med* 1985; **10**: 818–29.

2

The standardized mortality ratio (SMR)

For a cohort of patients numbering 200 or more, the accepted method of comparing outcome after adjusting for presenting factors that might influence it (e.g. the severity of physiological derangement, age and diagnosis – i.e. case-mix adjustment), is to use the SMR. This represents the ratio of observed deaths in the cohort, to the number of deaths predicted by a scoring system. If the SMR is 1 then the cohort is acting as predicted; if the SMR is significantly greater than 1 this suggests there is excess mortality. If scoring systems were perfect, transferable and able to adjust for case-mix equally well in both development and external datasets, the SMR might reflect ICU performance. These assumptions are not always valid and there are other confounding variables, such as lead-time bias and poor treatment in the ICU leading to a physiological deterioration, that limit the use of the SMR for the audit of ICU performance.

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Ventilatory Modes

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Vesalius first discussed tracheostomy and ventilation as a means of resuscitation in 1555 but it was another 300 years before the first ventilator, an iron lung, was built in Paris by Woillez. Early in the 20th century, positive-pressure ventilation during anaesthesia allowed the development of more complex surgery, but only in the 1950s did the early versions of today's ICU ventilators become available.

Over time, ICU ventilators have become increasingly sophisticated and complicated, so that they now provide intensivists with a variety of modes to use in different clinical situations. However, the terminology used to describe these modes is not standardized. For much of this article, the terminology of the Siemens 300 ventilator is used because of its wide use in the UK.

To avoid confusion, the authors focus on two fundamental characteristics of all the modes available on ICU ventilators:

- the way each breath is delivered (i.e. constant pressure versus constant flow)
- whether the breaths are controlled or supported.

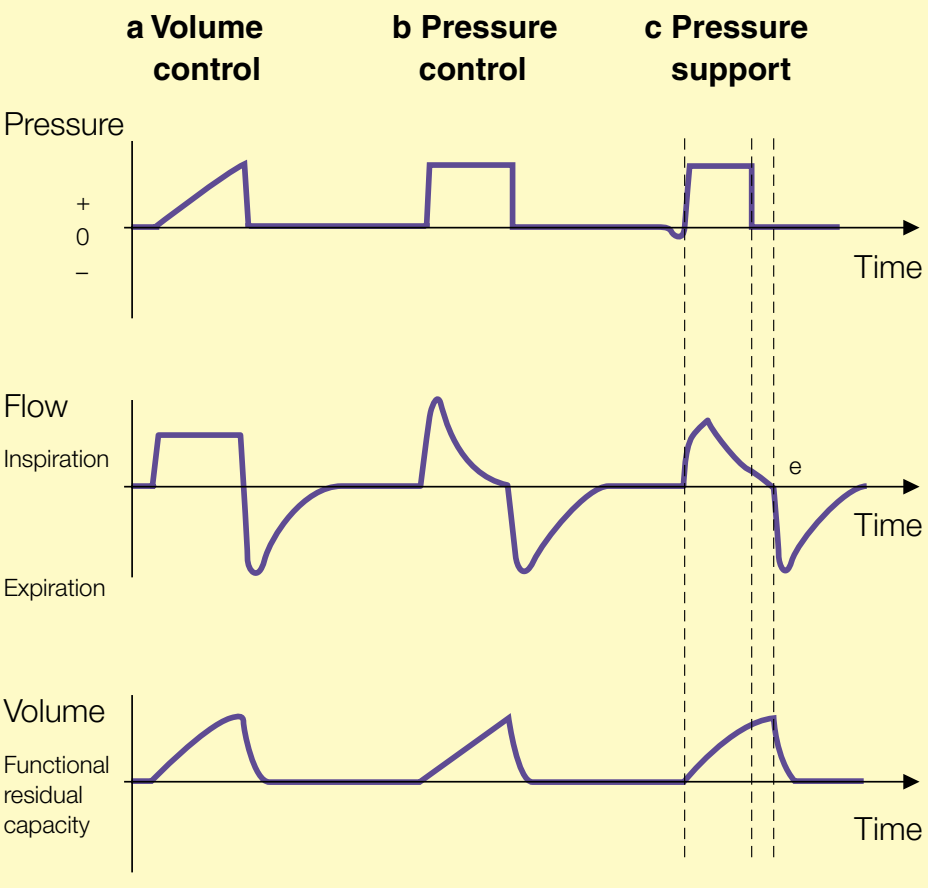
In all modes, exhalation is passive. Indications for and complications of mechanical ventilation are dealt with elsewhere.

Controlled modes

Controlled mechanical ventilation (CMV) is the ultimate 'controlled' mode because it delivers only a pre-selected tidal volume at a set rate. Apart from alarm settings, the only other parameter that can be adjusted is the inspiratory flow rate. This is controlled either directly (which determines the inspiratory:expiratory (I:E) ratio) or indirectly by altering the I:E ratio. In the latter case, any change in inspiratory time (with tidal volume and rate fixed) changes the flow rate. A disadvantage of using I:E ratios to govern inspiratory flow rate (as with the Siemens 300) is that the latter changes whenever rate, tidal volume or inspiratory time are adjusted. The waveforms are as represented for volume control in Figure 1a.

In the CMV mode, exhalation commences once the set tidal volume has been delivered. CMV is suitable only for apnoeic patients (e.g. in the operating theatre or during transport when the patient is paralysed). It should not be used when there is any possibility for spontaneous breathing because synchrony between patient/ventilator is difficult to attain. On some ventilators, 'CMV' is an assist-control (A–C) mode (see below).

Representative single breaths in three commonly used modes



In pressure support, the support ceases in the terminal phases of inspiration – the patient then determines the onset of exhalation (e). This differs from the control modes where the onset of exhalation is time (or volume) cycled.

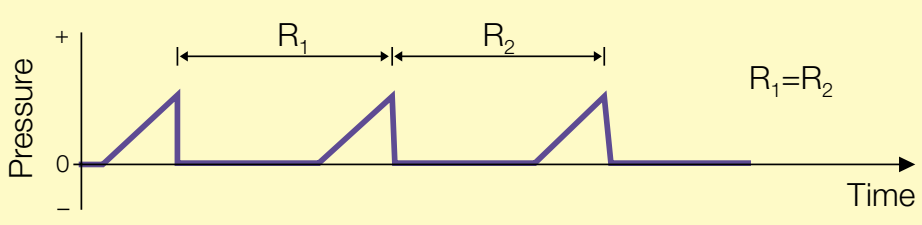
1

Assist-control – volume control sets a baseline rate and tidal volume as in CMV, but allows inspiratory effort by the patient to initiate additional breaths. The patient can therefore set their own respiratory rate, but all patient-triggered breaths (Figure 2) will be of the pre-set volume. This encourages better synchrony between patient and ventilator (and hence reduces the sedation requirements) while markedly reducing the inspiratory work of breathing. The possibility of weaning can be considered once the patient starts to trigger the ventilator. Exhalation occurs as in CMV (Figure 2).

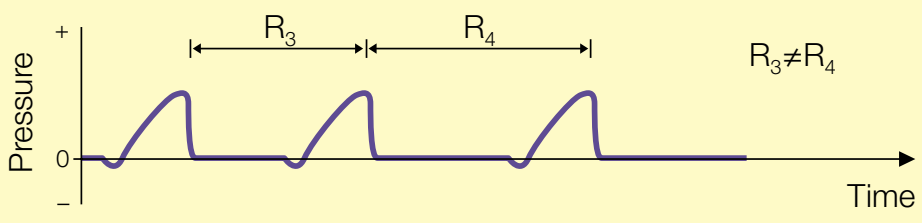
In assist-control, the inspiratory flow rate may be adjusted as in CMV. When patient-triggered breathing occurs, the inspiratory flow should be set to meet, but not exceed, the patient's inspiratory flow demands. This improves synchrony and maximizes the reduction in work of breathing. Many modern ventilators respond to high respiratory drive in patients by delivering a tidal volume above the set value in assist-control.

Pressure versus time waveforms comparing controlled and assist-control ventilation

a Control mode



b Assist mode



The graphs show the negative pressure generated by the patient to trigger assisted breaths at their own rate (thus R–R intervals are not constant). In control mode, the breaths are delivered at a predetermined interval irrespective of patient effort

2

Pressure control (PCV) is also an assist-control mode, but instead of applying a constant inspiratory flow, the ventilator provides a constant inspiratory pressure that is applied for a set inspiratory time – a 'square' wave of pressure (see Figure 1b). Flow is provided solely to maintain the set inspiratory pressure. Therefore, initial flow is high but decreases throughout inspiration. Expiration starts immediately on completion of inspiration (i.e. is time cycled), so close attention to the I:E ratio is essential in this mode.

At longer inspiratory times, the flow and pressure curves are different in PCV from those of volume control or assist-control (see Figure 1). However, at shorter inspiratory times, the flow and pressure curves are similar to assist-control using a decelerating inspiratory flow pattern – a facility that many ventilators provide in the belief that it is more natural.

In PCV, the tidal volume delivered is dependent on the respiratory system impedance as well as inspiratory time, and therefore changes with the changing clinical situation. Tidal or minute volume alarms should therefore be set to give adequate warning of excessive or under ventilation.

The main advantage of PCV is its potential to recruit atelectatic lung units while reducing the risk of barotrauma. When lung compliance is low because of acute respiratory distress syndrome or acute lung injury (ARDS/ALI), there is a broad distribution of time constants between different lung units. In assist-control, such a 'stiff' lung requires high end-inspiratory pressures to inflate units with a longer time constant, but such pressures applied to normally compliant lung units can result in over-inflation and barotrauma. By definition, PCV limits the maximum pressure applied to any part of the lung, and therefore reduces the risk of over-inflation. In PCV, lung recruitment is achieved by applying this constant pressure for a long inspiratory time, even to the extent of reversing I:E ratios. With reversed I:E ratios, as frequency rises, expiratory time progressively shortens and may reach a value that prevents full exhalation during each cycle. This results in the generation of intrinsic positive end-expiratory pressure (PEEP) and consequent hyperinflation. Since intrinsic PEEP may be either helpful or detrimental, its presence should always be sought and its potential consequences noted, particularly if obstructive airways disease co-exists with ARDS/ALI.

Triggering

Control modes use time cycling to determine the respiratory rate, but during assisted ventilation, this time cycling is over-ridden by the patient's inspiratory efforts. Most commonly, a set negative pressure must be generated by the patient in order to trigger the ventilator to deliver a breath. The trigger sensitivity (which uses electronic logic systems to compare the signal with a reference) is normally set at 1–2 cm H_2O below PEEP but this setting can be altered (if it is decreased, the work of breathing is increased and vice versa). Once the ventilator detects that the trigger sensitivity has been exceeded, the demand valve opens and inspiration commences. Too high a setting can lead to auto-cycling especially if water collects in the breathing circuit. Because pressure triggering can lead the patient to inhale for a short time against a closed system (until the demand valve opens), some newer ventilators have established a flow-triggered system. Here, a constantly monitored flow is delivered to the circuit (flow-by) during exhalation, and the ventilator initiates inspiration whenever this bias flow is reduced by the patient's inspiratory effort. As with pressure triggering, the level of inspiratory effort (reduction in bias flow) required by the patient to initiate inspiration can be adjusted. Although it is claimed that flow triggering can reduce the inspiratory work of breathing more than pressure triggering, it is difficult to prove an advantage of one over the other.

Pressure support (PS)

PS is widely used in the ICU, particularly during weaning. It allows excellent matching of the patient's respiratory drive with the ventilator so that less sedation is required. In addition, the cardiovascular consequences of PS may be less than those of controlled modes since the maximal inspiratory support pressures are generally lower and are not maintained throughout inspiration.

PS can be used only in a spontaneously breathing patient because each breath must be triggered by the patient. Each triggered breath is then supported to a pre-set pressure level. Support ceases when the inspiratory flow falls to less than 5–10% of its peak value, at which point the ventilator opens the expiratory port (see Figure 1c). Thus, the patient is never faced with attempting to exhale against a closed system. With PS, the patient can control not only the respiratory rate but also tidal volume and I:E ratio. PS reduces the work of breathing in proportion to the set pressure, which can vary from zero (weaned) to full support (equivalent to PCV). As PS is progressively reduced, the patient takes up an increasing proportion of the inspiratory work until he is breathing spontaneously (although a low level of PS may be required to overcome the resistance of the ventilator circuit and tracheal tube). This makes PS the best available weaning mode in the opinion of many.

In PS, a square pressure waveform is delivered once a breath is triggered. At high support pressures in a patient with increased respiratory drive, the initial flow required to generate this pressure can be very high and therefore uncomfortable to the patient. The rate of rise of inspiratory flow can be adjusted by the 'slope' control to allow a more progressive achievement of the pre-set pressure and therefore better synchrony between patient and ventilator. Apnoea and low minute volume alarms must be available with this mode. Many ventilators now provide an assist-control backup should apnoea arise.

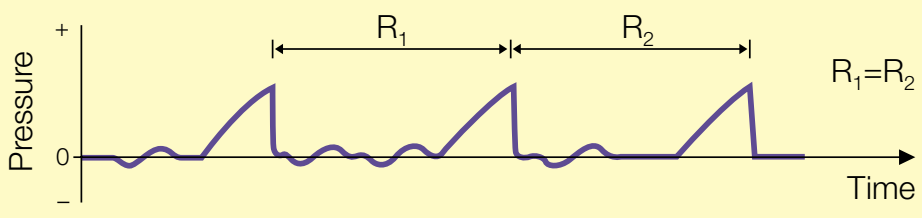
Hybrid modes

Many modern ventilators provide a variety of hybrid modes, a few of which are discussed below.

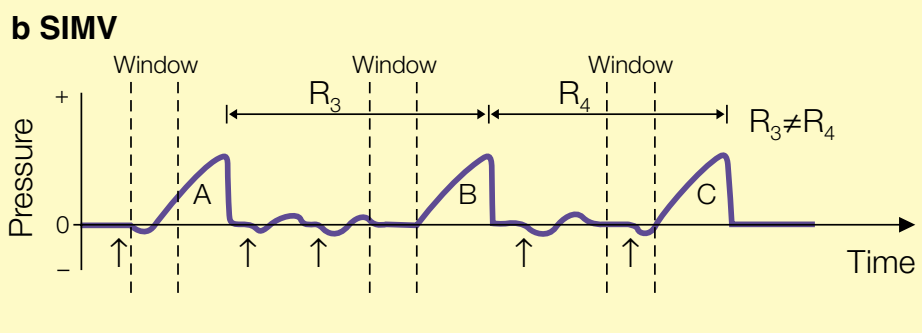
Intermittent mandatory ventilation (IMV) allows the patient to breathe spontaneously between mandatory breaths. The mandatory breaths are delivered at a pre-set time regardless of patient effort (Figure 3a). Thus, the mandatory breath may come at any point in the patient's spontaneous respiratory cycle. This may be difficult for the patient to tolerate and may increase the work of breathing, because the patient is fighting the ventilator. Inspiratory work may also be increased if the spontaneous respiratory efforts are inadequate and hence waste energy without ventilatory benefit.

Spontaneous breaths are possible between mandatory breaths in intermittent mandatory ventilation (IMV) and synchronized IMV (SIMV)

a IMV



b SIMV



IMV breaths are regular (as in controlled ventilation). In SIMV breaths are patient triggered (as in A–C) if the spontaneous inspiratory effort (↑) is detected during the machine-determined windows (breaths A and C); if no inspiratory effort is detected, a mandatory breath is delivered (breath B)

Synchronized intermittent mandatory ventilation (SIMV) was introduced over 20 years ago to avoid the problems of IMV. Modern ventilators invariably have SIMV not IMV, though they sometimes call it IMV. In SIMV, the patient receives a mandatory predetermined rate of either volume- or pressure-controlled breaths. The minute is broken into SIMV periods, determined by the rate set, during which each SIMV breath will be delivered, either triggered by the patient or time (see Figure 3b). On top of this the patient may trigger one or more spontaneous breaths between each SIMV breath; these breaths may be unsupported but, to avoid wasted respiratory effort, are often assisted by a preset level of PS (also possible in IMV). SIMV is therefore similar to assist-control in which the mandatory breaths are patient triggered and is hybrid because it also allows either spontaneous or supported breaths between the mandatory breaths.

SIMV can potentially be a bridge from assist-control to PS in weaning only if the patient's spontaneous breaths are adequate in rate and depth to tolerate a progressive reduction in the SIMV rate. Therefore, the patient must be examined to assess the adequacy of the spontaneous breaths even if arterial blood gases are reassuring.

Volume support (VS) is a pressure support mode in which a minimum tidal and minute volume are set. The ventilator progressively adjusts the inspiratory support pressure to whatever level is necessary (limited by the peak pressure alarm) to ensure that both targets are met or exceeded. In this mode, neither minute nor tidal volume can drop below the pre-set values. Predictably, if tidal volume decreases, the ventilator increases the PS until the volume target is again met. If the respiratory rate drops, tidal volume (i.e. PS) is adjusted to meet the target minute ventilation. If the rate rises, PS is adjusted to meet the target tidal volume, even if set minute volume is thereby exceeded. If both minute and tidal volume targets are exceeded, the PS is reduced until one or other target is again met.

Theoretically, this mode should allow 'automatic' ventilator-controlled weaning. However, the authors' experience suggests that this mode delays weaning, perhaps because it is difficult to define the 'right' settings for each patient and to follow the pattern of ventilator changes. If set too high, support is always provided and the patient cannot be weaned; if too low, the support is withdrawn too soon and weaning fails.

Pressure-regulated volume control (PRVC) attempts to combine PCV and VC. The ventilator adjusts the pressure control level to give a pre-set tidal volume at the lowest possible inspiratory pressure. Effectively, the ventilator tests the patient's compliance with an initial breath at 10 cm H_2O above PEEP. It then varies the delivery pressure incrementally to find the minimum PC value that delivers the required tidal volume. This mode is designed to compensate for the unavoidable variation in tidal volume with PCV as clinical conditions change. Because volume is fixed in PRVC, inflation pressure must be monitored to give warning of changes in patient compliance or resistance.

Adjuncts to oxygenation

PEEP sets an elevated pressure baseline during mechanical ventilation to prevent expiratory airway closure and aid oxygenation by increasing functional residual capacity (FRC) and reducing respiratory workload. Although labelled PEEP, it is applied throughout the ventilatory cycle. PEEP is achieved by a variety of methods that function as Starling resistors to raise the expiratory pressure without significantly increasing expiratory resistance. Excessive PEEP can lead to lung hyperinflation and so impair cardiac output and increase dead space. It may also contribute to barotrauma. PEEP must be optimized for each patient.

Continuous positive airway pressure (CPAP) is an elevation in baseline pressure throughout the respiratory cycle during spontaneous ventilation. It can be applied via a mask or a tracheal tube, and by a ventilator or a freestanding device. The aim is to prevent or reverse airway closure, thus maintaining or increasing functional residual capacity (FRC) and therefore oxygenation. Increasing FRC may place the patient's lungs on a more favourable point on the compliance curve and thus minimize the work of breathing. CPAP is maintained at a pre-set level during inspiration and expiration.

During ventilator CPAP, inspiratory flow is made available in proportion to the patient's inspiratory efforts, but only to maintain the required CPAP level. If the demand valve is slow to respond, or the patient has an excessive respiratory drive, flow delivery may be inadequate initially, leading to a drop in the CPAP level and increased respiratory work. For external circuits, sufficient flow must be provided throughout the respiratory cycle so that patient demands are always met.

Other modes of ventilation

Non-invasive ventilation (NIPPV) is increasingly used with a nasal or full face mask in the management of respiratory failure or acute pulmonary oedema, as an alternative to tracheal intubation and conventional ventilation. Easily portable, NIPPV has the advantages of lessening respiratory work and having fewer cardiovascular effects, but the mask can be difficult to tolerate (pressure sores and necrosis may occur with prolonged use) and gastric distension can arise. NIPPV is well established for patients with ventilatory failure secondary to chest wall deformity or neuromuscular disease; together with CPAP, it has its place in sleep-related disorders.

NIPPV can be delivered by a ventilator with all modes possible, although some are not well tolerated, or more commonly via a stand-alone machine. These machines are pressure generators, behaving similarly to PS on mechanical ventilators, in that a pre-set pressure is delivered to support triggered breaths in addition to having a baseline PEEP. On some models, the machine can be set for the breaths to be time cycled, similar to mechanical ventilation. Humidification can be added to the circuit to prevent the drying of secretions by the gases delivered. To be effective, patient selection and close monitoring are essential.

Others: in this brief overview, it is not possible to describe recently released modes (such as proportional assist or pressure release ventilation) or methods that have been used when conventional ventilation is not succeeding (e.g. high-frequency ventilation or partial liquid ventilation).

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Neurosurgical

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Acute Head Injury: Initial Resuscitation and Transfer

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Initial resuscitation

In the UK each year, about 1 million patients present to hospitals with head injury. These injuries range from the relatively trivial to the fatal and some form of classification is necessary. The most useful clinical classification of head injury is by severity. For adults, the Glasgow Coma Scale (GCS) is the best method for initially classifying the severity of head injury (Figure 1):

- mild GCS 14–15
- moderate GCS 9–13
- severe GCS 8 or less.

Initial assessment and resuscitation should follow the guidelines suggested by the ATLS (advanced trauma life support) protocol. The identification of compromised airway, inadequate ventilation or circulatory insufficiency must take precedence over detailed assessment of the neurological state.

Glasgow Coma Scale (GCS)

Eye opening response	
Spontaneously	4
To speech	3
To pain	2
None	1
Best motor response	
Obeys commands	6
Localization to painful stimuli	5
Normal flexion to painful stimuli	4
Spastic flexion to painful stimuli	3
Extension to painful stimuli	2
None	1
Best verbal response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Normal adult total score	**15**

1

Airway management: the priority is to secure, maintain and protect a clear airway. Remove secretions and foreign bodies by manual extraction or suction. Provide oxygen by non-rebreathing mask (10–12 litres/minute). Hold the neck immobile in line with the body, apply a rigid or semi-rigid cervical collar and (unless the patient is very restless) secure the head to the trolley with sandbags and tape. This is achieved with two sandbags, one on each side of the head, and two pieces of tape, one across the forehead and one across the chin, to secure the head and the sandbags to the trolley. Cervical spine injury can be difficult to diagnose in the unconscious patient and should be assumed to be present until it can confidently be excluded. A normal lateral radiograph of the cervical spine does not exclude the possibility of important cord injury. Maintain aligned immobilization of the neck when turning the patient during examination and treatment. Criteria for tracheal intubation are listed in Figure 2.

Indications for intubation and ventilation after head injury

Immediately

- Coma (not obeying, not speaking, not eye opening; GCS < 8)
- Loss of protective laryngeal reflexes
- Ventilatory insufficiency (as judged by blood gases):
  hypoxaemia (PaO_2 < 11 kPa on oxygen)
  hypercarbia ($PaCO_2$ > 6 kPa)
- Spontaneous hyperventilation causing $PaCO_2$ < 3.5 kPa
- Respiratory arrhythmia

Before the start of transfer to the neurosurgical unit

- Deteriorating consciousness (GCS has decreased by 2 points or more since admission to A&E, not caused by drugs) even if not in coma
- Bilaterally fractured mandible
- Copious bleeding into mouth (e.g. from skull base fracture)
- Seizures

An intubated patient must also be ventilated:
aim for PaO_2 > 11 kPa, $PaCO_2$ 4.5–5.0 kPa

2

The choice of anaesthetic drugs and neuromuscular blockers used for intubation is an individual decision that is modified by drug availability and clinical circumstance. Intravenous anaesthetic agents are indicated before intubation, even in neurologically obtunded patients, because they attenuate the rises in intracranial pressure associated with intubation. Most of these patients require a rapid sequence intubation with cricoid pressure and in-line cervical immobilization with removal of the collar, tape and sandbags. In such circumstances, the rapid onset of action of suxamethonium outweighs any theoretical risk that it might cause an increase in intracranial pressure. The use of opiates in a patient who is intubated and ventilated is not contraindicated, but large bolus doses of fentanyl or alfentanil may cause reductions in mean arterial pressure (MAP) and reflex rises in intracranial pressure (ICP), even in the ventilated patient. Tracheal tubes should be secured with adhesive tape that does not pass round the neck, or with loosely tied tape (to avoid compressing venous return from the head). It is advisable to pass an orogastric tube to empty the stomach, which commonly dilates after trauma. Nasogastric tubes or nasotracheal intubation are best avoided in patients in whom a basal skull fracture has not been excluded.

Clearing the cervical spine: there is no consensus about how the cervical spine should be cleared of significant injury when it is safe to remove immobilization. Purists claim that the cervical spine can only truly be cleared in a conscious patient, not intoxicated, with normal neurological examination, normal plain radiographs and with no painful distracting injury. This is impossible in a patient with a moderate or severe head injury because they will have a decreased level of consciousness. In such patients, it is acceptable to clear the cervical spine with the aid of plain radiographs and CT. A lateral radiograph of the cervical spine should delineate all seven cervical vertebrae and the cervico-thoracic junction. Anteroposterior radiographs of the cervical spine are difficult to interpret in intubated patients, and when doubt exists a CT is indicated. Radiological assessment of the cervical spine is discussed in *Anaesthesia and Intensive Care Medicine* **3:5:** 163. Plain radiographs and CT delineate bony injury only and may miss significant ligamentous injury. There is increasing interest in using MRI to exclude such injuries.

Breathing: a mechanical ventilator should be used whenever possible, and the adequacy of ventilation assessed clinically and by arterial blood gas analysis. If possible, an indwelling cannula should be inserted when the initial arterial sample for blood gas analysis is obtained, thus allowing serial blood gas measurement and continuous recording of blood pressure. Pulse oximetry is valuable for indirect measurement of how well the patient is being oxygenated, but provides no information about arterial carbon dioxide tension. Avoid excessive hyperventilation, which can depress the myocardium and induce cerebral ischaemia.

Circulation: the circulatory management of patients with significant head injury is given in Figure 3. Hypotension is a late sign of hypovolaemic shock, especially in children and fit young adults. Pulse rate, respiratory rate and capillary refill time are useful ways of assessing the circulation after injury. An isolated head injury is almost never the cause of shock, especially in adults. Maintenance of cerebral perfusion pressures (CPP = MAP–ICP) above 60 mm Hg is the intervention that best improves outcome. The ICP is not measured at this stage, but is certain to be high if the CT scan suggests raised intracranial pressure. Assume the ICP is greater than 20–30 mm Hg, and maintain MAP above 90 mm Hg. Avoid severe hypertension (MAP > 120 mm Hg).

Systemic and cerebral haemodynamic management in acute head injury

Suspect hypovolaemia, even in the absence of hypotension
Tachycardia, arterial respiratory swing, delayed capillary refill, source of bleeding, oliguria

Confirm hypovolaemia
Measure central venous pressure (CVP) if necessary

Find a cause for hypovolaemia (unlikely to be isolated head injury)
Multiple fractures, thoracic or abdominal haemorrhage (consider body CT)

Correct hypovolaemia
Targets: CVP = 8–10 cm H_2O; haematocrit 30% normal clotting, Na^+, K^+
Use 0.9% saline, Hartmann's solution, *Gelofusine, Haemaccel*, blood, fresh frozen plasma
Avoid 5% dextrose, hetastarch and hypotonic solutions

Catheterize bladder and measure urine output
Polyuria is usually the consequence of mannitol, and may require colloid supplements
If polyuria is disproportionate or persistent consider diabetes insipidus

Assume elevated intracranial pressure
Assume intracranial pressure > 20 mm Hg unless proven otherwise in patients with GCS < 12

Maintain mean arterial pressure at 90–100 mm Hg
This will ensure cerebral perfusion pressure ≥ 60 mm Hg; use vasopressors or inotropes if needed

If resistant hypotension consider
Myocardial contusion, tamponade, tension pneumothorax, high spinal cord injury, coning

3

It is advisable to set up two large-bore, peripheral, intravenous infusions and rapidly infuse an electrolyte solution such as normal saline or Hartmann's solution (not dextrose). Under-infusion is a more common error than overinfusion and the loss of more than 15% of blood volume must be corrected by blood transfusion. In patients with obvious hypovolaemia, early direct monitoring of arterial pressure and central venous pressure is helpful for assessing the adequacy of resuscitation. The sources of blood loss should be identified and controlled. Delay in recognizing thoraco-abdominal injuries and major pelvic and limb fractures is common and is associated with a high incidence of hypovolaemic shock and a poor outcome. A patient in persistent clinical shock despite fluid resuscitation must not be transported for CT or to the neurosurgical unit until the source of blood loss has been identified and controlled – in theatre if necessary.

Dysfunction: GCS measurements should be recorded as soon as possible and repeated frequently (at least every 10 minutes during the first hour in hospital). In a drunken patient with head injury, never assume the altered conscious level is simply a result of alcohol. Record any asymmetry of limb movements and compare the pupils repeatedly for size and reaction to light. Any deterioration in conscious level or the development of focal neurological signs must be recorded and acted on; the patient may have become hypoxaemic or shocked, or have an expanding intracranial haematoma. An infusion of mannitol, 0.25–1.0 g/kg, may allow transfer to a neurosurgical unit. Conscious level and limb movements cannot be measured in a patient who is pharmacologically paralysed and ventilated. Repeated assessment of pupil size and reaction is important in such neurologically inaccessible patients.

Exposure (other injuries): remove all the patient's clothing and check for injuries from head to toe, front and back. Some injuries do not need treatment at once but will do later, and all should be documented. Consider the need for abdominal and thoracic CT scans when the head is being scanned (Figures 4 and 5). Patients with major thoracic or abdominal injuries may require urgent exploration in theatre. CT of the torso is best used in patients who are not so unstable as to require exploration, but would benefit from having such injuries excluded before transfer.

Indications for neurosurgical referral and/or urgent CT scan

- GCS < 9 persisting after resuscitation
- Deterioration in level of consciousness or progressive focal neurological deficit
- Skull fracture with any of the following
  - Confusion or deteriorating impairment of consciousness
  - Seizures
  - Neurological symptoms or signs
- Open injury
  - Depressed open fracture of skull vault
  - Base of skull fracture
  - Penetrating injury
- Patient fulfils the criteria for a CT of the head but this cannot be obtained within a reasonable time (2 hours)

4

Indications for CT of the head before referral to neurosurgeons

- Skull fracture and GCS of 15
- Seizures
- Confusion or neurological symptoms or signs persisting after initial assessment and resuscitation
- Unstable systemic state precluding transfer to neurosurgery
- Diagnosis uncertain
- Tense fontanelle or suture diastasis
- Significant head injury requiring general anaesthesia

Indications for referral to neurosurgeons after head CT

- Abnormal CT
- Normal CT but unsatisfactory progress

5

Monitoring: the minimum standards of monitoring for anaesthesia apply equally to a seriously injured patient during resuscitation and transfer. They are continuous monitoring of blood pressure, ECG, oxygen saturation and urine output. Ventilated patients require monitoring of end tidal carbon dioxide concentrations and repeated arterial blood gas measurement.

Antimicrobial prophylaxis: booster doses of tetanus immunization are indicated in most patients. A suitable anti-staphylococcal agent is appropriate for patients with significant open injuries. Specific antimicrobial prophylaxis is ineffective and possibly harmful if there is CSF leak or a skull fracture.

Referral and transfer

Much time may be saved if the information outlined in Figure 6 is available when speaking to the neurosurgeon, and at the time of transfer.

What the neurosurgeon needs to know at referral

Patient's age and previous medical history (if known)
History of injury

- Time of injury
- Cause and mechanism (e.g. height of fall, approximate velocity of impact)

Neurological state

- Talked or not after injury
- Conscious level on arrival at the A&E Department
- Trend in conscious level after arrival (sequential GCS)
- Pupil and limb responses

Cardiorespiratory state

- Blood pressure and pulse rate
- Arterial blood gases, respiratory rate and pattern

Injuries

- Skull fracture
- Extracranial injuries

Imaging findings

- Haematoma, swelling, other

Management

- Airway protection, ventilatory status
- Circulatory status and fluid therapy (? mannitol)
- Treatment of associated injuries (? emergency surgery)
- Monitoring
- Drug doses and times of administration

6

Patients with head injuries are at risk during intra- and inter-hospital transfer. Adequate resuscitation and the optimization of systemic haemodynamics can reduce the risks and allow the maintenance of physiological homeostasis during transfer. Undesirable changes in the patient's homeostasis may be unnoticed or untreated because of inadequate monitoring, lack of equipment and drugs, or inexperienced escorts. Failures of communication can compound the problem and it is important that protocols and admission procedures facilitate a comprehensive handover.

Timing – the decision that a patient has been rendered stable for transfer (Figure 7) requires experience and follows a period of monitoring in the resuscitation room. This can legitimately delay the transfer, and it is helpful to telephone the neurosurgical unit as the journey starts to give the estimated time of arrival. Never start a journey with an unstable patient because of the high risk of complications during the journey.

Checklist before transfer of patient with head injury to a neurosurgical unit

Respiration

- Is the PaO_2 > 11 kPa?
- Is the $PaCO_2$ 4.5–5 kPa?
- Is the airway adequately protected for the journey?

Circulation

- Is the mean arterial pressure > 90 mm Hg?
- Is the pulse rate < 100/minute?
- Is peripheral perfusion adequate?
- Is there reliable and adequate venous access?
- Has enough volume/blood been given to replace losses?
- Is there a suggestion of continuing bleeding?
- Is the patient catheterized (essential if mannitol has been administered)?

Head injury

- What is the GCS score?
- What is the trend in GCS score?
- Is there any focal neurological deficit?
- Is there a skull fracture?

Other injuries

- Has a cervical spine injury been excluded?
- Have broken ribs/pneumothorax been excluded/dealt with (chest drain)?
- Could there be an intrathoracic or abdominal bleed?
- Are there pelvic or long bone fractures?
- Have extracranial injuries been splinted (cervical collar, limb splints)?

Imaging

- If the patient is sufficiently stable, was the need for CT of thorax, abdomen or cervical spine considered at the time of head scan?

7

Escort – the minimum escort for a patient with severe head injury is a doctor and a trained nurse or paramedic. They are professionally responsible for the patient until they hand over at the neurosurgical unit. They must be well informed about the patient before the journey starts, and ideally should have been involved in the patient's care in the resuscitation room. They must know what can go wrong during the journey and must have the skills and equipment to identify and deal with these problems. A doctor competent in airway procedures must escort every intubated and ventilated patient. Patients who are at substantial risk of deterioration during transfer are best intubated before leaving the referring hospital. When the risk of deterioration is less, the presence of an appropriately equipped and skilled doctor during transfer will ensure airway protection should the patient deteriorate during transfer. If in doubt, intubate before transfer.

Monitoring – it is unwise to rely solely on eyes and ears when monitoring a patient in the back of a noisy, dark, moving ambulance. The monitoring started in the resuscitation room should be continued. There must be reliable intravenous access. The ECG should be monitored continuously as should the blood pressure (sphygmomanometry is unreliable in a noisy, moving ambulance). Invasive blood pressure monitoring is ideal; failing this an automated non-invasive blood pressure machine is mandatory, but may be inaccurate in the back of a fast moving ambulance. All lines must be secured, and arterial and central venous lines should be clearly labelled to prevent inadvertent drug injection through them. A pulse oximeter is mandatory. Capnography during transport is ideal, but is often unavailable. An injured patient quickly becomes cold in an ambulance and should be wrapped in blankets (preferably a foil blanket). It is not essential to correct mild hypothermia ($\geq$ 36.0°C) because it may contribute to cerebral protection. The ventilator should have a pressure dial to indicate inflation pressure and a blow-off valve to avoid barotrauma. There should be a system to deliver high-flow oxygen to the patient, and two oxygen cylinders should be carried, both full and checked before use.

Other equipment and drugs – even if the patient has been intubated before transfer it may be necessary to reposition or replace a tube which obstructs or falls out, and the ambulance must carry a range of tracheal tubes and two working laryngoscopes. The oxygen supply can fail, and it is always advisable to carry a self-inflating bag. Intravenous lines inserted before transfer may block or fall out or may have to be supplemented for rapid fluid infusion during transfer. A range of cannulas and fluids should be carried. If blood has been cross-matched before the journey it should travel in the ambulance, not in a separate taxi. The escorts should carry drugs for cardiac resuscitation, non-depolarizing muscle relaxants, short-acting analgesics and sedatives for controlling ventilation, anticonvulsants and mannitol.

Ambulance and trolley – modern ambulances do not always offer a smooth, quiet ride but usually provide reasonable space and lighting. The problems of working in any moving vehicle make it vital to stabilize the patient and set up monitoring before transfer. The ambulance seldom needs to travel at great speed, which can worsen cardiovascular instability; a smooth ride at constant speed is safer. The patient should be placed in the ambulance head first because this allows better tolerance of any sudden deceleration during the journey. Most centres suggest that the head is elevated by about 15° throughout transfer. If life-saving procedures (e.g. tracheal intubation) are required during the journey it is best to stop the ambulance briefly rather than attempt heroics under poor conditions.

Handover – the escorts should give the neurosurgical staff an accurate description of all injuries, the trends in conscious level and neurological signs since injury or admission, and the drugs and intravenous fluids given. They should not leave until this has been done. The neurosurgical team may need further information later and must know whom to contact. All medical and nursing clinical notes, observation charts, drug prescription sheets, radiographs and scans should be left with the neurosurgical team.

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Anaesthesia and the Cervical Spine: Surgery and Trauma

Ian Calder

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The main considerations in anaesthesia for cervical spine surgery are the risk of neurological deterioration and airway problems.

Risk of neurological deterioration (spinal cord injury)

Patients with disease of the cervical spine or spinal cord run an increased risk of developing spinal cord injury during anaesthesia. The mechanism of the damage is uncertain. MRI shows that the shape of the spinal cord and the anterior and posterior spinal arteries changes with posture. People with healthy spines, kept in abnormal postures for several hours, or exposed to low blood pressure, have developed spinal cord injury. Prolonged cord deformation can result in spinal cord injury and patients with an abnormal spine have developed a spinal cord injury after short periods (less than 1 hour) of anaesthesia. The risk of general anaesthesia may stem from the immobility it induces. A position that would be tolerated only briefly by a conscious patient can be maintained for a dangerously long time under anaesthesia. Anaesthetists should be aware that some patients deteriorate neurologically for no discernible reason following cervical trauma and that absence of radiological evidence of damage does not mean that a spinal cord injury will not occur. Up to 50% of patients with spinal cord injury after traumatic neck injuries have no radiological evidence of trauma. Cervical injury may compromise the homeostatic mechanisms safeguarding the spinal cord.

Instability of the cervical spine is thought to be a risk factor for the development of a spinal cord injury during anaesthesia. Instability is hard to define. White and Panjabi defined it as 'loss of the ability, under normal physiologic loads, to maintain relationships between vertebrae in such a way that there is neither initial nor subsequent damage to the spinal cord or nerve roots, and there is neither development of incapacitating deformity, nor severe pain'. The mechanism of injury may involve several factors, such as deformation of the blood supply of the cord, reductions in spinal cord perfusion pressure and cord compression. 40% of patients with fractures or dislocations of the spine have vertebral artery damage.

Direct laryngoscopy may have caused a spinal cord injury in patients with cervical spine disease but there is no convincing case report in the literature. Direct laryngoscopy causes the same small amount of movement in cadaver spines rendered unstable by surgical preparation as jaw thrust or chin lift. A comparative study of different airway control systems (laryngeal mask airway (LMA), intubating LMA, lightwand, fibrescope, direct laryngoscopy) showed no significant difference between the methods, in terms of movement of an unstable C3 vertebra. Flexible fibre-optic laryngoscopy and intubation is useful in cervical spine disease because direct laryngoscopy is often difficult. The use of the gum-elastic bougie to minimize the amount of glottic exposure is deservedly popular in the UK.

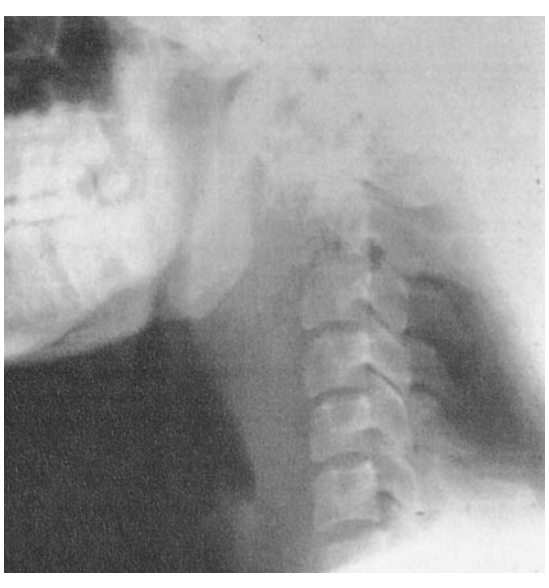
Manual in-line neck stabilization: there is conflicting evidence about whether this practice results in any worthwhile reduction in movement at unstable cervical sites. Enthusiastic application may make direct laryngoscopy difficult. There is an analogy with cricoid pressure application because in both situations the airway difficulty induced could be hazardous for the patient.

Pathology

Spinal cord injury may be associated with spondylosis, herniation of intervertebral discs, spinal stenosis, tumours, syringomyelia, infections, rheumatoid arthritis, ankylosing spondylitis or trauma.

Cervical rheumatoid arthritis: spinal involvement in rheumatoid arthritis is common, with the upper cervical joints being affected most often. There are three main patterns of involvement in the cervical spine:

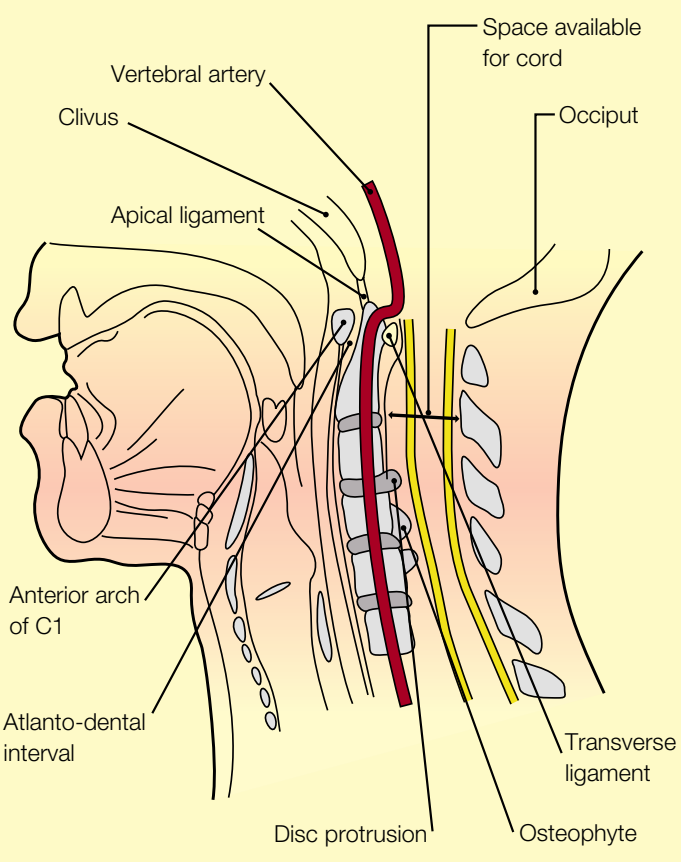
- atlanto-axial subluxation (Figure 1) (65%)
- 'vertical' subluxation (20%)
- sub-axial subluxation (15%).



1 Radiograph of the neck showing tuberculous abscess eroding C2 and causing atlanto-axial subluxation.

All three types may be present. The amount of atlanto-axial subluxation has been assessed by measuring the distance between the anterior arch of the atlas to the odontoid peg on lateral radiographs (Figure 2), the distance being known as the atlanto-dental interval (ADI). The size of the ADI does not correlate well with neurological symptoms and signs, or cord compression seen at MRI. Whether there is any correlation between the size of the ADI and the risk of spinal cord injury during anaesthesia is unknown. The clinical presentation of cervical rheumatoid disease is seldom acute. An insidious progression of neck pain, occipital headache, stiffness and crepitus occurs. L'Hermitte's phenomenon of an electric shock sensation up and down the spine can occur. Temporomandibular joint and arytenoid joint involvement is common. Rheumatoid cervical disease may be symptomless, therefore the question arises whether patients should have flexion/extension lateral radiographs before anaesthesia for procedures unrelated to the cervical spine. Requesting radiography demonstrates the anaesthetist's concern and appreciation of the possibilities.

Section through the neck



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Prevention of injury during anaesthesia for cervical surgery

There is an increased risk of spinal cord injury in:

- patients with preoperative myelopathy
- cranio-cervical junction surgery
- multi-level surgery
- insertion of fixation devices.

Great care should be taken with positioning. The position should look comfortable. Hypotension may reduce spinal cord blood flow. Hypertension causes oedema formation in experimental cord injury models. Normotension is recommended. Many practitioners avoid muscle relaxant drugs after intubation, so that irritation of the cord or a nerve root produces limb movement.

Spinal cord monitoring during cervical surgery: there is no evidence that monitoring improves outcome. Sensory evoked potentials are routine in many centres (stimulus applied to median nerve and recorded from the scalp over the sensory cortex). They are reasonably robust to volatile agents, unlike motor evoked potentials, which are easily abolished with volatile agents. Motor monitoring involves stimulation of the motor cortex with an electrical discharge, and is not routinely used in many centres.

High-dose steroids: NASCIS I, II and III (North American Spinal Cord Injury Study) have shown that large doses of methylprednisolone improve outcome after spinal cord injury. The current recommendation is an initial dose of 30 mg/kg, then 5.4 mg/kg over 24 hours if the treatment is begun within 3 hours, or over 48 hours if treatment commences 3–8 hours after injury. However, whether there is any real benefit is still debated.

Airway problems

Direct laryngoscopy is often difficult in patients with disease of the upper three vertebrae. The Mallampati examination is useful in cervical disease; the test can be regarded as a way of testing cranio-cervical extension. Mandibular protrusion is often impaired in high cervical disease as temporomandibular joint disease tends to be associated with cranio-cervical junction pathology. Grade C protrusion is always predictive of difficult laryngoscopy (see *Anaesthesia and Intensive Care Medicine* **3:7:** 246).

Anterior cervical haematoma can cause airway obstruction after surgery. In some cases there may be only a small, or even no, haematoma. The obstruction is caused by swelling of the periglottic tissue, which may make direct laryngoscopy difficult. Both the LMA and gum-elastic bougie have proved life saving. The wound should be opened as soon as possible. An inhalational induction with sevoflurane or halothane is generally regarded as the wisest option. Extubation should be delayed for about 24 hours. ◆

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Anaesthesia for Posterior Fossa Surgery

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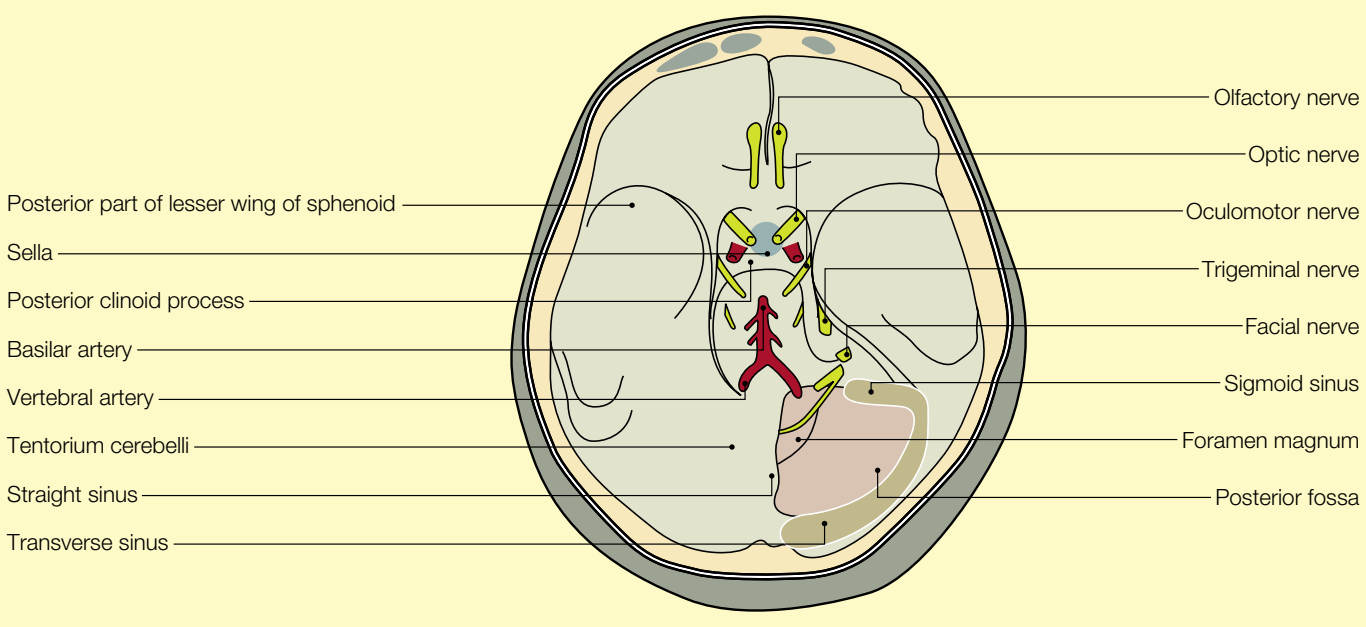
Anatomy
The posterior cranial fossa is a rigid, deep compartment that is almost circular in outline and contains the cerebellum and brainstem. These structures are covered by a dural sheet (the tentorium cerebelli) which separates them from the cerebrum superiorly (Figure 1). Anteriorly lie the dorsum sellae, the clivus, the posterior part of the sphenoid and the basilar part of the occipital bone. The squamous part of the occipital bone, the transverse sinus and the superior sagittal sinus lie posteriorly and the petrosal and mastoid part of the temporal bone, the internal auditory meatus and the sigmoid sinus lie laterally. The occipital bone, foramen magnum, jugular foramen and hypoglossal canal lie inferiorly. Compared with the supra-tentorial compartment, the posterior fossa is small, and a small increase in its volume can rapidly result in life-threatening brainstem compression.

Relationship of posterior fossa to other intracranial landmarks



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Pathology
Tumours – primary tumours are the most common indication for posterior fossa surgery and are more common in children than in adults. Up to 70% of all childhood brain tumours originate in the posterior fossa and include medulloblastomas, ependymomas, tumours of the choroid plexus, gliomas and astrocytomas. In contrast, 15–20% of adult brain tumours lie in the posterior fossa. Metastatic tumours, usually from the lung, kidney, breast and skin are the most common posterior fossa lesion in adults. Other primary tumours include meningiomas, acoustic neuromas (Schwannomas arise from the VIIIth cranial nerve, often in the cerebellopontine angle), clival tumours, glomus jugulare tumours, arachnoid and epidermoid cysts. Haemangioblastomas can develop in the cerebellum and often secrete erythropoietin, resulting in polycythaemia.

Vascular lesions – 15% of aneurysms occur in the posterior circulation with half of these appearing at the basilar bifur-cation. Haemorrhage or vasospasm from posterior circulation aneurysms may have a profound effect on brainstem blood flow. Arteriovenous malformations of the posterior fossa often involve the brainstem with a haemorrhage rate of 2–3% per year. Cerebellar haematoma is usually a result of systemic hypertension and cerebellar infarct may cause swelling and obstructive hydrocephalus. Both conditions may represent neurosurgical emergencies. Small vessels impinging on cranial nerves in the posterior fossa can result in symptoms such as trigeminal neuralgia. Surgical decompression has a good success rate.

Craniocervical abnormalities may require posterior fossa decompression. In the young this is usually for congenital abnormalities such as Arnold–Chiari malformation; in the elderly, degenerative changes are more common.

Positioning
Patient positioning for optimal surgical access during posterior fossa surgery may have major implications for the anaesthetist.

Supine position: patients with cerebellopontine angle tumours (e.g. acoustic neuromas) are often operated on in this position. However, access to the posterior fossa often requires substantial lateral rotation of the head, resulting in stretching of the jugular veins and brachial plexus. These problems can be reduced by placing a sandbag under the ipsilateral shoulder. Maximizing exposure through a relatively small craniectomy site may require lateral rotation of the operation table, and the use of 'safety belts' will ensure that patients do not slide off.

The prone position offers good access to midline structures but bleeding can obscure the surgical field. Head-up tilt is used to reduce haemorrhage but this increases the risk of air embolism. The chest and iliac crests should be well supported to ensure free movement of the abdomen during respiration. Obese patients are at particular risk because of restricted diaphragmatic movement and high intrathoracic pressure. Pressure on the iliac vessels should be avoided, reducing the risk of deep venous thrombosis and improving emptying of the epidural venous sinuses. The head is fixed in clamps in preference to a horseshoe to minimize pressure on the face and eyes. Pressure points should be well padded and the tracheal tube kept as secure as possible.

The lateral position is suitable for approaches to lesions not in the midline, particularly the cerebellopontine angle. This position facilitates gravitational retraction of the dependent cerebellum and facilitates CSF and venous drainage. A variation called the 'park bench' position is often used; so-called because of its resemblance to the way a tramp sleeps on a park bench. A pad should be placed under the body in the axilla to minimize weight on the lower arm and shoulder. The pelvis should be fixed with supports in front and behind. The lower leg is flexed at the hip and knee. The upper leg is kept straight and slightly externally rotated to lock the knee with the foot on a firm support, which will prevent the patient sliding down the table if significant head-up tilt is used. A pillow is placed between the legs. The lower arm is flexed across the body and the upper arm is taped along the upper side of the body. The head is fixed in pins. Excessive flexion of the neck can obstruct the internal jugular veins. This can be avoided by ensuring a two or three fingers-breadth gap between chin and sternal notch.

The sitting position provides good surgical access to midline structures, improves surgical orientation and allows good drainage of blood and CSF. Functional residual capacity and vital capacity are improved and access to the airway is facilitated. However, there are increased risks of cord compression, pneumocephalus and venous air embolism. Macroglossia and peripheral nerve injuries are also more common in the sitting position. Hypotensive techniques increase the risks of ischaemic damage. Many authorities now contend that with modern anaesthetic techniques there is no place for the sitting position in neuroanaesthesia. Excessive head-up tilt in other positions, however, exposes the patient to similar risks.

Anaesthetic management
Preoperative assessment
In addition to the routine assessment for patients undergoing general anaesthesia and specific assessment for patients scheduled for craniotomy, information relevant to posterior fossa surgery needs to be obtained during the preoperative visit. Any cranial nerve impairment needs to be documented, with particular reference to the lower cranial nerves, which may affect the gag reflex. Patients with impaired gag reflexes may have a history of aspiration pneumonia. Furthermore, this may impair airway protection postoperatively and extubation at the end of surgery may need to be delayed or elective tracheostomy considered. Patients are often dehydrated with associated biochemical derangements because of reduced oral fluid intake, or vomiting owing to raised intracranial pressure. Preoperative fluid replacement may be required.

Consultation with the surgeon will reveal the required position for surgery, and the patient should be assessed for the proposed position. In some cases, alternative positioning may have to be considered (e.g. obese patients requiring the prone position).

Premedication should include all regular medication, with a short-acting benzodiazepine reserved for those who are neurologically intact and who are particularly anxious.

Intraoperative management
Induction: as with any craniotomy, induction is achieved using an appropriate induction agent, normally an intravenous induction agent in adults, though a smooth inhalational induction with sevoflurane may be appropriate in children. Neuromuscular paralysis and an opioid facilitate tracheal intubation. The hypertensive response to intubation and head-pin insertion can be obtunded by supplementation of appropriate intravenous agents. If hypotension occurs, it should be treated promptly. An armoured tracheal tube should be inserted and secured firmly. A nasogastric tube should also be placed if there is any risk of postoperative bulbar dysfunction or the patient is to be ventilated postoperatively.

Direct arterial pressure monitoring is essential and can be established before induction if clinically indicated, or more commonly after induction. A central venous line is usually required. Access to the internal jugular veins may be difficult, and subclavian cannulation, or antecubital fossa or femoral long lines are useful alternatives. Core temperature and urine output must also be monitored during surgery. Especially in surgery where there is a risk of high venous air embolism, an oesophageal stethoscope and/or precordial Doppler probes are essential additional monitors.

Maintenance: the choice of particular agents is not critical but stable anaesthesia is paramount. The effects of a particular drug on blood pressure and neurophysiological monitoring should be considered. Muscle relaxation is best provided by continuous infusion of short- or medium-acting agents, which helps ventilation and prevents movement in a relatively lightly anaesthetized patient. If motor nerve function is monitored as a guide to resection (e.g. the facial nerve monitoring during acoustic neuroma surgery), muscle relaxation must be discontinued and sufficient depth of anaesthesia must be provided to obtund airway reflexes using other agents.

Neurophysiological monitoring is often used. Facial nerve monitoring is routine with all large acoustic neuroma excisions. Auditory evoked potentials are used as a safeguard during dissection near the brainstem, particularly during acoustic neuroma surgery. When somatosensory and motor evoked potentials are monitored, they can be suppressed during deep anaesthesia. Furthermore, paralysis can occur in the absence of somatosensory evoked potential changes.

Deliberate hypotension should be employed with caution if significant head-up tilt is used. It is also important to remember that surgery near the brainstem can induce further hypotension and bradycardia.

Postoperative management
Patients with good preoperative neurology may be extubated at the end of surgery providing the intraoperative course was uncomplicated. Coughing and straining should be avoided during the emergence period. Extubation at the end of surgery should not occur if significant brainstem or cranial nerve injury has occurred. This may manifest as repeated episodes of intraoperative haemodynamic instability. Pulmonary oedema may be precipitated by large venous air embolism or after surgery to the floor of the fourth ventricle. Respiratory failure can occur suddenly, even when awake.

Complications of posterior fossa surgery
Arrhythmias are often caused by manipulation of the brainstem. Bradycardia can occur when the periventricular grey matter and the reticular formation are stimulated. Most arrhythmias occur during surgery near the pons and the roots of nerves V, IX and X. Surgeons should be made aware of bradycardic episodes, which should stop when the offending surgical stimulation ceases. Anticholinergics should be used only as a last resort after discussion with the surgical team, because abolition of vagally induced bradycardia removes a useful indicator of potential brainstem injury. Severe hypertension can result from stimulation of the trigeminal nerve.

Airway problems: macroglossia and upper airway swelling can occur following prolonged surgery in the prone position. This is due to obstruction of venous and lymphatic drainage. Cranial nerve damage can also cause serious airway problems.

Neurological complications: extreme neck flexion can cause midcervical quadriplegia. Prolonged surgery and hypotension are contributory factors. Surgery near the roots of nerves VII–X may lead to loss of airway reflexes, dysphagia and dysphonia. Peripheral nerve damage can result from faulty positioning. The brachial plexus, ulnar nerve and common peroneal nerve are most vulnerable.

Pneumocephalus: following a craniotomy, an air-filled space between the dura and arachnoid remains after CSF has leaked away during surgery and brain bulk is reduced. In the recovery period, brain bulk increases again as cerebral oedema develops, arterial carbon dioxide concentrations increase and CSF reaccumulates. The trapped air then comes under increasing pressure and tension pneumocephalus can occur, which if left untreated can result in brain herniation and cardiac arrest. Nitrous oxide worsens the situation. Pneumocephalus presents as delayed recovery or deteriorating neurological state and should always be considered if this occurs. Pneumocephalus can be reduced by discontinuing nitrous oxide 15 minutes before surgery finishes and by allowing the arterial carbon dioxide tension to rise towards the end of the operation. Air may remain within the cranium for 2 weeks postoperatively and nitrous oxide should be avoided for this period after posterior fossa surgery.

Venous air embolism: a vein cut during surgery will normally collapse, preventing air being sucked into the circulation. In posterior fossa surgery, cut veins may not collapse: veins in the skull are held open by the surrounding bone; suboccipital veins are held open by cervical fascia; and the large venous sinuses are held open by the dura. Air can thus readily enter the circulation if these veins are opened. The incidence of air embolism in the sitting position is reported at 25–50%. However, recent use of transoesophageal echocardiography has reported an incidence as high as 75%. In most cases, the amount of air entering the circulation is small and may have little clinical importance. When larger volumes of air enter the right heart, cardiac output is reduced leading to systemic hypotension. Air also passes into the pulmonary arterial circulation, leading to a rise in pulmonary vascular resistance and an increase in pulmonary artery pressure. The ECG shows signs of right ventricular strain and right ventricular failure may occur. Physiological dead space increases as air blocks the pulmonary circulation with many alveoli ventilated but not perfused. This in turn leads to a decrease in carbon dioxide excretion and a fall in end-tidal carbon dioxide tension. Central venous pressure rises as a result of obstruction to right ventricular outflow. This increase in central venous pressure, together with arrhythmias and the classical mill-wheel murmur on auscultation are late signs. Occult atrial septal defects or a probe patent foramen ovale may be present in up to 35% of all individuals in autopsy studies. The rise in pulmonary pressures associated with venous air embolism that may predispose to right-to-left shunting in such individuals may result in systemic air embolism. In practice, though some degree of air embolism occurs in up to 75% of patients; clinically significant air embolism remains an uncommon complication.

Detection of air embolism

- Precordial Doppler device – the altered reflection of ultrasonic beams from an air–gas interface means that precordial Doppler probes can detect bubbles of air in the circulation and can indicate air emboli as small as 1 ml (some critics claim that the device is oversensitive). An experienced observer is required. Diathermy machines interfere with probe function.
- Capnography – a continuous capnograph shows a fall in end-tidal carbon dioxide concentration as air enters the pulmonary circulation. It is less sensitive than the Doppler but is much easier to use. However, other causes of a fall in end-tidal carbon dioxide tensions, such as reduced cardiac output can cause confusion.
- End-tidal nitrogen – entry of air into the pulmonary circulation results in a rise in end-tidal nitrogen, which mirrors the decrease in end-tidal carbon dioxide. However, nitrogen increase is more specific than end-tidal carbon dioxide and is not influenced by other cardiovascular changes.
- Pulmonary artery pressure – air embolism increases the pulmonary artery pressure proportionally to the size of the embolism.
- Pulse oximetry detects air embolism that results in significant cardiorespiratory compromise, but is best viewed as an indicator of the magnitude of circulatory disturbance and an index of the progress of treatment.
- Transoesophageal echocardiography is a highly sensitive method of detecting intracardiac air and of diagnosing atrial septal defects.

Prevention of air embolism – volume loading patients to raise their central venous pressure reduces the hydrostatic pressure gradient and reduces the likelihood of air embolism. Similarly, raising end-expiratory pressure may reduce the negative pressure in an open vein in the posterior fossa. However, positive end-expiratory pressure reduces venous return and may cause systemic hypotension.

Anti-gravity suits and medical anti-shock trousers help to reduce venous pooling in the lower limbs. The increase in venous pressure reduces postural hypotension and decreases the negative hydrostatic pressure in the posterior fossa.

Nitrous oxide diffuses into embolic bubbles and increases their size. If there is a significant air embolism, nitrous oxide should be discontinued. A central venous catheter is a useful cardiovascular monitor and is a helpful diagnostic tool if air enters the circulation. It also provides a useful method of attempting to aspirate air from the right atrium.

Management of air embolism

- Flood the operative field with saline and cover the wound with wet swabs to prevent further air entrainment.
- Ventilate with 100% oxygen, discontinue nitrous oxide.
- Raise the venous pressure at the operative site, which can be done by squeezing the veins in the neck.
- Aspirate from the cerebral venous pressure catheter to try to aspirate air from the right atrium.
- If cardiovascular collapse occurs, standard resuscitative measures should be used.

◆

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Anaesthesia for Supratentorial Craniotomy

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Surgery in the supratentorial region is required for a variety of pathologies including vascular malformations and space-occupying lesions. This article describes the general principles of patient management for such surgery and provides specific details about anaesthesia for mass lesions. Vascular malformations are discussed on pages 143–4.

Anatomy
The supratentorial compartment contains the cerebral hemispheres. the floor is formed by the anterior and middle cranial fossae along with the tentorium cerebelli, and the cavity is roofed by the calvarium.

Pathology and pathophysiology
Space-occupying lesions comprise:
- primary tumours (gliomas, meningiomas of the olfactory groove, medial sphenoidal wing and the base of the anterior cranial fossa)
- secondary tumours, vascular lesions (aneurysms and arteriovenous malformations)
- abscesses
- haematomas (spontaneous or traumatic).

Patients with anterior fossa lesions may present with seizures, neurological deficits or signs and symptoms of raised intracranial pressure (headache, nausea, vomiting, hypertension and bradycardia). The neurological deficits may be visual, caused by pressure on the optic nerve and chiasma, alteration or loss of smell due to involvement of the olfactory nerve, compression of the internal carotid artery or middle cerebral artery. Invasion through the superior orbital fissure may lead to proptosis.

Anaesthetic management

Anaesthesia for supratentorial surgery requires an understanding of intracranial physiology to facilitate manipulation of intracranial pressure (ICP), cerebral blood flow (CBF) and cerebral metabolic requirement of oxygen ($CMRO_2$) to optimize perioperative conditions. The aims of anaesthetic management are listed in Figure 1.

Aims of anaesthetic management in supratentorial craniotomy

- Preoperative assessment and optimization of associated medical conditions
- Haemodynamic stability (hypotension can lead to ischaemia in areas of impaired autoregulation; hypertension increases the risk of haemorrhage and vasogenic oedema)
- Maintain cerebral perfusion and prevent increases in intracranial pressure
- Facilitate surgery by providing a slack brain
- Provide cerebral protection if required
- Rapid recovery to enable neurological assessment in the immediate postoperative period

1

Preoperative assessment
A complete history and clinical examination of the patient provides an opportunity to identify associated diseases as well as to obtain specific information regarding the surgery. Underlying cardiac or respiratory disease must be controlled before surgery. Common associated conditions such as chronic untreated hypertension need to be controlled to reduce the risk of perioperative myocardial and cerebral ischaemia owing to the rightward shift in the autoregulatory limits of CBF.

The acute neurological condition must be assessed including the preoperative Glasgow Coma Score (GCS), an examination of radiological images and an evaluation of concurrent disease. Preoperative examination of CT and/or MR images provides information about lesion size, ease of surgical access, positioning of the patient and indirect information regarding likelihood of blood loss. It also allows assessment of pathology that may cause intracranial hypertension or reduced intracranial compliance. It must be remembered, however, that intracranial hypertension may exist in the absence of imaging signs. A substantial risk of venous air embolism or bleeding may be associated with lesions encroaching on the sagittal sinus.

A full drug history is important because some drugs affect anaesthetic management. Steroids, diuretics and anticonvulsants affect plasma biochemistry, glucose tolerance, the risk of upper gastrointestinal bleeding, intravascular volume and drug pharmacokinetics. Anticonvulsants and steroids should be continued.

Premedication (e.g. a short-acting benzodiazepine) is only given if the patient is particularly anxious, provided there is no evidence of raised ICP.

Induction
Induction is performed using an intravenous anaesthetic agent, titrated to minimize the reduction in blood pressure, together with a nondepolarizing muscle relaxant and a short-acting opiate. Normotension should be maintained by anticipating stimuli and preventing haemodynamic responses. The hypertensive response to laryngoscopy and intubation can be obtunded with an additional bolus of intravenous induction agent, a short-acting opioid or β-blocker, or intravenous lidocaine (lignocaine). Insertion of skull pins for cranial fixation provides a potent stimulus and the hypertensive response should be pre-empted by local anaesthetic infiltration, an additional dose of induction agent and/or a supplemental dose of opiate.

When the airway has been secured with an armoured tracheal tube, the tube should be carefully taped and secured on the side contralateral to the operation. The eyes should be taped and padded.

Monitoring
In addition to establishing routine monitoring before induction, invasive arterial blood pressure monitoring may be established before induction if the patient is unstable or at high risk, or after induction in patients who are more stable. After induction, a nasopharyngeal temperature probe and urinary catheter should be inserted. A central venous line is helpful in most patients, and is mandatory if there is a clinical indication (e.g. cardiorespiratory disease, large anticipated blood loss). A pulmonary artery catheter may be required in severe cardiac disease. Other neuromonitoring such as EEG, somatosensory evoked potentials and a jugular bulb catheter can also be established if required.

Intra-operative management
Positioning: access is usually through a frontal, parietal or temporal craniotomy, which allows the patient to remain in the supine position. A neutral position of the head with a reversed Trendelenburg tilt (15° head up) favours venous drainage from the cranium and helps to reduce ICP. Extreme head rotation for parietal and temporal access may impair venous drainage by kinking the internal jugular vein. A shoulder roll placed on the ipsilateral side reduces the impact of this position on venous drainage. The prolonged duration of certain neurosurgical procedures demands close attention to pressure points, nerve compression and thromboembolism prophylaxis. Thromboembolism deterrent stockings or sequential pneumatic calf compression devices may be used to reduce the incidence of deep vein thrombosis.

Maintenance of anaesthesia: the anaesthetic technique largely depends on the ability to control ICP, maintain haemodynamic stability and provide rapid emergence. Total intravenous anaesthesia with propofol infusion has been used successfully in a number of studies. Propofol reduces $CMRO_2$, thereby reducing CBF and cerebral blood volume (CBV) by preserving flow metabolism coupling. This helps to maintain cerebral perfusion and oxygenation to areas of brain that may be at risk of ischaemia. Propofol also preserves carbon dioxide reactivity thus allowing manipulation of CBF and CBV with changes in arterial carbon dioxide levels.

The addition of an opioid contributes to haemodynamic stability and reduces the requirement for anaesthetic agents. Most short-acting opioids are equally effective for haemodynamic stability, but remifentanil allows more rapid emergence compared with fentanyl and alfentanil, probably because its metabolism gives it a short context-specific half-life. All fluorinated volatile inhalational agents increase CBF and CBV by a direct intrinsic effect causing vasodilatation. The magnitude of this increase in vascular diameter depends on the balance between the intrinsic vasodilatory action and the reduction in blood flow secondary to the dose-related decrease in $CMRO_2$. Reactivity to carbon dioxide may be impaired with older anaesthetic agents, though it tends to be better preserved with the newer agents such as isoflurane and sevoflurane. Isoflurane and sevoflurane also have minimal effects on ICP in concentrations less than 1.5 minimum alveolar concentration, and the vasodilatory effects can be attenuated by mild hypocapnia. In contrast, nitrous oxide causes an increase in $CMRO_2$ with a coupled increase in CBF which is unaffected by hypocapnia, which makes its use unfavourable in patients with raised ICP.

Although there is debate about the most appropriate com-bination of agents for craniotomy, Todd and colleagues have shown that propofol/fentanyl, high-dose isoflurane/nitrous oxide and fentanyl/nitrous oxide are equally satisfactory.

An infusion of short- or medium-duration neuromuscular blockers (e.g. atracurium, vecuronium) facilitates ventilation at lower intrathoracic pressure. The lungs are ventilated aiming for a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) of 4.0–4.5 kPa. Many anaesthetists allow body temperature to drift to 35–36°C when neural tissue is at risk of ischaemic injury as part of the procedure, though there is no evidence that this is beneficial. Rewarming should begin as soon as this risk is over, and certainly by the time dural closure begins.

Optimization of surgical conditions: a ‘slack’ brain facilitates surgical access with minimal retraction, which reduces the likelihood of ischaemic damage. The dura should be observed at the time of craniotomy to ensure that it is not tense or bulging out of the craniotomy site. Mannitol, 0.5–1 g/kg, may be infused about 30 minutes before dural opening to reduce brain bulk. It is an osmotic diuretic that was thought to act by drawing water from the brain, but it is now also thought to improve the rheological properties of the blood in the cerebral circulation, increase CBF and reduce CBV and ICP. Limiting plasma osmolality to 320 mosm/litre reduces the risk of rebound oedema. Mannitol may also theoretically worsen oedema by crossing a damaged blood–brain barrier. Furosemide (frusemide), 0.25–1 mg/kg, reduces the ICP to the same extent as mannitol, and lowers cerebral venous pressure, thereby optimizing CSF reabsorption.

Hyperventilation has been used in neuroanaesthesia for many years to reduce ICP. However, evidence from patients with traumatic brain injuries suggests that it may be detrimental by causing cerebral vasoconstriction and a reduction in CBF below a critical threshold. The evidence has lead to guidelines recommending that such patients should not be hyperventilated prophylactically below an arterial carbon dioxide concentration of 35 mm Hg (4.7 kPa) during the first 24 hours after injury. If hyperventilation is required, $PaCO_2$ levels should be monitored and maintained above 4.0 kPa, and the use of jugular oximetry considered, with the aim of maintaining jugular bulb oxygen saturation above 55%. Intraoperative complications specific to such surgery include haemorrhage and acute cerebral oedema. The management of intraoperative cerebral oedema is outlined in Figure 2.

Management of intraoperative cerebral oedema

- Optimize ventilation and blood gases
- Maximize venous drainage
- Deepen anaesthesia – bolus intravenous anaesthetic agent, adjust inhalational agent concentration
- Diuretics – mannitol, 0.5–1.0 g/kg
  ± furosemide (frusemide), 0.25–1.0 mg/kg
- CSF drainage
- Minimize cerebral metabolic requirement of oxygen – bolus lidocaine (lignocaine); thiopental (thiopentone) or propofol infusion
- Consider further doses of diuretic and CSF drainage

2

Fluid management: central venous pressure is used as a guide to maintain normovolaemia. Reduced osmolality of extracellular fluid results in brain oedema. Normal saline is slightly hyperosmolar and Hartmann's solution is slightly hypo-osmolar compared with extracellular fluid. Net transfusion of free water should be avoided and dextrose-containing solutions should not be used. Fluid replacement is required if patients are dehydrated (often the case in those who have an impaired conscious level) or in those who have had a rapid diuresis owing to mannitol. Colloid solutions are appropriate to restore intravascular volume following diuresis, fluid deprivation or moderate blood losses. Patients who have lost more than 1 litre of blood generally require transfusion. It is essential to ensure that haemostasis is monitored intraoperatively and abnormalities are corrected promptly.

Emergence from anaesthesia

During closure of the craniotomy, the anaesthetic may be reduced with the aim that the patient rapidly regains consciousness at the end of the procedure. It is important to normalize mean arterial pressure and $PaCO_2$ before closure to reveal any bleeding points, and to ensure that intraoperative brain swelling does not increase the likelihood of intracranial hypertension when the patient is normocapnic. Obvious brain oedema may prompt a decision to leave the bone flap out, institute ICP monitoring, or opt for a period of postoperative sedation and ventilatory support. The ideal emergence should be free from coughing, straining, hypertension and allow rapid and reliable neurological assessment in the immediate postoperative period. These complications lead to increased venous or arterial bleeding and oedema formation at the operated site. In poorly autoregulating areas, hypertension leads to vascular engorgement and further brain swelling. If the paranasal air sinuses have been breached, coughing after extubation may lead to tension pneumocephalus. Hypertension during emergence may be controlled by bolus doses of labetalol or esmolol. Neuromuscular paralysis should be reversed at the time of dressing application so that coughing and straining are minimized. Lidocaine (lignocaine), 1.5 mg/kg intravenously, is a useful adjunct to reduce coughing towards the end of an anaesthetic. Patients with a preoperative GCS of 13–15 can be extubated when they open their eyes to command and have demonstrated the ability to protect their airway.

Postoperative care

Assessment of pupillary size and its reaction to light should be undertaken soon after the procedure and documented. The neurological state is assessed as soon as possible in the recovery room and any gross abnormality should be brought to the notice of the surgical team. Simple analgesics such as paracetamol or opioids (e.g. codeine phosphate) are traditional and may be adequate, however, many patients require more potent analgesia. In patients who have been extubated, any sudden deterioration in GCS or neurological deficit should be viewed seriously and an urgent CT scan should be considered. ◆

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Anaesthesia for Imaging Relevant to the CNS

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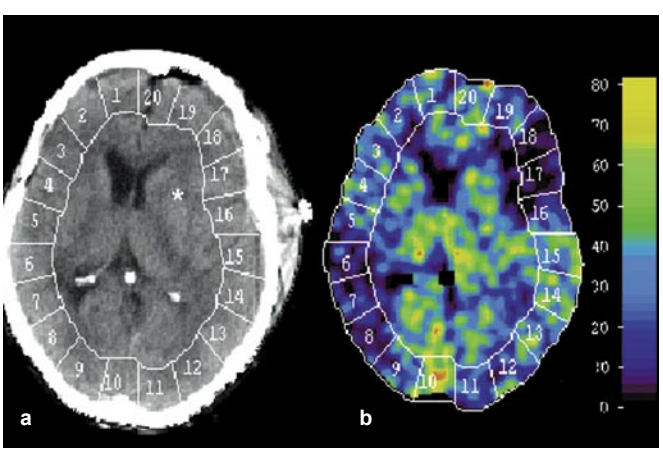
Neuroradiology is an expanding field and likely to involve an increasing input from the anaesthetist. Many patients need careful anaesthesia and perioperative care during procedures carried out in sites remote from the normal operating theatre or ICU.

Imaging techniques

CT provides wide access to tomographic structural imaging. Rapid imaging following administration of intravenous contrast or inhalation of xenon allows computation of cerebral blood flow and blood volume (Figure 1). Image-guided stereotactic surgery allows access to intracranial lesions without craniotomy. A mechanical frame is attached to the patient's head, a CT scan is performed, and a computer calculates three-dimensional co-ordinates within the brain. In frameless stereotaxy, the initial CT or MRI is stored on computer and fixed points on the skull are mapped on to the image using a sensor wand.



1a CT and **b** xenon CT of a patient following surgery for cerebral artery aneurysm. On the CT there is evidence of oedema within the left hemisphere (∗) with compression of the ipsilateral ventricle and midline shift. The xenon CT shows low regional cerebral blood flow, particularly in regions 17 and 18, suggestive of infarction. Scale: ml/100 g/minute.

γ **cameras** are commonly used for imaging following the injection of γ-emitting labels. Single photon emission CT (SPECT) uses conventional γ-emitting nuclear medicine isotopes with multiple detectors to generate tomographic images that are non-quantitative. Positron emission tomography (PET) uses isotopes such as ^{15}O and ^{18}F, which emit positrons. The annihilation of these positrons can be localized in space by pairs of γ detectors, and provides quantitative images of cerebral physiology.

Interventional neuroradiology (INR): flow-directed microcatheters are introduced into blood vessels via the femoral artery under local or general anaesthesia and manipulated through the carotid or vertebral vessels. A variety of devices and drugs including microcoils, stents, balloons, glues, thrombolytics, sclerosing and chemotherapeutic agents can be introduced for diagnostic angiography, coiling or ablation of cerebral aneurysms and arteriovenous malformations, percutaneous transluminal angioplasty, or intravascular thrombolysis.

MRI and magnetic resonance spectroscopy (MRS): magnetic resonance images are produced using powerful static magnetic fields and intermittent oscillating radiofrequency electromagnetic fields that elicit signals from the nuclei of certain atoms. MRI and MRS allow structural and functional imaging and *in vivo* biochemical analysis. Magnetic field strengths are measured in Tesla (1 T = 10000 Gauss (G)). The magnetic field strength at the surface of the earth is 0.5–1.5 G. Field strengths of 0.05–3.0 T are used in clinical MRI and tend to be based on cryogenic superconducting magnets, which are maintained at –273°C by immersion in liquid helium.

Safety

Biological safety: all the above techniques, excluding MRI, involve exposure to ionizing radiation, which is defined by the estimated dose equivalent in milliSieverts (mSv). In the UK, the range of background radiation is 2–8 mSv/year (chiefly from naturally occurring radioactivity). Radiation safety is based on the 'as low as reasonably achievable' (ALARA) principle. The maximum distance from the X-ray source should be maintained wherever possible. Lead glass shields, lead aprons and thyroid shields should be used (together with radiation exposure badges in selected settings) to assess cumulative radiation burden. The available data generally support the safety of exposure to magnetic fields, but unnecessary exposure to high magnetic fields should be avoided, based on general safety principles.

MRI

Projectile risks from ferromagnetic objects – ferromagnetic objects (e.g. oxygen cylinders, identification badges, paging devices) can become dangerous projectiles and should not be taken into the MR suite unless they are known to be safe.

Implanted devices may be ferromagnetic and move in the magnetic field. Such movement may be disastrous if the implant is large or in a critical location (e.g. intraocular foreign bodies, cerebral aneurysm clips). Patients with an intracranial aneurysm clip should not be imaged using MR, unless the clip has been documented to be non-ferromagnetic, or the patient has already been imaged at the same field strength with no problems. Even non-ferromagnetic implants can result in significant image distortion, or cause local burns because their temperature is increased in the presence of radiofrequency currents. Fatalities have been reported in patients with cardiac pacemakers. The magnetic field causes the reed switch on pacemakers to stick, and revert to fixed rate mode where delivery of a pacing spike on the upstroke of a T wave can result in an R on T phenomenon and trigger ventricular fibrillation. MRI is contraindicated in the presence of pacemakers and other implanted electronic devices, unless it is known with absolute certainty that it will function safely. If there is doubt, the implants should be tested with a powerful hand-held magnet and checked against the manufacturer's specifications. MR units usually have a checklist for patients and staff to exclude the presence of implants.

Monitoring devices – in addition to the above hazards, monitoring devices may dysfunction as a consequence of exposure to magnetic fields. Leads from such devices present a particular hazard because induced currents may result in burns. Simple precautions can help to ensure safety (Figure 2). Devices are described as MR safe when they do not represent a risk to the patient, and MR compatible when they also continue to function in the MR environment without degrading imaging.

Other issues – the most commonly used MR contrast agent (gadopentate dimeglumine – Gd-DTPA, *Magnevist*®), has an ex-cellent safety record. The helium contained in cryogenic magnets can boil off (quench) rapidly when the temperature rises. This dilutes room oxygen and the cold vapour gives frostbite and burns.

Precautions to avoid problems with monitoring devices in magnetic resonance environments

- Check insulation on all monitoring wires and magnetic resonance (MR) cables is intact
- Do not cross cables or form large diameter loops of wire, instead plait leads around each other
- Remove any equipment not in use
- Separate all cables from the skin (using padding)
- Keep monitoring equipment as far away from the examination area as possible
- Use only MR-compatible devices
- Ensure limb extremities do not contact each other

2

Monitoring

Neuroradiology often requires the transport of the patient, and monitoring in an unfamiliar environment. Minimal monitoring standards outside the operating theatre should apply:

- circulatory function including ECG, blood pressure, and auscultation of heart sounds or pulse oximetry
- oxygenation, including oxygen analyser, and pulse oximetry
- ventilation if general anaesthesia is induced, ideally by capnography
- temperature, if changes in body temperature are intended, anticipated or suspected.

Monitoring in MRI suites

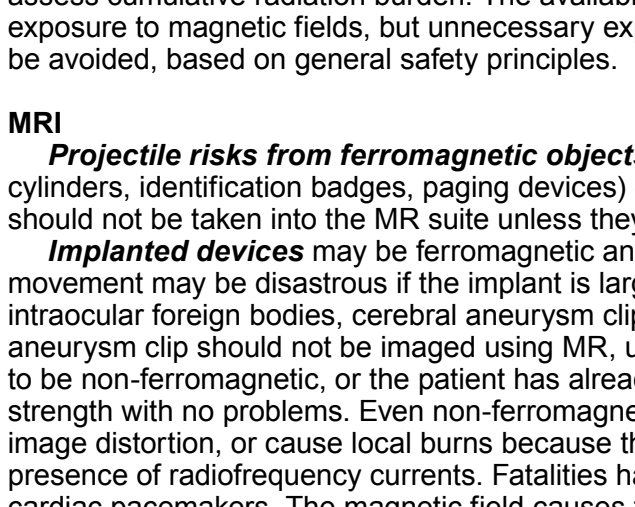
Integrated monitoring systems based on technology developed for the MRI environment are widely available, and represent the standard of care (Figure 3). Even MR-compatible devices should be used with special attention to ensure their safe application (see Figure 2). Other monitoring problems include ECG distortion. Changes occur in early T waves and late ST segments that mimic hyperkalaemia or pericarditis and radiofrequency currents produce ECG artefacts (Figure 4). Intracranial pressure can be measured accurately via a ventriculostomy. Several intra-parenchymal sensors are MR safe, but not MR compatible.

Magnetic resonance compatible monitoring and anaesthetic equipment

• Medrad Inc. USA	www.medrad.com
• Invivo Research Inc. USA	www.invivoresearch.com
• Datex-Ohmeda, Finland	www.datex-ohmeda.com
• North American Drager, USA	www.nad.com
• Sims Pneupac, USA	www.pneupac.com
• Mammendorfer Institut fur Physik und Medizin, Germany	www.mimpm.com

3

Interference with ECG tracing during magnetic resonance imaging following induction of currents in leads by radiofrequency and gradient fields



ECG with: **a** the subject outside the magnet bore; **b** the subject in the magnet bore (note the ST-T changes); and **c** the ECG trace during operation of the imaging sequence.

4

Anaesthesia and sedation

General issues common to most neuroradiological settings include:

- isolated unfamiliar environment
- hard narrow scanning table that will not tilt rapidly
- potential for disconnection of equipment during movement within the scanner
- rapid heat loss in the air-conditioned environment.

The choice of sedation or anaesthesia for patients undergoing imaging should be discussed by the anaesthetist and neuroradiologist. High-dose sedation may be inappropriate in patients with potential respiratory problems and raised intracranial pressure. General anaesthesia and airway protection is required for prolonged and uncomfortable procedures, extreme cases of anxiety and claustrophobia, failed sedation and for critically ill patients requiring intermittent positive-pressure ventilation. The anaesthetic technique should aim to maintain stable cerebral perfusion pressure and minimize cerebral oedema. Both volatile and intravenous anaesthesia can be used; the choice depends on clinical circumstances.

INR: patient immobility is crucial to ensure success and prevent complications such as rupture or intimal tearing of small vessels. Patient management may need to allow for the following.

- Rapid titration of sedation or anaesthetic depth. Rapid neurological assessment may be required. Problems include patient anxiety, comfort on prolonged immobility, and discomfort following contrast injection.
- Haemodynamic manipulation. To aid therapy, assess vascular reserve and treat ischaemic episodes. This may have adverse effects in unstable patients with neurological disease and should be used with caution.
- Management of complications. These include vessel rupture and haemorrhage, ischaemic episodes (following thromboembolism, vasospasm, hypoperfusion, vessel dissection, stenosis or venous outflow obstruction), neurological complications, radio-contrast reactions and pulmonary embolization of particles.
- Anticoagulation. Heparin is commonly given to achieve an activated clotting time two to three times baseline and prevent thrombosis.

CT: most procedures involve little stimulation and anaesthesia is required only for unstable patients in intensive care and for children. Propofol is commonly used for fast titration of levels of sedation and rapid return of consciousness. Small infants tolerate scanning procedures without sedation if fed, wrapped well and placed prone. Supplemental oxygen can improve the safety margin of sedation in children.

MRI requires an immobile patient to be placed in a noisy, dark, cold and uncomfortable space that is isolated from radiology and anaesthetic staff. Induction and recovery of anaesthesia should ideally take place with dedicated equipment incorporating commercially constructed MR-compatible anaesthetic machines, ventilators and infusion devices. Sedation techniques in children include ketamine, barbiturates, benzodiazepines, high-dose chloral hydrate (50–150 mg/kg) and low-dose propofol infusions.

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Applied Cerebrovascular Physiology

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Understanding the principles of the physiology of the brain, and the effects of drugs and pathological processes on it, is of fundamental importance for anaesthetists in the management of patients with brain injury, and for the provision of anaesthesia in neurosurgical patients.

Cerebral metabolism and blood flow

The ability of the brain to maintain membrane ionic gradients and transmit electrical impulses depends on a continuous supply of metabolic substrates. Glucose is the primary energy source of the brain and is actively transported across the blood–brain barrier. The cerebral metabolic rate of glucose utilization is about 5 mg/100 g brain/minute, with 90% taken up in aerobic metabolism. During starvation, however, the brain is able to adapt and use different substances for metabolism (e.g. ketones, lactate, amino acids: see **PHYSIOLOGY**). In normal circumstances, oxygen consumption closely parallels glucose consumption (3.5 ml/100 g brain/minute or 50 ml/minute). In adults, stores of glycogen are exhausted in less than 3 minutes in the face of normal brain activity and there are no significant stores of oxygen. Owing to the high brain oxygen consumption, cessation of cerebral blood flow results in unconsciousness within 10 seconds.

The brain accounts for 20% of basal oxygen consumption and 25% of basal glucose consumption, which under normal circumstances is more than adequately met by the 15% of cardiac output that the brain receives (750 ml/minute in adults). The mean resting cerebral blood flow in young adults is about 50 ml/100 g brain/minute. There are, however, regional differences in blood flow, with mean values for grey and white matter being 80 and 20 ml/100 g brain/minute, respectively. Blood flow also parallels metabolic activity, varying between 10 and 300 ml/100 g brain/minute. Functional impairment results from reductions in cerebral blood flow; the EEG slows at flow rates below 20–25 ml/100 g brain/minute, it is flat at a rate of 15–20 ml/100 g brain/minute, and irreversible brain damage occurs at rates below 10 ml/100 g brain/minute.

The blood–brain barrier

Endothelial cells in cerebral capillaries contain few pinocytic vesicles and are sealed by tight junctions (zona occludens), with no anatomical gap. Consequently, unlike other capillary beds, the endothelial barrier of cerebral capillaries presents a high electrical resistance and is remarkably non-leaky. This property of the cerebral vasculature is termed the blood–brain barrier, and comprises three cellular components (i.e. endothelial cell, astrocyte and pericyte), and one non-cellular structure (endothelial basement membrane). The blood–brain barrier is a function of the cerebral microenvironment rather than an intrinsic property of the vessels themselves. Passage of substances through the blood–brain barrier is directly proportional to lipid solubility and the presence of active transport mechanisms, but indirectly proportional to molecular weight, ionic charge and the degree of plasma protein binding. Thus lipophilic substances, such as carbon dioxide, oxygen and anaesthetic agents, freely enter the brain, whereas ions, proteins and large molecules penetrate the blood–brain barrier poorly. Water moves freely by bulk flow, whereas there is some impedance to small ions such as sodium. Acute changes in plasma electrolyte concentrations (and osmolality) produce changes in the osmotic gradient between plasma and brain interstitial fluid. Although these changes are transient, they result in rapid fluid shifts in the brain, leading to altered neurological function. Thus, marked abnormalities in serum sodium or glucose should be corrected slowly. Disease processes, such as severe hypertension, stroke, infection, tumours, trauma, sustained seizure activity, marked hypercapnia and hypoxia, can cause disruption of the blood–brain barrier. If this occurs, fluid movements across the barrier become dependent on hydrostatic gradients rather than osmotic gradients.

CSF

The main function of CSF is to protect the brain from trauma. It also recirculates interstitial proteins back to plasma (there are no brain lymphatics). The volume of CSF in an adult is about 150 ml (with a turnover of 21 ml/hour) with roughly equal proportions in the cranial and spinal compartments. Most CSF is formed (secretion and ultrafiltration) in the choroid plexus of the cerebral ventricles (mainly lateral). It is iso-osmolar compared with plasma, but has a lower concentration of K^+, Ca^{2+}, HCO_3^-, H^+ (pH 7.33), protein and glucose, and a higher concentration of Na^+, Cl^-, Mg^{2+} and carbon dioxide. CSF flows from the lateral ventricles, through the foramen of Monro, to the third ventricle and then the fourth ventricle (via the aqueduct of Sylvius). It then passes through the foramen of Magendie (medial) and foramina of Luschka (lateral) into the cisterna magna to continue into the subarachnoid spaces around the brain and spinal cord. Reabsorption of CSF occurs at the arachnoid granulations.

Intracranial pressure and volume relationships

In adults, the skull is a rigid structure, which forms an almost completely closed box. It contains four components: brain parenchyma and interstitial fluid (80%), blood which is mainly venous (12%) and CSF (8%). Each fluid component is essentially incompressible, and any increase in the volume of one component if unaccompanied by a compensatory decrease in the volume of another, will result in a rise in intracranial pressure (ICP), as the intracranial volume is fixed (Monro–Kellie doctrine). The normal ICP is less than 15 mm Hg, but varies with arterial pulsations, respiration, coughing and straining (venous pressure). Blood flow to the brain is governed by cerebral venous pressure only when it exceeds ICP; in such situations, cerebral blood flow is dependent on arteriovenous pressure differences. In most instances, however, cerebral blood flow is dependent on the pressure difference between the mean arterial pressure (MAP) measured at the level of the brain and ICP. This is the cerebral perfusion pressure (CPP):

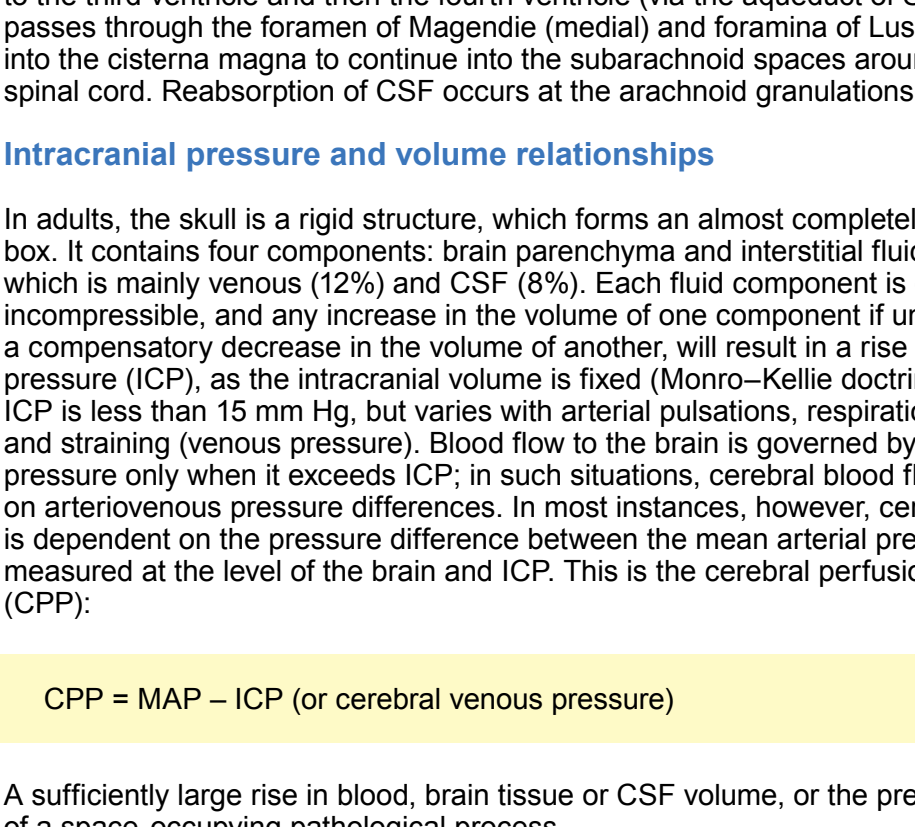
$$CPP = MAP - ICP \text{ (or cerebral venous pressure)}$$

A sufficiently large rise in blood, brain tissue or CSF volume, or the presence of a space-occupying pathological process (e.g. haemorrhage, tumour, abscess), will result in an increase in ICP. However, compensatory mechanisms can initially prevent rises in ICP. These include:

- displacement of CSF from the cranial to spinal compartment
- increased CSF absorption
- decreased CSF production
- decreased cerebral blood volume.

Intracranial compliance is initially high due to these processes. However, as intracranial space occupation continues (by physiological or pathological means), the limits of these mechanisms are exceeded. Intracranial compliance falls and ICP rises dramatically with small increases in intracranial volume, such as 5–10 ml of blood (Figure 1). Therefore, although the cerebral blood volume forms only a small part of the intracranial volume, inappropriate anaesthetic management may cause it to increase as a result of coughing, positive end-expiratory pressure (PEEP), or severe hypertension. Conversely, physiological and pharmacological interventions by the anaesthetist may result in marked reductions in ICP in the presence of intracranial hypertension. Although the absolute magnitude of such a decrease in volume may be small, it may result in a marked fall in ICP.

Intracranial pressure–volume curve



1

Physiological determinants of cerebral blood flow and volume

Regional metabolism

Increases in local neuronal activity are accompanied by increases in regional cerebral metabolic rate. This is termed flow–metabolism coupling. It has now been shown that increases in regional cerebral blood flow during functional activation tend to track glucose utilization, but may be far in excess of an increase in oxygen consumption. This results in regional anaerobic glucose utilization, and a consequent decrease in the local oxygen extraction ratio and increase in local oxyhaemoglobin saturation. The cellular mechanisms underlying these observations have highlighted the role played by astrocytes in the regulation of cerebral metabolism. These data suggest that astrocytes utilize glucose glycolytically and produce lactate, which is transferred to neurons where it serves as a fuel in the citric acid cycle. Astrocytic glucose utilization and lactate production appear to be, in large part, coupled to the astrocytic reuptake of glutamate released at excitatory synapses.

The regulatory changes involved in flow–metabolism coupling have a short latency (about 1 second) and may be mediated by metabolic or neurogenic pathways. The metabolic pathways include the increases in perivascular K^+ or adenosine concentrations that follow neuronal depolarization. Dopamine, acetylcholine, nitric oxide and, possibly, 5-hydroxytryptamine, substance P and neuropeptide Y, released by nerves that supply cerebral vessels, may mediate neurogenic flow–metabolism coupling.

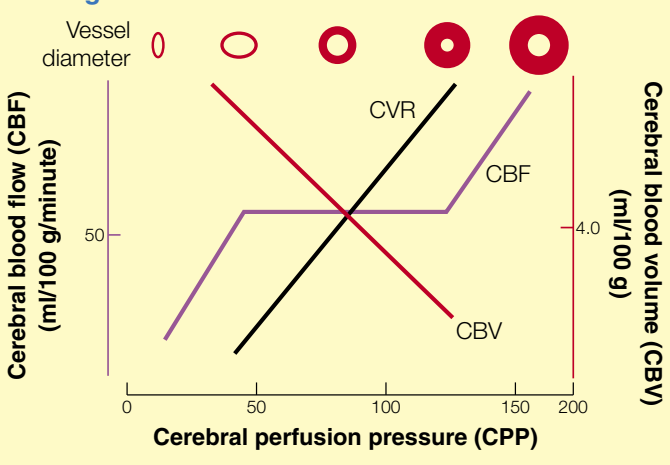
Cerebral perfusion pressure

The ability of the cerebral circulation to maintain cerebral blood flow at a relatively constant level, in the face of changes in cerebral perfusion pressure, by altering cerebrovascular resistance is termed autoregulation (Figure 2). In normal circumstances, as both ICP and cerebral venous pressure are low, systemic arterial perfusion pressure (i.e. mean arterial pressure) becomes the primary determinant of cerebral perfusion pressure. However, in pathological states, ICP becomes a significant factor for cerebral perfusion pressure. Autoregulation has limits above and below which cerebral blood flow is directly related to perfusion pressure. Above the higher limit of autoregulation, increases in mean arterial pressure lead to forced dilatation of cerebral arterioles, disruption of the blood–brain barrier and formation of cerebral oedema with a resultant increase in cerebral blood volume and ICP. Below the lower autoregulatory limit, cerebral blood flow falls linearly with decreasing perfusion pressure.

Unlike flow–metabolism coupling, autoregulatory responses are not immediate; estimates of the latency for compensatory changes in regional cerebrovascular resistance range from 10 to 60 seconds. Changes in cerebrovascular resistance probably arise as a result of myogenic reflexes in the resistance vessels, but these may be modulated by sympathetic nervous system activity or the presence of chronic systemic hypertension. Thus, sympathetic blockade or cervical sympathectomy shifts the autoregulatory curve to the left, while chronic hypertension or sympathetic activation shifts it to the right. These modulatory effects may arise from angiotensin-mediated mechanisms. Primate studies suggest that nitric oxide is unlikely to be important in pressure autoregulation.

In reality, the clear-cut autoregulatory thresholds with varying cerebral perfusion pressure shown in Figure 2 are not observed; the autregulatory 'knees' tend to be more gradual, and there may be wide variations in regional cerebral blood flow for a given value of cerebral perfusion pressure. Symptoms of cerebral ischaemia have been shown to appear when the mean arterial pressure falls below 60% of an individual's lower autoregulatory threshold. However, generalized extrapolation from such individualized research data to the production of 'safe' lower limits of mean arterial pressure for general clinical practice is hazardous for several reasons. These include the wide individual scatter in regional cerebral blood flow autoregulatory efficiency and the coexistence of local fixed vascular obstruction (e.g. carotid atheroma or vascular spasm).

Autoregulation



A change in cerebrovascular resistance (CVR) occurs in response to changes in CPP to maintain CBF. Note that cerebral vasodilatation, and thus a decrease in CVR, maintains CBF with reductions in CPP. This increases CBV which results in critical increases in intracranial pressure in patients with poor compliance (e.g. B in Figure 1)

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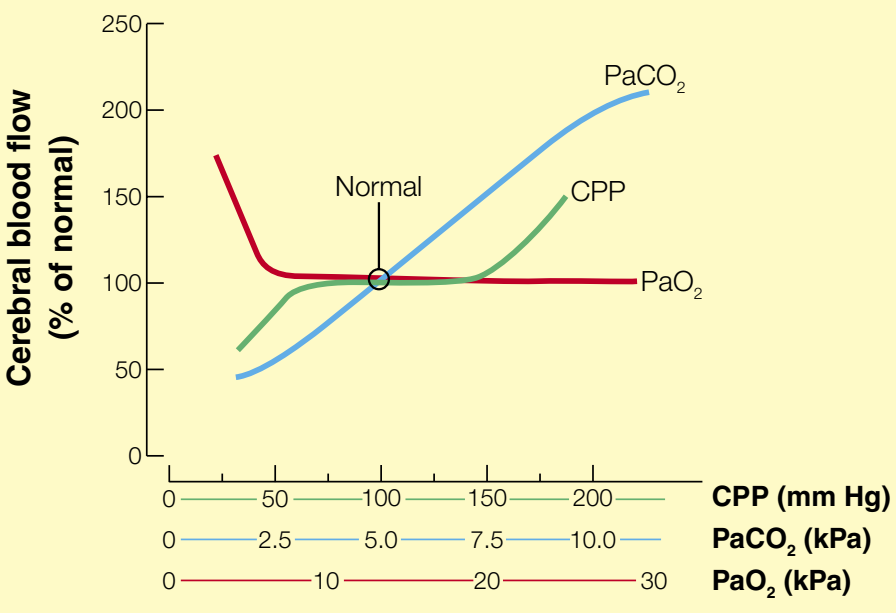
Partial pressure of carbon dioxide in arterial blood ($PaCO_2$)

Cerebral blood flow is proportional to $PaCO_2$, subject to a lower limit, below which vasoconstriction results in tissue hypoxia and reflex vasodilatation, and an upper limit of maximal vasodilatation (Figure 3). On average, in the middle of the physiological range, each kPa change in $PaCO_2$ produces a change of about 15% in cerebral blood volume and 20% in cerebral blood flow. In patients with low intracranial compliance, this decrease in cerebral blood volume can result in dramatic reductions in ICP. However, moderate hypocapnia ($PaCO_2$ of about 3.5 kPa) is no longer recommended to reduce cerebral blood volume in intracranial hypertension because these levels of hypocapnia in head-injured patients can result in dangerously low regional cerebral blood flow levels. Prostaglandins and nitric oxide mediate the vasodilatation produced by carbon dioxide.

Arterial oxygen content

Classical teaching is that cerebral blood flow is unchanged until the partial pressure of oxygen in arterial blood (PaO_2) falls below about 7 kPa, but rises sharply with further reductions (Figure 3). However, recent transcranial Doppler data suggest cerebral thresholds for cerebral vasodilatation as high as 8.5 kPa (about 89–90% oxygen saturation). This nonlinear behaviour is because tissue oxygen delivery governs cerebral blood flow, and arterial oxygen content is related primarily to haemoglobin oxygen carriage (and thus oxygen saturation) rather than PaO_2. The vasodilator responses to hypoxaemia show little adaptation with time, but may be substantially modulated by $PaCO_2$ levels. Nitric oxide does not play a role in the vasodilatory response to hypoxia. Blood haematocrit (and hence viscosity) was also thought to play a role in determining cerebral blood flow. However, it is more likely that changes in cerebral blood flow caused by alterations in haematocrit are the consequence of changes in arterial oxygen content, rather than in blood viscosity.

Effect of pressure changes on cerebral blood flow



The curve for cerebral perfusion pressure (CPP) for patients with chronic systemic arterial hypertension is shifted to the right. $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood.

3

Temperature

Cerebral blood flow changes by about 5–7%/°C. Hypothermia decreases both cerebral metabolic rate and cerebral blood flow so that, at 27°C, metabolic utilization of oxygen is 50% of normal. These reductions in cerebral metabolic rate allow safe circulatory standstill for up to 40 minutes in patients maintained at temperatures of 18°C. In healthy brains at this temperature, autoregulation, flow–metabolism coupling and carbon dioxide reactivity remain intact. An increase in temperature to 42°C leads to an increase in the utilization of oxygen and cerebral blood flow. Temperatures exceeding 42°C appear to cause neuronal damage and reduced oxygen uptake.

Autonomic nervous system

The autonomic nervous system mainly affects the larger cerebral vessels, up to and including the proximal parts of the anterior, middle and posterior cerebral arteries. β_1-adrenergic stimulation results in vasodilatation while α_2-adrenergic stimulation leads to vasoconstriction. The effects of systemically administered α- or β-agonists are less significant. However, significant vasoconstriction can be produced by extremely high concentrations of catecholamines (e.g. in haemorrhage) or centrally acting α_2-agonists (e.g. dexmedetomidine). The autonomic nervous system may be involved in cerebral vasospasm after brain injury (e.g. subarachnoid haemorrhage).

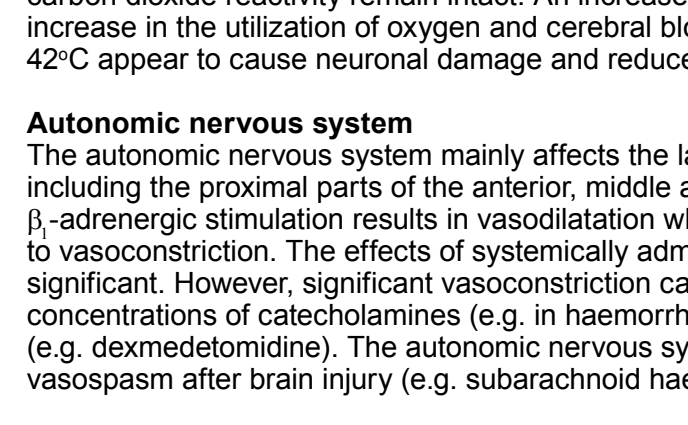
Cerebral venous pressure

Venous obstruction can be caused by supine or head-down positioning, coughing, straining, incomplete muscle relaxation, or tight tracheal tube ties in ventilated patients. While PEEP levels that result in cerebral venous pressures greater than ICP can exacerbate intracranial hypertension, in most instances moderate applications of PEEP will improve arterial oxygenation and potentially result in reductions in ICP. Obstruction of cerebral venous drainage increases ICP by increasing cerebral blood volume and by promoting cerebral oedema formation due to hydrostatic pressure changes. Such oedema can produce microcirculatory disturbances that add to the detrimental effects of intracranial hypertension on cerebral blood flow via cerebral perfusion pressure changes.

Mechanisms in regional cerebral blood flow control

Some of the mechanisms involved in cerebrovascular control are shown in Figure 4, several of which have been referred to earlier. In addition, the level of free Ca^{2+} is important in determining vascular tone, and arachidonate metabolism can produce prostanoids that are either vasodilators (e.g. prostacyclin) or vasoconstrictors (e.g. thromboxane A_2). Endothelin (ET), produced by endothelin-converting enzyme in endothelial cells, balances the vasodilator effects of nitric oxide in a tonic manner by exerting its influences at ET_A receptors in the vascular smooth muscle.

Mechanisms involved in the regulation of regional cerebral blood flow in health and disease



The figure shows a resistance vessel in the brain in the vicinity of a neuron and an astrocyte (A). E, endothelium; M, muscular layer; PGs, prostaglandins; TXA_2, thromboxane A_2; ET, endothelin; ECE, endothelin-converting enzyme; ET_A, ET_A receptor; NO, nitric oxide; CO, carbon monoxide; DA, dopamine

4

Nitric oxide in the regulation of cerebral haemodynamics

Recent interest has focused on the role of nitric oxide (NO) in the control of cerebral haemodynamics. NO is synthesized in the brain from the amino acid L-arginine by the constitutive form of the enzyme NO synthetase. This form of the enzyme is calmodulin dependent and requires Ca^{2+} and tetrahydrobiopterin for its activity. Under basal conditions, endothelial cells synthesize NO, which diffuses into the muscular layer and, via a mechanism mediated by cyclic guanosine monophosphate (cGMP), produces relaxation of vessels. There is strong evidence to suggest that NO exerts a tonic dilatory influence on cerebral vessels. Some of the endothelium-derived relaxant factor (EDRF) activity in cerebral vessels may be due to compounds other than NO. For example, carbon monoxide produced by heme-oxygenase may be responsible for significant cerebral vasodilatation, especially when NO production is reduced.

NO plays an important role in cerebrovascular responses to functional activation, excitatory amino acids, hypercapnia, ischaemia and subarachnoid haemorrhage. Furthermore, NO may also play an important part in mediating the vasodilatation produced by volatile anaesthetic agents, although other mechanisms, including a direct effect on the vessel wall, cannot be excluded.

Neurogenic flow–metabolism coupling

In the last 10 years, focus has been placed on flow–metabolism coupling being effected by a diffusible extracellular mediator. However, there is now accumulating evidence to suggest that dopaminergic neurons may play a major part in such events and, in addition, may control blood–brain barrier permeability.

Measurement of cerebral blood flow and oxygenation

All clinical and many laboratory methods of measuring global or regional cerebral blood flow are indirect and may not produce directly comparable measurements. It is also important to treat results from any one method with caution, and attribute any observed phenomena to physiological effects only when demonstrated by two or more independent techniques. Methods that provide absolute estimates of regional cerebral blood flow use one of two principles: they either measure the distribution of a tracer, or estimate blood flow from the wash-in or washout curve of an indicator. Other techniques do not directly estimate regional cerebral blood flow, but can be used either to measure a related flow variable (such as arterial flow velocity) or to infer changes in flow from changes in metabolic parameters. Some techniques that have been used for the measurement of cerebral blood flow and oxygenation are described briefly in Figure 5.

Techniques for measuring cerebral blood flow and oxygenation

Technique	Global/regional	Features
Kety–Schmidt minute	Global	Invasive (requires jugular bulb and arterial catheters). Time consuming (10–20 data collection). Repeated measures possible. Can be performed in ICU
Intracarotid ^{133}Xe	Regional	Invasive. One hemisphere only. Primarily looks at superficial cortex. Washout or dynamic CT method. Repeated measures possible
Inhaled ^{133}Xe	Regional	Non-invasive. Primarily looks at superficial cortex. Washout or dynamic CT method. Repeated measures possible but not at rapid intervals. Extracranial tissue contamination
SPECT	Regional	Distribution of photon-emitting tracer estimates rCBF. Cheaper than PET, but poorer resolution. Difficult to repeat measurements. Not bedside test
PET	Regional	Distribution of positron-emitting tracer estimates rCBF. Good resolution. Expensive and complex. Repeated measures possible. Not bedside test
Functional MRI	Regional	Intravenous contrast label used or utilizes change in regional oxygenation during functional activation. Excellent resolution. Repeated measures easy with non-contrast method. Not bedside test. Non quantitative in most settings
TCD ultrasound	Regional	Measures flow velocity and therefore CBF indirectly. Measures relative, not absolute CBF. Non-invasive bedside measurement for continuous monitoring. Repeatable but needs same probe angle and vessel diameter to compare values
$SjvO_2$	Regional	Permits continuous monitoring of jugular venous bulb oxygen saturation. Fibre-optic catheter commonly used. Invasive bedside measurement. Indicates balance between oxygen supply and demand
NIROS	Regional	Spectroscopic measurement of regional haemoglobin oxygenation and cytochrome redox state in restricted and poorly defined volume (transcranial cerebral oximetry).Non-invasive bedside measurement for continuous monitoring

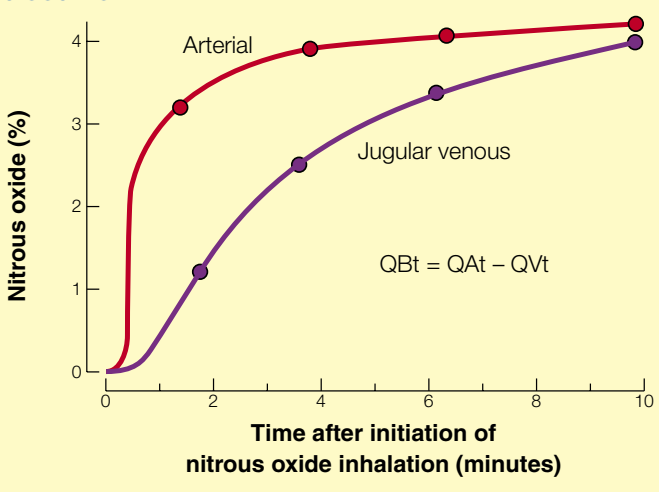
Abbreviations: rCBF, regional cerebral blood flow; SPECT, single photon emission tomography; PET, positron emission tomography; TCD, transcranial Doppler; $SjvO_2$, jugular venous oxygen saturation; NIROS, near infrared optical spectroscopy.

5

The Kety–Schmidt technique

The Kety–Schmidt technique involves the insertion of catheters into a peripheral artery and the jugular bulb. An inert, freely diffusible tracer, such as 10–15% inhaled nitrous oxide, is administered, and paired arterial and jugular venous samples of blood are obtained at rapid intervals for measurement of nitrous oxide levels. The resultant plot of concentration versus time produces an arterial and a venous curve (Figure 6). The jugular venous level of nitrous oxide rises more slowly than the arterial levels because delivered nitrous oxide is taken up by the brain. The rate of equilibration of the two curves measures the rate at which nitrous oxide is delivered to the brain, and thus provides a means of measuring global cerebral blood flow.

Kety–Schmidt method of measuring global cerebral blood flow



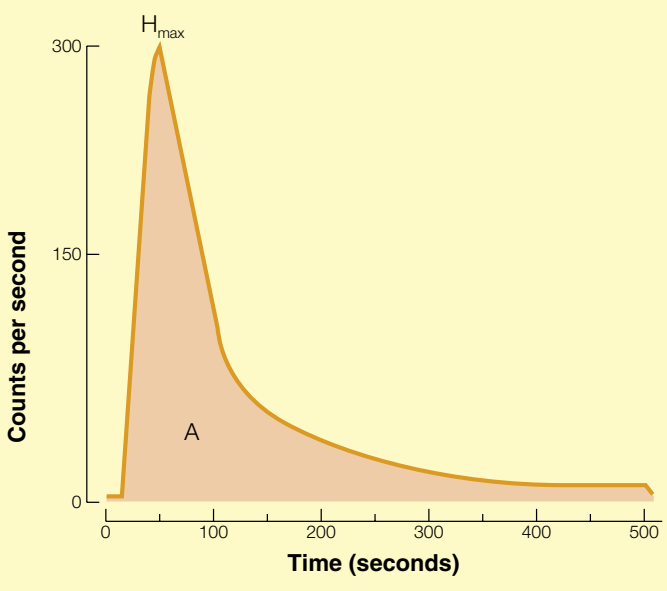
The rate of increase in arterial and jugular venous concentrations of a diffusible tracer gas (e.g. nitrous oxide) are compared. A rapid equilibration implies a high cerebral blood flow (CBF), while a slow equilibration is evidence of a low CBF. QBt, quantity of tracer taken up by brain in unit time; QAt, quantity of tracer delivered to brain by arterial blood in unit time; QVt, quantity of tracer removed by cerebral venous blood in unit time.

6

Xenon-133 washout

An array of collimated scintillation counters positioned over the head can be used to measure the regional decay in radioactivity after the intracarotid or intra-aortic injection of ^{133}Xe. The slope of the washout curve for radioactivity is proportional to regional cerebral blood flow. This washout curve is bi-exponential (Figure 7) and may be resolved into two mono-exponential components, which represent fast and slow washout components. Although these are often referred to as grey matter and white matter components, there is no basis to support such an anatomical distinction because the two curves represent pharmacokinetic compartments, rather than specific neuroanatomical structures. The technique provides two-dimensional information regarding regional cerebral blood flow, but is invasive and primarily evaluates superficial cortical blood flow. Furthermore, intra-carotid injection permits the assessment of only a single cerebral hemisphere at a time. One modification involves the inhalational or intravenous administration of ^{133}Xe; although this makes the technique less invasive, problems arise because of recirculation and contamination by extracranial tissues. The simultaneous presence of activity in both cerebral hemispheres also leads to the 'look-through' phenomenon, where regional cerebral blood flow reductions on one side may be missed because of activity sensed in deeper areas of contralateral brain tissue.

Measurement of cerebral blood flow using intracarotid injection of xenon-133



Blood flow is calculated from the maximal height (H_{max}) and integration of the area under the curve (A).

7

Tomographic regional cerebral blood flow measurement

Tomographic information regarding regional cerebral blood flow may be obtained by quantitative studies of the washout of a radiodense contrast agent, using rapid sequential X-ray CT imaging (dynamic CT scanning). Inhaled stable xenon has been used most often as the contrast agent. Xenon-enhanced CT gained popularity owing to its high spatial resolution and the availability of the equipment. In addition, it can be performed in neurological emergencies because of the short examination time. Recent studies have been performed using standard radioiodinated intravenous contrast agents.

Single photon emission tomography (SPECT) and positron emission tomography (PET) use γ-emitting (e.g. ^{99}Tc) and positron-emitting isotopes (e.g. ^{15}O, ^{18}F, ^{11}C, ^{13}N), respectively, to produce tomographic images of regional cerebral blood flow. PET, in addition to imaging cerebral blood flow, can provide information about cerebral blood volume, oxygen metabolism, and the oxygen extraction fraction. Functional MRI (fMRI) produces tomographic images of regional cerebral blood flow in one of two ways. One technique uses an intravenous contrast agent in the same way as the techniques previously mentioned use other agents. MRI can also produce, without the use of external contrast agents, tomographic images of changes in regional cerebral blood flow. The technique maps the increases in magnetic resonance signal intensity produced by the decreases in regional deoxyhaemoglobin levels that occur during regional activation.

In general, continuous clinical monitoring of the adequacy of cerebral perfusion tends to use techniques other than those outlined above. The parameter most commonly monitored in head-injured patients is cerebral perfusion pressure, though many centres are increasingly using fibre-optic jugular venous oximetry and transcranial Doppler measurement of middle cerebral artery flow velocity. Monitoring of the processed EEG or evoked potentials provides information regarding the consequences of reduced cerebral blood flow, and this technique has been used in the context of cardiopulmonary bypass and carotid endarterectomy. Near-infrared optical spectroscopy and laser Doppler flowmetry are investigational techniques the roles of which have not been clearly defined.

Transcranial Doppler (TCD) ultrasonography

TCD measures the velocity of RBCs flowing through the large vessels at the base of the brain using the Doppler shift principle. Since the diameter of these basal vessels is unaffected by common physiological variables, such as mean arterial pressure and $PaCO_2$, flow velocity in these vessels provides an index of flow. Although many of the intracranial arteries may be studied, the middle cerebral artery is most commonly insonated because it is easy to detect, receives a substantial proportion of the blood flow from the internal carotid artery and allows easy probe fixation. Provided the angle of insonation and the diameter of the vessel insonated remain constant, relative changes in cerebral blood flow velocity correlate closely with changes in cerebral blood flow. Changes in TCD velocities and waveform patterns can be used to detect cerebral ischaemia, hyperaemia and vasospasm. In addition, the characteristics of the TCD waveform may be used to provide a non-invasive estimate of cerebral perfusion pressure.

Jugular venous oximetry

Cerebral oxygenation has conventionally been assessed by jugular bulb oximetry. Traditionally, the superior sagittal sinus is thought to drain primarily into the right internal jugular vein, and it is common practice to place jugular bulb catheters on this side in order to monitor the oxygenation in the supratentorial compartment. More recent data suggest that supratentorial venous drainage is less lateralized, and a case has been made for bilateral jugular bulb catheterization. Normal jugular bulb oxygen saturations tend to be 65–70%. Reductions in the jugular bulb oxygen saturation or increases in arterio-jugular difference in oxygen content of more than 9 ml/dl provide useful markers of inadequate cerebral blood flow and can guide therapy. Values of jugular bulb oxygen saturation below 50% have been shown to be associated with a worse outcome in head injury. Conversely, marked elevations in jugular bulb oxygen saturation may provide evidence of cerebral hyperaemia.

FURTHER READING

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Clinical Neuroprotection

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Neuroprotection begins with basic resuscitation comprising airway, respiratory and cardiovascular support. Unless normoxia and normotension are maintained, the application of drugs is ineffective. While this article focuses on agents that achieve neuroprotection by reversing one or more of the secondary injury processes, other therapeutic interventions can reduce neuronal injury by optimizing cerebrovascular physiology. Drugs such as mannitol and dexamethasone, can reduce post-traumatic and peritumoral oedema, respectively, and thus augment cerebral perfusion pressure and oxygen delivery. Similarly, haemodynamic augmentation for hypervolaemia and hypertension can enhance cerebral blood flow in the setting of intracranial hypertension or cerebral vasospasm. Agents that antagonize most recognized injury mechanisms have been shown to be neuroprotective in animal models. This contrasts with the clinical setting, where one of the major disappointments in recent years has been the repeated failure of neuroprotective agents.

Neuroprotective interventions
Categories of drugs that have been evaluated in animal models of CNS ischaemia and trauma are outlined below. Specific issues that need to be considered when evaluating the clinical relevance of experimental studies are listed in Figure 1.

Critical issues in assessing preclinical neuroprotective studies

- Species in which studies are performed (effectiveness in more than one species is reassuring; primate models are increasingly seen as relevant)
- Is the model well characterized? (especially problematic in traumatic brain injury)
- Is intervention at a relevant time point? (pre-ischaemic interventions may be irrelevant to clinical stroke therapy)
- Duration of follow-up (increasing evidence supports a need to follow up animals for several days to weeks, because neuronal loss may be delayed)
- Does the study address outcome or only modification of mechanistic changes?
- Have age and gender of the experimental animals been specified and/or controlled? (older animals may show less benefit, there may be gender variations)

Excitatory amino acid antagonists (EAAs): raised levels of glutamate in the extracellular fluid (ECF) have been demonstrated following ischaemia and trauma, and neuroprotective interventions have been targeted at all three glutamate receptor subtypes (*N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA/kainite) and metabotropic) and at various regulatory sites on the NMDA receptor (e.g. the glycine site). The reference compound in this category is dizocilpine (MK-801), a non-competitive antagonist at the NMDA receptor, which had significant CNS side-effects and never reached clinical trials. Newer compounds and regulatory site agents (e.g. glycine and polyamine antagonists) may be better. NMDA receptor antagonists may provide additional neuroprotection when used in combination with antioxidants or thrombolysis, suggesting a possible role for multidrug combinations in neuroprotection.

Experimental data attest to the efficacy of EAAs in animal models. However, a variety of EAAs, including cerestat (a non-competitive NMDA blocker), selfotel (a competitive NMDA blocker) and eliprodil (a polyamine regulatory site antagonist), have proved disappointing in stroke and head injury.

Sodium channel blockers: the neuroprotective potential of drugs such as phenytoin (and its prodrug fosphenytoin), lamotrigine, lubeluzole and riluzole has been shown experimentally. They block sodium channels and attenuate glutamate release. No clinical successes have been reported.

Antioxidants and free radical scavengers: several antioxidants have been effective in animal models, including superoxide dismutase and catalase, the spin-trap phenyl-t-butyl nitrone (PBN), iron chelators (e.g. desferroxamine) and the aminosteroid tirilazad. They all exhibit neuroprotective efficacy in animal models but there have been no successful clinical trials. Initial optimism regarding pegorgotein (PEG conjugated superoxide dismutase) and tirilazad mesylate has been unfounded. One of the few exceptions to the list of failures is the use in acute spinal cord injury of methylprednisolone at high doses (30–35 mg/kg, followed by 5.4 mg/kg/hour for 24 hours) which may provide part of its benefit through antioxidant effects.

Inflammation and corticosteroids: inhibition of tumour necrosis factor α (TNFα), interleukin-1 (IL-1), and IL-8 release or activity improves outcome in focal cerebral ischaemia and trauma models. Inhibition of leukocyte-endothelial interactions is also neuroprotective, and antagonism of adhesion molecules such as ICAM-1, E-selectin and P-selectin reduces neuronal injury.

Despite experimental success with anti-inflammatory therapy, a recently reported trial of anti-ICAM-1 antibody (*Enlimomab*) in acute stroke showed increased morbidity and mortality in treated patients, and recent guidelines covering the intensive care management of patients with head injury have emphasized the lack of objective benefit from corticosteroids. Animal data provide evidence of both harm and benefit from corticosteroid therapy. However, a recent meta-analysis of corticosteroid therapy in head injury concluded that available clinical evidence cannot exclude a benefit from corticosteroid therapy. These conclusions have been widely discussed and have triggered a large (10,000 patients) MRC-sponsored randomized trial of corticosteroid therapy in head injury (the CRASH trial; http://www.crash.lshtm.ac.uk).

Anaesthetic neuroprotection does not depend exclusively on the extent of metabolic suppression and may involve several mechanisms (Figure 2). There is increasing interest in the neuroprotective effects of non-barbiturate anaesthetics. Barbiturates, propofol and isoflurane provide neuroprotection. Ketamine, in addition to its anaesthetic effects, may provide neuroprotection by acting as an NMDA receptor antagonist.

Recent clinical studies of anaesthetic neuroprotection are inconclusive. One study addressing the relative merits of intravenous anaesthetic agents and isoflurane in the clinical setting of temporary clip application during aneurysm surgery showed that pre-treatment with intravenous anaesthetics improved tolerance to ischaemia, but patient numbers were small and it is not clear whether comparable metabolic suppression was achieved. In another study, while barbiturate coma was effective in treating refractory intracranial hypertension following stroke, it produced no improvement in outcome.

Mechanisms by which anaesthetic agents may exert their neuroprotective effects

- Reduction in synaptic transmission
- Reduction in calcium influx
- Ability to block sodium channels
- Membrane stabilization
- Improvement in distribution of regional cerebral blood flow
- Suppression of cortical EEG activity
- Reduction in cerebral oedema
- Free radical scavenging
- Potentiate γ-aminobutyric acid (GABA)-ergic activity
- Alteration of fatty acid metabolism
- Suppression of catecholamine-induced hyperactivity
- Reduction in CSF secretion
- Anaesthesia, de-afferentation and immobilization
- Facilitates uptake of glutamate in synapses

Nitric oxide and the endothelin system: the vasoconstrictor effects of endothelin are normally balanced by vasodilatation produced by endothelial nitric oxide. Overactivity of the endothelin system represents a potential therapeutic target in stroke and subarachnoid haemorrhage. However, neuronal nitric oxide can worsen secondary injury, and nitric oxide synthase inhibition in experimental animals has variable effects, depending on the selectivity of the inhibitor, the model and the systemic haemodynamic perturbations that are produced. Reduced nitric oxide production may be one of the mechanisms by which hypothermia (see below) effects neuroprotection; no clinical studies are available.

Calcium channel blockade: studies continue to show neuro-protection by calcium blockers active at several calcium channel subtypes. Failures in other studies may be explained by the relative importance of the N, Q and P subtypes of voltage-gated calcium channels in neuronal injury, because they may be relatively resistant to block by common calcium-blocking agents. The use of prophylactic nimodipine in aneurysmal sub-arachnoid haemorrhage is one of the few clinically neuroprotective interventions that has been successful, with reductions in morbidity and improvements in outcome.

Hypothermia: several reports document continued experimental success with mild hypothermic neuroprotection. It causes metabolic suppression above 30°C, but other mechanisms are also important. Mild-to-moderate hypothermia (≥ 28°C) can reduce excitatory amino acid release, nitric oxide production, cytokine responses, adhesion molecule expression, neutrophil infiltration, arachidonate release and production of free radicals. The effects of hypothermia result in better preservation of the blood–brain barrier, reduced intracranial hypertension, preservation of cytoskeletal integrity, a lower frequency of spreading depolarization and modulation of gene expression.

Clinical hypothermia – the ischaemic brain tends to be warmer than systemic temperature, and this finding has been confirmed in clinical head injury and stroke. Use of an extracorporeal heat exchanger has been described for rapid cooling following brain trauma, but forced convective cooling seems to be the best means of inducing hypothermia in patients. Pharmacological methods of temperature reduction have non-sustained effects. Selective cooling of the brain during retrograde perfusion in hypothermic circulatory arrest for major cardiovascular surgery may enhance cerebral hypothermia and give added protection while reducing systemic risks.

A series of pilot studies in 1993 suggested significant benefit from induced hypothermia in patients with closed head injury, and formed the basis of an NIH multicentre trial of nearly 400 patients using mild hypothermia (33°C for 48 hours) following head trauma. The initial results were encouraging, but the final results suggest that hypothermia is ineffective in this setting. This is disappointing because many of the expected mechanistic effects of mild hypothermia have been documented in clinical disease. One explanation for this discordance is that hypothermia worsens outcome in patients with head injuries without intracranial hypertension, suggesting that the risk to benefit ratio from hypothermia is maximal in patients with refractory intracranial hypertension in whom the benefits are maximal. A more recent case-controlled pilot study suggests that mild hypothermia (33°C for 12 hours) may improve outcome in patients who experienced cardiac arrest out of hospital.

Miscellaneous and emerging neuroprotective targets
Calpain is a protease implicated in several events in the injury cascade. The potent calpain inhibitor MDL 28,170, rapidly penetrates the brain, prevents cleavage of structural and regulatory proteins and produces significant neuroprotection with therapy initiated up to 6 hours after the onset of ischaemia.

Immunophilins – the immunosuppressant drugs cyclo-sporin A and FK506 bind to specific receptors in the brain and inhibit calcineurin and nitric oxide synthase, modulate neurotransmitter release and cytosolic calcium increases, and mediate nerve growth and regeneration following ischaemia. They are beneficial in ischaemia models.

Caspases are a family of cysteine aspartate proteases (including interleukin converting enzyme (ICE) and CPP32 or caspase 3) involved in apoptotic neuronal death. Their inhibition has been associated with neuroprotection in transient focal ischaemia.

Poly (ADP-ribose) polymerase (PARP) is an abundant nuclear enzyme activated as a DNA repair mechanism by DNA nicks that are typically mediated by oxidant or nitric oxide. PARP transfers ADP monomers from NAD^+ and depletes cellular adenine nucleotide and hence ATP stores when the demand and supply balance of cellular energy is critical. Inhibition or genetic inactivation of the enzyme is neuroprotective.

Matrix metalloproteases are upregulated in a variety of experimental brain injury models, and result in damage to the extracellular matrix with disruption of the blood–brain barrier following ischaemia. Matrix metalloprotease inhibitors can reduce peri-haemorrhagic oedema formation and neuronal injury in ischaemia models.

Adenosine may have neuroprotective effects at A_1 receptors by modulating glutamate-induced rises in cytosolic calcium. Adenosine may also improve microvascular flow, inhibit platelet aggregation, reduce inflammatory responses, and at low concentrations may protect against apoptosis. Adenosine is thought to play a role in ischaemic preconditioning, and exogenous adenosine agonists may potentiate the neuroprotective effects of transient brief ischaemia. The synergistic effects of aspirin and dipyridamole in stroke prevention may be at least partly due to dipyridamole acting as an adenosine reuptake inhibitor.

Neural repair, regeneration and gene therapy – neurotrophins and neural transplantation have been used extensively in neuronal culture preparations, in animal models of ischaemia, Parkinson's and Huntingdon's disease, and these interventions are now being clinically tested for Parkinson's and Huntingdon's disease. Epidermal growth factor, brain-derived neurotrophic factor, nerve growth factor and hepatocyte growth factor all improve neuronal survival or behavioural outcome following experimental ischaemia or trauma. Published clinical trials of neurotrophic therapy have been disappointing, and there are no clinical data addressing the use of these substances in acute neuro-protection. Grafting neural cell lines into ischaemia lesioned brains has improved behavioural outcome, and temporar gene transfer for therapy may be feasible in acute brain injury.

Failure of clinical neuroprotection

For most neuroprotective agents, the translation of experimental success into clinical benefit has been disappointing. Clinical trials that have recently been halted or shown no benefit are listed in Figure 3. Figure 4 lists possible reasons for the failures.

Results from clinical outcome studies of neuroprotective agents

Mechanism of action	Agent	Outcome data
Non-competitive NMDA blocker	Aptiganel	Studies in stroke and acute head injury terminated at interim analysis due to lack of benefit
	Magnesium	No benefit in in-hospital cardiac arrest
Competitive NMDA blocker of benefit	Selfotel	Stroke study halted by steering group due to lack
NMDA polyamine site antagonist	Eliprodil	Stroke study halted by pharmaceutical sponsor
GABA agonist	Chlormethiazole	No benefit in acute stroke within 12 hours in study population Possible benefit in large strokes
Anti-ICAM-1 antibody	Enlimomab	No benefit in acute stroke
Antioxidants	Ebselen	No benefit in stroke on intention-to-treat basis Possible subgroup efficacy
	High-dose tirilazad	Stroke study stopped after 126 patients: no significant benefit
Poorly defined	Lubeluzole	Multinational study showed no benefit in acute stroke within 6 hours
	Piracetam	No benefit with therapy within 12 hours Post hoc analysis suggests benefit with early treatment Possible neuroprotective benefit in cardiopulmonary bypass
	Citicholine	No benefit on intention-to-treat basis Possible subgroup efficacy

GABA, γ-aminobutyric acid; ICAM-1, intercellular adhesion molecule; NMDA, *N*-methyl-D-aspartate.

3

Possible causes of failure of clinical neuroprotection trials

- Experimental demonstration of neuroprotection incomplete (functional end-points?)
- Inappropriate agent: mechanism of action not relevant in humans
- Inappropriate dose of agent (plasma levels suboptimal either globally or in subgroups)
- Poor brain penetration by agent
- Efficacy limited by side-effects that worsen outcome (e.g. hypotension)
- Inappropriate timing: mechanism of action not active at time of administration
- Inappropriate or inadequate duration of therapy
- Study population too sick to benefit
- Study population too heterogeneous: efficacy only in an unidentifiable subgroup[1]
- Study cohort too small to remove effect of confounding factors
- Failure of randomization to distribute confounding factors equally[1]
- Insensitive, inadequate or poorly implemented outcome measures[1]

[1]May benefit from small mechanistic studies in homogeneous, well characterized, clinical subgroups.

4

The future

The success of experimental neuroprotection is undeniable and several publications have explored exciting new therapeutic targets. However, the challenge facing clinical neuroscientists is the failure to translate these successes into positive results from outcome trials. Two approaches have been suggested for overcoming the problems of patient heterogeneity and lack of sensitivity of outcome measures. The first is to accept that these problems are unavoidable and mount larger outcome trials of 10,000–20,000 patients which will address benefits of a magnitude less than the 10% improvement in outcome that most drug trials are designed to detect. The alternative is to mount smaller, more detailed, studies in homogeneous subgroups of patients whose physiology is characterized by modern monitoring and imaging techniques. Repeated application of these techniques during the course of a trial can provide evidence of reversal of pathophysiology and hence mechanistic efficacy. Such surrogate end-points could be used to select drugs or combinations of drugs for larger outcome trials. ◆

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Critical Care Management of Head Injury

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Head injuries account for up to half of all trauma-related deaths and often cause severe functional impairment in survivors. The in-patient case fatality rate varies widely between centres with mortality ranging from 15 to over 50%. Good outcome, defined as a Glasgow outcome scale (Figure 1) of 1 or 2, varies from less than 50% to nearly 70%. Few of the interventions used by specialist centres in severe head injury have been subject to prospective, randomized clinical trials. Recommendations for their use are based largely on clinical experience.

Glasgow outcome scale

1 Good recovery
- Resumption of normal life
- Minor neurological or psychological deficits may persist

2 Moderate disability
- Able to travel independently, work in sheltered environment or at reduced level to that before injury
- May have deficits in speech and memory and personality change

3 Severe disability
- Usually dependent in activities of daily living and institutionalized
- May live at home with large amount of support
- Unable to work even in sheltered environment

4 Persistent vegetative state
- Eyes open, sleep–wake cycles
- No speech, communication or response to external stimuli

5 Death

Timing of assessment should be stated.

1

Determinants of outcome: cerebral injury from trauma can be divided into primary and secondary types. Primary injuries result from mechanical disruption of brain tissue occurring at the time of the initial trauma. Secondary insults occur in the period following the initial injury and can be related to outcome (Figure 2). The severity of secondary insults has an additive effect on outcome. Management of head injury in the critical care unit aims to avoid, detect and treat secondary injuries. It is important to emphasize the role of rapid resuscitation and appropriate transfer of such patients to neurological critical care units.

Effects of physiological insults following head injury on mortality and neurological outcome

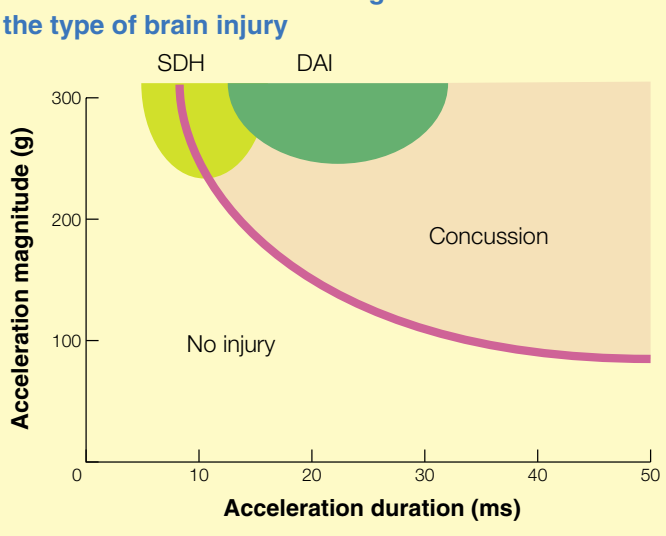
Insult	Mortality	Grades within Glasgow outcome score
Duration of hypotension (systolic blood pressure ≤ 90 mm Hg)	Yes	Yes
Duration of hypoxia (SaO_2 ≤ 90%)	Yes	No
Duration of pyrexia (core temperature > 38°C)	Yes	No
Intracranial hypertension (intracranial pressure > 30 mm Hg)	Yes	No
Cerebral perfusion pressure (< 50 mm Hg)	Yes	No

2

Pathophysiology of acute head injury

Macroscopic and microscopic changes: the severity and type of impact affects the structural changes that occur following head injury (Figure 3). Acceleration and deceleration forces can produce axonal injury, brain contusions and intracranial haematomas. Microscopic injury includes ischaemia, astrocyte swelling with microvascular compromise, disruption of the blood–brain barrier and recruitment of inflammatory cells.

Effect of the duration and magnitude of forces on the type of brain injury



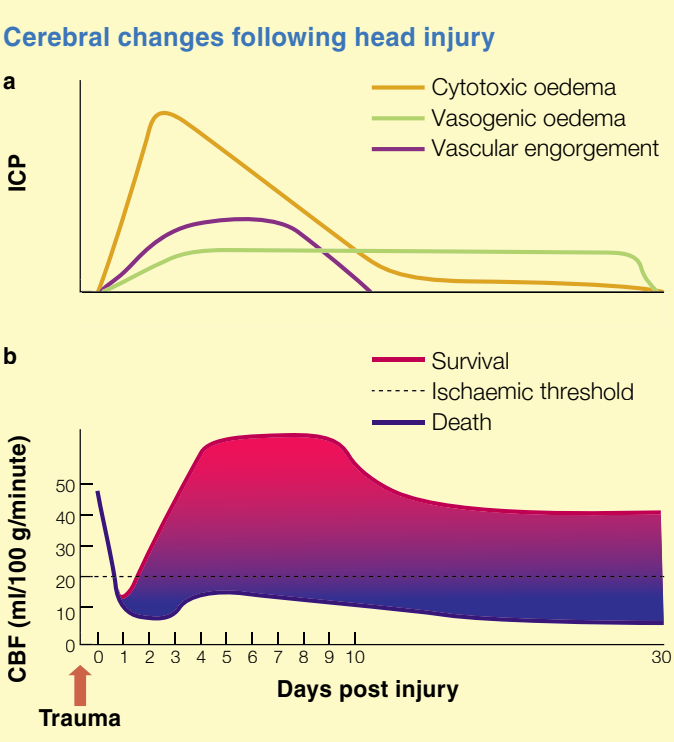
DAI, diffuse axonal injury; SDH, subdural haemorrhage.

3

Cerebral haemodynamics and intracranial pressure: cerebral blood flow (CBF) shows a triphasic response following head injury (Figure 4). In the first 12 hours, global blood flow is reduced, the magnitude being directly related to the severity of the injury. Between 12 and 24 hours, CBF increases and the brain may exhibit supranormal CBF, which is often described as hyperaemia, but may be coupled to hypermetabolism in many patients. CBF begins to fall again several days after injury. In some patients, the fall in CBF may be associated with significant increases in large vessel flow velocity suggesting vasospasm.

Apart from intracranial haematomas, elevation of intracranial pressure (ICP) in the early phase following head injury is usually a result of cytotoxic oedema. From the second day, elevations of CBF and cerebral blood volume make vascular engorgement an important contributor to raised ICP. The blood–brain barrier becomes leaky between days 2–5 post injury and vasogenic oedema then contributes to raised ICP (Figure 4).

Cerebral changes following head injury



Temporal patterns of **a** mechanisms responsible for intracranial pressure (ICP) elevation and **b** cerebral blood flow (CBF) changes following head injury. (Modified from Bullock R, Chesnut R M, Clifton G *et al.* Guidelines for the Management of Severe Head Injury. *J Neurotrauma* 1996; **13:** 643–734)

4

Secondary neuronal injury: several mechanisms have been implicated in secondary neuronal injury including excitatory amino acid release, intracellular calcium overload, free-radical mediated injury and activation of inflammatory processes. Production of pro-inflammatory cytokines with upregulation of adhesion molecules leads to early neutrophil influx and later recruitment of lymphocytes and macrophages. Mononuclear cells may contribute to a prolonged inflammatory response associated with amyloid deposition. Head injury is a risk factor for the deposition of amyloid in the brain and for Alzheimer's disease.

Genetic influences: polymorphism of the apolipoprotein-E (ApoE) genotype directly affects outcome from severe head injury. Possession of the ApoEε4 genotype confers an increased risk of poor outcome. Identification of further genetic markers of outcome may allow targeted neuroprotection strategies.

Management of severe head injury

There is no universally accepted treatment algorithm for patients with severe brain injury but that used at the authors' hospital is given in Figure 5. Widespread variations in practice have led to the recent production of two sets of guidelines from the European Brain Injury Consortium, and a collaboration of the Brain Trauma Foundation, the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. Basic physiology supports the benefits of maintaining CBF and oxygenation. Hypotension (systolic blood pressure < 90 mm Hg) and hypoxia (partial pressure of oxygen in arterial blood (PaO_2) < 60 mm Hg (8 kPa)) worsen outcome.

Cerebrovascular autoregulation may be impaired in patients with severe head injuries. CBF is maintained at a cerebral perfusion pressure (CPP = mean arterial pressure – ICP) above 60–70 mm Hg, a figure higher than in healthy subjects. Although there is controversy over appropriate therapeutic targets, most centres aim for a CPP above 70 mm Hg and an ICP less than 20 mm Hg. A CPP below 50 mm Hg is significantly related to increased mortality. ICP is an independent, albeit weaker, determinant of outcome. Elevations in blood glucose and body temperature may also worsen outcome in acute brain injury.

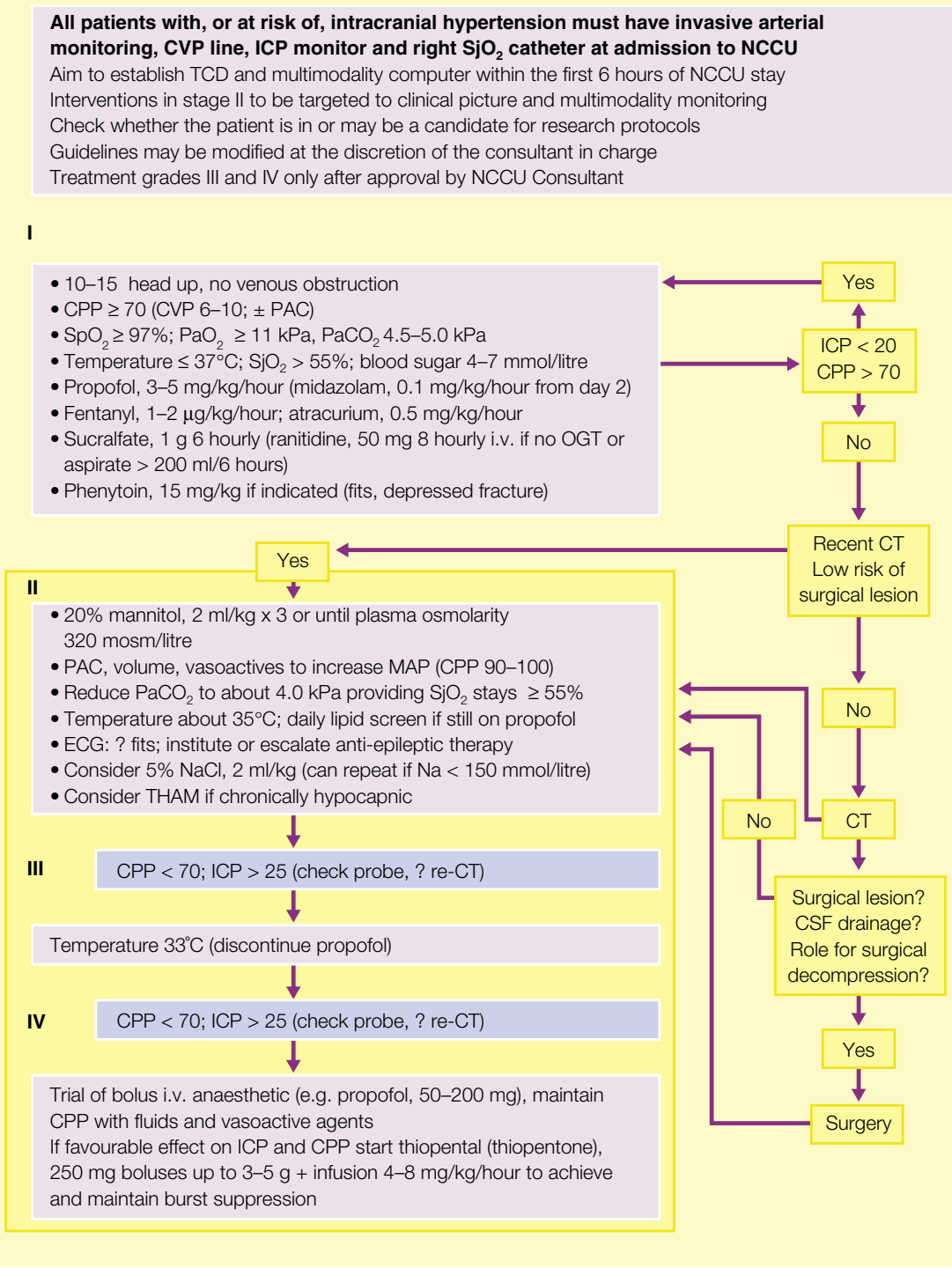
Systemic monitoring: invasive monitoring of arterial blood pressure, continuous pulse oximetry, core temperature monitoring and regular analyses of arterial blood gases and blood glucose are required to optimize physiology. Manipulation of mean arterial pressure may require the placement of central venous or pulmonary artery catheters.

Intracranial pressure monitoring: the need to optimize CPP mandates the need for ICP monitoring. ICP monitoring allows early detection of mass lesions or increasing cerebral oedema in sedated and paralysed patients. The most accurate monitoring method is an intraventricular catheter, but intraparenchymal micromanometers (Codman, USA) or fibre-optic probes (Camino, USA) are increasingly used owing to ease of insertion and lower infection rates. Intraventricular catheters offer the advantage of being able to drain CSF to control ICP. The choice of monitoring technique depends on local preference and expertise.

Other monitoring techniques

Jugular venous oximetry – placement of a catheter high in the jugular bulb allows continuous recording of jugular venous oxygen saturation (SjO_2). SjO_2 varies with the ratio of cerebral oxygen consumption to CBF. Reductions in SjO_2 (< 50%) and increases in SjO_2 (> 75%) may be associated with worse outcomes. The technique averages SjO_2 from the whole brain and may be normal when ischaemia and hyperaemia coexist. SjO_2 monitoring is technically difficult and up to half the episodes of cerebral desaturation may be false-positive results.

Management of intracranial pressure (ICP) and cerebral perfusion pressure (CPP)[1]



[1]Algorithm used in the Neurosciences Critical Care Unit (NCCU), Addenbrooke's Hospital, Cambridge, UK.

Note sequential escalation of therapy and targeting of multiple mechanisms for ICP control.

Abbreviations: CVP, cerebral venous pressure; SjO_2, jugular venous oxygen saturation; PAC, pulmonary artery catheter; SpO_2, oxygen saturation; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; OGT, orogastric tube; MAP, mean arterial pressure; TCD, transcranial Doppler; THAM, Tris (hydroxymethyl) amino methane

Transcranial Doppler (TCD) ultrasound can be used to measure blood flow velocity in major cerebral arteries. The most commonly imaged artery is the middle cerebral artery. Reductions in flow velocity are a useful indicator of reduced intracranial perfusion if ICP is raised. Increased flow velocities may result from either hyperaemia or arterial vasospasm. Vaso-spasm can occur in patients suffering traumatic subarachnoid haemorrhage and increases the incidence of poor neurological outcome. Hyperaemia and vasospasm may be distinguished by relating intracranial velocities to those in the carotid artery in the neck.

Newer techniques – near infra-red spectroscopy, direct tissue oximetry, cerebral microdialysis, xenon-enhanced CT scanning and PET imaging are being investigated in acute head injury.

Basic intensive care

Exclusion of surgically treatable lesions

CT scanning should be used routinely for all patients with severe head injury to exclude any surgically treatable mass lesions. CT scans should be repeated for any new episode of unexpected intracranial hypertension.

Ventilatory support

Patients with a Glasgow Coma Score (GCS) less than 8 require intubation for airway protection. Mechanical ventilation ensures that oxygenation is adequate and that the partial pressure of carbon dioxide (pCO_2) is controlled in the low normal range. The use of hyperventilation to reduce cerebral blood volume and hence ICP is controversial. Even moderate hyperventilation may reduce CBF to ischaemic levels and patients without intracranial hypertension are managed at near-normal partial pressures of carbon dioxide in arterial blood ($PaCO_2$ 4.5–5.0 kPa). Controlled hypocapnia can be used to reduce an elevated ICP, but $PaCO_2$ levels are generally maintained above 4.0 kPa, and cerebral oxygenation monitored using jugular bulb oximetry.

Sedation: intravenous anaesthetic agents decrease CBF, cerebral metabolism and ICP. Autoregulation and the cerebrovascular response to carbon dioxide are preserved. Continuous infusions of propofol or midazolam have largely replaced barbiturates because of their better pharmacokinetic profiles. The lipid load resulting from continuous infusion of propofol should be taken into account when calculating daily calorific intake. The routine use of neuromuscular blockers varies between centres, but they may be useful in preventing the rises in ICP associated with coughing or patient–ventilator asynchrony. Long-term use of neuromuscular blockers (especially the corticosteroid-based agents) has been associated with the development of acute neuromyopathy and prolonged neuromuscular blockade.

Fluid management: fluid replacement in the patient with head injuries should be guided by repeated measurement of volume status. Fluid movement across the intact blood–brain barrier is governed by osmolarity rather than oncotic pressure. As such, hypotonic fluids such as dextrose-containing solutions should be avoided. Residual free water after dextrose metabolism can worsen cerebral oedema and elevated plasma glucose levels are associated with worse outcomes.

Osmotherapy: mannitol, 0.25–1 g/kg, may be used to elevate plasma osmolality and reduce brain oedema when ICP is elevated. Volume status must be measured and plasma osmolality should not be allowed to exceed 320 mosm/litre. Hypertonic saline (5–25%) has also been used to treat intracranial hypertension, and may produce ICP reductions without the large volume shifts that are triggered by mannitol-induced diuresis.

Feeding and stress ulcer prophylaxis: enteral feeding should be established early. Patients with head injuries have high nutritional requirements and the aim should be to replace 140% of resting metabolic expenditure by the seventh day following trauma. Parenteral nutrition should be considered for patients who cannot be fed enterally, but it is associated with a higher incidence of hyperglycaemia. Patients in whom enteral feeding has not or cannot be established should receive stress ulcer prophylaxis with sucralfate or H_2-blockers.

Anti-epileptic therapy: the incidence of post-traumatic seizures is highest in patients with a GCS less than 10 and in those in whom an intracranial haematoma, contusion, penetrating injury or depressed skull fracture is present. Seizure prophylaxis with phenytoin or carbamazepine can reduce the incidence of early post-traumatic epilepsy but has little effect on late seizures, neurological outcome or mortality.

Second-line therapy

Induced hypertension: the rationale for maintaining CPP stems from the finding that CBF is commonly reduced following traumatic brain injury, and that cerebral ischaemia is consistently found on post-mortem examination of fatal head injury. Inadequate CPP may result in ischaemia-induced secondary brain injury. Cerebral vasodilatory responses to CPP reductions increase cerebral blood volume and further increase ICP. The optimum target for CPP is unclear and may vary between patients and in the same patient at different times following injury. Most centres agree on the range 60–70 mm Hg for maintaining CPP. If ICP is increased, mean arterial pressure may be elevated using volume expansion, inotropes and vasopressors. The relative efficiency and safety of these interventions has not been studied.

Therapeutic hypothermia is widely used in cardiac and neurological surgery to protect the brain during cardiac standstill, and reduces elevated ICP. In animal studies, mild- to-moderate hypothermia (33–36°C) has been shown to be neuroprotective in cerebral ischaemia, but the clinical benefit remains unproven in patients who do not have refractory intracranial hypertension. Although early studies of moderate hypothermia in head injury suggested benefit, recent publication of the largest study to date has shown a lack of effect. Mortality and poor neurological outcomes were similar in the hypothermia and the normothermia groups, with patients in the hypothermia group having more hospital days with complications.

Barbiturate coma: intravenous barbiturates have been used to reduce ICP in acute head injury for many years. Although their use may improve ICP when other measures have failed, the effects on outcome are unclear. Barbiturates are administered as a continuous infusion; titrated to produce burst suppression on the EEG. This achieves near-maximal suppression of cerebral metabolism and blood flow. Further increasing the dose of barbiturates may increase complications without therapeutic benefit. The most common side-effect is cardiovascular depression and hypotension. Barbiturates should be used only with appropriate cardiovascular support. The prolonged period required for recovery after barbiturates is another drawback to their use.

Decompressive surgery: drainage of CSF via a ventriculostomy is effective in reducing ICP especially (but not exclusively) in patients with hydrocephalus. Two other surgical options are available for the management of resistant intracranial hypertension, craniectomy and lobectomy. Removing part of the skull allows room for the brain to swell. Although ICP usually falls acutely, the pressure may rise over time as swelling continues. Lobectomy of either the non-dominant temporal or frontal lobe also reduces ICP. These techniques have not been subject to a prospective, randomized, controlled study. The decision to perform decompressive surgery lies with the individual neurosurgeon.

Brain volume regulation (Lund therapy) is based on concepts that are contrary to many conventional beliefs regarding the management of intracranial hypertension, and focuses on the prevention and control of cerebral oedema rather than CPP. Transcapillary filtration is controlled by using clonidine and metoprolol to reduce mean arterial pressure. Cerebral blood volume is reduced using a combination of low-dose thiopental (thiopentone) as a sedative, and dihydroergotamine to constrict large veins. Normal colloid oncotic pressure is maintained by infusion of albumin or plasma. Neurological outcome is favourable, but a randomized, controlled trial is awaited.

Investigational neuroprotective agents

Calcium channel blockers – nimodipine has been used successfully for the treatment of vasospasm associated with primary subarachnoid haemorrhage. Trials in traumatic subarachnoid haemorrhage are inconclusive.

Corticosteroids – although the use of early high-dose methylprednisolone is of benefit in traumatic spinal cord injury, the use of corticosteroids in acute head injury is controversial. The use of high-dose, short-duration methylprednisolone therapy is the subject of an ultra-large, randomized, controlled trial, the Corticosteroid Randomization After Significant Head injury (CRASH) trial.

Excitatory amino acid antagonists have a role in experimental head injury and antagonists of their action can afford neuroprotection. However, they have not been effective in outcome trials.

Antioxidants – animal studies suggest that free radicals play a prominent role in head injury and that this may be ameliorated by the use of antioxidants. Two antioxidants (pergorgotein and tirilazad) have been studied in large scale, human trials but have demonstrated no improvement in clinical outcome. ◆

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General Principles of Neurosurgical Postoperative Care

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The postoperative period can be critical for neurosurgical patients, who may present with intracranial hypertension, altered sensorium and/or depressed airway reflexes. The deterioration in physiological homeostasis produced by anaesthesia and surgery poses additional risks. Failure to detect and correct alterations in systemic and cerebral physiology rapidly can result in irretrievable neurological damage. The main groups of neurosurgical patients requiring intensive or high dependency care following neurosurgery are listed in Figure 1.

Neurosurgical patients requiring postoperative intensive or high dependency care

- Patients with preoperative cardiorespiratory illness
- Long surgery, large blood loss, coagulopathy, incidental hypothermia, unstable haemodynamics
- Patients at risk of, or documented to have, intracranial hypertension
- Patients requiring ventilation to provide stability for venous haemostasis
- Patients requiring or recovering from a period of hypothermia induced for cerebral protection
- Patients requiring postoperative intracranial pressure monitoring
- Requirement for blood pressure manipulation as a part of induced hypertension for cerebral perfusion pressure maintenance or as a part of triple-H therapy
- Induced hypotension for treatment of hyperaemia following carotid surgery or surgery for arteriovenous malformations

1

Monitoring

Clinical assessment is the primary form of monitoring. Other basic monitoring includes blood pressure, ECG monitoring, pulse oximetery and careful recording of fluid balance.

Arterial blood gases and invasive blood pressure

Arterial access is required in all ventilated patients for the measurement of arterial blood gases. Direct arterial pressure measurement is indicated following neurovascular procedures (clipping of ruptured aneurysms, resection of arteriovenous malformations, and the early postoperative period following carotid endarterectomy) in patients with haemodynamic instability, intracranial hypertension, and those requiring vasoactive agents for blood pressure control.

Central venous pressure (CVP) monitoring and pulmonary artery catheterization
CVP monitoring is needed for patients with large volume losses, cardiac disease, vasoactive infusions, and hypotension or oliguria not readily responsive to fluid challenge. CVP monitoring may also be essential in the patient with pathological polyuria due to diabetes insipidus or the condition of 'cerebral salt wasting' that occurs following subarachnoid haemorrhage. However, the CVP is an indirect measure of intravascular volume status, which is influenced by right heart compliance, pulmonary or right heart disease, intrathoracic pressure and posture. Measurement of pulmonary artery wedge pressure provides a more reliable index of intravascular volume status in the critically ill patient, and the use of thermodilution catheters allows the monitoring of cardiac output and systemic vascular resistance. These data are of particular benefit in patients with concurrent severe cardiorespiratory disease or sepsis. Pulmonary artery catheters are also valuable to guide the use of complex vasoactive interventions as a part of cerebral perfusion pressure augmentation in intracranial hypertension or triple-H therapy (see *Anaesthesia and Intensive Care Medicine* **3:4:** 143) for vasospasm following subarachnoid haemorrhage.

Neurological examination

Changes in conscious level or new focal deficits may provide the first evidence of postoperative intracranial bleeding or cerebral oedema. Neurology should be reviewed with particular regard to the operation performed and preoperative neurological status. Regular observations should include the measurement of pupillary size and reaction, limb power and the Glasgow Coma Score (GCS; see *Anaesthesia and Intensive Care Medicine* **3:4:** 132). Although originally designed to quantify the severity of head injury, the GCS allows wider quantification of neurological dysfunction and facilitates the detection of trends in neurological status. One crucial decision is whether to undertake CT in a patient whose GCS is substantially worse than in the preoperative period. While many decisions are clear-cut, a short period of observation may help in others. Gradual improvement in GCS, absence of new focal neurology and the presence of normally reacting pupils and acceptable haemodynamics suggest residual anaesthetic effects. However, clinical signs of intracranial events may be nonspecific, and it is better to err on the side of over-investigation rather than to miss an early intracranial event.

Intracranial pressure (ICP) monitoring

ICP monitoring should be considered in all patients who have intracranial hypertension or are at risk of developing it. It is particularly indicated in patients who remain sedated and cannot be assessed by regular neurological examination. It is essential to relate ICP measurements to mean arterial pressure (MAP), and to monitor cerebral perfusion pressure (CPP; where CPP = MAP–ICP) continuously, because many therapies to treat neurosurgical patients target ICP or CPP. They include a reduction in cerebral oedema by cerebral dehydration, administration of corticosteroids, hyperventilation, blood pressure control, reduction of CPP, surgical decompression, CSF drainage and hypothermia.

Other monitoring modalities

Transcranial Doppler ultrasound, jugular venous saturation monitoring, and EEG and evoked potential monitoring may be useful in individual patients. Their use is discussed in *Anaesthesia and Intensive Care Medicine* **3:4:** 127.

Investigations

Routine postoperative tests including a full blood count, clotting screen, urea and electrolytes are required after most major neurosurgical procedures, along with arterial blood gases if the patient is ventilated or has a low oxygen saturation. A chest radiograph is indicated if the patient is ventilated, a central line has been inserted or gas exchange is abnormal. Imaging of the CNS should be undertaken if there is deterioration in the patient's neurological state or a rise in ICP.

ICU management

Airway and ventilation

Inability to protect or maintain the airway or maintain acceptable blood gases mandates intubation and ventilation. Airway protection should also be considered in patients with a GCS of 8 or less, haemodynamic instability, inadvertent post-operative hypothermia, sepsis or those who require controlled hyperventilation in order to reduce ICP.

While conventional ventilation strategies are generally applicable to neurosurgical patients, some specific issues need attention. It is important to maintain partial pressure of carbon dioxide in arterial blood ($PaCO_2$) within tight limits (the author uses an initial target value of 4.5–5 kPa), because even mild hypercapnia can result in cerebral vasodilatation and a rise in ICP. Conversely, profound hypocapnia may result in dangerous cerebral vasoconstriction and ischaemia. Central ventilatory drive may be compromised by drugs or disease, therefore the use of ventilatory modes that do not assure a near constant minute volume (e.g. pure pressure support ventilation) may be inappropriate. Similarly, while mild arterial desaturation (SaO_2 < 90%) is often well tolerated by non-neurosurgical patients, the resulting hypoxic cerebral vasodilatation can markedly increase ICP in a non-compliant brain.

Haemodynamic management

Intraoperative blood loss can be difficult to estimate, and the pulse rate, blood pressure, urine output and CVP provide a guide to the patient's haemodynamic state. Blood or colloid replacement should be guided by these modalities in conjunction with the haematocrit. Fluid and electrolyte balance must be monitored closely with regular assessment of blood gases, urea and electrolytes. Glucose-containing solutions should be withheld from neurosurgical patients at risk of cerebral oedema or ischaemia, because the residual free water after glucose is metabolized reduces plasma osmolality and accelerates cerebral oedema formation; also, increases in blood sugar can worsen outcome in the ischaemic brain. Prompt normalization of coagulation and platelet levels is essential in patients who have undergone intracranial procedures.

Analgesia, sedation and muscle relaxation

Postoperative pain after brain surgery is an important clinical problem. Pain most often occurs within the first 48 hours after surgery but a significant number of patients endure pain for longer. The subtemporal and suboccipital surgical routes result in the highest incidence of postoperative pain. Appropriate analgesia for spontaneously breathing patients includes codeine phosphate, 30–60 mg up to 6 hourly i.m./p.o./n.g., paracetamol, 1 g 6 hourly p.o./n.g./p.r., and/or diclofenac, up to 150 mg/day (if the patient has no bleeding problem or renal insufficiency). Traditionally, powerful opiates have not been used in patients undergoing cranial surgery, but there is increasing recognition that some of these patients may be in significant pain, and many centres are now beginning to use small doses of intravenous opiates in selected patients with careful monitoring of CNS state. Parenteral opiates, preferably using a patient-controlled analgesia system, are widely used following spinal surgery where changes in the level of sedation are not a critical part of postoperative monitoring. Patients undergoing simple discetomies often do not require strong opiates for postoperative analgesia.

Sedatives are used to decrease anxiety and diminish awareness of noxious stimuli in ventilated patients. Propofol, 1–5 mg/kg/hour, is appropriate for short periods of sedation, while longer periods of ventilation may be facilitated by midazolam. Prolonged or high-dose propofol use presents problems of cost, cardiovascular depression and lipid loading. Low-dose fentanyl, 1–2 μg/kg/hour, is commonly used, but there may be a role for shorter acting opioids (e.g. alfentanil, remifentanil) which facilitate rapid recovery and weaning from ventilatory support.

Neuromuscular blockade is sometimes required to facilitate ventilation and prevent increases in ICP. Prolonged neuromuscular blockade and myoneuropathy are most commonly reported with the long-acting or steroid-based neuromuscular blockers, therefore atracurium is commonly used if paralysis is indicated.

Complications specific to neurosurgical operations

Management of raised ICP

Intracranial hypertension is multifactorial and may result from hydrocephalus, vascular congestion and/or cerebral oedema. A patent airway, adequate oxygenation and mild hyperventilation, along with maintenance of an adequate CPP, provide the foundation of care in such patients. There is no role for fluid restriction in patients with raised ICP, because cerebral hypoperfusion will worsen cerebral ischaemia and cause further increases in ICP by promoting cerebral vasodilatation. Reduction in vasogenic oedema can be achieved using osmotic agents. Both 20% mannitol, 5 ml/kg, and 5% hypertonic saline, 2 ml/kg, are effective, and may improve cerebral perfusion via micro-circulatory and rheological effects. Furosemide (frusemide) can be used as an adjunct.

Corticosteroids are effective in reducing vasogenic oedema associated with mass lesions (e.g. intracerebral tumour or haematoma). The ICP effects of corticosteroids require many hours to become apparent and they are ineffective (and possibly detrimental) in brain trauma and ischaemic stroke.

Hypocapnia causes cerebral vasoconstriction and reduces cerebral blood volume, thereby reducing brain bulk and ICP. Aggressive hyperventilation should be avoided, because there is a danger of severe vasoconstriction with resultant ischaemia. Mild-to-moderate hyperventilation ($PaCO_2$ of about 4.5 kPa) may be relatively safe, but is best used with the safeguard of jugular bulb oximetry, which provides a warning against cerebral ischaemia.

Changes in CVP can have a marked influence on ICP. Flexion or torsion of the neck can obstruct cerebral venous outflow and increase brain bulk and ICP. Application of positive end-expiratory pressure (PEEP) or other ventilatory patterns that increase intrathoracic pressure can theoretically increase ICP, but seldom do so in practice, because CVP dictates ICP only when ICP is less than CVP. There is no reason to withhold PEEP if it is required to optimize gas exchange. Muscle relaxation and sedation can indirectly reduce elevated ICP by decreasing mean intrathoracic pressure and spikes in pressure caused by coughing.

It is generally accepted that reducing brain temperature lowers metabolism, cerebral blood flow, cerebral blood volume and CSF secretion with resultant reductions in ICP. However, there is debate as to whether hypothermia may be neuroprotective in the absence of intracranial hypertension. There is no doubt that elevations in body temperature are injurious to the ischaemic or traumatized brain, and aggressive treatment of pyrexia is essential in neurosurgical patients.

In the event of intractable intracranial hypertension with preserved electrical activity on EEG, the use of high-dose intravenous anaesthetics such as thiopental (thiopentone), titrated to burst suppression, may reduce metabolic needs and result in cerebral vasoconstriction and ICP reduction.

Intracranial hypertension can be reduced by CSF drainage, especially (but not exclusively) in the presence of hydrocephalus. External ventriculostomy allows controlled drainage of CSF and permits catheter flushing in the event of blockage, but it is associated with a significant risk of infection, and microbiological surveillance is mandatory. Surgical removal of intracranial tissue or masses reduces ICP, and can reduce shifts in brain tissue that are associated with herniation and/or focal neurological dysfunction. Intractable intracranial hypertension may respond to decompressive craniectomy.

Intracranial bleeding
Awake patients may suffer reductions in GCS and/or focal neurological deficits related to the site of bleeding. In sedated patients, ICP monitoring may provide an early indication of postoperative intracranial haemorrhage, which should prompt early CT scanning for confirmation.

Seizures
Prolonged seizure activity produces irreversible cerebral damage, independent of any accompanying hypoxia and acidosis, as a result of the excessive metabolic demands and energy depletion in continuously firing neurons. Cerebral oedema and lactic acid accumulation ensue. Intravenous benzodiazepines are commonly used as initial treatment for seizure control, followed by phenytoin (intravenous loading dose 15 mg/kg over 1 hour, with maintenance at 3–4 mg/kg/day) because it does not cause significant depression of the conscious level.

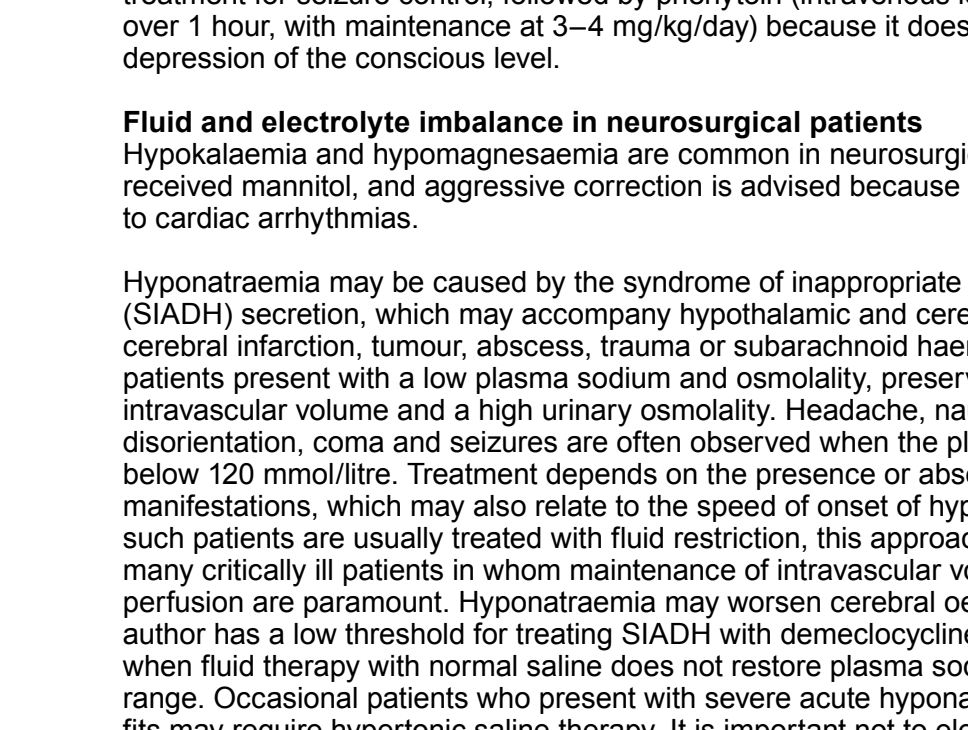
Fluid and electrolyte imbalance in neurosurgical patients
Hypokalaemia and hypomagnesaemia are common in neurosurgical patients who have received mannitol, and aggressive correction is advised because they may predispose to cardiac arrhythmias.

Hyponatraemia may be caused by the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, which may accompany hypothalamic and cerebral lesions, including cerebral infarction, tumour, abscess, trauma or subarachnoid haemorrhage. Such patients present with a low plasma sodium and osmolality, preserved or expanded intravascular volume and a high urinary osmolality. Headache, nausea, confusion, disorientation, coma and seizures are often observed when the plasma sodium falls below 120 mmol/litre. Treatment depends on the presence or absence of clinical manifestations, which may also relate to the speed of onset of hyponatraemia. While such patients are usually treated with fluid restriction, this approach is inappropriate in many critically ill patients in whom maintenance of intravascular volume and cerebral perfusion are paramount. Hyponatraemia may worsen cerebral oedema, therefore the author has a low threshold for treating SIADH with demeclocycline, 300–1200 mg/day, when fluid therapy with normal saline does not restore plasma sodium to the normal range. Occasional patients who present with severe acute hyponatraemia, coma and fits may require hypertonic saline therapy. It is important not to elevate plasma sodium levels too rapidly in patients who have been chronically hyponatraemic, because this may predispose to the development of central pontine myelinolysis. In such patients, plasma sodium should not be raised at a rate greater than 1 mmol/hour or 12 mmol in 24 hours.

Hyponatraemia in other neurosurgical patients, especially following subarachnoid haemorrhage, may be the consequence of ‘cerebral salt wasting’. Such patients present with a low plasma sodium and high urinary sodium output, and are usually fluid depleted. This syndrome may be the consequence of excessive secretion of brain natriuretic peptide, and is treated with aggressive volume expansion with sodium-containing crystalloid or colloid.

Many neurosurgical conditions including trauma, intracranial hypertension, tumours, subarachnoid haemorrhage and brainstem death can lead to diabetes insipidus. The relative lack or absence of antidiuretic hormone in these patients results in the passage of large volumes of dilute urine (up to 0.5–1 litre/hour) with the rapid development of hypovolaemia, plasma hyperosmolality and hypernatraemia. Diagnosis is made by detecting high plasma osmolality coupled with low urinary osmolality. Treatment is with deamino-D-arginine vasopressin (DDAVP, 1–8 μg boluses, repeated as required) and hypotonic fluids. Mild elevations in plasma sodium should be left untreated, because they may help to minimize vasogenic oedema. Also, the aggressive and rapid reduction of plasma sodium and osmolality in patients who have been chronically hypernatraemic may result in cerebral oedema. Diagnosis of changes in plasma osmolality in neurosurgical patients is facilitated by reference to nomograms that relate plasma and urine osmolality (Figure 2).

Nomogram relating plasma and urine osmolality showing diagnostic categories for different abnormalities



Classically, the syndrome of inappropriate antidiuretic hormone (SIADH) results in concentrated urine with high osmolalities and sodium levels (> 25 mmol/litre) despite hyponatraemia, low plasma osmolality and intravascular volume repletion or expansion. Patients with cerebral salt wasting (CSW) also have high urinary sodium levels (25 mmol/litre), but excrete large urine volumes and are volume depleted. Unlike CSW, fluid restriction in SIADH results in reduction in urinary sodium, but the volume depletion produced by this diagnostic intervention is inappropriate in critically ill patients. These differentiating features may be confounded in critically ill patients by variable volume loading and use of diuretics.

Modified from: Moses A M, Blumenthal S A, Streeten D H. Acid–base and Electrolyte Disorders associated with Endocrine Disease: Pituitary and Thyroid. In: Arief A I, Defronzo R A, eds. *Fluid Electrolyte and Acid-Base Disorders.* New York: Churchill Livingstone, 1985; 851–92.

Intrahospital transfers
Tomographic imaging is commonly needed in the postoperative neurosurgical patient, and for some patients this may involve multiple journeys. Such transfers expose the sick brain to the risk of physiological insults, and careful planning, appropriate monitoring, and the presence of an anaesthetist is essential for patients who are ventilated or haemodynamically compromised. Communication with the imaging department is a priority to prevent delays. Monitoring levels should be similar to those used in the ICU, and should include pulse oximetry, ECG, blood pressure (invasive if arterial line *in situ*), ICP monitoring and capnography. Infusions required on the ICU should continue, including appropriate doses of sedation, analgesia and muscle relaxant. Haemodynamic control in a ventilated patient can be difficult during transfer with periods of hyper- or hypotension. Gentle movement, with carefully timed boluses of sedation can help to minimize this problem. Resuscitative drugs should be carried with the patient. During the time spent in the scanner careful attention must be paid to the patient’s physiological state with particular regard to airway, breathing and circulation. Ideally, the scanning room should have its own piped oxygen and compatible mains electricity supply to avoid the hazards of running out of oxygen or battery power. Any intervention to stabilize the patient must take priority over the scanning procedure. ◆

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Neuromonitoring

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Neuromonitoring has become an important aspect of neuro-anaesthesia and intensive care because it is assumed that the early detection of insults to the brain is possible and can reduce injury. Various monitoring technologies are available, but there is little evidence that their use improves outcome. Although most clinical monitoring is based on sound physiological premises, the absence of such evidence makes the objective choice of best monitoring technique for a particular patient or procedure difficult.

Monitoring cerebral function

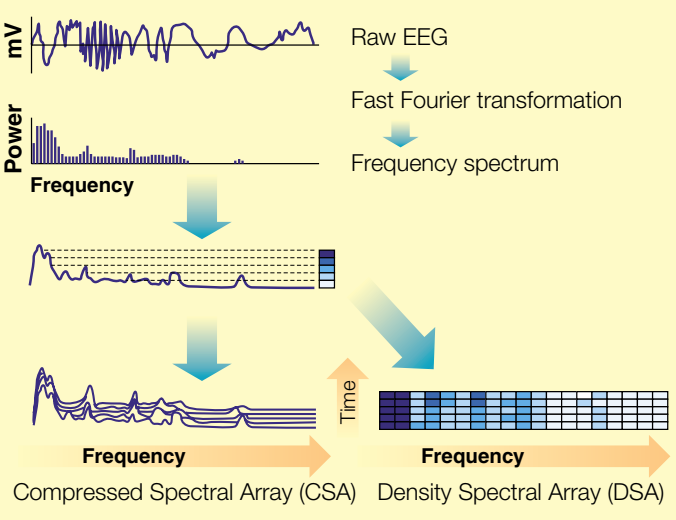
EEG

The EEG signal is predominantly generated by postsynaptic potentials of cortical pyramidal neurons. When neighbouring cells have synchronous changes of these potentials, their current loops are summed in the extracellular fluid, which creates a regional current flow that is large enough to be detected by scalp electrodes (the normal range of EEG amplitude in adults is 10–100 μV). The EEG is therefore predominantly a cortical phenomenon. Magnitude and frequency of the EEG signal are determined by the synchronicity of postsynaptic potentials. Synchronicity is strongly influenced by neuronal circuits connecting the cortex with the thalamus and the brainstem. Higher cortical function is associated typically with desynchronization while anaesthesia and other factors that depress cortical function are associated with increasing synchronicity.

Indications for EEG monitoring in neuroanaesthesia and intensive care include diagnosis and management of seizures, assessment of drug effects (e.g. dose control for EEG burst suppression), making specific diagnoses (e.g. certain types of encephalitis), monitoring for ischaemia during carotid surgery and monitoring depth of anaesthesia.

Processed EEG: a standard EEG consists of an 8–32 channel trace printed on paper at 30 mm/second (or 300 pages/hour) and provides an enormous amount of data, which requires interpretation by a specialist who assesses frequency, amplitude and specific waveform patterns. The standard EEG is not well suited for intraoperative use. Various approaches have been used to summarize such information in a format that can be rapidly understood and allows recognition of trends. The number of tracings is reduced (typically one per hemisphere) and after artefact detection the signal is further processed. The technique most commonly used calculates a spectral array. This calculation results in a set of frequency bins, with the power in each bin representing the magnitude of the signal. Two display methods are popular. The Compressed Spectral Array (CSA) displays a temporal series of frequency versus power histograms in a three-dimensional manner, while the Density Spectral Array (DSA) transforms the power of each frequency bin into a grey-scale intensity and plots this versus time (Figure 1). Both techniques allow display of up to 1 hour of data on a single screen.

Two common methods for transforming EEG data



The CSA and DSA formats can be interpreted easily intraoperatively and allow rapid detection of trends

Bispectral index (BIS): bispectral analysis provides a new approach to computerized EEG analysis. It analyses the frequency and phase angles of the components of a signal and takes into account the interactions of some waves with others. It calculates new summary measures of EEG activity. The BIS, as calculated by a commercially available device (Aspect Medical Systems, Natick, MA, USA), makes use of this approach. Its calculation involves the determination of several ECG descriptors, including information from bispectral analysis. Each of these descriptors performs best in a specific range of anaesthetic effects. The displayed BIS value is the result of a proprietary combination of these descriptors, which has been selected using a database incorporating EEG recordings from thousands of patients undergoing anaesthesia with different anaesthetic regimens and clinical information relating to anaesthetic depth.

The BIS is a dimensionless number ranging from 0 to 100 that gives information on depth of anaesthesia. Using propofol, midazolam or isoflurane, 95% of patients are unconscious at a BIS of 50. However, caution must be used when choosing a single value as a threshold for non-responsiveness or awareness. Many questions remain concerning the effects of various classes of drugs (e.g. anticonvulsants, anxiolytics) or effects of temperature on the BIS. The BIS has not been validated for titrating sedation in the ICU, and its utility in patients with organic CNS disease is unknown.

Evoked potentials

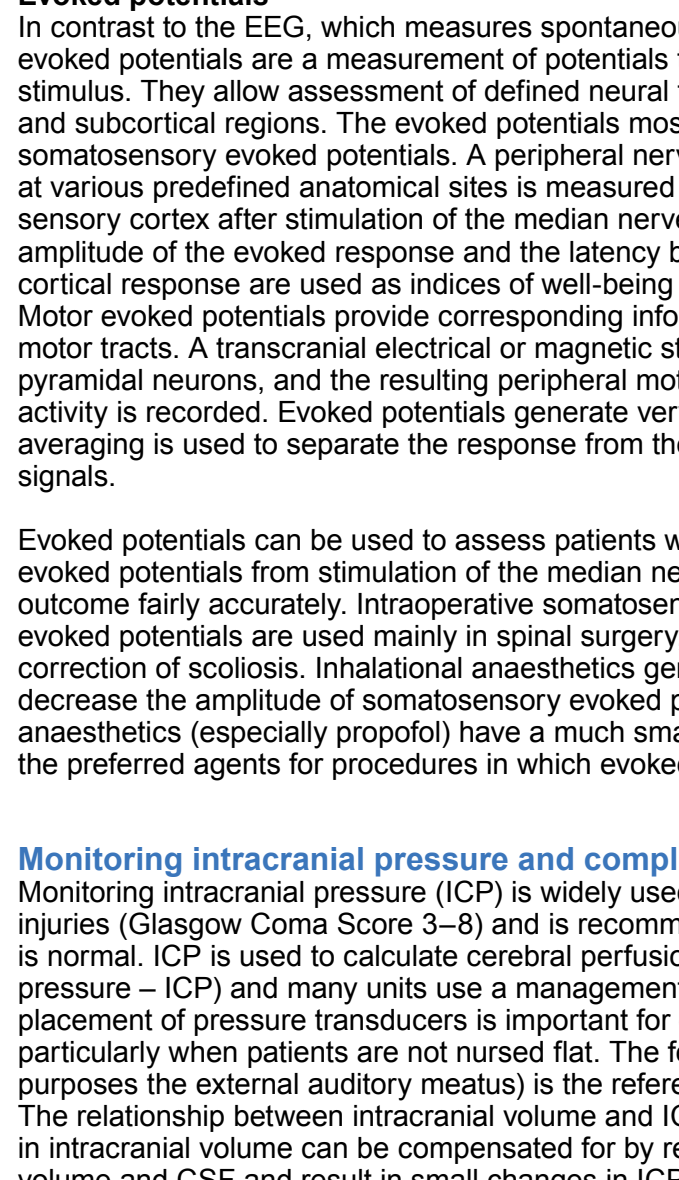
In contrast to the EEG, which measures spontaneous electrical activity of the cortex, evoked potentials are a measurement of potentials that are produced in response to a stimulus. They allow assessment of defined neural tracts including peripheral nerves and subcortical regions. The evoked potentials most often used in anaesthesia are somatosensory evoked potentials. A peripheral nerve is stimulated, and the response at various predefined anatomical sites is measured (e.g. Erb's point, cervical spine, sensory cortex after stimulation of the median nerve at the wrist). Typically, the amplitude of the evoked response and the latency between stimulus application and cortical response are used as indices of well-being of the monitored neural pathways. Motor evoked potentials provide corresponding information regarding the integrity of motor tracts. A transcranial electrical or magnetic stimulus is used to activate cortical pyramidal neurons, and the resulting peripheral motor nerve response or muscle activity is recorded. Evoked potentials generate very small signals (< 10 μV) and signal averaging is used to separate the response from the much stronger EEG and ECG signals.

Evoked potentials can be used to assess patients with head injury. Somatosensory evoked potentials from stimulation of the median nerve can predict unfavourable outcome fairly accurately. Intraoperative somatosensory evoked potentials and motor-evoked potentials are used mainly in spinal surgery, typically during procedures for correction of scoliosis. Inhalational anaesthetics generally increase the latency and decrease the amplitude of somatosensory evoked potentials. Opioids and intravenous anaesthetics (especially propofol) have a much smaller influence on the signals and are the preferred agents for procedures in which evoked potentials are monitored.

Monitoring intracranial pressure and compliance

Monitoring intracranial pressure (ICP) is widely used in patients with severe head injuries (Glasgow Coma Score 3–8) and is recommended even when the CT scan is normal. ICP is used to calculate cerebral perfusion pressure (CPP = mean arterial pressure – ICP) and many units use a management strategy based on CPP. The placement of pressure transducers is important for obtaining a correct value of CPP, particularly when patients are not nursed flat. The foramen of Monroe (or for clinical purposes the external auditory meatus) is the reference point for zeroing transducers. The relationship between intracranial volume and ICP is not linear. Initial increases in intracranial volume can be compensated for by reductions in intracranial blood volume and CSF and result in small changes in ICP, however, with rising ICP these mechanisms are exhausted and small increases in intracerebral volume lead to large rises in ICP (Figure 2a). This is illustrated by the fact that the amplitude of the ICP curve, which is brought about by the small increase in cerebral blood volume that every cardiac contraction causes, is normally in the range of a few mm Hg, but is much larger when the intracranial compliance is reduced. In the presence of reduced intracranial compliance, changes in cerebral blood volume caused by changes in CPP are reflected in ICP (Figure 2b).

Measurement of intracranial pressure (ICP)



a Intracranial pressure–volume relationship. Initially, increases in intracerebral volume can be compensated and small changes in ICP ensue (A), after exhaustion of these mechanisms (B) small changes in volume lead to a massive increase in ICP.
b Relationship between cerebral perfusion pressure (CPP), vasodilatation or vasoconstriction, cerebral blood volume (CBV) and ICP. This sequence of events is only observed when cerebrovascular pressure autoregulation is intact and intracranial compliance is reduced.

The gold standard in ICP monitoring is the direct measurement of intraventricular fluid pressure via a catheter inserted into one of the lateral ventricles. In addition to monitoring pressure, these catheters allow withdrawal of CSF to treat raised ICP, however, the infection rate is up to 10%. The best alternatives to the ventricular catheter are probes that use a miniature strain gauge pressure sensor mounted at the tip of a thin catheter (change of ICP results in a change in resistance) or a fibre-optic catheter (change of ICP results in a change of reflection of the light beam). These catheters are inserted into the brain parenchyma and have a low infection rate. Their main problem is a small drift of the zero line. It is important to realize that an intraparenchymal reading probe reflects a local value and that ICP is not necessarily uniform within the skull; significant pressure gradients may exist in patients with intracranial hypertension (e.g. supratentorial measurements do not necessarily reflect infratentorial pressure). When it is impossible to insert an ICP monitoring device (e.g. because of severe coagulopathy) it is possible to estimate CPP from a transcranial Doppler examination. Pressure measured in the lumbar CSF space is not a reliable estimate of ICP, and such measurements may be dangerous in patients with space-occupying lesions.

A recent development is the Spiegelberg Compliance Monitor. It uses an intraventricular catheter with an air-filled pouch at its tip. By repetitively injecting small volumes of air into this pouch and measuring the pressure response, the cranio-spinal compliance can be calculated. Whether this information improves the management of patients with head injuries is unknown.

Monitoring cerebral blood flow and metabolism

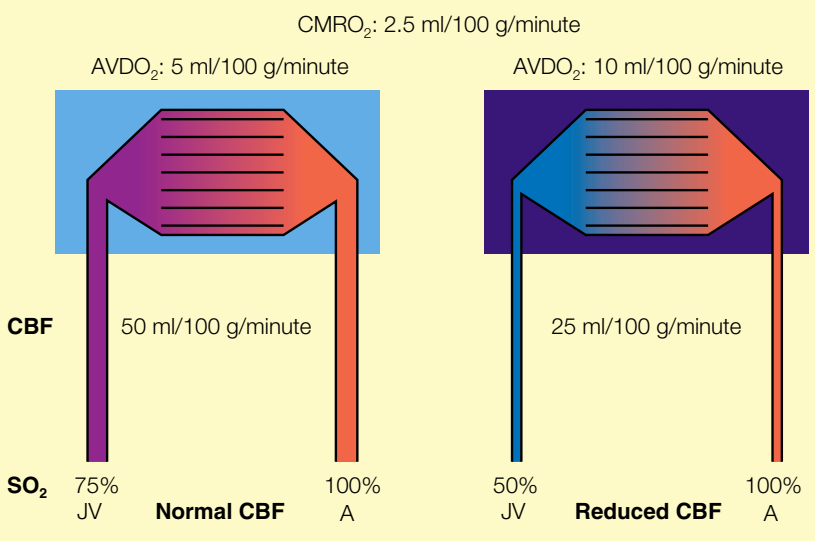
Inadequately low cerebral blood flow (CBF) significantly contributes to the occurrence of (secondary) brain insults. This suggests that monitoring CBF would detect and prevent such insults and thus improve treatment and outcome in neurosurgical patients. There is no ideal method of monitoring CBF; most methods produce non-quantitative measurements of physiological variables, which are assumed to be proportional to CBF. Many methods to measure CBF are available, but in most centres they are not routine procedures in patients with brain injuries. The most common approach is to assess the adequacy of CBF using jugular bulb oximetry.

Jugular bulb oximetry

Jugular bulb oximetry provides information about the adequacy of global CBF in relation to metabolic demands. A catheter is inserted into one of the internal jugular veins and advanced upwards into the jugular bulb where blood draining from the hemispheres can be sampled. All methods that rely on blood sampling from one of the jugular bulbs are prone to the influence of asymmetry of cerebral venous drainage. This may introduce an unquantifiable risk of acquiring misleading data and there is no consensus on which side should be cannulated. Generally, the right internal jugular vein is preferred because it is often the dominant vessel. The position of the catheter should be checked radiologically. A catheter tip at the level of the first or second cervical vertebral body lies above the point at which the jugular vein receives its first extracranial tributary (the common facial vein), and samples intracranial venous drainage. Blood can be sampled intermittently or a fibre-optic catheter can be used to determine jugular venous oxygen saturation (SjO_2) continuously. Intermittent sampling can give erroneous results because a certain amount of extracranial blood can be aspirated, especially if the sample is withdrawn too quickly. The fibre-optic technique needs regular recalibration of the sensor to deliver accurate readings and is susceptible to artefact because of suboptimal catheter position inside the vessel. Normal values for SjO_2 are thought to be 55–85%. Low CBF (ischaemia) raises oxygen extraction, increases the arterio-jugular oxygen content difference and leads to lower values for SjO_2, whereas hyperaemia leads to a decrease in arterio-jugular oxygen content difference and high values for SjO_2 (Figure 3). Some centres use SjO_2 to optimize hyperventilation in patients with head injuries, but it has not been demonstrated convincingly that this approach is superior to CPP oriented management, one reason being the low sensitivity of SjO_2 to detect ischaemia.

Use of jugular bulb oximetry

With a normal cerebral blood flow (CBF) of 50 ml/100 g/minute, an arterial (A) oxygen saturation (SO_2) of 100%, and a cerebral metabolic rate for oxygen ($CMRO_2$) of about 2.5 ml/100 g/minute, the extraction of oxygen by the brain results an arterio-venous difference in oxygen content ($AVDO_2$) of 5 ml/dl and a jugular venous (JV) saturation of 75%. In the face of a reduction in CBF (to 25 ml/100 g/minute as shown on the right), the only mechanism by which $CMRO_2$ can be maintained is by increased oxygen extraction, with an increase in $AVDO_2$ and a decrease in jugular bulb saturation. Jugular bulb saturations are therefore an indicator of the adequacy of CBF, with low values (< 50%) in ischaemia, and high values (> 85%) in hyperaemia



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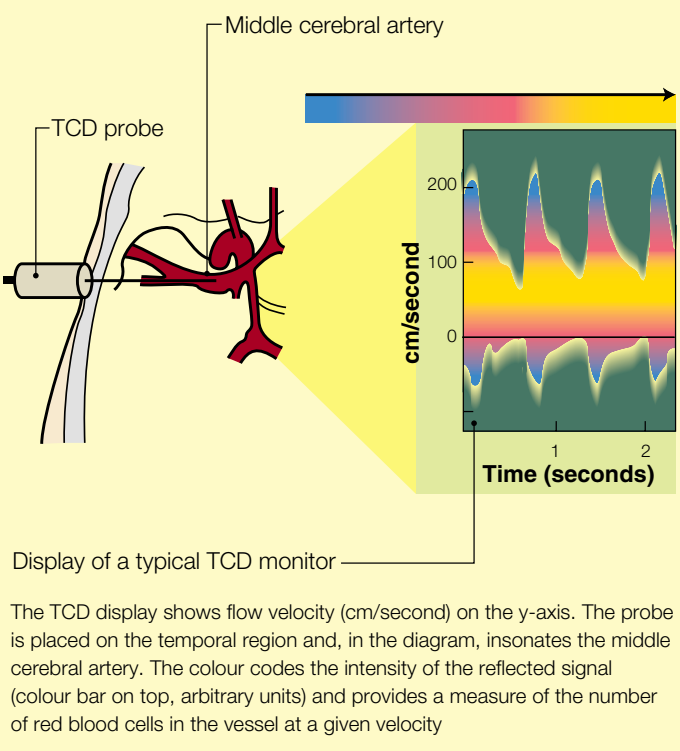
Recently, two techniques for quantitative determination of global CBF at the bedside using jugular bulb catheters have been proposed. One uses continuous jugular thermodilution the other a double-indicator (dye and iced water) method providing non-continuous measurements. The usefulness of both methods is currently being evaluated.

Transcranial Doppler (TCD) ultrasonography

TCD ultrasonography makes use of the fact that the temporal bone can be penetrated by ultrasound and uses the Doppler shift principle to measure blood flow velocity in the basal cerebral arteries (Figure 4). It is easy to use and non-invasive. However, the assumed linear relationship between flow velocity and CBF (CBF ~ FV x area of the insonated vessel x angle of insonation) is present only if the diameter of the insonated vessel does not change during the examination. This assumption is fulfilled for most clinical situations because changes in common physiological variables (e.g. blood pressure, partial pressure of carbon dioxide in arterial blood) do not change the diameter of the investigated vessels significantly. The main disadvantage of TCD is that although continuous measurements are possible they are prone to artefact. TCD is a valuable tool for rapid estimation of CBF and can differentiate vasospasm from hyperaemia, which influences the treatment of patients after subarachnoid haemorrhage or head injury. TCD can be used to assess cerebrovascular autoregulation and vasoreactivity to carbon dioxide, which can give prognostic information about patients with head injuries. Mean flow velocity (the time averaged mean of the signal) is mainly used for interpretation. Further pulsatility of the Doppler wave form is often reported and mainly graded by the (Gosling) pulsatility index, which is calculated as the signal amplitude divided by mean flow velocity. The pulsatility index is not a reliable estimator of cerebrovascular resistance and should be interpreted with caution because it is influenced by many uncontrollable variables (Figure 5).

Transcranial Doppler (TCD) ultrasonography



The TCD display shows flow velocity (cm/second) on the y-axis. The probe is placed on the temporal region and, in the diagram, insonates the middle cerebral artery. The colour codes the intensity of the reflected signal (colour bar on top, arbitrary units) and provides a measure of the number of red blood cells in the vessel at a given velocity

4

Interpretation of transcranial Doppler results

Diagnosis	FVm MCA	FVm ICA	MCA:ICA ratio	Pulsatility
Normal	60–70 cm/s	40–50 cm/s	1.76 ± 0.1	0.7 ± 0.1
Hyperaemia	↑	↑	→	↓
Vasospasm	↑	→	↑	↑↓
ICP↑	→	→	→	↑

FVm, mean flow velocity; ICP, intracranial pressure; MCA, middle cerebral artery. Normal values for FVm MCA are reported over a wide range and influenced by age, gender, haematocrit and metabolic factors. ICA, internal carotid artery. An MCA:ICA ratio (or Lindegaard ratio) > 3 in combination with FVm MCA > 120 cm/second indicates MCA spasm. This ratio has not been validated for vasospasm of the anterior or posterior cerebral artery.

5

Near infrared spectroscopy (NIRS)

NIRS measures changes in the chromophore levels of oxygenated and deoxygenated haemoglobin (i.e. 'cerebral haemoglobin saturation'). It is a non-invasive monitor that is placed on the forehead and allows estimation of relative changes in cerebral oxygenation and blood flow. The main limitation of NIRS is the inability to discriminate between extracranial and intracranial blood flow changes. NIRS is the most controversial method for monitoring the brain. This is reflected in the conflicting results correlating NIRS measurements with other modalities to monitor CBF and cerebral oxygenation.

Thermal diffusion and laser Doppler flowmetry

Measuring microcirculatory blood flow to estimate CBF is an alternative to monitoring CBF. The thermal diffusion probe is inserted through a burr hole and placed on a cortical region of interest. The probe consists of two small metal plates, one of which is heated. Blood flow is calculated from the temperature difference between the plates. Recently an intraparenchymal thermal diffusion probe has been evaluated. Its values of CBF are in good agreement with values obtained by stable xenon CT for a volume of about 5 cm^3 around the probe. Laser Doppler flowmetry allows continuous real-time measurements of local microcirculatory blood flow. However, the sample volume is small (1–2 mm^3) and only relative changes in flow can be assessed.

Partial pressure of oxygen (pO_2) in brain tissue

Recently, intraparenchymal catheters that measure tissue pO_2 and in the case of the *Neurotrend*™ monitor pCO_2, pH and temperature have been introduced. Two methods of measurement are available, one uses a miniature Clark-type electrode, the other uses fibre-optic technology. Normal brain tissue pO_2 is in the range 3.5–4.0 kPa. The role of brain tissue pO_2 monitoring has yet to be defined.

Microdialysis

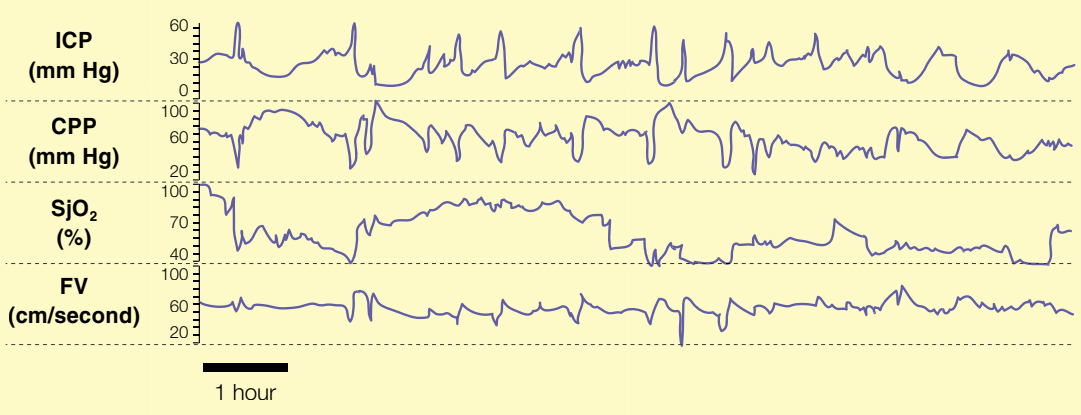
Microdialysis samples extracellular brain fluid. It is based on the transfer of molecules (5–20 kD) over a semipermeable membrane. A thin catheter lined with a dialysis membrane is placed in the brain parenchyma and perfused continuously at a slow rate (0.3–2.0 μl/minute) with a physiological solution. The concentration of glucose, lactate, glutamate, aspartate and other neurotransmitters, drugs and cytokines can be determined in the dialysate. Studies to determine the value of cerebral microdialysis in clinical decision-making are under way.

Multimodality monitoring

Secondary ischaemic insults can be short-lived and may be missed because of limited temporal and spatial resolution as well as the limited sensitivity of monitoring devices. This led to the concept of multimodality monitoring. The combination of several monitors can improve understanding of the continuing pathophysiology and also increases the likelihood of detecting relevant insults (Figure 6). ◆

Multimodality monitoring in a patient with head injury

Values for intracranial pressure (ICP), cerebral perfusion pressure (CPP), jugular bulb oximetry (jugular venous oxygen saturation, SjO_2) and transcranial Doppler (TCD) are integrated. Repetitive waves of raised ICP lead to changes in the recorded parameters, however, insults are not always detected by all modalities. FV, flow velocity (Courtesy of Dr M Czosnyka, Academic Neurosurgery, Addenbrooke's Hospital, Cambridge, UK).



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Neuromuscular Disorders: Relevance to Anaesthesia and Intensive Care

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Guillain-Barré syndrome

Guillain-Barré syndrome is an acute inflammatory poly-neuropathy characterized by a progressive neuropathic weakness and areflexia. The incidence is 1–2/100,000 and affects all age groups. Up to 75% of patients have preceding infection, usually of the upper respiratory tract or gastrointestinal tract. Various bacterial and viral organisms have been implicated, including *Campylobacter jejuni* and *Mycoplasma pneumoniae*.

The mechanism of the disease is unclear, but the association with preceding infection suggests an immune mechanism for the demyelination of peripheral nerves. The presence of circulating antibodies against neural gangliosides supports this view. It is possible that the immune response to the infection generates self-reactive antibodies that mediate the inflammatory demyelination.

Diagnosis

Guillain-Barré syndrome is diagnosed by the presence of:

- progressive weakness of more than one limb (due to neuropathy)
- areflexia
- duration of progression of less than 4 weeks.

Laboratory features include an increase in CSF protein (in 90%) a normal white cell count (in 90%), and an electromyograph suggestive of demyelination and axonal damage. Other supportive diagnostic criteria are presented in the clinical features below. Figure 1 lists the differential diagnoses.

Differential diagnosis of Guillain-Barré syndrome

- Acute myasthenia gravis
- Diabetes mellitus
- Poliomyelitis
- Botulism
- Acute intermittent porphyria
- Polymyositis
- Lead poisoning
- Organophosphate poisoning
- Shellfish poisoning
- Transverse myelitis

1

Clinical features

Guillain-Barré syndrome can present with symmetrical weakness, pain and sensory impairment. The weakness commonly ascends from the legs, with 90% of patients affected maximally at 3–4 weeks. Proximal limb weakness is usually the earliest motor sign. Paraesthesia occurs in 50% of patients, and is often in a 'glove and stocking' distribution. Neuropathic pain (which may be severe) commonly occurs in the back, sides and between the scapulae. The Miller-Fisher syndrome is an atypical variant of the condition characterized by a classical triad of areflexia, ataxia and ophthalmoplegia. About one-third of patients have respiratory muscle weakness requiring positive pressure ventilation. Bulbar weakness often occurs in association with respiratory muscle weakness and predisposes to pulmonary aspiration, which necessitates adequate airway protection.

Autonomic dysfunction occurs in 65% of patients. Sinus tachycardia is the most common manifestation and requires treatment only if severe. Vagal stimulation may precipitate dangerous bradyarrhythmias. Other autonomic features include urinary retention, postural hypotension, sweating and ileus.

Management

The management of patients in ICU involves supportive therapy and specific treatments. Vigilant nursing is essential. Careful, regular turning prevents pressure sores. Passive physiotherapy (and use of limb splints) reduces the risk of tendon contractures. Patients often require long-term ventilation. Tracheostomy should be performed early if prolonged ventilation is likely.

Deep vein thrombosis prophylaxis is mandatory, because thromboembolic complications remain a major cause of morbidity and mortality. All patients should receive prophylactic subcutaneous low molecular weight heparin, and wear thromboembolic disease prevention stockings. Adequate nutritional support can be provided via enteral feeding. If ileus is severe and unresponsive to prokinetic agents such as metoclopramide, parenteral nutrition may be required. Autonomic disturbances such as persistent tachycardia and hypertension should be treated appropriately, usually with β-blockers. Temporary or permanent cardiac pacing may occasionally be indicated for severe episodes of bradycardia. Infection, particularly of the respiratory tract is common, and should be treated promptly and effectively.

Pain is common, and can be particularly distressing at night. Despite sometimes being responsive to simple analgesics, stronger pain relief is often indicated. The constipating effects of opioids should be avoided if possible. Neuropathic pain can be relieved by carbamazepine or amitriptyline.

Specific therapy includes two immunomodulatory interventions: plasma exchange and intravenous immunoglobulin. Plasma exchange is most beneficial if given within 2 weeks of diagnosis and instituted before positive pressure ventilation is required. Typically 200–250 ml/kg of the patient's plasma is exchanged with 4.5% human albumin solution. This exchange is repeated up to five times.

Intravenous immunoglobulin (IvIg) is easier to administer than plasma exchange but is expensive. Patients with autonomic dysfunction or cardiovascular disease may tolerate IvIg better, but it also has adverse effects. Anaphylaxis, aseptic meningitis and renal failure have been reported, and the risks of transfusing a blood product are also present. A recent study has suggested that the combination of IvIg and methylprednisolone may be more effective than IvIg alone. However, despite the clear therapeutic benefit of immunotherapies on reducing length of hospital stay and residual disability, there appears to be no reduction in mortality rate compared with that of untreated patients. Typical mortality for patients with Guillain-Barré syndrome is 5%, and 25% are left with a degree of disability 1 year after the onset of symptoms.

Myasthenia gravis

Myasthenia gravis is a rare disease of the neuromuscular junction, with an incidence of 1/20,000. It is an autoimmune disease characterized by fatiguable muscle weakness resulting from failure of neuromuscular transmission. This is a result of production of IgG antibodies to the postsynaptic membrane (anti-acetylcholine receptor antibodies), which reduce receptor density at the neuromuscular junction. It may be congenital or acquired later in life. It is more common in females, and has a peak incidence in the third decade of life. 3–4% of patients with myasthenia gravis have other autoimmune disease (e.g. thyrotoxicosis, pernicious anaemia, rheumatoid arthritis, systemic lupus erythematosus). Myasthenia gravis is characterized by fluctuating weakness of the muscles of the head, face and neck. Classic presentation is with diplopia and ptosis due to weakness of the ocular muscles. Bulbar weakness may present as dysarthria and dysphagia. Moderate proximal muscle weakness may occur, as may respiratory muscle weakness, especially during exacerbations. Weakness increases with exercise and improves with rest.

Diagnosis is from the history and confirmed by a high titre of receptor antibodies on immunoassay. Diagnosis can also be confirmed clinically by a positive 'Tensilon' (an anticholinesterase) test. Edrophonium (Tensilon) is administered and improved muscle function is observed when compared with administration of placebo. Electromyography studies show decreased amplitude following a single twitch, fade on tetanic stimulation and post-tetanic facilitation.

Management: patients may present to the ICU during a myasthenic crisis, often precipitated by infection, or as a consequence of over-treatment with anticholinesterases, causing a cholinergic crisis. Treatment for myasthenia gravis includes anticholinesterases (pyridostigmine), immunosuppression (corticosteroids, azathioprine, cyclosporin (ciclosporin)), removal of antibodies (plasma exchange) or thymectomy. Thymectomy is indicated in patients with a thymoma, younger patients (< 50 years), and women of child-bearing age (in whom immunosuppressants may be inappropriate).

Anaesthetic considerations

Preoperatively, the ability to swallow should be assessed. Respiratory function should be optimal before surgery, and adequacy of ventilation checked with an arterial blood sample. Plasma exchange may be necessary. A chest radiograph may reveal signs of aspiration, a thymoma with upper mediastinal widening or an anterior mass (lateral film). Anticholinesterase therapy should be reduced by 20% preoperatively, and withdrawn on the day of surgery. Patients are better slightly myasthenic than cholinergic.

Patients with myasthenia gravis are relatively resistant to small doses of suxamethonium, and tend to get a dual (phase II) block with high doses. Conversely, they are extremely sensitive to non-depolarizing neuromuscular blocking drugs, and these should be avoided if possible. Drugs such as atracurium should be administered at one-tenth the normal dose. Spontaneous return of neuromuscular function should be allowed, to avoid clinical confusion caused by the administration of anticholinesterase agents. It is also essential not to exacerbate muscle weakness by avoiding hypokalaemia, aminoglycosides, quinine and ciprofloxacin.

Regional anaesthesia should be used if possible to avoid the use of neuromuscular blocking drugs. Additionally, intubation may also be achieved via deep inhalational anaesthesia and local anaesthetic spray to the vocal cords.

During anaesthesia for thymectomy, it is essential to place intravenous access in a lower limb vein, because there is a risk of damage to the superior vena cava during surgery.

Postoperatively, patients may require ventilation. Anticholinesterases should be restarted, but the initial dose required may be less than the preoperative dose.

Lambert–Eaton myasthenic syndrome

Lambert–Eaton myasthenic syndrome is characterized by severe muscle weakness. It occurs in 1% of patients with bronchial carcinoma. It is also associated with thyroid disease and connective tissue disease, and is mediated by decreased release of acetylcholine from the presynaptic membrane. It can be distinguished from myasthenia gravis because:

- it causes proximal rather than bulbar/ocular weakness
- muscle power increases with exercise
- tendon reflexes are diminished
- there is no fade on tetanic stimulation
- tetanic stimulation increases muscle strength
- the Tensilon test is negative
- muscle pains are common.

Treatment is by removal of the bronchial tumour, or admin-istration of 3,4-diaminopyridine. Patients are sensitive to both depolarizing and non-depolarizing neuromuscular blocking drugs.

Myotonic syndromes

Myotonic syndromes are a group of hereditary diseases characterized by delayed muscle relaxation following contraction. Myotonic dystrophy is the most common, with an incidence of 1/25,000. Inheritance is autosomal dominant with anticipation (increasing severity in successive generations). Males and females are equally affected. Patients typically present between 20 and 40 years with a reduced life expectancy. A characteristic facies is present, with frontal balding, an expressionless face, smooth forehead, ptosis, presenile cataracts and a lateral (or inverted) smile. Masseter and sternocleidomastoid muscle wasting occurs, and bulbar weakness can predispose to aspiration and chest infections. Once muscle wasting develops, tone and reflexes are reduced and foot drop is common. Myotonia is secondary to abnormal closure of sodium/chloride channels following depolarization, leading to repetitive discharge and contraction. It is precipitated by:

- cold
- exercise
- shivering
- pregnancy
- hyperkalaemia
- suxamethonium
- neostigmine.

Associations include a low IQ, gonadal atrophy, diabetes mellitus, dysphagia, constipation, delayed gastric emptying, respiratory muscle failure, obstructive sleep apnoea and thyroid adenoma. Cardiac involvement includes conduction defects, valve defects and cardiomyopathy. There is a progressive worsening of cardiac conduction, with an increasing risk of tachyarrhythmia and sudden death.

Anaesthetic considerations
Cardiorespiratory function must be thoroughly investigated preoperatively, because cardiac pacing may be necessary. Invasive cardiac monitoring may be indicated. Monitoring of body temperature and neuromuscular blockade is essential. Patients are sensitive to all depressant drugs, therefore sedative premedication is avoided. There is also increased sensitivity to induction agents, opioids and non-depolarizing neuromuscular blocking drugs. Suxamethonium may produce a generalized myotonic response rendering laryngoscopy, tracheal intubation and ventilation difficult or impossible. This may not be reduced by subsequent administration of non-depolarizing neuromuscular blocking drugs. If neuromuscular blockade is required, atracurium is the agent of choice, with spontaneous reversal (because neostigmine may precipitate myotonia). Myotonic contraction may also occur with surgical diathermy. Regional anaesthesia can be useful, although the myotonic reflex is not blocked.

Admission to intensive care may be required if there is cardiovascular instability, or if the patient is slow to regain consciousness or adequate neuromuscular function. Swallowing and gastric emptying are often impaired, therefore asymptomatic aspiration is common, necessitating a delay in feeding postoperatively.

Myotonia congenita
Myotonia congenita is less prevalent than myotonic dystrophy, with little systemic involvement and a normal life expectancy. There is generalized muscular hypertrophy and stiffness on initiating movement, which is relieved by exercise. There is no muscle weakness, although the myotonia may be severe. Anaesthetic problems are the same as for myotonic dystrophy, although there is an important association with malignant hyperthermia.

Muscular dystrophies
Muscular dystrophies are a hereditary group of conditions of unknown aetiology, characterized by atrophy of some muscle groups and pseudohypertrophy of others. The most common is Duchenne muscular dystrophy (transmitted as an X-linked recessive condition, occurring in 1/3500 live male births). Symmetrical weakness of the proximal and pelvic muscles is evident from 2 years of age, which progressively worsens, with patients becoming wheelchair bound due to contractures and scoliosis. Cardiorespiratory problems and mental retardation are common. Serum creatine kinase is often elevated from birth and can be 30–300 times the normal value. Death usually occurs before 30 years of age as a result of cardiorespiratory failure.

Anaesthetic considerations
Preoperatively, assessment of cardiorespiratory function by exertion is problematic because effort is limited by the muscular disease and most patients are extremely immobile. Echocardiography is essential and often reveals chamber hypertrophy and mitral valve prolapse (25%). If respiratory function is severely compromised (vital capacity < 20 ml/kg), the risk of death is high. During the perioperative period, physiotherapy is essential and antibiotics are often indicated. There is an increased risk of malignant hyperthermia in these patients, and suitable precautions, including the availability of dantrolene, are recommended. Suxamethonium is additionally contraindicated because of the risks of hyperkalaemia and cardiac arrest. Volatile anaesthetic agents and suxamethonium have both been implicated in precipitating rhabdomyolysis and cardiac arrest. Intravenous anaesthetic agents and opioids appear to be safe. Patients are sensitive to non-depolarizing neuromuscular blocking drugs and they should be used incrementally with appropriate monitoring. There is still a risk of delayed recovery associated with skeletal muscle weakness. Regional anaesthesia should be used if possible, avoiding many of the above complications and providing good postoperative analgesia. High dependency postoperative care is essential, with aggressive physiotherapy and clearance of secretions. Despite all the above precautions, cardiac arrest resistant to resuscitation may occur.

Neuromuscular complications of intensive care
Muscle weakness in critically ill patients is not a result of inactivity, as previously thought, but caused by neuromuscular disorders arising during the ICU stay. It usually presents as a failure to wean patients from the ventilator. Three causes are recognized:
- critical illness polyneuropathy
- prolonged neuromuscular blockade
- necrotizing myopathy.

Motor neuron disease
Motor neuron disease is a group of disorders characterized by a progressive degeneration in motor function, while sensory and higher function remain normal. Males are affected more commonly than females. The diagnosis is made clinically and using EMG studies. No treatment is of any proven benefit. Patients typically present with weakness and wasting of muscle groups with fasciculation. The disease affects smooth, striated and cardiac muscle. Death occurs within 3–5 years of diagnosis.

Anaesthetic problems relate to the increased sensitivity to intravenous induction agents and both depolarizing and non-depolarizing neuromuscular blocking agents. Respiratory muscle involvement is commonplace and must be managed appropriately in the perioperative period. If the brainstem is involved, there is a significant risk of aspiration due to bulbar weakness. ◆

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Neurovascular Anaesthesia and the Management of Ischaemic Stroke

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Neurovascular anaesthesia covers the preoperative resuscitation and optimization, intraoperative management and postoperative neurointensive care of patients with intracranial vascular lesions. This article deals mainly with subarachnoid haemorrhage (SAH) and arteriovenous malformations (AVM) and briefly describes the management of ischaemic stroke.

Regardless of the cause of intracranial haemorrhage, many pathological mechanisms operate to precipitate cerebral ischaemia. Management of intracranial haemorrhage centres around adequate neuroprotection, via maintenance of adequate cerebral blood flow (CBF) and prevention of secondary cerebral ischaemia.

Subarachnoid haemorrhage (SAH)

Cerebral aneurysms account for 75–80% of SAH, cerebral AVM for 4–5%, and in the remaining 15–20%, no source of haemorrhage can be found.

Cerebral aneurysms

Aneurysms arise from vessels of the circle of Willis, usually at a bifurcation. They occur in 2–5% of the population, and are three times more common in women than in men. 90% of aneurysms involve the anterior circulation and 10% the posterior circulation. 20% of patients have multiple aneurysms. SAH accounts for 10% of cerebrovascular disease and has an annual incidence of 15/100,000. It can occur at any age, with a peak incidence between 55 and 60 years of age. Aneurysm formation is more likely in those with hypertension, some genetic and collagen abnormalities and in those who smoke or are pregnant.

Risk of rupture is 0.05–6%. Rupture is often, but not always, related to hypertensive episodes. One-third of patients die before reaching hospital, one-third have a poor outcome and one-third are functional survivors. The main risks facing patients who reach hospital include recurrent haemorrhage, development of delayed ischaemic neurological deficits (vasospasm) and hydrocephalus. For those who survive the initial haemorrhage, the peak risk of re-bleed occurs in the first 48 hours. On the first day of SAH, there is a 4% risk of re-bleeding, which decreases to 1.5% by the third day. By day 14, the cumulative re-bleeding incidence is 19%. Six months after SAH, 50% of patients have re-bled, and the long-term risk stabilizes at 3% per year.

Presentation of SAH

Headache is the presenting symptom in 85–95% of patients. Classically, it is severe and of sudden onset. Other symptoms include loss of consciousness, photophobia, nausea, vomiting, lethargy and neurological deficits. Signs of meningism are also common. Bleeding increases intracranial pressure (ICP), leading to a reduced cerebral perfusion pressure (CPP). A sudden rise in ICP prevents continuing bleeding from the aneurysm site. If ICP subsequently decreases, CBF recovers, allowing function to improve. Non-survivors show no recovery of CBF.

Grading SAH

The severity of SAH is assessed and graded according to the Hunt and Hess classification (Figure 1), or the World Federation of Neurological Surgeons (WFNS) SAH Scale (Figure 2), which uses the Glasgow Coma Scale (GCS). A higher WFNS grade results in worse outcome as a result of increased initial damage, an increased risk of developing intracranial hypertension, reduced CBF autoregulation (Figure 3) and reduced carbon dioxide vasoreactivity (Figure 4). These physiological abnormalities expose the injured brain to ischaemic insults and reduce its ability to cope with them.

Management

Hunt and Hess classification of intracranial aneurysms

Category	Criteria
0	Unruptured aneurysm
I	Asymptomatic or minimal headache and slight nuchal rigidity
II	Moderate to severe headache, nuchal rigidity ± cranial nerve palsy
III	Drowsiness, confusion or mild focal deficit
IV	Stupor, moderate-to-severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances
V	Deep coma, decerebrate rigidity, moribund appearance

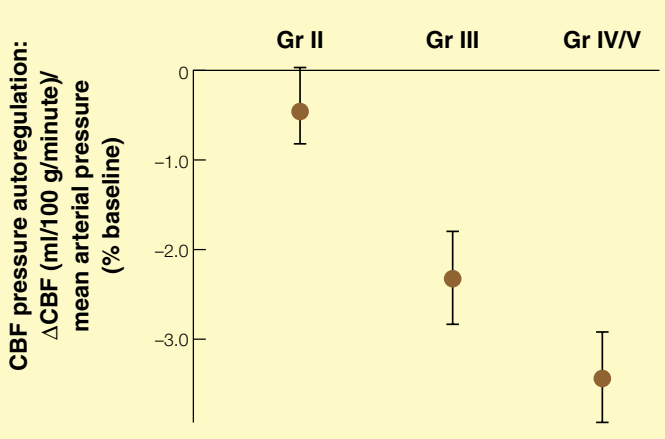
1

World Federation of Neurological Surgeons (WFNS) SAH Scale

WFNS grade	GCS score	Motor deficit
I	15	Absent
II	13–14	Absent
III	13–14	Present
IV	7–12	Present or absent
V	3–6	Present or absent

2

Change in cerebral blood flow (CBF) pressure autoregulation with grade of subarachnoid haemorrhage



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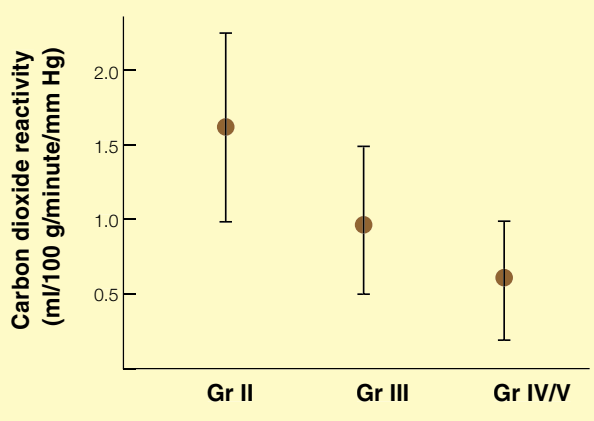
Change in carbon dioxide reactivity with grade of subarachnoid haemorrhage



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Conservative non-surgical management of SAH is associated with a higher mortality than surgical management (40% versus < 10%). Reasons include reduction in the risk of re-bleeding, removal of the blood clot, irrigation and toilet of the operative site, and improved acute functional outcomes, which improve long-term survival.

Timing of surgery: surgery can be early (1–3 days post SAH) or late (10–14 days post SAH). Early surgery, soon after aneurysm rupture, reduces the risk of re-bleeding (and subsequent morbidity and mortality). Early surgery is technically more difficult because of oedema and inflammation. However, because the risk of vasospasm relates to the presence and extent of cisternal blood, some studies suggest that early removal of clot may reduce the risk of developing a delayed ischaemic deficit. Surgery typically involves ablation of the aneurysm with specialized clips (clipping). In some cases, operative access may make this impossible, and the aneurysm is wrapped in muslin to induce fibrosis (wrapping). While this does not ablate the aneurysm immediately it does secure it over time. Increasingly, interventional neuroradiology is being used as an alternative to surgery, usually by placing thrombogenic coils in the aneurysm (coiling). Early clipping or coiling facilitates the medical and neuroradiological treatment of vasospasm.

Cardiovascular dysfunction: ECG changes following SAH are common, and occur more often in those with severe neurological impairment. The degree of myocardial dysfunction does not correlate with the SAH-induced ECG changes, however, the greatest degree of myocardial dysfunction occurs in patients with worse WFNS grades. Pathological Q waves can develop after an SAH, and can be misinterpreted as evidence of a recent myocardial infarction. Diffuse myocardial ischaemia occurs in 50% of patients, with widespread ST segment and T wave changes. Mechanisms for this cardiovascular dysfunction include catecholamine release triggered by SAH, direct trauma to cerebral autonomic control centres, and a hypothalamic neurogenic mechanism. It is difficult to differentiate between SAH-associated ECG changes and actual myocardial ischaemia. Most patients with ECG changes have acceptable perioperative cardiovascular risk, but further investigation (with echo-cardiography) may be needed in some patients, and delayed surgery may be justified in patients with major left ventricular dysfunction, or in those with new Q waves or bundle branch block, who are at high risk of malignant dysrhythmias.

Blood pressure commonly rises after SAH, and is often a normal compensatory response to maintain CPP, in response to a rising ICP. Hypertension in this setting should only be treated if it is severe. Systolic pressures above 160 mm Hg may increase the risk of re-bleeding and rupture, and antihypertensive treatment may be indicated, preferably using drugs that do not produce cerebral vasodilatation (e.g. labetalol). It is also important to avoid hypotension, and the pressure at which neurological deterioration occurs should be recorded so it can be used to guide blood pressure goals intraoperatively.

Volume status and electrolyte imbalance: hypovolaemia and intravascular volume depletion are common and fluid resuscitation is essential. Volume depletion may be the result of poor intake, autonomic hyperactivity, bed-rest or increased urinary volume loss. Inappropriate diuresis may be the consequence of diuretics, diabetes insipidus or the syndrome of cerebral salt wasting, which result in increased urinary losses of sodium ions and water. Hyponatraemia occurs in up to 40% of patients and, when severe, is associated with an impaired level of consciousness, cerebral oedema and vasospasm. This may be due to cerebral salt wasting, inappropriate secretion of antidiuretic hormone or administration of hypotonic maintenance fluids. Invasive monitoring may be required to guide fluid management. Normoglycaemia should be maintained, to prevent the poor outcome associated with hyperglycaemia after brain injury.

Anaesthetic management

Premedication: the use of sedative premedication is controversial and probably best avoided. Grade III–V patients seldom require premedication, and it is best reserved for particularly anxious grade I–II patients. Antacid prophylaxis is mandatory for those at risk of aspiration.

Monitoring should include ECG, pulse oximetry, end-tidal capnography, urinary output and temperature. Invasive arterial blood pressure measurement should be established before induction, allowing accurate observation of blood pressure as well as allowing sampling for blood gas and haemoglobin measurements. Central venous catheters are inserted after induction, to guide fluid management when using diuretics and mannitol. Pulmonary arterial pressure monitoring should be used if impaired myocardial function is present. Such monitoring is also useful in elderly patients, and those with poor grade SAH, because hypertensive, hypervolaemic and haemodilutional therapy is often used in these patients. More specialized intraoperative monitoring may include jugular bulb oximetry, transcranial Doppler, electroencephalography (EEG), intraparenchymal probes and cerebral function monitors.

Induction of anaesthesia involves titration of the depth of anaesthesia and the blood pressure to match surgical need. The ICP must be controlled and cerebral metabolic demands minimized to prevent cerebral ischaemia and provide good operating conditions. Aneurysmal rupture is related to transmural pressure across the wall of the aneurysm. Abrupt increases in arterial pressure or sudden decreases in ICP may cause a re-bleed. Aggressive hyperventilation and hypocapnia can also predispose to rupture. The incidence of rupture at induction is 1–2%, and is associated with high mortality and postoperative morbidity. Rupture should be suspected when a sustained rise in blood pressure occurs on, or shortly after, induction or intubation. Intubation is ideally preceded by a short trial of laryngoscopy with careful monitoring of blood pressure; a significant hypertensive response should trigger administration of a supplemental dose of induction agent before intubation is attempted. Supplemental doses of induction agent or high dose opiates may also be required to avoid the pressor responses associated with the placement of surgical pins. If an aneurysm re-bleeds at induction, surgery should be deferred to allow detailed assessment of the patient. Management of intraoperative rupture is discussed below.

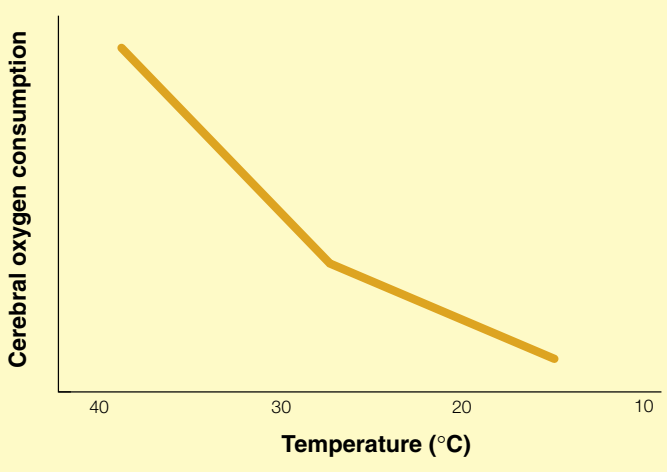
Maintenance: the ideal technique produces a ‘slack’ brain (to minimize retraction pressure), while ensuring maximal cerebral protection by keeping cerebral metabolic requirements to a minimum. No evidence favours one particular technique. Total intravenous anaesthesia, using propofol and an opioid (e.g. remifentanil), is increasingly used for maintenance of anaesthesia during aneurysm surgery. Propofol allows rapid adjustment of anaesthetic depth and has better recovery characteristics than other agents.

Brain relaxation: several methods are used to reduce the brain bulk, CSF volume and cerebral blood volume (CBV), including a 15–30° head-up tilt, mild hypocarbia, mannitol and furosemide (frusemide). A head-up tilt facilitates venous return and reduces ICP. Mild hypocarbia (about 4.5 kPa) can be used, however the potential ischaemic effects of hyperventilation must be balanced against the benefits of reducing CBV. Hyperventilation is a quick method of reducing CBV, but its application is best guided by a monitor of the adequacy of cerebral oxygenation, such as a jugular bulb saturation (SjO_2) monitor. Hyperventilation should be titrated to keep the SjO_2 above 55%.

Mannitol is an osmotic diuretic administered as a 20% solution at a dose of 0.5–1.0 g/kg. Brain bulk is reduced by osmotic dehydration and a transient increase occurs in intravascular volume and CBF. CBV is reduced as a consequence of these changes, and by improved rheology of red blood cells, and CSF production is reduced. These effects result in a decrease in ICP, which peaks at 45–60 minutes. Furosemide (frusemide) is often used in conjunction with mannitol or alone in patients whose cardiovascular system may be compromised by mannitol. Bolus administration of propofol, thiopental (thiopentone) or lidocaine (lignocaine) also reduces CBV by reducing cerebral metabolism and thus CBF.

Hypothermia: most drugs reduce only the active component of cerebral metabolism. However, hypothermia reduces the active and basal components, which increases the time of ischaemia tolerated. Cerebral metabolism is 15% of normal at 20°C (Figure 5). Other mechanisms (e.g. suppression of cytokine, free radical and glutamate release) are thought to contribute to the neuroprotection offered by hypothermia in addition to the reduction in cerebral metabolism. Prophylactic hypothermia during aneurysm clipping is the focus of a multicentre Phase III trial (Intraoperative Hypothermia during Aneurysm Surgery Trial 2; IHAST 2). Deep hypothermia is not without risks. Problems include the accuracy of temperature measurement, optimal temperature used, method of rewarming, delayed awakening, postoperative shivering, coagulation disorders and aggravation of cardiovascular disease.

Relationship between temperature and cerebral oxygen consumption



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Temporary clipping/induced hypotension: intraoperative rupture of an aneurysm is an emergency. Management should include administration of 100% oxygen and prompt volume replacement, with blood if necessary. Other measures that may be used include the application of temporary vascular clips on the feeding artery, controlled hypotension, anaesthetic neuroprotection (usually with barbiturates) or the prophylactic use of hypothermia in high-risk cases.

Temporary clips applied to the feeding vessel are used to reduce the risks of intraoperative rupture, or the risk of bleeding from a ruptured aneurysm. This results in focal ischaemia in the vessel territory, which may be worsened by systemic hypotension. Brisk haemorrhage from a ruptured aneurysm may obscure the surgical field and make clipping of the aneurysm or application of a temporary clip impossible. Under these circumstances, the induction of systemic hypotension using potent anaesthetic agents, short-acting vasodilators or β-blockers may allow visualization of the surgical field and stop haemorrhage. The minimum mean arterial pressure required to prevent ischaemia is unknown. Temporary clipping is becoming more popular and induced hypotension is practised less. This distinction is crucial, because induced hypertension during temporary clipping may permit improved collateral flow and reduce the risk of infarction. The risk of infarction is high if clipping is prolonged beyond 15 minutes. Bolus doses of intravenous anaesthetic agents or the application of hypothermia may be neuroprotective in this setting, but strong evidence is lacking. While many intravenous agents are used in this setting, what little evidence there is supports the use of barbiturates (typically thiopental (thiopentone), 250–1000 mg), which may be effective even when administered after the application of the temporary clip.

Recovery: a rapid return to consciousness allows early neurological assessment. It is important to normalize mean arterial pressure and the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) before closure, to reveal any bleeding points and ensure that intraoperative brain swelling does not increase the likelihood of intracranial hypertension in a normocapnic patient. Obvious brain swelling may prompt a decision to leave the bone flap out, institute ICP monitoring, and/or opt for a period of postoperative sedation and ventilatory support. Assuming a smooth intraoperative course, grade I–II patients are extubated. Grade III–V patients often require a period of postoperative ventilation, unless their preoperative conscious level permits more rapid recovery. Blood pressure must be closely monitored in recovery. Hypertension is often seen as a response to restore CPP and CBF. Uncontrolled hypertension in the immediate postoperative period can precipitate intracerebral haemorrhage and/or vasogenic oedema. Boluses of short-acting opioids, propofol or lidocaine (lignocaine) can facilitate blood pressure control at extubation. More prolonged hypertension, despite adequate analgesia, needs prompt treatment with nifedipine, labetalol or esmolol.

Failure to recover to an expected GCS level is usually related to anaesthetic factors, though this must not be assumed to be the case. Factors that need to be considered include:

- partial neuromuscular blockade
- residual opioid and sedative drugs
- hypoxia and hypercarbia
- metabolic factors (e.g. hyponatraemia)
- postictal state
- brain swelling
- hydrocephalus
- postoperative haemorrhage
- ischaemia (surgical/vasospasm).

The time-course of recovery or deterioration may suggest surgical causes of poor recovery. Once drug-related effects have been excluded and/or treated, a CT scan is performed to exclude hydrocephalus, cerebral oedema, intracranial haemorrhage, haematoma or a re-bleed. A negative CT may prompt a cerebral angiogram to exclude vascular occlusion or vasospasm.

Management of delayed ischaemic neurological damage

Delayed ischaemic neurological damage classically presents as a focal deficit in the second week after SAH, and has been attributed to reductions in large vessel calibre (vasospasm). However, the presentation and presumed cause may be different. Reductions in large vessel calibre may be observed at presentation and deficits may persist into the fourth week post-bleed. There is also increasing evidence that while large vessel vasospasm may contribute to ischaemic deficit, microcirculatory and autoregulatory abnormalities are also important.

The differential diagnosis includes aneurysmal re-bleed, postoperative haemorrhage, retraction injury (which follows long periods of intraoperative brain retraction), epilepsy with postictal Todd’s paralysis, hydrocephalus and electrolyte abnormalities. The history, radiographs, CT and routine biochemistry help to exclude these diagnoses and an EEG is occasionally required to exclude non-convulsive seizures. A clear history of deficit modulated by blood pressure alterations strongly supports a diagnosis of delayed ischaemic neurological damage.

Confirmation of the diagnosis requires angiography, but strong supportive evidence is provided by transcranial Doppler ultrasound, with perfusion imaging that demonstrates reductions in regional CBF. Patients with significant deficits that constitute a neurological emergency must be treated within hours. Prompt and effective therapy can reverse ischaemia and substantially improve outcome. Management includes the following three therapies.

Prophylactic therapy with calcium channel blockers – nimodipine therapy over the first 3 weeks after aneurysmal SAH has been shown significantly to reduce incidence of vasospasm and improve outcome. Both enteral, and more commonly, intravenous nimodipine may result in significant hypotension requiring haemodynamic support.

Triple H’ therapy includes the induction of controlled **h**ypervolaemia (with monitoring of CVP or PA pressures), **h**aemodilution (to a haematocrit of 30–33%, ostensibly to improve flow characteristics through the narrowed vessel) and **h**ypertension to improve flow through narrowed arteries. Mean arterial pressure tends to be maintained below 110 mm Hg in patients with unclipped aneurysms, but levels of 130–140 mm Hg are occasionally required (and achieved) in some patients with clipped aneurysms.

Interventional neuroradiology – selective intra-arterial vasodilator infusions or angioplasty may be beneficial in resistant vasospasm or in patients who develop cardiovascular complications of triple H therapy.

Arteriovenous malformations (AVMs)

AVMs are congenital abnormalities of the cerebrovascular bed. Most are supratentorial and superficial, the remainder are infratentorial or dural. They usually present at 20–40 years of age. The risk of bleeding is 2% per year and the annual rate of death and disability is 4%. 5–10% are associated with cerebral aneurysms (most of which resolve following AVM resection).

Most patients present with an intracranial haemorrhage. Presenting symptoms include seizures, headache and signs of intracranial hypertension. A steal syndrome manifesting as a progressive neurological deficit may also occur. In contrast to cerebral aneurysms, haemorrhage is unrelated to blood pressure and is usually venous in origin.

Most AVMs are treated by embolization particularly if the surgical risk is high. Surgical risk depends on size, anatomy of feeding arteries and venous drainage, and location and eloquence of adjacent brain areas. Surgical resection tends to be reserved for small, superficial AVMs.

Perioperative management: blood products should be readily available because bleeding from AVMs can be torrential. Increases in jugular venous pressure can be transmitted to the cerebral circulation and further enhance bleeding from the AVM. Care must be taken with head-down positioning, tracheal tube tapes, central lines and the application of positive end-expiratory pressure. Induced hypotension may promote visualization of the surgical field, but at the risk of inducing venous thrombosis or ischaemia in non-autoregulating adjacent brain. Blood pressure management should be discussed with the surgical team.

Postoperative haemorrhage may occur from a residual AVM. In addition, hyperaemia is a major source of postoperative morbidity and mortality, producing oedema or haemorrhage and intracranial hypertension, which may be caused by two factors.

- Normal perfusion pressure breakthrough occurs when the brain bordering the lesion is subjected to ‘steal’ from the low resistance circuit of the AVM and adapts by lowering its autoregulatory thresholds. Resection of the AVM exposes this brain to the normal CPP, which may exceed its upper limit of autoregulation. Hyperaemia, microhaemorrhages and vasogenic oedema may result. Staged removal by excision or embolization may allow the brain to regain autoregulatory mechanisms.
- Occlusive hyperaemia. Venous outflow obstruction may cause haemorrhage if arterial feeders are not occluded completely. Venous obstruction may also result in hypoperfusion, owing to stagnation of CBF.

The risk of seizures following AVM resection is about 50%. Blood pressure control is of paramount importance in the postoperative period. Hypertension must be avoided to prevent hyperaemia. β-blockers can be used to control blood pressure, without delaying emergence. Blood pressure should be maintained in the low to normal range. Postoperative ventilation is indicated for patients who suffer excessive bleeding, or have brain swelling. ICP monitoring may be needed.

Management of ischaemic stroke

The annual incidence of stroke is 1–2/1000 population. 80% are caused by ischaemic cerebral infarction, 10% by SAH and 10% by primary intracerebral haemorrhage.

The publication of the National Institute of Neurological Disorders and Stroke (NINDS) trial of alteplase (rtPa) for acute stroke patients in 1995, and its subsequent approval by the US Food and Drug Administration, has increased interest in acute stroke treatment. If given within 3 hours of onset of stroke, rtPa resulted in a trend towards neurological recovery at 24 hours, and at 3 months 50% of survivors had no or minimal disability compared with 38% in the control group. Mortality at 3 months was the same in both groups, despite the rate of symptomatic brain haemorrhage increasing tenfold. There is controversy about its safety, its wider applicability outside clinical trials and its availability. Furthermore, recent studies from Europe do not confirm the positive results of the NINDS study. At present, only 6–12% of stroke patients are likely to be eligible for thrombolysis. Advancements in investigating acute stroke, particularly MRI, may improve the targeting of thrombolysis to those patients most likely to benefit. Any increasing use of thrombolysis will have major implications on stroke services in the future.

There is increasing interest in using intensive care in patients with ischaemic stroke in specific settings. The first of these is to provide physiological optimization in patients in whom cardiorespiratory dysfunction exposes the ischaemic brain to risks of secondary insults. Specific issues include airway and blood gas maintenance in patients with low GCS levels, and thresholds for intervention to treat hypertension in the early stroke period. In general, it is important to maintain near-normal arterial blood gas levels and to avoid treating mild-to-moderate hypertension in the acute period. Sustained blood pressure elevation above 200/120 mm Hg may provide a reasonable threshold for considering antihypertensive therapy.

A second indication is the care of patients who have undergone thrombolysis and require careful monitoring, either because of comorbidities, or complications of the procedure. Finally, there is increasing interest in the use of ICP and CPP oriented therapies (including decompressive craniectomy) in patients with massive non-dominant hemisphere infarctions. ◆

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Pharmacological and Pathological Modulation of Cerebrovascular Physiology

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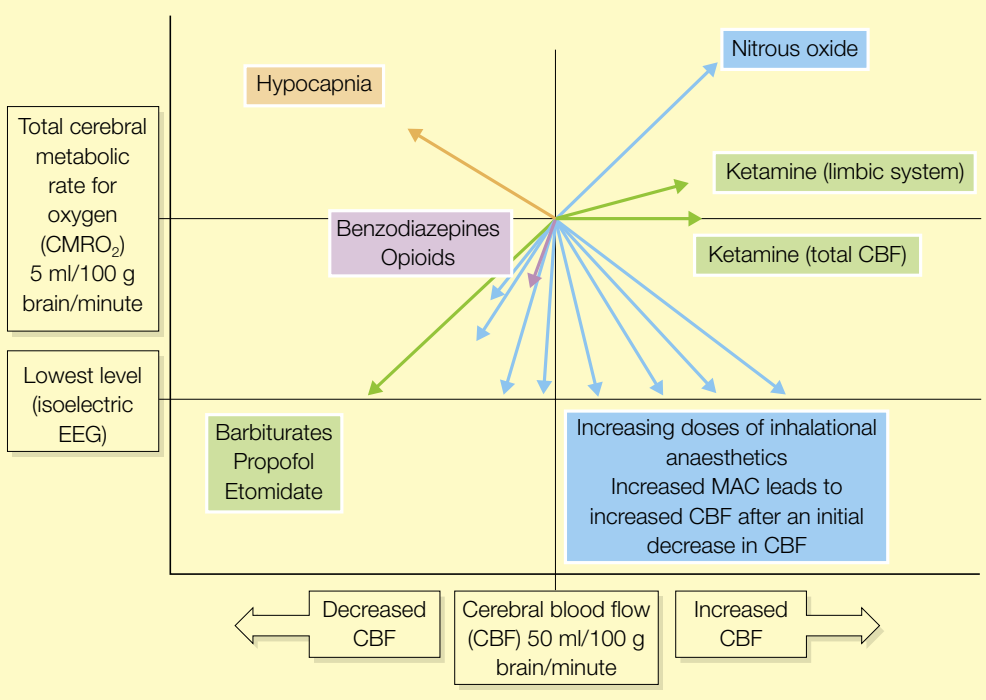
Pharmacological modulation of cerebral physiology

The importance of understanding the effects of drugs used in anaesthetic practice on cerebral physiology cannot be overemphasized. Drugs can exert changes in cerebral blood flow, cerebral metabolic rate and cerebral perfusion pressure, and on cerebral blood volume and intracranial pressure (ICP). These effects may be desirable, for example by reducing intracranial volume and ICP, and thereby improving neurosurgical conditions, or undesirable, for example increasing intracranial volume and ICP, and thereby predisposing to brain herniation in patients with intracranial hypertension (Figure 1).

Effect of drugs used in anaesthetic practice and hypocapnia on cerebral metabolic rate and cerebral blood flow



Hyperventilation and the resulting hypocapnia can lead to vasoconstriction (decreased CBF) and an increase in $CMRO_2$, which is a particularly unfavourable situation. Increasing the inhalational anaesthetic agent concentration (minimum alveolar concentration – MAC) does not decrease CMR below a lower limit. However, it does increase CBF thereby increasing cerebral blood volume and intracranial pressure. This is hazardous for patients with poor intracranial compliance.

1

Fluorinated volatile anaesthetic agents

Fluorinated volatile anaesthetic agents have previously been thought to cause a disturbance in flow–metabolism coupling and attenuate or abolish autoregulation with increasing concentrations, leading to an increase in cerebral blood volume, and thus ICP, despite a reduction in cerebral metabolic rate. However, it is now appreciated that commonly used agents (e.g. isoflurane) preserve flow–metabolism coupling and autoregulation at clinically useful concentrations. There is a dose-dependent decrease in cerebral metabolic rate (to a lower limit), which predisposes to cerebral vasoconstriction as flow–metabolism coupling is preserved. Superimposed on this is the dose-dependent vasodilatory effect of these agents. The effect on cerebral blood volume is a balance between these two antagonistic processes. For example, isoflurane, although a more potent vasodilator of cerebral vessels than halothane, causes more of a reduction in cerebral metabolic rate at equipotent doses. This leads to greater vasoconstriction (secondary to flow–metabolism coupling), which antagonizes the greater dilating effect of isoflurane. Carbon dioxide reactivity of the cerebral circulation is preserved in a normal brain despite the use of these agents, and hypocapnia can further reduce their vasodilatory effect.

The initial popularity of halothane as a neurosurgical anaesthetic agent was reversed by the discovery that it was a potent cerebral vasodilator and could result in clinically significant elevations in ICP in patients with intracranial space-occupying lesions. Enflurane was shown to produce epileptogenic activity, causing an increase in cerebral metabolic rate, cerebral blood flow and thus cerebral blood volume and ICP. As a result, its use in the context of neuroanaesthesia also declined. Halothane reduces cerebral metabolic rate to a lower level than isoflurane. It also has the greatest attenuating effects on autoregulation compared with the other volatile agents. Halothane at 1 MAC (minimum alveolar concentration) almost completely abolishes autoregulation, whereas isoflurane significantly impairs it only above 1 MAC. There is little difference between the two agents in the reduction in global cerebral blood flow at levels of about 1 MAC. Halothane selectively increases cortical blood flow while markedly decreasing subcortical blood flow, whereas isoflurane produces a more generalized reduction in cerebral blood flow. As with all volatile agents, cerebral blood flow increases with increasing concentrations of isoflurane (> 1 MAC) towards the levels in awake patients. Isoflurane has been shown to have a beneficial effect on CSF dynamics by increasing reabsorption.

Initial studies suggested that desflurane and sevoflurane have effects on the cerebral vasculature very similar to isoflurane (e.g. similar reductions in cerebral metabolic rate). However, more recent studies have shown distinct differences between these agents. Desflurane, like isoflurane, can produce EEG burst suppression, but this effect may be attenuated over time. Initial clinical reports suggest that desflurane may cause a clinically significant rise in ICP in patients with supratentorial lesions, despite its proven ability to reduce cerebral metabolic rate. These increases in ICP may be related to cerebral vasodilatation and/or changes in CSF production and reabsorption.

Sevoflurane is non-irritant and has desirable pharmaco-kinetics for neuroanaesthesia. Unlike other volatile agents, sevoflurane up to 1.5 MAC preserves autoregulation. Although reductions in cerebral metabolic rate are similar with both agents, the vasodilatory effect of sevoflurane is about one-third of that seen with isoflurane.

Nitrous oxide

In equi-MAC doses, nitrous oxide is a more powerful vasodilator than any of the fluorinated volatile anaesthetic agents. It also leads to an increase in cerebral metabolic rate, which results in increases in cerebral blood flow and volume, producing a particularly unfavourable pharmacodynamic profile in patients with raised ICP (Figure 1). Furthermore, the vasodilatation produced by nitrous oxide is not decreased by hypocapnia. The effects of nitrous oxide in neuroanaesthesia need to be considered in relation to the effects of the other anaesthetic agents used. Sevoflurane (like all the volatile agents) reduces cerebral blood flow compared with the awake state, but the addition of nitrous oxide can increase cerebral blood flow to a level greater than that in the awake state. Conversely, when propofol is used to maintain anaesthesia, the addition of nitrous oxide has no effect on cerebral blood flow or cerebral metabolic rate, which is an effect that is also seen when barbiturates are used in combination with nitrous oxide.

Intravenous anaesthetics

Intravenous anaesthetic agents, with the exception of ketamine, all reduce global cerebral metabolic rate to a minimum of about 50% of baseline (which corresponds to an isoelectric EEG), coupled with similar reductions in cerebral blood flow (Figure 1). As flow–metabolism coupling is unaffected, these agents have an indirect vasoconstrictive effect, thereby reducing cerebral blood volume and ICP. Autoregulation and carbon dioxide responsiveness are unaffected.

Propofol has a favourable pharmacokinetic profile for neuroanaesthesia and is the only agent that can provide a realistic alternative to volatile agents for maintenance of anaesthesia. As a result, it is being used increasingly in neuroanaesthesia and critical care. However, it is a potent cardiodepressant and systemic vasodilator, and can cause significant reductions in mean arterial pressure. Consequently, it is important to be aware of its potential for causing a fall in cerebral perfusion pressure.

Experimental studies have indicated that intravenous anaesthetic agents may have a neuroprotective role in patients with intracranial disease. Both thiopental (thiopentone) and propofol have significant anticonvulsant activity, reduce intracellular calcium influx, scavenge free radicals and inhibit N-methyl-D-aspartate (NMDA) responses *in vitro*. However, direct evidence of clinical benefit from these agents is scanty.

Ketamine dilates cerebral vessels and increases global cerebral blood flow and ICP. Total cerebral metabolic rate is unchanged, but regional increases occur particularly in limbic structures. Seizure activity is also a concern and CSF absorption is impaired. These changes may be partially attenuated by hypocapnia, propofol, benzodiazepines and halothane. Recently, there has been renewed interest in the use of ketamine, an NMDA antagonist, for its neuroprotective properties. The results of further studies are awaited.

Opioids

If ventilation is not controlled, increases in cerebral blood flow, volume and ICP, secondary to respiratory depression and hypercapnia, can occur after opioid use. During controlled ventilation, however, the administration of small-to-moderate doses of opioids does not adversely affect cerebral blood flow and cerebral metabolic rate. Autoregulation and carbon dioxide reactivity are also maintained. Nevertheless, high doses of fentanyl and sufentanil have been shown to depress cerebral metabolic rate and cerebral blood flow. Chest wall rigidity, causing a rise in central venous pressure, may also occur. Bolus administration of fentanyl, sufentanil or alfentanil may be associated with increases in ICP in patients with intracranial hypertension. This is probably due to autoregulatory vasodilatation of cerebral vessels that follows an initial decrease in cerebral blood flow (due to reductions in mean arterial pressure and thus cerebral perfusion pressure), which leads to an increase in cerebral blood volume. These effects are unlikely to be clinically significant if detrimental haemodynamic and blood gas changes can be avoided. Remifentanil, like alfentanil, has similar minimal effects on cerebral haemodynamics when given as an infusion.

Muscle relaxants

Most nondepolarizing neuromuscular blockers have little effect on cerebral blood flow or cerebral metabolic rate, although atracurium, mivacurium and D-tubocurarine may increase cerebral blood volume and ICP secondary to histamine release and vasodilatation. Succinylcholine can produce increases in ICP, probably secondary to increases in cerebral blood flow mediated via muscle spindle activation. However, these effects are transient and mild and can be blocked by prior precurarization if necessary; they provide no basis for avoiding succinylcholine in patients with raised ICP when its rapid onset of action is desirable for clinical reasons.

Other drugs

Benzodiazepines tend to produce small decreases in cerebral metabolic rate and cerebral blood flow, but there is a ceiling on this effect whereby increasing doses produce no further reductions in these variables. Droperidol has no effect on cerebral metabolic rate and minimally reduces cerebral blood flow. α_2-agonists, such as clonidine, dexmedetomidine and xylazine, reduce cerebral blood flow if there is no significant reduction in mean arterial pressure. Vasodilators, such as nitrates and sodium nitroprusside, increase cerebral blood flow and volume in the absence of hypotension, so predisposing to raised ICP. Vasopressors increase cerebral perfusion pressure, cerebral blood flow and volume when autoregulation is impaired (with disease processes or outside the autoregulatory pressure limits). However, increases in CPP in the presence of intact autoregulation result in reductions in CBV and hence ICP. Mannitol is an osmotically active diuretic that does not normally cross the blood–brain barrier. It decreases ICP in two ways. First, it has an almost immediate effect by improving microcirculatory flow and oxygen delivery; reflex vasoconstriction reduces cerebral blood volume. Secondly, it causes a reduction in brain water thereby reducing intracranial volume.

Pathological modulation of cerebral physiology

Ischaemia

Graded reductions in cerebral blood flow are associated with specific electrophysiological and metabolic consequences (Figure 2). Ischaemia is thus a continuum between normal cellular function and cell death; cell death, however, is not merely a function of the severity of ischaemia, but is also dependent on its duration and several other circumstances that modify its effects. Thus, the effects of ischaemia may be ameliorated by the cerebral metabolic depression produced by hypothermia or drugs, exacerbated by increased metabolic demand associated with excitatory neurotransmitter release, or compounded by other mechanisms of secondary neuronal injury (such as cellular calcium overload or reperfusion injury).

Electrophysiological and metabolic consequences of graded reductions in cerebral blood flow

Cerebral blood flow (ml/100 g brain/minute)	Electrophysiological/metabolic consequence
> 50	Normal neuronal function
?	Immediate early gene activation
?	Cessation of protein synthesis
?	Cellular acidosis
20–23	Reduction in electrical activity
12–18	Cessation of electrical activity
8–10	ATP rundown, loss of ionic homeostasis
< 8	Cell death (also depends on other modifiers, such as duration and metabolic rate)

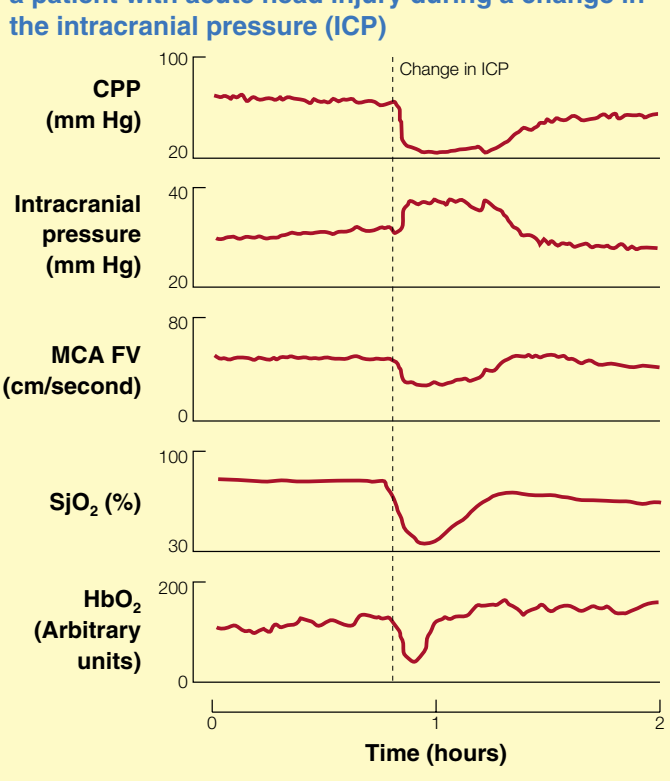
2

Head injury

Severe head injury is accompanied by both direct and indirect effects on cerebral blood flow and metabolism. Cerebral blood flow may be high or normal but is more usually low soon after the ictus. Studies have shown that 30% of patients have significant cerebral ischaemia within 6–8 hours of a head injury. Global hypoperfusion in these studies was associated with 100% mortality at 48 hours, and regional ischaemia with significant deficits. Patterns of cerebral blood flow also vary in relation to the time after injury. Initial reductions are replaced, especially in patients who achieve good outcomes, by a period of relative increase in cerebral blood flow. Towards the end of the first week after injury, this may be replaced by reductions in cerebral blood flow resulting from vasospasm associated with traumatic subarachnoid haemorrhage. Changes in cerebral blood flow are non-uniform in the injured brain. Blood flow tends to be reduced in the immediate vicinity of intracranial contusions, and so cerebral ischaemia associated with hyperventilation may be extremely regional and not reflected in global monitors of cerebrovascular adequacy.

Elevations in ICP result in reductions in cerebral perfusion pressure and cerebral ischaemia, which lead to secondary neuronal injury (Figure 3). There is strong evidence that maintenance of a perfusion pressure above 60 mm Hg improves outcome in patients with head injury and raised ICP. Traditionally, patients with intracranial hypertension have been nursed head-up in an effort to reduce ICP. It is important to realize, however, that such manoeuvres will also reduce the effective mean arterial pressure at the level of the head, and run the risk of reducing cerebral perfusion pressure. A 30° head-up elevation may provide the optimal balance by reducing ICP without decreasing cerebral perfusion pressure.

Continuous record of multimodality monitoring in a patient with acute head injury during a change in the intracranial pressure (ICP)



Note the fall in cerebral perfusion pressure (CPP) and reduction in the middle cerebral artery flow velocity (MCA FV) measured using transcranial Doppler, suggesting reduced MCA flow. The ischaemia associated with the reduction in CPP produces jugular venous desaturation (SjO_2) and a fall in oxyhaemoglobin signal (HbO_2) measured by near infrared optical spectroscopy (NIROS).

3

Hypertensive encephalopathy

Current concepts of the causation of hypertensive encephalopathy are based on the forced vasodilatation hypothesis. Severe acute or sustained elevations in mean arterial pressure overcome autoregulatory vasoconstriction in the resistance vessels and result in forced vasodilatation. These vasodilated vessels, exposed to high intraluminal pressures, leak fluid and protein and result in cerebral oedema, which is multifocal and later diffuse. In the absence of actual encephalopathy, it is important to recognize that untreated hypertension results in a shift of the autoregulatory curve to the right, with elevation of cut-off points for loss of autoregulation.

Subarachnoid haemorrhage

Cerebral autoregulation and carbon dioxide responsiveness are grossly distorted after subarachnoid haemorrhage, more so in patients with worse clinical grades. Such patients may be unable to compensate for reductions in mean arterial pressure produced by anaesthetic agents and develop clinically significant deficits. Significant vasospasm after subarachnoid haemorrhage occurs in up to 30–40% of patients, typically several days after the initial bleed, and may be due to one or more mechanisms. Nitric oxide may be taken up by haemoglobin in the extravasated blood or be converted to peroxynitrite (a highly reactive free radical species) by superoxide radicals produced during ischaemia and reperfusion. Alternatively, spasm may be secondary to lipid peroxidation of the vessel wall by various oxidant species, including superoxide and peroxynitrite. Other authors have proposed a role for endothelin. Vasospasm tends to be worst in patients with the largest amounts of subarachnoid blood, suggesting that the blood contributes to the phenomenon. Vaso-spasm is associated with parallel reductions in regional cerebral blood flow and cerebral metabolic rate in the regions affected.

The clinical impact of late vasospasm has been substantially modified by the routine use of calcium channel antagonists, such as nimodipine, and by the routine use of hypertensive hypervolaemic haemodilution (triple H therapy). Triple H therapy involves the use of colloid administration (with venesection if needed) to increase filling pressures and reduce haematocrit to 30–35%. If moderate hypertension is not achieved with volume loading, vasopressors and inotropes are used to maintain mean blood pressures as high as 120–140 mm Hg. The hypertensive element of this therapy protects non-autoregulating portions of the cerebral vasculature from hypoperfusion, while the haemodilution improves flow and oxygen delivery through vessels, the calibre of which is reduced by spasm. Such interventions produce clinically useful improvements in cerebral blood flow in regions of ischaemia.

Preoperative Assessment of the Patient with Neurological Disease

Catherine Duffy

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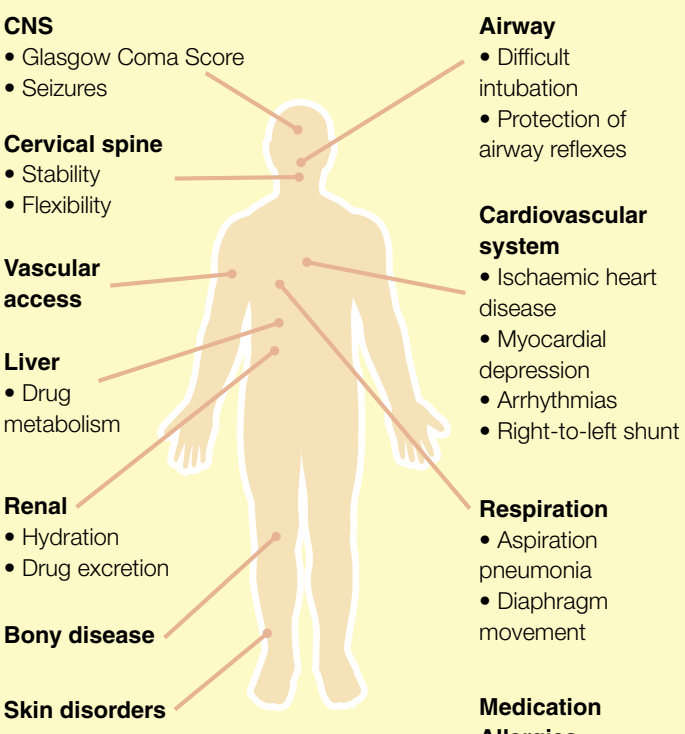
The role of the anaesthetist in neurosurgery is to provide the safest possible operating conditions for the surgeon and the patient. To achieve this, a comprehensive knowledge of CNS physiology and the effects of drugs on the brain are required. The anaesthetist must assess the patient's presenting neurological condition and any underlying medical disease that may affect neurosurgery (Figure 1). The urgency of surgery tends to be determined by the patient's presenting neurology. The Glasgow Coma Score (GCS) (Figure 2) provides a useful and easily communicated means of rapidly assessing neurological status.

Preoperative checklist



1

Glasgow Coma Score

Eye opening	
• spontaneous	4
• to speech	3
• to pain	2
• none	1
Best verbal response	
• orientated	5
• confused	4
• inappropriate words	3
• incomprehensible sounds	2
• none	1
Best motor response	
• obeys commands	6
• localizes pain	5
• withdraws to pain	4
• abnormal flexion to pain	3
• extension to pain	2
• none	1
Total	3–15

2

Airway and ventilation: patients with a GCS less than 9 are at risk of developing hypoxia and hypercarbia, which exacerbate intracranial hypertension. To control intracranial pressure and protect the airway, tracheal intubation and ventilation should be instituted at the earliest opportunity in neurologically obtunded patients.

Fluid and electrolyte balance should be optimized before surgery. To maintain adequate cerebral perfusion, it is important to correct dehydration, which occurs as a result of reduced intake or use of diuretics (including mannitol) in the preoperative period. An attempt should be made to correct electrolyte abnormalities that may occur as a result of syndrome of in-appropriate antidiuretic hormone secretion (SIADH) or diabetes insipidus. Corticosteroids are used preoperatively to control tumour-related cerebral oedema. They cause hyperglycaemia, which has to be controlled, often using an insulin sliding scale regimen. This may have to be continued intraoperatively because hyperglycaemia worsens neurological outcome in the event of an ischaemic injury.

Cardiovascular disease: patients with ischaemic heart disease should be assessed and optimized before neurosurgery. Chronic hypertension causes rightward shift of the cerebral blood flow autoregulation curve such that hypotensive episodes are more likely to cause cerebral hypoperfusion. It is therefore important that blood pressure is well controlled preoperatively.

Preoperative investigations: the anaesthetist should ensure that appropriate preoperative investigations have been performed and the results are available. In particular, it is vital that clotting abnormalities are assessed and corrected before surgery. Depending on the anticipated blood loss, blood should be grouped and saved or cross-matched.

Concurrent medication: the patient's usual medications, including corticosteroids, anticonvulsants, antihypertensives, antacids and antibiotics should be continued throughout the perioperative period. Sedative premedication is best avoided in neurologically compromised patients. In anxious patients with a GCS of 15, oral benzodiazepines are useful. In patients with a history of postoperative nausea and in those undergoing posterior fossa surgery, which predisposes to nausea and vomiting, an oral anti-emetic should be included in the premedication. In patients undergoing spinal surgery, and in whom there is no contraindication, a non-steroidal anti-inflammatory drug (NSAID) premedication is effective in reducing postoperative analgesic requirements. An antisialagogue may be used in patients in whom awake fibre-optic bronchoscopic intubation is planned.

Planning perioperative care: for major neurosurgical procedures, appropriate provision should be made for intensive care or high-dependency nursing in the postoperative period. Some factors specific to the site and nature of neurosurgery warrant special consideration; this article is restricted to the neurological diseases encountered by the neurosurgical anaesthetist.

Craniotomy for supratentorial masses

Masses in the supratentorial compartment fall into three groups.

Tumours – primary lesions range from benign meningiomas to highly malignant glioblastomas. Secondary tumours are the most common intracranial neoplasm; 50% of secondaries originate in the lung. The patient should have been investigated for primary disease and a thorough assessment of the primary site should be made.

Haematomas – traumatic acute extradural and subdural haematomas are often associated with other injuries, which must be prioritized. Major chest or abdominal injuries cause cerebral hypoperfusion as a result of hypotension and necessitate urgent surgery to stop blood loss. In trauma patients, the cervical spine should be treated as unstable until radiographs or CT scans prove otherwise. To achieve optimal neurological results, acute haematomas must be evacuated within 4–6 hours of onset.

Abscesses – patients with an abscess may be immuno-compromised and are often systemically unwell due to infection. Surgery should not be delayed. Antibiotics must be continued perioperatively.

CT scans should be reviewed by the anaesthetist for evidence of raised intracranial pressure, looking in particular for oedema, hydrocephalus and midline shift. Proximity to venous sinuses should be noted, because of the high risk of severe intraoperative haemorrhage. Preoperative angiography provides useful information about the vascularity of tumours. Occasionally, large vascular meningiomas can be embolized in the neuroradiology suite before surgery. This can limit intra-operative blood loss but successful embolization requires that surgical removal take place within 48 hours because the process of necrosis can trigger marked cerebral oedema.

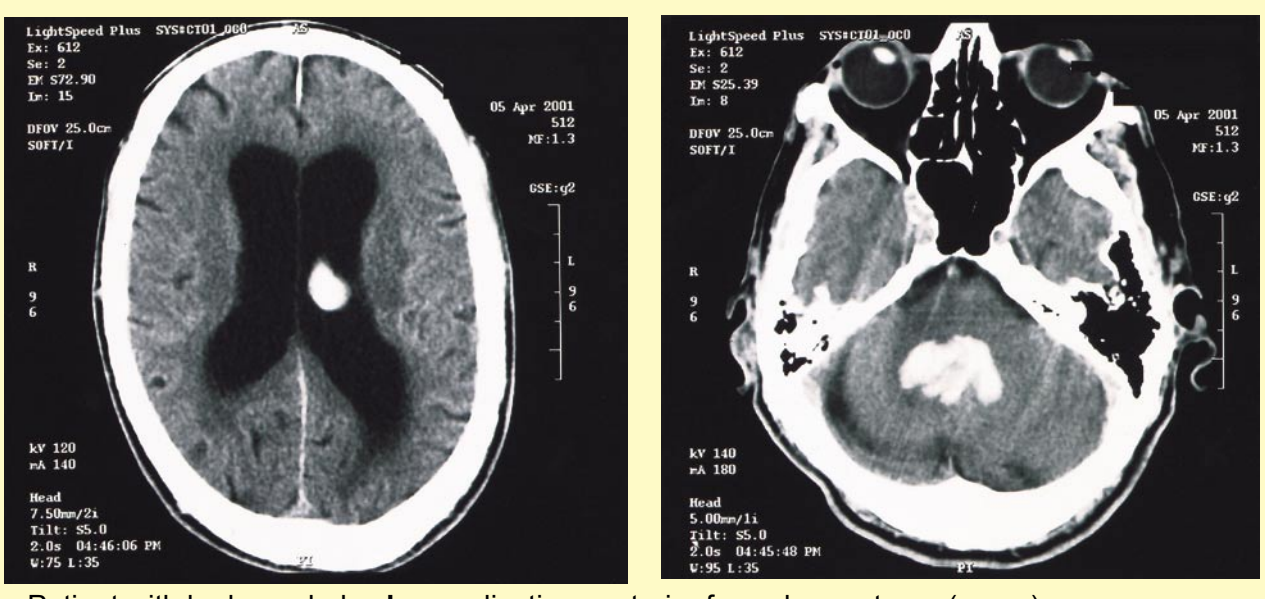
Posterior fossa surgery

The posterior fossa is a small rigid compartment that contains vital structures and through which there is a narrow outflow of CSF. Patients with posterior fossa lesions can present as life-threatening emergencies. Expansion of a posterior fossa lesion can cause acute intracranial hypertension due to hydrocephalus which must be drained urgently (Figure 3).

As with the supratentorial compartment, posterior fossa tumours, haematomas and abscesses may require surgical removal. Posterior fossa surgery is also undertaken to decompress cranial nerves and to correct craniocervical abnormalities.

To allow surgical access, the patient may have to be placed in the prone, lateral, 'park bench' or sitting position. Preoperatively, the patient's suitability for the proposed surgical position must be assessed. For example, obese patients are not suited to lying prone for a prolonged period. Because of its significant risk of morbidity and mortality, the sitting position is reserved for patients in whom it provides the only means of accessing the surgical lesion. Patients with cervical spine disease are unsuitable for this position because neck flexion stretches the spinal cord causing hypoperfusion and potential quadriplegia. The sitting position is contraindicated in patients with known right-to-left shunts because of the risk of paradoxical air embolism following entrainment of venous air. Exclusion of a right-to-left heart defect on preoperative echocardiography does not rule out the risk of paradoxical air embolism. Transpulmonary passage of air can probably still occur in the absence of a right-to-left shunt.

Large posterior fossa masses compress the brainstem resulting in lower cranial nerve palsies. Patients should be examined for impaired gag reflex and evidence of chronic aspiration. If it is anticipated that the patient will be unable to maintain airway protection after surgery, appropriate support in intensive care should be arranged at the time of preoperative evaluation.



a Patient with hydrocephalus **b** complicating posterior fossa haematoma (arrow).

3

Neurovascular surgery

Cerebral aneurysms
Cerebral aneurysms are present in 2–5% of the population. Rupture occurs at a rate of 0.05–6% per year and is related to hypertensive episodes. In the event of a subarachnoid haemorrhage, one-third of patients do not reach hospital, one-third have a poor outcome and one-third are functional survivors. Outcome correlates with neurological condition at presentation which is graded according to Hunt and Hess (Figure 4) or World Federation of Neurological Surgeons (Figure 5) scales. Early surgery (within 48 hours of subarachnoid haemorrhage) reduces the risk of rebleeding but does not change the incidence of vasospasm, which typically occurs 4–9 days after the haemorrhage. Nimodipine improves outcome following subarachnoid haemorrhage and should be started on admission and continued throughout the perioperative period.

Of major concern to the anaesthetist is the cardiac dysfunction that is often associated with patients with a poor grade. This manifests as arrhythmias and depression of ventricular wall function secondary to diffuse myocardial ischaemia. The underlying mechanism is thought to be massive catecholamine release triggered by subarachnoid haemorrhage. These patients are usually in an ICU or high-dependency environment in the preoperative phase. Cardiac function should be assessed and optimized before surgery.

Hunt and Hess classification of patients with intracranial aneurysms

Category	Criteria
0	Unruptured aneurysm
I	Asymptomatic or minimal headache and slight nuchal rigidity
II	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
III	Drowsiness, confusion or mild focal deficit
IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances
V	Deep coma, decerebrate rigidity, moribund appearance

4

World Federation of Neurological Surgeons (WFNS) Subarachnoid Haemorrhage Scale

WFNS Grade	Glasgow Coma Score	Motor deficit
I	15	Absent
II	14–13	Absent
III	14–13	Present
IV	12–7	Present or absent
V	6–3	Present or absent

5

Carotid artery surgery
Multi-centre trials in Europe and North America have shown carotid endarterectomy to be worthwhile in symptomatic high-grade (> 70%) carotid artery stenosis. The place of surgery in low-grade and intermediate stenosis is not established. Patients with vascular disease are often elderly and have coexisting medical conditions that must be optimized before surgery.

55% of patients presenting for carotid artery surgery have evidence of ischaemic heart disease. The risk of postoperative myocardial infarction is ten times greater in these patients than in those without coronary artery disease. Given that myocardial infarction accounts for 40–60% of postoperative mortality, it is essential that ischaemic heart disease is optimized preoperatively using medical therapy.

70% of patients with carotid endarterectomy have a history of hypertension. Poorly controlled blood pressure increases myocardial oxygen demands, thereby increasing the risk of myocardial ischaemia. Postoperative hypertension is associated with hyperperfusion syndrome in which an area of brain that has lost the ability to autoregulate owing to chronic underperfusion is suddenly reperfused following endarterectomy. Hyperperfusion can lead to cerebral oedema and intracerebral haemorrhage. To minimize the risk of surgery, blood pressure must be controlled.

Smoking is a risk factor for vascular disease and many patients presenting for carotid endarterectomy have chronic obstructive pulmonary disease. Some improvement in lung function may be achieved with preoperative bronchodilator and corticosteroid therapy. To benefit from surgery, patients should stop smoking permanently.

20% of carotid endarterectomy patients have diabetes mellitus, which is associated with renal impairment, ischaemic heart disease and autonomic neuropathy. Diabetic patients should be assessed for evidence of end-organ disease. A sliding scale may be needed to achieve tight control of blood glucose in the perioperative period.

The patient's preoperative neurological condition should be carefully documented. Progressive neurological deficits are associated with an increased risk of postoperative deficit.

Spinal surgery

Spinal injuries
In patients with spinal injuries, care must be taken to minimize the risk of secondary spinal cord damage. Hypoxia, hypercarbia and hypovolaemia should be treated aggressively and a neutral position should be maintained whenever the patient is moved.

The anaesthetist is often involved in the airway management of patients with cervical spine injuries. To minimize the risk of neurological injury in a patient with an unstable cervical spine, patients should be intubated using manual in-line traction and stabilization. The neck is immobilized using a hard collar or sand bags, while an assistant applies gentle traction to the mastoid processes. Fibre-optic intubation may provide the best alternative for securing the airway in some patients.

If the patient deteriorates neurologically, early surgery may be required to stabilize the spine. The anaesthetist needs to be aware of the systemic effects of spinal injury and make a thorough preoperative assessment.

Within the first 3–5 days of injury, these patients present a picture of spinal shock. Patients with high spinal injuries are bradycardic due to the loss of T1–4 sympathetic cardiac innervation. In subsequent months, they develop autonomic hyperreflexia and, in the chronic phase, postural hypotension.

Patients with spinal injuries at or above C5 need ventilatory support and are at risk of chest infections. Below C6, there may be some respiratory impairment due to paralysis of intercostal muscles. Provision for appropriate postoperative respiratory support should be made at the time of preoperative assessment. Patients with chronic spinal damage may have renal failure with electrolyte abnormalities secondary to long-term bladder dysfunction.

Chronic spinal disease
Of particular concern to the anaesthetist is the patient with ankylosis of the cervical spine in whom intubation can be difficult, especially when temporomandibular joint movement is restricted, as in rheumatoid cervical joint disease, or when dentition is abnormal. When difficulty is anticipated, preparation should be made for awake fibre-optic intubation. This must be discussed in advance with the patient. The anaesthetist should ensure the anaesthetic room is equipped for providing topical airway anaesthesia and fibre-optic intubation. Sedation and an antisialagogue can be administered intravenously on arrival in the anaesthetic room.

Patients with connective tissue disorders must be assessed for cardiac, respiratory, renal and haematological manifestations of their disease. These patients are often taking long-term corticosteroid or other immunosuppressive therapy. The side-effects of such medication must be considered and care paid to the sterility of technical procedures.

Pituitary surgery

Pituitary lesions present as a mass effect or as endocrine changes. 30% of tumours are hormonally inactive and present with headaches or visual field defects due to compression of the optic chiasm. The remainder present with a range of symptoms due to hyper- or hypo-secretion of one or more hormones. Expansion of one cell-type adenoma can compress surrounding normal areas resulting in undersecretion of other cell types. Large pituitary lesions compress the hypothalamo-pituitary stalk, reducing the effect of hypothalamic neuroregulatory hormones. Because of the complex nature of pituitary lesions, these patients are assessed by the endocrinology team in conjuction with the neurosurgeon.

The usual surgical approach is trans-sphenoidal; the nasal mucosa is vasoconstricted using intranasal cocaine post-induction. The anaesthetist should ensure that the patient does not have any conditions (e.g. ischaemic heart disease) that contraindicate the use of cocaine. Patients should be warned that they will have nasal packs at the end of the procedure and will have to breathe orally. A transcranial approach is preferred for tumours that have spread extensively beyond the pituitary fossa but it is associated with a higher rate of morbidity.

Patients undergoing pituitary surgery receive perioperative corticosteroid therapy. An appropriate dosage regimen is usually prescribed by the endocrinology team. Posterior pituitary damage is rare when the trans-sphenoidal approach is used so vasopressin replacement therapy is seldom required.

Acromegaly
Enlargement of soft tissues and cartilage makes patients with acromegaly difficult to intubate. A history of hoarseness and stridor should alert the anaesthetist to airway problems. Indirect laryngoscopy may be helpful in the preoperative work-up. If difficulty is anticipated, plans should be made for awake fibre-optic intubation.

A history of sleep apnoea should be sought. This is usually peripheral in origin owing to airway changes but there may also be a central component as a result of elevated levels of growth hormone. 30% of patients with acromegaly have hypertension. Occasionally they may have cardiomyopathy, in which case a preoperative echocardiogram to assess left ventricular function is useful. Appropriate intraoperative invasive monitoring should be planned in advance. 25% of patients develop diabetes, which should be controlled preoperatively.

Cushing's disease
The classic features of Cushing's disease (central obesity with a short thick neck) can make patients with this disease difficult to intubate. There may be an associated history of sleep apnoea. If there is a history of gastro-oesophageal reflux or peptic ulcer disease, preoperative antacid therapy should be prescribed and plans made for rapid sequence induction. 85% of patients with Cushing's disease have hypertension, which can be refractory to treatment. Left ventricular hypertrophy and congestive cardiac failure are not uncommon. Appropriate cardiac investigations should be available preoperatively. 60% of patients with Cushing's disease have diabetes mellitus. Due to osteoporosis and a tendency to bruising, care should be taken when transferring and positioning these patients. Vascular access may be trouble-some due to fragile skin and loss of connective tissue.

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Secondary Neuronal Injury Mechanisms

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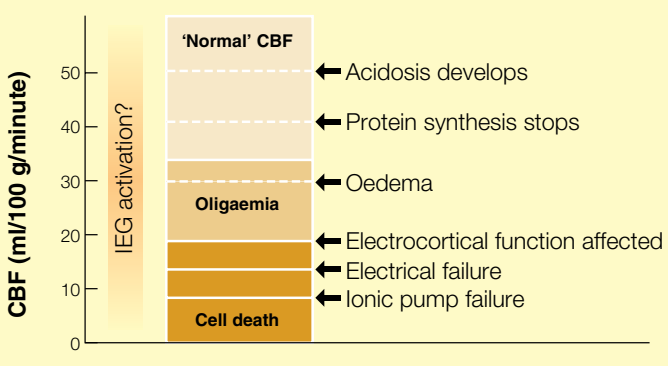
Cerebral injury is common and results in substantial morbidity and mortality. Neuronal systems are fragile owing to structural and functional complexity, the post-mitotic status of neurons and their specialized metabolic requirements.

Primary neuronal injury occurs when there is trauma causing physical disruption of neurons, or when the oxygen supply is deficient owing to inadequate oxygenation of blood or perfusion of brain tissue. It is common to cite cerebral blood flow thresholds at which several physiological or pathophysiological processes occur, but little is known about what triggers these important biological processes (e.g. immediate early gene expression)(Figure 1).

'Ischaemic thresholds' for pathophysiological events in acute brain injury



Some of the figures are clinically relevant (e.g. cerebral blood flow (CBF) of about 10 ml/100 g/minute for irreversible neuronal injury), but others are speculative, and few data are available for CBF thresholds for key neurobiological processes in ischaemia such as immediate early gene (IEG) expression

1

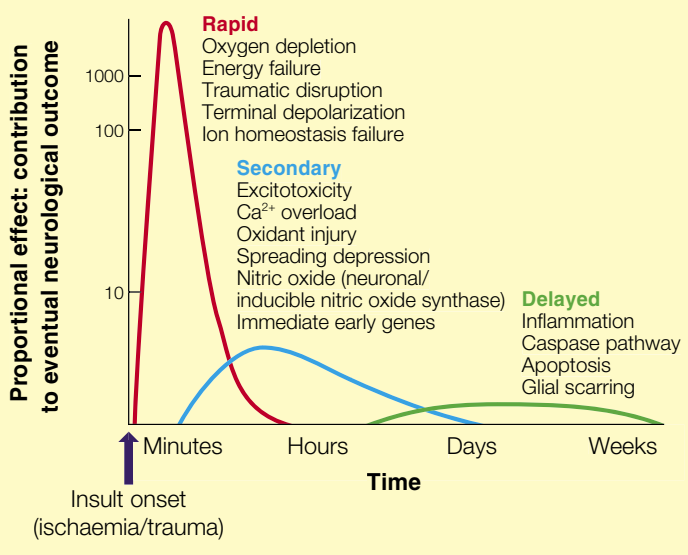
Secondary neuronal injury is caused by damaged and dying neurons releasing factors that have a detrimental effect on other cells, especially neighbouring cells in the CNS. Increasing knowledge of secondary injury mechanisms may provide further useful treatments. The mechanisms may be directly cytotoxic or may compound the imbalance between oxygen supply and demand by:

- further reducing cerebral perfusion through pathological vasoconstriction (vasospasm), autoregulatory dysfunction or microcirculatory occlusion
- increasing neuronal oxygen requirements by inducing ionic shifts, inducing epileptiform activity or precipitating slow waves of depolarization (spreading depression)
- compromising systemic cardiorespiratory physiology.

Reducing secondary injury – simple measures are important. Rapid correction of cerebral hypoperfusion and hypoxia reduce secondary injury. A fuller understanding of the molecular mechanisms of secondary neuronal injury may allow neurons to be protected from secondary injury by other means. However, current application of such knowledge is limited, and clinical trials of drugs inhibiting some secondary injury mechanisms have proved disappointing.

Most knowledge about secondary neuronal injury mechanisms comes from experiments in cell cultures or animal models, some of which produce contradictory results. The importance and timing of many of these mechanisms remains speculative in humans (Figure 2) and direct observation of human pathophysiology may be required to understand clinical disease.

Time course and outcome relevance of pathophysiological processes in cerebral ischaemia



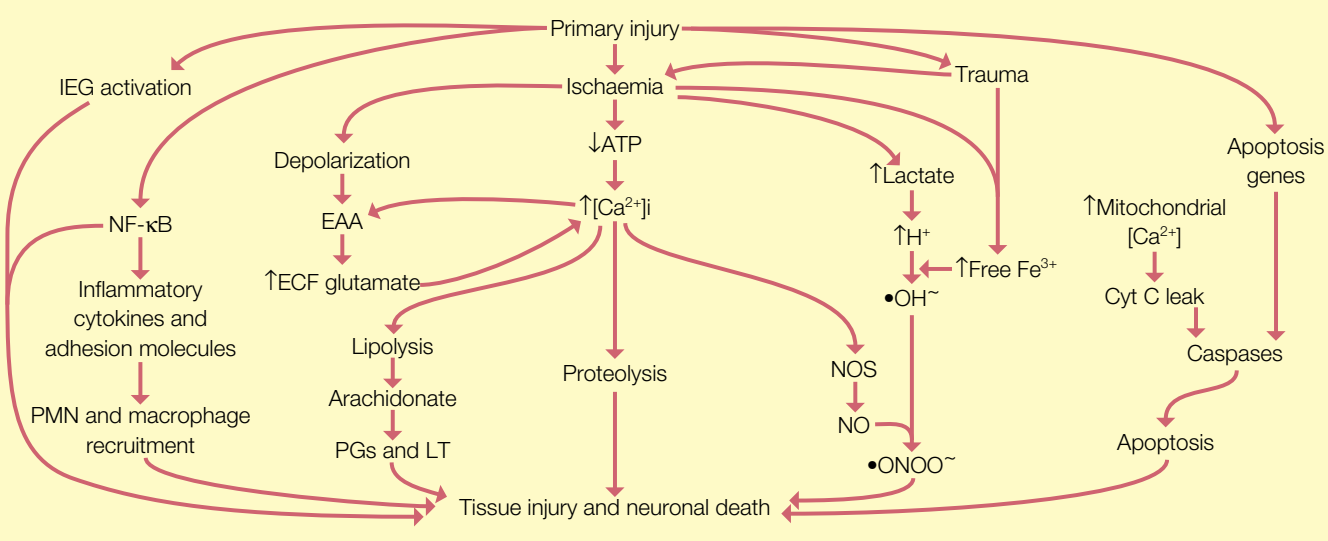
2

Neuronal death is complex. Cells may die by necrosis when cell membrane pumps fail and cells burst, or death may be triggered by an active process ('programmed suicide') called apoptosis. Necrosis and apoptosis can both occur in the same cell, and dying or struggling cells can switch between them as their environment and metabolic demands change. Cellular damage eventually leads to an inflammatory response, which may contribute to late CNS damage. This article concentrates on what kills neurons rather than the means by which they die.

Pathways that damage neurons

Figure 3 shows the main pathways that damage and kill neurons. They are interlinked and can form positive feedback systems.

Processes in secondary neuronal injury



ATP, adenosine triphosphate; $[Ca^{2+}]i$, cytosolic calcium concentration; cyt C, cytochrome C; EAA, excitatory amino acid; ECF, extracellular fluid; IEG, immediate early gene; LT, leukotrienes; NF-κB, nuclear factor NF-κB; NO, nitric oxide; NOS, nitric oxide synthase; ONOO, peroxynitrite; PMN, polymorphonuclear leukocytes; PGs, prostaglandins

3

Glutamate-mediated neurotoxicity and calcium homeostasis

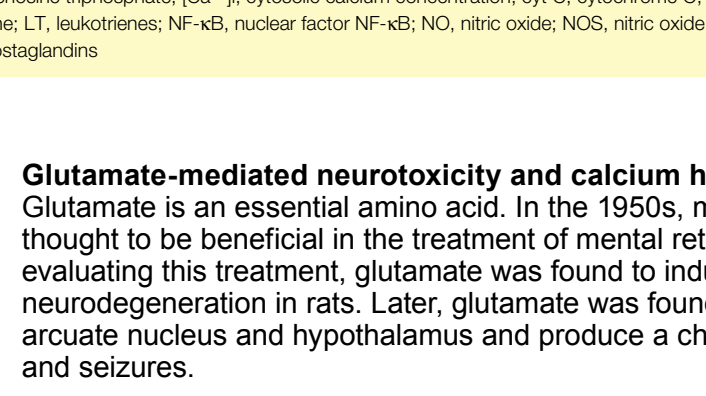
Glutamate is an essential amino acid. In the 1950s, monosodium glutamate was thought to be beneficial in the treatment of mental retardation and seizures. While evaluating this treatment, glutamate was found to induce rather than alleviate retinal neurodegeneration in rats. Later, glutamate was found to be toxic to neurons in the arcuate nucleus and hypothalamus and produce a characteristic syndrome of vomiting and seizures.

Other excitatory amino acids (EAAs) and neurotransmitters (e.g. aspartate) were found to have similar effects and introduced the concept of 'excitotoxicity'. When a neuron is injured or is depleted of energy stores, its cell membrane depolarizes and large amounts of glutamate are released. More glutamate leaks out of damaged cell membranes. Glutamate reuptake systems also fail, and extracellular glutamate levels rise precipitously. Neighbouring cells are depolarized by the excessive glutamate and release more glutamate causing positive feedback, resulting in a vicious spiral of increasing extracellular glutamate concentration. Glutamate damages neurons by depolarizing their membranes, allowing a huge influx of sodium and calcium. The swollen neuron can survive if it has sufficient ATP to power its Na^+/K^+-ATPase pumps and handle the osmotic load, but exhibits cytotoxic oedema following metabolic failure, with eventual loss of viability. Human intracerebral glutamate levels are markedly elevated in brain injury, but there is doubt as to whether synaptic levels are truly toxic. In experimental models, inhibition of glutamate-induced depolarization and cytosolic Ca^{2+} overload improves neuronal survival.

Receptors: the fact that glutamate can damage discrete areas of brain and leave others untouched implied the effect was receptor-mediated. Two classes of glutamate receptor have been identified: ionotropic and metabotropic.

- Ionotropic receptors are coupled directly to ion channels and their activation causes sodium and calcium influx. Depending on their subunit assembly and specific agonist sensitivity, ionotropic receptors are either classified as *N*-methyl-D-aspartate (NMDA) receptors, or α-amino-3-hydroxy-5-methyl-4-isoxazole propionate/kainic acid binding (AMPA/kainite) receptors.
- There are eight subtypes of metabotropic receptor expressed on specific neuron subpopulations and coupled to different secondary messenger systems. Their effects range from excitatory to anti-excitatory. There are several regulatory sites on the NMDA receptor complex that modulate calcium influx when the receptor is activated (Figure 4). Regulatory sites that increase calcium influx (e.g. the glycine site) provide additional targets for neuroprotective interventions.

NMDA (N-methyl-D-aspartate) receptor



The NMDA receptor is an ionotropic glutamate receptor directly coupled to an ion channel that allows Na^+ and Ca^{2+} to enter the cell and K^+ to leave it. NMDA, glutamate and glycine are potent agonists. Other modulatory sites include the polyamine and redox regulatory site. Mg^{2+} is an antagonist, blocking the centre of the ion channel

4

Calcium influx acts as an important effector of glutamate neurotoxicity. The arrival of extracellular calcium triggers the release of intracellular calcium stores from the endoplasmic reticulum. The cytosolic calcium concentration rises to such an extent that protein kinase C, nitric oxide synthase (NOS) and a cascade of phospholipases, endonucleases and proteases are activated, which destroy the cell and its contents. The process has been described as an 'osmotic explosion'. It is possible to block calcium channels and spare the cell. The main calcium channels responsible for extracellular influx are the N, P and Q channels. There are no selective pharmacological blockers for these channels, but nimodipine improves outcome in spontaneous and traumatic subarachnoid haemorrhage. Whether this is due to prevention of catastrophic calcium influx into struggling neurons or its effect on vasospasm is unknown.

Increases in cytosolic calcium concentrations are partly buffered by mitochondrial calcium uptake. However, mitochondrial calcium overload can change the permeability of the inner mitochondrial membrane to macromolecules (a change in the properties of the mitochondrial permeability transition pore). The subsequent leak of cytochrome C is one trigger for apoptosis via the caspase pathway (see below). Drugs such as cyclosporin and tacrolimus can inhibit this process, and may be useful neuroprotective agents.

Glutamate, nitric oxide synthase and free radicals
When NMDA receptors are activated, nitric oxide (NO) is generated in the presence of calcium. NO is mildly cytotoxic. It is synthesized from L-arginine by the three isoforms of nitric oxide synthase (NOS). NO and $\bullet O_2^-$ react to form peroxynitrite ($\bullet ONOO^-$). With a relatively long half-life of about 1 second, this highly reactive free radical can diffuse over several cell diameters and breaks down into the damaging hydroxide radical ($\bullet OH^-$).

It would be reasonable to expect that high glutamate levels would cause secondary neuronal injury via these pathways too. The corollary of this is that inhibiting NOS might limit injury. Surprisingly, NOS inhibition has been found to reduce, to not affect, or even to increase secondary neuronal injury. These contradictory results may result from the specific isoform of NOS inhibited, the time at which NOS inhibition occurs, and the levels of NO present in injured tissue. Soon after injury, endothelial NOS (eNOS) produces NO, which dilates cerebral blood vessels and inhibits platelet aggregation, processes that result in improved blood flow and oxygen delivery. Low levels of NO may also modulate the redox regulatory site at the NMDA receptor to prevent calcium influx. Later, neuronal NOS (nNOS) and inducible NOS (iNOS) in inflammatory cells become the dominant source of NO production. The high levels of NO produced by these routes in the brain parenchyma overwhelm the beneficial effects of eNOS and NO becomes predominantly neurotoxic.

Cells generate free radicals as byproducts of normal and aberrant activity. In health, free radicals are scavenged and inactivated by a number of enzymes (superoxide dismutase, catalase, glutathione peroxidase) and chelators (ferritin, transferrin, vitamin E, uric acid). If oxygen and ATP are scarce, these energy-requiring safety mechanisms are compromised. An excess of free radicals breaks DNA strands, modifies DNA bases, alters protein structure and function and damages lipid bilayers. Free radical production and protection by free radical antagonists is well established in experimental CNS injury.

Immediate early genes and transcription factors
Acute insults to the brain trigger the expression of immediate early genes (IEGs) via a highly complex alteration in the balance of secondary messenger enzyme activity. IEGs most commonly expressed in CNS injury include c-*jun*, c-*fos*, *jun-B* and *jun-D*. The gene products are transcription factors, which activate another cascade of proteins via activator protein-1 (AP-1). AP-1 alters the expression of genes involved in the cell cycle, cell survival and regeneration. Several key genes also have a role in preventing (*bcl-2, bcl$_x$*) or producing (*bad, bax*) apoptosis.

Nuclear factor-κB (NF-κB) is another transcription factor independent of the AP-1 family. It can transduce a signal directly from the cell membrane to the nucleus without the need for enzyme cascades, implying a rapid response time. NF-κB release results in upregulation of a variety of proinflammatory mediators including cytokines and adhesion molecules, and may injure neurons through non-inflammatory mechanisms. Paradoxically, NF-κB expression may be neuroprotective in some settings.

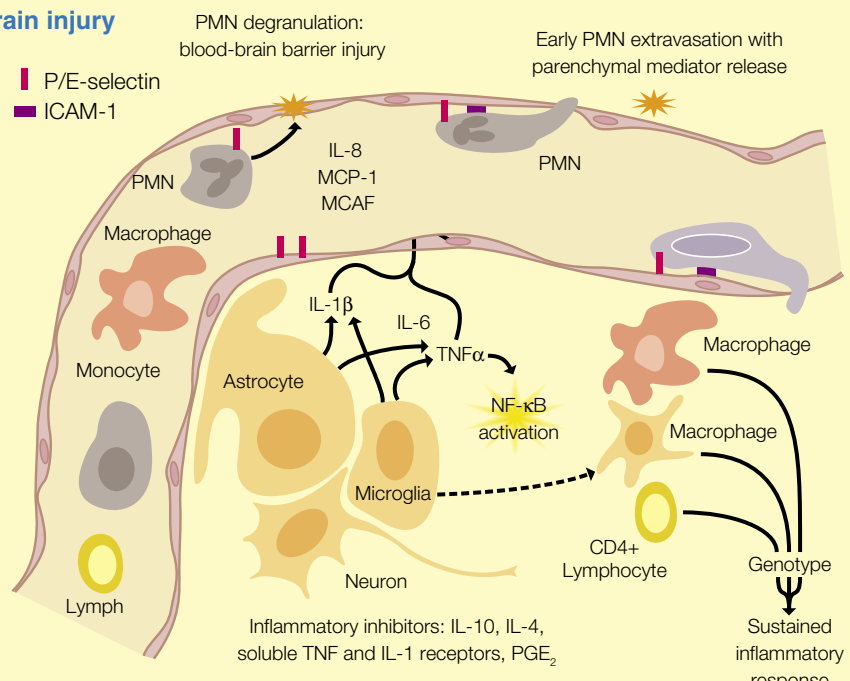
Proteases: caspases and calpains
Caspases (*c*ysteinyl *a*spartate-*sp*ecific prote*ases*) are a family of proteases fundamental to apoptosis. Their role was first elucidated in the nematode *Caenorhabditis elegans*. Three genes (*ced* genes) were found to regulate cell death as the worm developed, two causing cell death and one preventing it. Humans probably have 14 such genes, divided into the ICE (interleukin-1β converting enzyme) and CED-3 subfamilies. *In vivo* studies have shown that caspases are important in effecting neuronal apoptosis after cerebral injury.

Calpains are calcium-activated proteases belonging to a papain family of cysteine proteases. They are the enzymes that break down the cell's cytoskeleton, digest signal transduction enzymes and second messenger systems, and digest cell membrane receptors. They are the end-point of apoptosis, destroying its machinery and packaging it so that it can be phagocytosed. They may also be important in neuronal differentiation and long-term potentiation. As the end-point of apoptosis, they may be useful targets for future interventions.

The inflammatory response
The blood–brain barrier isolates the CNS from systemic inflammatory processes in health, but an inflammatory response is observed following acute CNS insults. The temporal pattern of inflammatory cell recruitment is modified in the CNS, but cytokine production, chemokine release, inflammatory adhesion molecule upregulation, and neutrophil recruitment are all observed in cerebral ischaemia and trauma (Figure 5). Neutrophils can be found at injury sites within hours, and remain for 24–48 hours. Macrophages arrive later, either recruited from the circulating monocyte population, or derived from the resident CNS macrophage population called microglia. Microglia behave differently from peripheral macrophages. In their resting state they have few of the features of macrophages and express few of the same genes. When activated they become phagocytic and secrete the inflammatory factors TNFα and TGFβ. The population of microglia in the CNS is small so the debris of a dead neuron is removed more slowly than in the peripheral nervous system. When the debris is cleared, astrocytes grow where the neuron once was, in response to IL-6 and TGFβ. This astrocytic scar forms a barrier to re-innervation.

Inflammatory responses following acute brain injury

The cytokines TNFα and IL-1β are secreted early by astrocytes and microglial cells, with later production of IL-6. Subsequently, both endothelial and parenchymal cells produce chemokines, including IL-8, monocyte chemoattractant protein-1 (MCP-1) and monocyte chemotactic and activating factor (MCAF), which attracts monocytes and macrophages. Leukocytes attracted by these chemokines undergo margination and extravasation subsequent to interaction with adhesion molecules such as P- and E-selectin and intercellular adhesion molecule-1 (ICAM-1), the endothelial expression of which is upregulated by cytokines and oxidants. The initial cellular response is mainly polymorphonuclear (PMN), and although this persists in man, later cellular responses predominantly consist of invading macrophages and CD4+ T lymphocytes. These cells, along with microglia-derived tissue macrophages, may be responsible for a sustained inflammatory response, the magnitude of which may show genetic polymorphism. TNFα also produces activation of the nuclear factor NF-κB, which has wide-ranging effects. Note that several anti-inflammatory mediators are also upregulated by injury and limit the intensity of the process



Intervening to prevent scar tissue formation and possibly to encourage re-innervation is attractive. However, the molecular relationship between neurons, microglia and astrocytes is poorly understood and likely to be highly complex. Many trophic factors are yet to be identified, but transplanting primary neurons and stem cells into injured areas is a mode of delivery that is generating much interest. ◆

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Obstetrics

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Anaesthesia for Operative Obstetrics

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Anaesthesia for obstetric operations must accommodate the physiological changes of pregnancy, and preserve maternal and fetal well-being. Delivery may be required rapidly when the fetus is at risk. Emergency procedures often occur outside working hours and in remote facilities. Obstetric surgery is associated with comparatively high mortality, and increasing medico-legal involvement.

Caesarean section

Elective lower segment caesarean section is performed for cephalopelvic disproportion, malpresentation, multiple pregnancies, placental insufficiency, and at maternal request following previous caesarean section. Emergency caesarean section is required when fetal or maternal well-being is acutely threatened.

Assessment: patients at high risk of operative delivery should be made known to the anaesthetic team and assessed. Women presenting for caesarean section are often well informed, and many have experienced it before. It is important to establish the woman's preference for anaesthesia and elicit information about any:

- obstetric history and previous caesarean sections
- previous anaesthetics used (or family history of suxamethonium apnoea or malignant hyperthermia)
- problems in this pregnancy (e.g. hypertension, diabetes, coagulation disorders)
- medications and allergies (e.g. latex, skin preparations, antibiotics).

Regional anaesthesia should be encouraged, and anxieties allayed, though potential complications must be discussed honestly. The presence of painful labour contractions may limit the extent of any discussion, but not its legal validity. An assessment of intubation difficulty must always be made and recorded. A simple bedside test such as Mallampati's classification is useful, but lacks a high positive predictive value. Difficult intubation (see page 218) should always be anticipated. Early insertion of an epidural catheter (for analgesia) is highly desirable when operative delivery is likely, particularly if general anaesthesia involves an added risk (e.g. known difficult intubation).

Emergency caesarean section: fetal distress is diagnosed from continuous fetal heart rate monitoring and fetal blood gas analysis, but remains an unreliable predictor of condition at birth. A briefer 'decision-to-incision' and 'incision-to-delivery' interval is associated with better initial fetal outcomes. Infants delivered by emergency caesarean section under general anaesthesia have been shown to have lower Apgar and other neurobehavioural scores compared with those under regional techniques. Both anaesthetist and obstetrician should decide which anaesthetic to use depending on the speed and safety required. All methods aim to prevent fetal acidosis by:

- ensuring adequate maternal oxygenation
- avoiding hypotension
- minimizing aortocaval compression
- preventing excessive maternal hypocapnia.

The left lateral position minimizes aortocaval compression (and improves uterine perfusion). Supplementary oxygen for the mother also improves fetal oxygenation. Maternal blood pressure should be maintained with non-glucose-containing crystalloid solutions and intravenous ephedrine. Discontinuing oxytocin infusions, and administering tocolytic agents (e.g. magnesium or β-agonists) reduces uterine activity and can improve acidosis. Fetal monitoring should be continued, because lasting improvement may allow time to convert to regional anaesthesia.

Regional anaesthesia

Regional techniques avoid many of the life-threatening complications of general anaesthesia. An increasing use of regional anaesthesia, has paralleled a fall in anaesthetic-related maternal mortality, though the absolute number of general anaesthetics has fallen only marginally. Apart from safety, regional anaesthesia has four other advantages.

- Fetal exposure to depressant drugs is minimized.
- Maternal participation at delivery is made possible, and the mother can bond with, and care for, her baby sooner.
- Blood loss is reduced.
- Postoperative analgesia is improved using spinal or epidural opioids.

Regional anaesthesia should be performed in a fully equipped operating theatre or anaesthetic room. Adequate resuscitation facilities must be available, together with the necessary drugs and equipment in case conversion to general anaesthesia is required. Reliable, large-bore (14 G or 16 G) venous access must be established before any regional procedure, and pulse oximetry and ECG monitoring established with frequent measurements of arterial blood pressure. Fluid pre-load of 1000–1500 ml of crystalloid solution is normally given. Correct aseptic technique includes wearing a gown, mask and gloves. Skin preparation with chlorhexidine in alcohol solution is effective, provided it is allowed to dry. Skin and deeper tissues are infiltrated with local anaesthetic (e.g. 2% lidocaine (lignocaine)) at the intended site.

Spinal anaesthesia is the quickest and simplest technique. It produces a superior quality of anaesthetic block, and requires anaesthetic doses that cause minimal toxicity to mother or fetus. However, there is no opportunity to provide intraoperative supplementation via the same route in the event of inadequate anaesthesia, or prolonged surgery.

Spinal injection can be performed in the lateral position, but in the obese patient the sitting position helps to identify the midline, and assists the mother to flex her back. The L3/4 or L4/5 interspaces are chosen to avoid direct trauma to the spinal cord. A 25 G or preferably 27 G pencil-point (Whitacre or Sprotte) needle causes a low rate of post-dural puncture headache (PDPH). These small-gauge needles often require an introducer needle. Commonly used regimens are listed in Figure 1.

Commonly used regimens for regional anaesthesia

Caesarean section

Spinal

- Bupivacaine (hyperbaric – usually 0.5% bupivacaine in 8% glucose), 10–12 mg, ± fentanyl, 25 μg, or diamorphine, 200–300 μg

Epidural

- Test dose: 0.5% bupivacaine, 3 ml (± adrenaline (epinephrine), 5 μg/ml)
- Loading dose: 0.5% bupivacaine, 20 ml (± adrenaline (epinephrine), 5 μg/ml) + fentanyl, 50–100 μg, or diamorphine, 2–5 mg (in saline, 10 ml)
- 0.5% levobupivacaine, 20 ml, + opioid
- 0.75% ropivacaine, 20 ml, + opioid

Extension of *in situ* epidural

- 2% lidocaine (lignocaine), 15–20 ml, + adrenaline (epinephrine), 5 μg/ml, ± opioid
- 0.5% bupivacaine, 15–20 ml, (± adrenaline (epinephrine), 5 μg/ml) ± opioid
- 50:50 mixture 0.5% bupivacaine and 2% lidocaine (lignocaine), 15–20 ml, (± adrenaline (epinephrine), 5 μg/ml, ± 8.4% sodium bicarbonate, 2 ml) ± opioid
- 0.5% levobupivacaine, 15–20 ml, ± opioid
- 0.75% ropivacaine, 15–20 ml, ± opioid

Operative vaginal delivery (forceps, ventouse)

***In situ* epidural catheter**

- 0.25–0.5% bupivacaine, 10–15 ml, + fentanyl, 25–50 μg

Spinal or combined spinal-epidural

- 0.5% bupivacaine (hyperbaric), 1.5–2 ml, ± fentanyl, 25 μg

1

Epidural anaesthesia: insertion of an epidural catheter is technically more difficult than spinal injection, and more time is required to produce an effective block. However, the block can be established incrementally if needed, and supplemented during surgery. Preparation, precautions and position are the same as for spinal anaesthesia. The two approaches to the epidural space are the midline and the paramedian; the former is most commonly used.

For the midline approach, the epidural needle is inserted into the interspinous ligament, normally below the L2/3 interspace, and the epidural inner stylet withdrawn. The epidural space is identified by loss of resistance to injection of saline. The saline technique reduces the incidence of dural puncture with the epidural needle. The epidural catheter is passed through the needle, which is itself removed, leaving only the epidural catheter *in situ*. The epidural catheter is then withdrawn leaving 4–5 cm in the epidural space, and finally taped to the skin and a bacterial filter attached to the distal end. A test dose of local anaesthetic should be administered to exclude subarachnoid or intravascular placement (Figure 1). If dural puncture has occurred, the catheter can be resited in an adjacent space, but the response to the test dose must be monitored carefully. Alternatively, the catheter can be advanced into the subarachnoid space, and used as a spinal catheter.

***In situ* epidural catheter:** an epidural catheter, that has been used for labour analgesia and is functioning correctly, can be used to extend the existing block for emergency caesarean section. No optimum solution has been found to do this rapidly and effectively, but choices are shown in Figure 1.

Combined spinal-epidural anaesthesia combines the speed of onset and quality of spinal anaesthesia, with the flexibility of an epidural catheter, though it is technically more difficult to perform. Concerns have been raised that 'drug flux' may occur from the epidural space once a hole has been made in the dura. This has been reported, but the risk is thought to be significant only if large-gauge spinal needles are used, and high local anaesthetic concentrations are subsequently injected epidurally.

This combined technique is most commonly performed as a 'needle through needle' technique, in which a long spinal needle such as a 119 mm, 27 G Whitacre spinal needle is advanced (once the epidural needle has been correctly located in the epidural space) through the dura mater into the subarachnoid space. The spinal injection provides rapid anaesthesia for surgery and the epidural catheter is used for intra-operative supplementation or for postoperative analgesia.

Infiltration and field block: direct infiltration of the anterior abdominal wall with local anaesthetic, layer by layer, can make surgery possible. Alternatively, intercostal and iliohypogastric blocks and/or rectus sheath block combined with direct infiltration of the incision line have been used. Visceral reflexes can also be obtunded to some degree by injection of local anaesthetic around the uterovesico fold and paracervical area. Up to 100 ml of 0.5% lidocaine (lignocaine) with 1:200,000 adrenaline (epinephrine) may be used. Most obstetricians have limited experience with this technique.

Intraoperative care of the patient: the patient should be placed in the full lateral position while the block develops, and supplementary oxygen given. Complaints of nausea normally indicate hypotension and require prompt treatment with ephedrine. Ethyl chloride spray or needle-prick testing will establish the extent of sensory blockade, which should reach an upper level of the T4 dermatome (See *Anaesthesia and Intensive Care Medicine* **1:1**: 42). Surgery should not proceed until this sensory level is achieved. Patients should be warned that some discomfort may be encountered at delivery, or if the uterus is brought out during closure. Continued reassurance is important. Oxytocin, 10 i.u., is routinely given after delivery and at the end of surgery, rectal analgesics (e.g. diclofenac sodium, 100 mg) can be administered.

Problems

Hypotension (defined as a 20% or greater fall in systolic blood pressure) is more common during spinal than epidural anaesthesia, and also in non-labouring women. Sympathetic blockade causes reduced venous tone, pooling of blood in the lower body, and decreased systemic vascular resistance. Hypotension adversely affects uterine perfusion and fetal acidosis, and precipitates maternal nausea and vomiting. It requires prompt treatment, including the adoption of the lateral position, intravenous fluids and vasoconstrictors. Ephedrine is the vasoconstrictor of choice, owing to its sparing effect on uterine vasculature.

Nausea and vomiting are common. They may potentially lead to the aspiration of gastric contents. Hypotension is the most common precipitant, though prior opioid administration contributes.

Inadequate block results from failure of technique, or allowing insufficient time for the block to develop. It is more common with epidural than with spinal anaesthesia, due partly to inadequate spread within the epidural space, and also catheter migration into paravertebral spaces. Poor block is the most common reason for conversion to general anaesthesia, and also a potential source of litigation.

Dural puncture has a theoretical frequency of 0.3% or 1/200 (to which units should aspire), but is often more common. The symptoms of PDPH can be severe and disabling in post-partum patients, and are also associated with significant sequelae (see page 222). Symptoms should be actively sought at follow-up, and established headaches treated actively with epidural blood patching. Many units treat milder headaches with conservative treatment including bed rest, oral analgesics, intramuscular ACTH, subcutaneous sumatriptan and oral or intravenous caffeine.

Total spinal blockade occurs when an epidural dose of local anaesthetic is inadvertently given intrathecally, causing complete motor and sensory blockade, profound hypotension, loss of consciousness and airway reflexes.

Side-effects of local anaesthetic drugs manifest as toxicity when upper safe limits are exceeded, or accidental intravenous injection occurs. Spinal or epidural opioids can cause pruritus and respiratory depression. Delayed respiratory depression with opioids is uncommon in obstetric patients and less likely to occur with more lipid-soluble compounds (e.g. fentanyl, diamorphine). Intrathecal or epidural diamorphine is probably the most common opioid used in the UK to provide postoperative analgesia after caesarean section under regional block.

Neurological complications are four times more likely to be caused by the fetus passing through the pelvis, or by iatrogenic injury. In contrast, complications from regional anaesthetic techniques occur in about 1/13,000 deliveries.

Paraplegia and cauda equina syndrome result from spinal cord compression by epidural haematoma, or abscess. Haematoma is extremely rare, but classically presents with sharp irradiating back pain and sensorimotor deficit. Early symptoms of epidural abscess include headache and backache, which may be most severe at the epidural site. Later signs of bladder and bowel disturbance may occur with or without signs in the lower limbs. Once symptoms have developed, urgent surgical decompression is required within 8 hours, to prevent permanent neurological damage.

Nerve injury can be caused by epidural or spinal needles. Direct contact with a nerve root for example, may produce transient paraesthesia, while nerve root trauma usually causes severe lancinating pain radiating to the dermatome it supplies. Patients may be left with areas of paraesthesia, hypoanalgesia or weakness, which take variable lengths of time to resolve. Adequate follow-up and reassurance are important, ideally involving a neurologist experienced in this area.

Meningitis is a rare but recognized complication of regional anaesthesia. Bacterial meningitis is usually caused by species of *Streptococcus* or *Staphylococcus*, resulting from direct haematological spread or poor aseptic technique on insertion. Aseptic meningitis may be caused by viral infection, equipment contamination, or in association with certain drugs.

Contraindications may be absolute or relative (Figure 2). The need for extremely urgent delivery may allow insufficient time for regional methods to be performed. Spinal deformities (e.g. scoliosis) make regional anaesthesia technically more difficult and less reliable. Neurological diseases (e.g. multiple sclerosis) are not a contraindication to epidural anaesthesia, though data on intrathecal injections are lacking.

Coagulopathy can place patients at risk of epidural haematoma, though most women are prothrombotic in late pregnancy. Adequate haemostasis depends on platelet numbers and function. Most UK centres agree that a count of over 100 x 10^9/litre is safe for performing neuraxial blockade, and the range 80–100 x 10^9/litre remains acceptable if coagulation tests are normal. Counts below 50 x 10^9/litre represent an absolute contraindication. Pre-eclamptic patients may present with falling platelet counts, or impaired coagulation, and recent values are essential. Prophylactic administration of heparin, particularly low molecular weight heparin (LMWH), is increasingly common. For unfractionated heparin, present guidelines state that neuraxial blocks can be performed 4 hours after the last dose, and the catheter removed 4 hours following a subsequent one. For LMWH, 12 hours should elapse. Recent consensus is that aspirin and other antiplatelet drugs when used alone are not a contraindication to regional block. In less clear-cut cases, point of care monitors such as the thromboelastogram may have a role, and advice from a haematologist should be sought.

Anticipation of significant haemorrhage – placenta praevia occurs where the placenta implants ahead of the presenting fetal part (in about 1/200 pregnancies). It remains a principal cause of massive obstetric haemorrhage, but is now better detected and managed by caesarean section. The exact grading depends on the extent to which the placenta covers the lower segment and os, but this does not dictate the choice of anaesthesia. There is no consensus, though modern practice is increasingly using regional techniques, except where urgent delivery is essential, or significant maternal hypovolaemia has occurred. In all cases, potential haemorrhage must be anticipated. It results from incision of the placenta (particularly when anterior), uterine atony, or the occurrence of placenta accreta. Reliable, large-bore venous access must be established before surgery, cross-matched blood should be available, and measures to promote uterine contraction may be needed.

Systemic sepsis – maternal pyrexia is common in labour, but does not generally indicate sepsis. Prolonged rupture of membranes (defined as over 24 hours) is the most important cause, and may be associated with chorioamnionitis in which 8% of women will be bacteraemic. Regional techniques may incur the risk of meningitis or epidural abscess, though a causal relationship is unproven, and the incidence of these complications remains low, even in febrile patients. Most authorities conclude that epidural catheters can be safely sited in patients with chorioamnionitis once antibiotic treatment has commenced, but should be avoided if there are signs of untreated sepsis.

Contraindications to the use of regional anaesthesia

Absolute
- Maternal refusal
- Coagulopathy
- Local sepsis
- Severe uncorrected hypovolaemia
- Known allergy to local anaesthetic agent

Relative
- Urgent delivery
- Spinal deformities
- Anticipation of significant haemorrhage
- Systemic sepsis

2

General anaesthesia
Large-bore venous access must be established (minimum calibre 16 G). The patient should be prepared on the operating table, in a left tilted position or with a left uterine wedge. Pulse oximetry, automated blood pressure cuff, and ECG are the minimum levels of monitoring required. Capnometry is also considered essential to confirm tracheal intubation, and satisfactory ventilation. A source of suction, gum elastic bougies, and smaller sized tracheal tubes (e.g. 5–7 mm internal diameter) must be available, together with short-handled laryngoscopes and alternative designs of blade (e.g. the McCoy laryngoscope). Equipment to assist with oxygenation in the event of failed intubation should be immediately accessible, and includes simple oral airways, laryngeal mask airways, and a cricothyroid puncture set.

The surgical team routinely prepare and drape the skin before induction, to minimize subsequent delay. Preoxygenation of the lungs is achieved by 3 minutes' breathing (or four vital capacity breaths) 100% oxygen through a close-fitting mask. Anaesthesia is induced intravenously as a rapid sequence with thiopental (thiopentone), 6–7 mg/kg, and suxamethonium, 1.5 mg/kg. Cricoid pressure is applied by an assistant. Tracheal intubation must be confirmed by observing the chest for equal expansion, auscultating the chest at both axillae and over the stomach, and by the presence of a regular capnograph waveform. Preparations for a potential failed intubation (see page 218) must be made beforehand, and a drill followed.

Anaesthesia should be ensured by administering adequate concentrations of a volatile agent (e.g. 1% isoflurane with oxygen:nitrous oxide 50:50), and a non-depolarizing muscle relaxant (e.g. atracurium). After delivery and clamping of the umbilical cord, the nitrous oxide concentration can be increased, and opioid analgesia given (e.g. morphine, 10 mg i.v.), together with prophylactic antibiotics. Oxytocin, 10 i.u., is routinely given once the fetus has been delivered, and may be followed by an infusion (e.g. 20–40 units over 2–4 hours). At the end of surgery, rectal analgesics (e.g. diclofenac sodium, 100 mg) can be administered, and patients recovered in the left lateral position and extubated when awake.

Problems

Failure of oxygenation is the most serious and life-threatening complication of general anaesthesia. Functional residual capacity is reduced in pregnancy, causing rapid desaturation in the apnoeic patient. Hypoxia results from an inability to manage a difficult airway, though this has usually followed unsuccessful tracheal intubation. Failed intubation in obstetric patients (see page 218) is eight times more common than in the general surgical population. Full dentition and enlarged breasts make insertion of the laryngoscope more difficult, while obesity and upper airway oedema impede direct laryngoscopy, and make the airway more difficult to manage. Additionally, cricoid pressure applied in the wedged position can displace the glottis laterally, and intubation attempted before suxamethonium is maximally effective will be more likely to fail.

Aspiration of gastric contents continues to cause maternal morbidity and mortality. Lower oesophageal sphincter tone is reduced in pregnancy and gastric emptying is delayed during labour, the delay being exacerbated by opioid administration. All women must receive antacid prophylaxis before caesarean section. Ranitidine, 150 mg, given orally at 12 and 3 hours before surgery effectively reduces acid secretion, and metoclopramide, 10 mg, on the morning of surgery contributes to reduced gastric volume, and increased lower oesophageal sphincter pressure. For emergency surgery, ranitidine, 50 mg, can be given intravenously. A non-particulate antacid (e.g. sodium citrate 0.3 M, 30 ml) should also be given within 20 minutes of surgery.

Hypertensive response to intubation may be exaggerated in patients with pre-eclampsia or pre-existing hypertension. It may be obtunded by β-blockade, or short-acting opioid drugs and, if hypertension poses an increased risk (e.g. cerebrovascular disease), intra-arterial blood pressure monitoring should be instituted.

Maternal awareness represents a terrifying ordeal with potentially long-lasting psychological consequences. In the past this has resulted from small induction doses of thiopental (thiopentone) causing inadequate anaesthetic drug concentrations before intubation, and from deliberate avoidance of volatile agents caused by concerns of uterine relaxation (leading to past awareness rates of 12–26%). Pregnant women may have higher anaesthetic requirements owing to increased cardiac output, and high catecholamine levels secondary to pain and anxiety.

Fetal depression is increased with a longer ‘induction-to-delivery’ interval.

Postoperative care
patients should ideally be cared for in a designated recovery area. Blood pressure, pulse rate, respiratory rate and arterial oxygen saturation must be monitored for at least 1 hour before return to the post-natal ward.

Postoperative analgesia after regional techniques (see page 214) can be provided with intrathecal opioids (e.g. diamorphine, 200–300 µg) administered together with the local anaesthetic at the time of spinal injection, or by subsequent top-ups of epidural opioid (e.g. diamorphine, 2.5 mg) via an epidural catheter. Respiratory depression, especially with less lipid-soluble opioids, is a serious complication, and if adequate observations cannot be made, these techniques should be used with caution. Lipid-soluble opioids (e.g. diamorphine) are seldom associated with delayed respiratory depression in the obstetric population and are routinely used in many UK units. Paracetamol and regular non-steroidal suppositories are highly effective (e.g. diclofenac sodium, 150 mg/day, in divided doses for 3–5 days).

Monitoring for complications of regional anaesthesia (as listed above) must include observation for signs of spinal cord compression or neurological deficit, and also headache and backache.

Thromboprophylaxis – in recent years, thromboembolism has been the leading cause of death in pregnancy, occurring frequently after caesarean section. Important risk factors are age over 35 years, obesity, grand multiparity, immobility, pre-eclampsia and emergency caesarean section. Women at moderate or high risk must receive thromboprophylaxis, for example unfractionated heparin starting at the time of surgery and continued until discharge from hospital.

Pregnancy-related illnesses

A number of maternal medical conditions can complicate pregnancy, but pre-eclampsia and cardiac diseases have particularly important implications for anaesthesia.

Pre-eclampsia complicates 5–10% of pregnancies, presenting as a syndrome of hypertension, proteinuria and/or oedema usually after 20 weeks’ gestation. The only definitive treatment is delivery for which caesarean section is commonly required. Regional anaesthesia is strongly indicated except where coagulopathy is present. In mild disease, most women have normal platelet counts and coagulation, though 20% may show evidence of a consumptive thrombocytopenia and platelet function abnormalities especially in severe pre-eclampsia. In the HELLP (Haemolysis, Elevated Liver enzymes, Low Platelets) syndrome variant, thrombocytopenia can be severe with counts of less than 50 x 10^9/litre. If a recent platelet count is above 100 x 10^9/litre, coagulation is unlikely to be abnormal. Below this level, a coagulation screen must be performed. Spinal and epidural techniques for caesarean section in patients with pre-eclampsia are equally acceptable, and the incidence of hypotension is equivalent. Fluid pre-loading in women with severe pre-eclampsia should be restricted to no more than 500 ml of crystalloid or colloid solution, and hypotension corrected with ephedrine.

With general anaesthesia, the hypertensive response to intubation must be obtunded, to reduce cerebral haemorrhage risk. Intravenous alfentanil, 10–20 µg/kg, or labetalol, 10–20 mg, can be used. Upper airway oedema is common, making intubation and airway management difficult. Smaller sized tracheal tubes may be required, and postoperative ventilation should be considered in cases of potential obstruction. Pre-eclamptic patients are increasingly receiving magnesium therapy, which potentiates non-depolarizing muscle relaxants, and reduced doses should be used.

Cardiac disease is causing increasing maternal mortality, as more women with congenital defects survive to reproductive age. Patients require care in specialist units, with individual assessment and planning, but some general points can be made. Elective caesarean section is commonly favoured. Epidural block may be considered if a slow incremental top-up technique with intra-arterial blood pressure monitoring is used. Sudden cardiovascular changes are reduced, and conditions such as aortic or mitral regurgitation may benefit from reduced systemic vascular resistance.

General anaesthesia may be unavoidable if anticoagulation is required, and in other individual instances. Cardiac considerations should dictate the choice of anaesthesia and, because intra-operative opioids improve haemodynamic stability, they will often be the agents of choice. However, fetal respiratory depression can occur, requiring ventilatory assistance or administration of naloxone.

Oxytoxic drugs can increase pulmonary vascular resistance, promote fluid retention and lead to cardiac decompensation. Many units avoid them at delivery but because this risks post-partum haemorrhage, it is preferable to administer dilute oxytocin over 30 minutes or administer it cautiously in incrementally diluted solutions.

Anaesthesia for other procedures

Cervical cerclage

Cervical incompetence can cause recurrent mid-trimester abortions. In most cases, the cervix can be re-enforced by cerclage, and this is typically performed at 12–18 weeks' gestation as a prophylactic procedure. It may also be attempted in an emergency for actively bulging membranes and, in this situation, reduction of intrauterine and intra-abdominal pressure is important. General anaesthesia has been advocated, because volatile agents can decrease intrauterine pressure and facilitate reduction of the membranes, but coughing and straining must be avoided. In contrast, a regional technique reduces these risks, but positioning, movement and vomiting may increase the possibility of membrane rupture. There is little definite evidence to support either approach. The procedure is performed transvaginally and, if a regional technique is chosen, blockade to T8/10 level is required for which epidural and spinal anaesthesia are both suitable.

Manual removal of retained placenta

The placenta must be manually removed if normal separation does not occur or fragments remain within the uterus. Post-partum haemorrhage may occur in both instances, and patients must be adequately resuscitated first. The choice of anaesthetic technique depends on the degree of haemorrhage and the presence of an *in situ* epidural catheter. Manual removal requires anaesthetic block to a sensory level of T6. If an epidural catheter is in place, incremental boluses of 0.5% bupivacaine or 2% lidocaine (lignocaine) with adrenaline (epinephrine) 1:200,000 up to a total volume of 20 ml may be used to provide anaesthesia. Alternatively, a spinal technique as outlined above can be used, using bupivacaine, 10 mg.

General anaesthesia is required if regional methods are contraindicated or at maternal request. Conduct is the same as for caesarean section, though opioids can be used at induction because fetal depression is not a consideration. Intraoperative uterine relaxation can be provided with transiently high concentrations of volatile agent. Alternatively, nitroglycerine, 50–500 µg i.v., has been used to relax the uterus. Haemorrhage and uterine inversion are potential complications.

Operative vaginal delivery

Additional analgesia or anaesthesia is often needed for ventouse or forceps delivery. The choice of technique is influenced by the presence of an existing epidural catheter, the degree of pain that the mother is likely to experience (e.g. forceps delivery compared with ventouse), the urgency of delivery and the likelihood of success; failed vaginal delivery usually necessitates immediate caesarean section. The following options can be considered.

- An existing epidural catheter can be used to augment the block (Figure 1).
- An epidural, spinal or combination catheter can also be inserted.
- The obstetrician can perform a pudendal nerve block to provide analgesia for a low forceps or ventouse delivery, or infiltrate local anaesthetic into the perineum before episiotomy. *Entonox* (oxygen: nitrous oxide) can be given to supplement the block.

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Anaesthetic Management of Labour (Induction and Augmentation)

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Labour management aims to ensure a safe delivery for both mother and baby. This is achieved through close monitoring of labour progress, together with assessment of maternal and fetal well-being. When problems arise, the options are to instigate more intensive surveillance, introduce therapeutic measures to correct pathology, or to deliver the baby. This article defines labour and its different stages and describes the methods for detecting problems and how to deal with them.

Diagnosis of labour

The correct diagnosis of labour is essential and can be difficult. Incorrect diagnosis leads to high rates of intervention. Labour is characterized by regular uterine contractions, dilatation of the cervix and descent of the presenting part. The key to diagnosing labour is observing a change in cervical state on consecutive vaginal examinations.

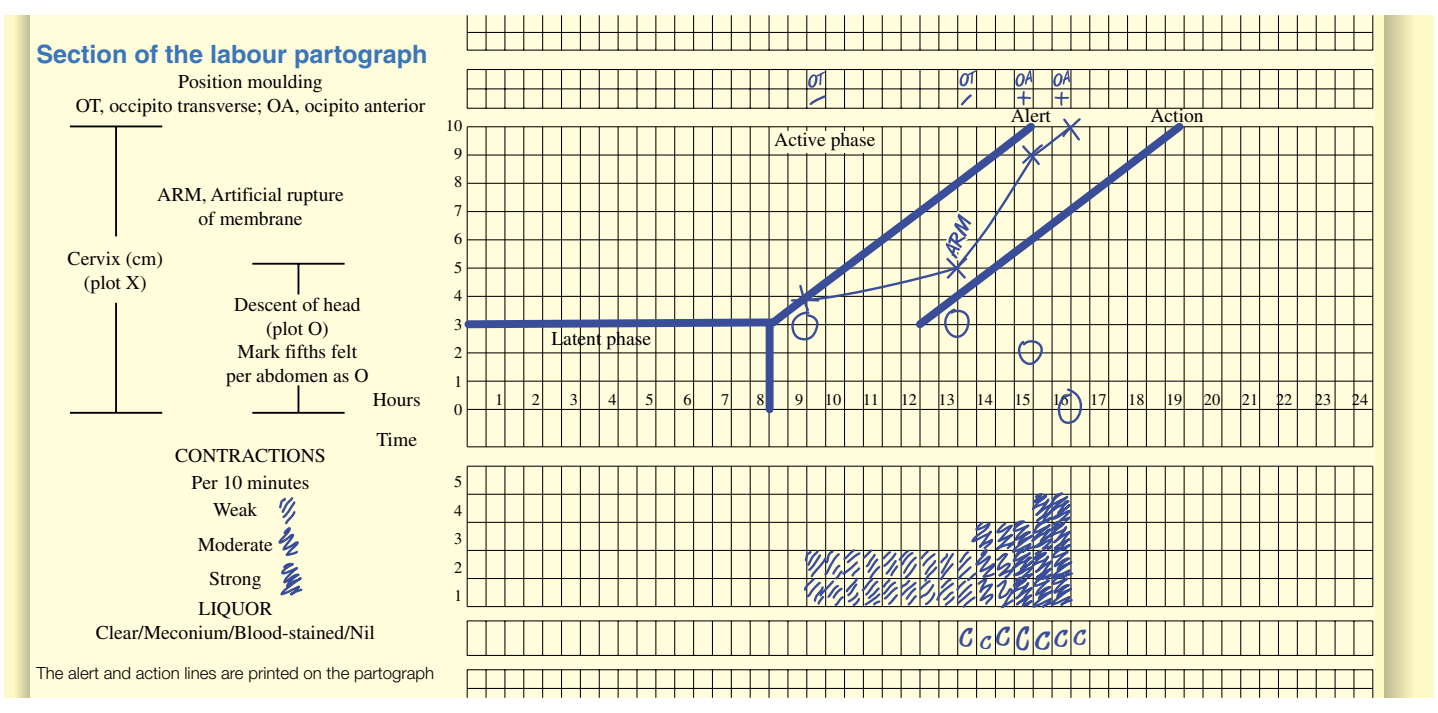
Partogram

The partogram is a graphical record of the progress of labour (Figure 1). The cervical dilatation is plotted against time, along with the descent of the presenting part (usually cephalic). Adequate and progressive descent of the fetal head is a good sign of labour progress. Descent should always be sought in addition to cervical dilatation, because the latter can occur in an obstructed labour. Abdominal assessment of descent is necessary because vaginal assessment can falsely suggest progress when there is increasing swelling on the head (caput). Lines are often drawn to indicate when progress (as judged by cervical dilatation) is slow; this indicates the need for action.

The strength and frequency of the contractions are noted, but they are not reliable signs of an adequate labour.

The state of the liquor is documented. Staining with meconium or blood indicates possible fetal compromise and warrants close fetal monitoring. No liquor with ruptured membranes may be a sign of fetal compromise.

Maternal temperature, pulse and blood pressure are recorded regularly. The fetal heart rate is also noted, primarily to identify a rise in baseline. Tachycardia may indicate fetal distress or infection, and the need for continuous monitoring by cardiotocogram.



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Assessing risk

The onset of labour: a spontaneous onset of labour is associated with the best chance of a normal delivery. Induction of labour is achieved by ripening the cervix (if necessary) usually with vaginal prostaglandins (PGE2), repeated as necessary. This is followed by an artifical rupture of the membranes when possible, which releases endogenous prostaglandins. Stimulation with oxytocin is used if labour does not become established, usually within a couple of hours. The indication for induction and the induction itself significantly increase the need for intervention in labour, including operative deliveries.

Parity: compared with a multiparous woman, a woman in her first labour (primiparous) is much more likely to require intervention, the progress of labour is slower, and oxytocin is needed more often. Caesarean section and operative vaginal delivery rates are higher in primiparous women (about tenfold). The same partogram is used for all women. A delayed labour in a multiparous woman is more likely to be a result of a serious cause, and is therefore more urgent.

Maternal and fetal disease: risk in labour is dependent on maternal and fetal well-being. A growth-restricted fetus, or a poorly functioning placenta (e.g. in pre-eclampsia) increases the risk of fetal distress. These types of labour are often induced, confounding the problems. Pregnancies of more than 42 weeks' gestation are prone to increased rates of fetal distress and intervention.

Regional analgesia: women having difficult labours often request epidural analgesia. A significant proportion of these women do not achieve a spontaneous vaginal delivery because a regional block increases the need for oxytocin stimulation and assisted vaginal delivery. However, it is unlikely to increase the need for caesarean section.

Support in labour: emotional and physical support in labour has been shown to improve outcome. Having a birthing partner or one-to-one midwifery care is probably the best way to avoid problems.

Stages of labour

Intervention in labour is aimed at preventing a long labour associated with fetal distress and infection.

First stage

The first stage occurs from the onset of cervical change to 10 cm dilatation. The first stage of labour can be divided into latent and accelerative phases (Figure 1). The latent phase can last up to 8 hours, without the need for intervention. A prolonged latent phase should be managed by artificial rupture of the membranes, followed by an oxytocin infusion if progress remains slow. At about 3 cm, the rate of cervical change increases. In about 75% of women in labour in their first pregnancy, the cervix will dilate at least 1 cm/hour during this later accelerative phase. Rates less than this may be abnormal, and indicate a dysfunctional labour or secondary arrest. A dysfunctional labour is usually caused by inadequate uterine activity and is common in primiparous women. It can be corrected using an oxytocin infusion. However, secondary arrest must be excluded. This can result from malposition (e.g. occipitoposterior position) or malpresentation (e.g. brow, which usually requires delivery by caesarean section). Whatever the cause of delay (as assessed on cervical dilatation and head descent), the degree and severity of obstruction can be assessed by the caput and moulding on the head, and the adequacy of the pelvis, during vaginal examination. This determines whether oxytocin can be used to augment the labour and if there is a need for caesarean section. Inefficient uterine action is uncommon in a multiparous women, and oxytocin must be used cautiously even when there are no other signs of obstruction, or the uterus may rupture. True cephalic–pelvic disproportion, a possible cause of secondary arrest (i.e. normal presentation with adequate uterine activity and delay) is rare. Women with a previous caesarean section also have the risk of scar rupture and should be assessed closely, but over 70% achieve vaginal delivery.

Vaginal examinations are performed every 4 hours in normal labour, but can be performed more often if delay develops (usually 2 hourly). If an intravenous infusion of oxytocin is used, it is titrated to contraction frequency so that there are no more than five contractions in 10 minutes. Increased frequency above this may not allow the uterus to relax and increases the risk of fetal distress. Women with prolonged labour should be adequately hydrated, and often require intravenous fluid. The fetus should be continuously monitored with an electronic fetal heart rate monitor. Slow progress between 7 and 10 cm has been associated with higher rates of instrumental vaginal delivery.

Second stage

The second stage occurs from full dilatation (10 cm) to delivery of the baby. A prolonged second stage may increase the risk of fetal distress and pelvic floor damage. The diagnosis depends on the time of the vaginal examination and, in practice, it is the length of pushing that equates best to risk and should be limited. If women do not have the desire to push, and the head still has room to descend, then a delay before pushing is often advised. This is often necessary with an epidural, when oxytocin is also more commonly used. It is unusual to wait for more than 2 hours before commencing pushing, but if delivery has not occurred after 1 hour of pushing, the need for assistance should be considered urgently. Maternal exhaustion usually requires intervention at this time. A ventouse is generally safer, particularly from the maternal viewpoint, and can be performed without an episiotomy in some cases. Forceps are more often used in difficult cases. Rotational forceps, although not widely used, can be employed when the presenting part is malpositioned, but their use requires more skill.

Third stage

The third stage occurs from delivery of the baby to delivery of the placenta. *Syntometrine* (a combination of oxytocin, 5 IU, and ergometrine, 0.5 mg) is given intramuscularly with the delivery of the anterior shoulder. This reduces the incidence of post-partum haemorrhage. Ergometrine can cause nausea and sickness. The placenta is delivered by cord traction, once the uterus has contracted and the placenta separated.

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Anatomy of the Uterus

Hazel Adams

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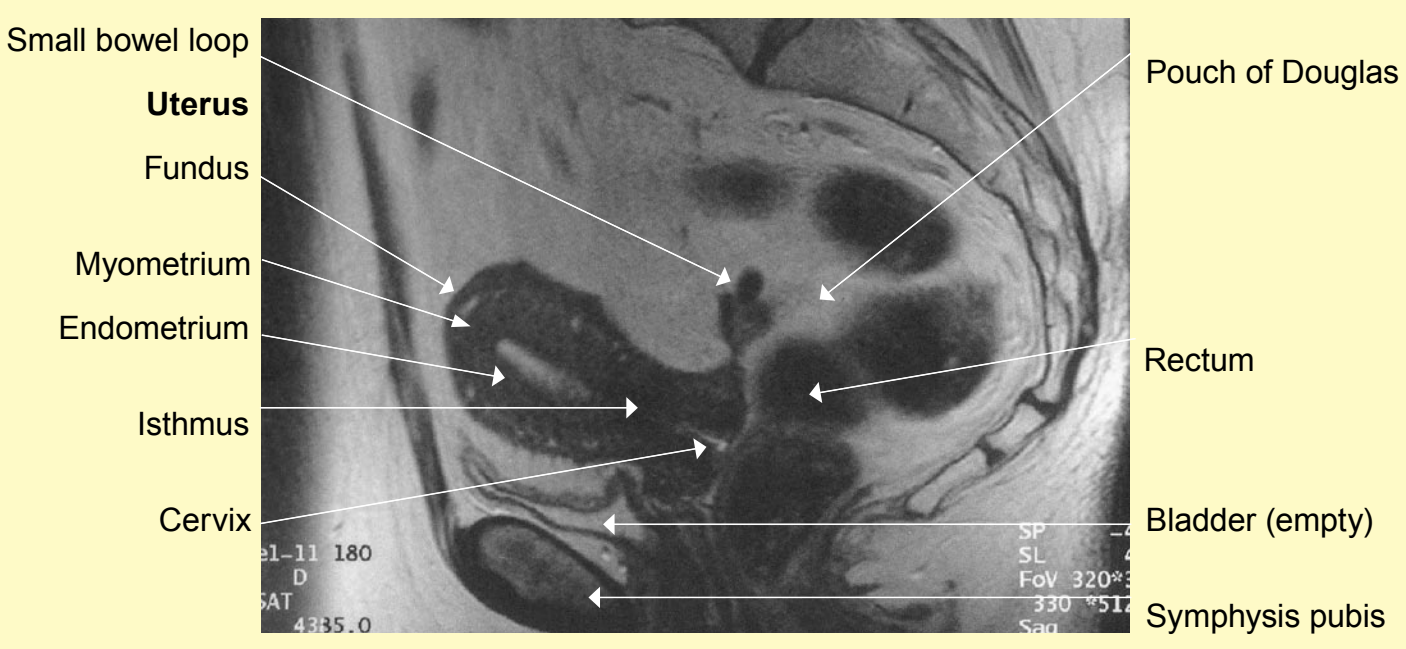
The uterus is a muscular tube, widest at the top and flattened anteroposteriorly (Figure 1). It lies between the bladder and the rectum and is separated from them by a layer of peritoneum. The uterine tubes are embedded in its upper lateral edges and extend laterally to the ovaries. The fundus is the domed area above the insertion of the tubes. The body is mainly smooth muscle (the myometrium) arranged in three ill-defined layers. The outer fibres tend towards longitudinal and the inner layers are more circular, acting like sphincters around the blood vessels. The lowest 3 cm of the uterus is the cervix and the part of the body adjacent to the cervix is the isthmus. During pregnancy, the isthmus forms the lower uterine segment, which is where the uterine incision is usually made during a caesarean section.



1 MRI of the female pelvis

The cervix protrudes into the anterior wall of the vagina. The ureters pass forwards to the bladder in the parametrium (the connective tissue surrounding the cervix). The ureters are closely related to the uterine arteries.

The vagina is a fibromuscular tube at 60° to the horizontal. The space between the cervix and vagina is the fornix. Anteriorly the vagina is in contact with the base of the bladder. The urethra is adherent to the anterior wall of the vagina.

The ovaries are attached to the posterior border of the broad ligament by a double fold of peritoneum. The obturator nerve (anterior primary rami of L2, 3, 4) and vessels lie laterally. Pain from the ovary may be referred to the inner thigh. During pregnancy the ovaries are pulled upwards.

Peritoneum: the uterus is enclosed by peritoneum, a double fold of which extends laterally to the walls of the pelvis as the broad ligament. Posteriorly, the peritoneum extends beyond the cervix to the wall of the vagina. It forms the recto-uterine pouch of Douglas, which contains small and large bowel. Anteriorly, the peritoneum is reflected on to the bladder at the level of the isthmus. During a lower segment caesarean section it must be divided in order to avoid damaging the bladder.
Blood supply

The uterus is supplied by the uterine arteries, which usually branch from the internal iliac artery. They pass medially across the pelvic floor in the broad ligament to reach the cervix and give branches to the cervix and vagina. There are anastomoses between both uterine arteries and the ovarian arteries, which increase during pregnancy.

Venous drainage is through the several pelvic plexuses to the internal iliac veins. These plexuses are the cause of the severe haemorrhage associated with a fractured pelvis. There are no valves in the pelvic veins. Raised intra-abdominal pressure may cause back flow through the sacral veins into the venous plexuses within the vertebral column. From there, blood drains into the superior vena cava via the posterior intercostal and the azygos veins.

The ovaries – the ovarian arteries are branches of the aorta below the renal arteries. They are retroperitoneal and enter the broad ligament each giving off a tubal branch.

Nerve supply

The sympathetic supply
Fibres from cell bodies at T11–L2 pass to plexuses continuing downwards in front of the aorta. They form the superior hypogastric plexus at the level of L5 along with fibres from L3 and L4. This plexus divides into right and left hypogastric nerves, which run into the pelvis to form the inferior hypogastric plexus. Each inferior hypogastric plexus lies lateral to the rectum on the side walls of the pelvis. They receive contributions from the sacral sympathetic ganglia.

The uterus is supplied by the superior and inferior hypogastric plexuses. The cell bodies of the sympathetic motor supply to the uterus are mainly at T11 or T12.

The ovaries are supplied by the aortic and coeliac plexuses.

The parasympathetic supply comes from S2, 3, 4. Sacral nerves join the inferior hypogastric plexuses. They continue to the lexuses surrounding the cervix where they synapse.

Function of the autonomic supply: the sympathetic supply is vasoconstrictor and facilitates muscular contraction, especially of fibres near the cervix.

Uterine muscle is mainly responsive to hormonal changes. Some authorities describe motor nerves from T6 and T7 accompanying the sympathetic nerves to the uterus. There is little evidence of parasympathetic innervation of muscle.

The sensory supply
Stretch, contraction, infection and possibly ischaemia all cause pain (Figures 2 and 3). Pain from the body of the uterus is transmitted by sympathetic sensory fibres that enter the sympathetic chain at L5 and ascend. They enter the cord between T10 and L1 and pain can be referred to the corresponding dermatomes. Early labour pain is often felt in the T11–12 dermatomes. As the pain becomes more severe it spreads to T10 and L1. Other fibres travel with the aortic, superior and inferior hypogastric plexuses (i.e. there are alternative pathways entering the spinal cord at different levels).

Pain pathways of relevance to the obstetric anaesthetist

- Sympathetic afferents T10–L1
- Parasympathetic afferents S2, 3, 4
- The rectal, perineal and pudendal branches of the sacral plexus (S2, 3, 4) transmit the pain of perineal stretching
- The ilioinguinal nerve (L1) supplies the root of the clitoris, the labia, the mons pubis and the upper and medial part of the groin
- The genitofemoral nerve (mainly L2) supplies the labia majora
- The posterior femoral cutaneous nerve (S1, 2, 3) supplies the posterolateral labia majora
- A pudendal nerve block will not anaesthetize the whole vulva

2

Important points for the obstetric anaesthetist

- The inferior hypogastric plexus receives fibres from the superior hypogastric plexus, which receives fibres from the coeliac plexus supplied by the splanchnic nerves from T5–T12
- Nerve fibres may enter the spinal cord higher than expected
- Synapses may occur several segments higher
- The peritoneum is supplied segmentally by the spinal nerves that innervate the overlying muscles. Without a block to T4, traction on the peritoneum can cause pain
- The diaphragm is supplied predominantly by C4 (via the phrenic nerve). About one-third of the fibres in the phrenic nerve are sensory and pain is referred to the shoulder tip. The periphery of the diaphragm has a sensory supply from the lower intercostal nerves
- A block from T4–S4 is required for a caesarean section even though the principal nerve supply to the uterus is from T10–T12. Even then sensation from the diaphragm is not completely blocked

3

Pain from the cervix is classically considered to be carried by the pelvic splanchnic nerves (S2, 3, 4). It may be referred to the area supplied by the sacral plexus extending from the lower back to the buttocks, thighs and the mid-calf.

Pain from the isthmus may also be carried via the same pathways as pain from the body of the uterus and be referred to the T12 and L1 dermatomes.

Somatic pain is also perceived during labour. Aδ and C fibres supply the uterus and cervix and accompany the sympathetic nerves. These nociceptive fibres enter the roots between T10 and L1 and synapse at the interneurons in the dorsal horn.

The ovaries: sympathetic vasoconstrictor fibres, with their cell bodies at T10 and T11, reach the ovaries from the aortic plexus. Sensory fibres travel with the sympathetic nerves. Pain from the ovary may be referred to the peri-umbilical area (as well as the inner thigh, see above).

The vagina: sympathetic fibres from the inferior hypogastric plexus and the paracervical plexus supply the blood vessels and smooth muscle. Sensory fibres travel via the pudendal nerve (anterior divisions of S2, 3, 4) to supply the lower vagina. ◆

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Antenatal Assessment of the Pregnant Mother

Anne May

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Preoperative assessment is a well-recognized part of the anaesthetist's clinical practice and many hospitals have preoperative assessment clinics run by anaesthetists or nursing staff. It is often assumed that pregnancy is a normal physiological condition without risk, but an anaesthetist will be involved with the care of over 50% of women at some time during their delivery. In the UK, the caesarean section rate is over 20% in many units and there are parts of the world where the rates are much higher. In the UK, epidural analgesia rates vary from 5% to 80%.

The need for anaesthetic assessment of the pregnant mother has been highlighted by successive reports on the Confidential Enquiries into Maternal Deaths (CEMD) 1981–84, 1985–87, 1988–90, 1991–93 and 1994–96. Antenatal anaesthetic assessment of pregnant women with cardiac disease was recommended in the 1985–87 CEMD report.

Though maternal mortality has fallen in the last 50 years, as reported in the triennial reports into maternal death, pregnancy still carries a significant risk, which is greatest for women with coexisting medical diseases. An increasing number of women who become pregnant have significant concomitant disease. Some years ago, many of these women would not have contemplated pregnancy, but advances in management and treatment of many diseases mean that such woman can now expect normal fertility. A good example is the excellent control that many women with insulin-dependent diabetes achieve. However, it is important to remember that the underlying condition is still present and may be influenced by the physiological changes of pregnancy and delivery.

Other women who may benefit from antenatal assessment by an anaesthetist include those who may present an anaesthetic problem and those who need to have their anxieties and fears about analgesia and anaesthesia allayed. It could be argued that all women should be seen by an anaesthetist in the antenatal period because they are all potentially in need of obstetric anaesthetic intervention. If a woman has had an antenatal consultation with an anaesthetist, the problems of assessment and consent are less than when the woman presents in a distressed state for anaesthetic intervention. Explanation and assessment are easier in the antenatal period when the woman is calm and pain free.

Women with coexisting medical problems

It is important for the practitioner to consider the effects of the physiological changes at each stage of pregnancy on the disease. The stress of labour and delivery (including pain), and the potential effects of any anaesthetic intervention should also be taken into account.

Cardiac disease

In the Western world, there has been a change in the pattern of cardiac disease, which is illustrated in the most recent CEMD. It is now less common to see women with rheumatic heart disease, while the number with congenital heart disease and ischaemic heart disease has increased. A number of physiological changes of pregnancy affect the cardiovascular system.

- Cardiac output increases to a maximum of 40% at 20–28 weeks' gestation.
- Stroke volume increases and heart rate increases by 10–20 beats/minute.
- Blood pressure decreases in the first and second trimesters and increases in the third trimester.
- Systemic and pulmonary vascular resistance decrease by 25–30%.
- Plasma oncotic pressure decreases by 10–15%, therefore the patient will be prone to pulmonary oedema.
- In labour, the cardiac output increases by 25–50%; mainly mediated through the sympathetic nervous system.
- Autotransfusion of blood from the placenta occurs.

Supine hypotension may cause a reduction in cardiac output of up to 20%. This occurs when the weight of the gravid uterus reduces blood flow through the large vessels (inferior vena cava and aorta) in the supine position.

All pregnant women with cardiac disease should have a full history and examination taken early in pregnancy. Where appropriate, ECG, echocardiography and chest radiography assessments should be undertaken. The team caring for the woman in pregnancy should plan her management in detail and liaise with the cardiologist. It is useful to classify the severity of the cardiac disease using the New York Heart Association (NYHA) classification (Figure 1).

Women with NYHA class 1 or 2 heart disease usually present little problem in pregnancy or labour. Those with more severe cardiac disease may not tolerate the physiological changes of pregnancy, especially as they approach 20–28 weeks' gestation, and will need to be managed by a multidisciplinary team. Caesarean section is required only for obstetric reasons.

In women with severe cardiac disease, epidural analgesia removes the stress response to the pain of labour. Modern low-dose epidural techniques cause little sympathetic block and therefore are safe for most women with cardiac disease. Epidurals are beneficial to women with left heart failure. However, in women with heart disease in whom a drop in systemic vascular resistance would be deleterious, epidural analgesia is not advised. Patients with hypertrophic cardiomyopathy and primary pulmonary hypertension are particularly at risk. Epidural analgesia may be considered in some cases of aortic stenosis where the gradient across the valve is not too great. It is essential to remember the autotransfusion that occurs in the third stage of labour as well as the effect of oxytocin.

Women with cardiac disease need careful monitoring and management throughout labour and the puerperium. Antibiotic cover is important as the CEMD has shown a continuing problem with endocarditis. Clear management plans should be written and agreed by all members of the multidisciplinary team in the antenatal period.

New York Heart Association (NYHA) Classification

NYHA 1
Known cardiac disease with no limitation of physical activity and no objective evidence of cardiovascular disease

NYHA 2
Slight limitation of normal physical activity and objective evidence of minimal disease

NYHA 3
Marked limitation of physical activity and objective evidence of moderate disease

NYHA 4
Severe limitation of activity including symptoms at rest and objective evidence of severe disease

Respiratory disease

The most common respiratory problems seen in pregnant women are asthma and cystic fibrosis. The lung disease may be primarily obstructive or restrictive.

- Obstructive conditions (e.g. asthma, bronchiectasis, cystic fibrosis) may improve after treatment with bronchodilators.
- Restrictive conditions include granulomatous (sarcoid) and fibrotic (postradiation fibrosis, fibrosing alveolitis) disease; they are characterized by fibrotic changes in the lungs, and may be progressive or stable.

Respiratory disease may be exacerbated by the increased respiratory demands of pregnancy. If the disease is severe, pre-pregnancy counselling is advisable. A number of important physiological changes need to be considered.

- Oxygen consumption increases by 20% and metabolic rate by 15%.
- The resting minute ventilation increases by 40–50% with the tidal volume increasing and the respiratory rate remaining unchanged.
- The functional residual capacity (FRC) is decreased in the third trimester, though the vital capacity remains unchanged.
- Forced expiratory volume in 1 second, peak expiratory flow rate and the partial pressure of oxygen in arterial blood remain unchanged while the partial pressure of carbon dioxide in arterial blood decreases to 4.0 kPa.
- Arterial pH is 7.44.

The respiratory centre is reset early in pregnancy as a result of progesterone enhanced by oestrogen, which increases the sensitivity of the chemoreceptors to carbon dioxide. Patients with respiratory disease, in particular those with asthma, are aware of the hyperventilation early in pregnancy and may need reassurance. Towards the end of pregnancy, the enlarging uterus displaces the diaphragm and reduces FRC. FRC remains greater than closing pressure in the upright posture though in the recumbent posture it falls. In the second trimester, airway closure falls within the normal tidal ventilation in a significant number of women.

The effects of these physiological changes may severely compromise the woman with respiratory disease. Pulmonary function tests carried out in the first trimester give a baseline value and these should be repeated in the third trimester or earlier if clinically indicated. Regular peak flow monitoring is a useful assessment in those with obstructive lung disease and may be used as a guide to therapy. Many women avoid taking medication when pregnant and it is important that they are encouraged to continue their maintenance medication.

Women who have treated malignancies may have restrictive lung function and cardiac damage, and require echocardiographic examination of the heart.

In general, women with significant respiratory disease should be encouraged to have a stress-free labour and delivery, minimizing pain and hyperventilation. Epidural analgesia is an integral part of the pain management of these women. If an operative delivery is required, regional anaesthesia is the anaesthetic of choice because general anaesthesia is poorly tolerated.

Haematological disease

In many parts of the world, including the UK, antenatal screening for anaemia, thalassaemia and sickle cell disease is routine. Women with haematological disease may have:

- reduced oxygen carrying capacity (e.g. sickle cell trait)
- increased risk of clotting (e.g. thrombophilia)
- increased risk of bleeding (e.g. idiopathic thrombocytopenia, von Willebrand's disease).

Antenatal assessment is best undertaken by a multidisciplinary team including a haematologist, ideally at a combined clinic. Detailed plans for the management of labour and delivery should include the risks and benefits of regional analgesia and anaesthesia. If regional analgesia is contraindicated, the woman should be told what options are available to her for pain relief including the use of patient-controlled opiate analgesia.

Musculoskeletal disease

Musculoskeletal diseases seen in pregnant women range from physical disability resulting from nonspecific back problems to those who are severely disabled and wheelchair bound. Assessment includes respiratory and cardiac function for those with severe disease (e.g. severe kyphoscoliosis).

The effect of each stage of the pregnancy on the disease needs to be assessed and this must include the possibility of vaginal delivery. The musculoskeletal abnormality should be assessed by an obstetric anaesthetist to balance the risks and benefits of a regional block; it is helpful if previous records of surgery and radiographs are available. Antenatal consultation is important so that informed consent is obtained for any anaesthetic intervention.

Endocrine disease

The most common endocrine diseases that present in the childbearing population are diabetes and thyrotoxicosis. These women are best managed in a combined clinic, where the obstetrician and endocrinologist manage the pregnancy and plan for delivery. For most of these women a stress-free delivery is advised and epidural analgesia is an integral part of management.

Neurological disease

Antenatal assessment is advisable for women with, or with a history of, neurological disease. Patients with a history of trauma, tumours, infection or cerebrovascular accidents need to be assessed to determine whether there is any residual problem that will be affected by the pregnancy or labour. Consultation with the obstetric anaesthetist is advisable because many of these women are frightened by the thought of a needle in their back or any sensation of numbness. They may have had a bad experience with a lumbar puncture or paralysis, for example in acute post-infective neuropathy. Careful explanation and reassurance about regional analgesia and anaesthesia is important.

Women with established neurological disease include those with spina bifida, myasthenia gravis, epilepsy, or multiple sclerosis. In all these conditions, the assessment should take account of the effect of the pregnancy and labour on the disease. Many women who cope with crutches will need a wheelchair in the later stages of pregnancy. Women with spina bifida may have other risk factors (e.g. associated kyphoscoliosis, tethered spinal cord). Early consultation allows time for full investigations including MRI, and to obtain records of previous investigations and surgery.

Traditionally, regional analgesia and anaesthesia have been avoided in patients with neurological conditions because of the fear of making the condition worse or being blamed if worsening should occur. Although randomized controlled trials are unavailable, there is increasing clinical experience of regional blocks being safely and successfully carried out in these women. Antenatal consultation with an obstetric anaesthetist is important so that the risks and benefits may be explained and a plan made for analgesia and anaesthesia during delivery.

Women with potential anaesthetic problems

General anaesthesia is associated with maternal mortality, although the incidence of death as a direct cause of general anaesthesia has fallen in recent years as demonstrated by successive CEMD reports. The increased risks of general anaesthesia in pregnancy are mainly a result of the physiological changes of pregnancy, in particular the cardiovascular and respiratory changes. These changes are compounded by the physiological changes of pain, the work of the contracting uterus, and the oxygen demands and stress response of labour. Weight gain, oedema, large breasts and swollen mucosa all increase the difficulty in visualizing the larynx at laryngoscopy. The physiological and anatomical changes of pregnancy make airway management and hypoxia more of a problem than in the nonpregnant state. Failed intubation associated with acid aspiration (Mendelson's syndrome) is still a major anxiety for anaesthetists in obstetrics. Failure to intubate the trachea occurs in about 1/300 pregnant women and is ten times more common than in nonpregnant women.

Women who have a potential anaesthetic problem include those with:

- coexisting disease
- obesity
- difficult intubation (known or potential)
- previous anaesthetic problems
- genetic conditions associated with general anaesthetic problems.

Obese women

Obese women have several potential anaesthetic problems. These range from difficulty in finding intravenous access and placing regional blocks to major difficulties in intubation and ventilation if general anaesthesia is required.

Difficult intubation

In women who have had a previous difficult or impossible intubation, the difficulty must be clearly stated in the medical record and clear guidelines for the labour and delivery set out. These women need to be told that regional anaesthesia is the anaesthetic of choice and this may indicate epidural analgesia in labour. If regional anaesthesia is not an option then these women may have to be delivered by caesarean section as an elective procedure using fibre-optic intubation techniques. Antenatal planning is essential for these women.

Genetic diseases

Genetic diseases associated with potential anaesthetic problems are malignant hyperpyrexia and suxamethonium sensitivity. Women with malignant hyperpyrexia are usually aware of the hazards of general anaesthesia and the safety of regional analgesia and anaesthesia for them. It is essential that a clear plan for their delivery is made in the medical record so that all carers are aware of the problem. Women who are suxamethonium sensitive usually have a reasonable knowledge of the problem of prolonged apnoea, though they may not be aware that suxa-methonium is a standard drug used in emergency anaesthesia in obstetrics. They should be encouraged to have regional anaesthesia but told that there are alternative drugs if they need a general anaesthetic. Antenatal assessment is important for these women.

Women with adverse drug reactions

Many women have drug allergies. The antenatal period allows time for records to be found and the advice of an immunologist and pharmacist to be sought where appropriate. Some women need reassurance because their reaction was a side-effect of a drug rather than an allergic reaction. The anaesthetist should ensure that there is clear documentation of true allergies that may be life threatening and that guidelines for suitable pain relief in labour are drawn up taking account of relevant drug allergies and sensitivities.

Women with specific anxieties about their delivery

Elective caesarean section

Women scheduled to have an elective caesarean section are usually admitted on the day of surgery and this makes it difficult to discuss the risks and benefits of regional anaesthesia with them. Many units have introduced leaflets to explain the basics of their anaesthetic. This is helpful, but there are still some women for whom this information is inadequate and who need an antenatal consultation with the anaesthetist. Ideally, this should be available to all women who are to be delivered by planned caesarean section.

Planned pain relief in labour

Information on pain relief in labour is available to all women but some may have particular anxieties and benefit from detailed discussion on epidurals. Women for whom an epidural has been suggested as a planned part of their labour management (e.g. for twins, breech or hypertensive disease of pregnancy) may also benefit from a more detailed discussion.

Previous anaesthetic or analgesic problems

Previous anaesthetic or analgesic problems include a previous bad obstetric experience or, for example:

- dural puncture
- difficult or failed epidural
- pain at caesarean section
- epidural did not extend for caesarean section
- bad experience of general anaesthesia
- bad opiate experience.

These women benefit from antenatal assessment so that plans for their labour and delivery can be made and recorded in their notes.

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Assessing the Fetus

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The two key assumptions underlying fetal assessment are that:
- fetal compromise is progressive and can be detected at an early stage before permanent damage has occurred to the fetus
- an effective intervention can prevent or ameliorate fetal damage.

Despite widespread use of fetal assessment techniques, these underlying assumptions are not always met. Fetal compromise has various aetiologies that progress at different rates. It is the underlying aetiology that determines whether the assessment of fetal well-being is successful in detecting a stage before permanent fetal damage occurs. The only intervention that can 'rescue' the fetus from an adverse intrauterine environment is delivery, which may result in death or disability from prematurity. In order to minimize the number of fetuses exposed to the risks of iatrogenic prematurity, a judgement must be made as to when fetal compromise becomes permanent damage. Delivery should be undertaken just before this point. Unfortunately, current assessment techniques do not predict this point accurately, and so some fetuses will be delivered more prematurely than necessary and others delivered after they are irreversibly damaged.

Ante-partum assessment

There is no single agreed method of assessing fetal well-being in the ante-partum period and in practice a variety of different parameters are used to provide an overall impression of fetal health. Individual units have different approaches to fetal assessment depending on the technology and expertise available. At its most simple, fetal well-being is assessed throughout pregnancy by health professionals asking the mother at each visit whether the baby is moving well. Ultrasound scanning is commonly used in fetal assessment with parameters such as fetal growth, amniotic fluid volume, placental maturity, and fetal and placental blood flow being measured.

Whatever the method used, effective assessment of fetal well-being depends on the background risk in the pregnancy. All methods of monitoring may give false-positive or false-negative results, the impact of which may be reduced by bearing in mind the likelihood of fetal compromise in the pregnancy being assessed. For example, a decline in movements may indicate a compromised fetus, but in most cases it will not. Decreased movements are most likely to represent compromise in a pregnancy at high risk of fetal problems, such as one complicated by fetal growth restriction, and so should be taken most seriously in this context.

Electronic fetal heart rate (FHR) monitoring to produce a cardiotocograph (CTG) is widely available, but research does not support its use in the ante-partum period. CTGs have never been shown to improve fetal outcome and their use is associated with a trend towards an increase in perinatal deaths (odds ratio 2.85, 95% confidence interval 0.99 to 7.12).

Intra-partum assessment

Fetal heart rate monitoring

The aim of intra-partum FHR monitoring is to identify those fetuses who become hypoxic and acidotic during labour so that delivery can be expedited before permanent damage or death ensues. It was hoped that this would reduced the incidence of cerebral palsy, but it has not done so. This partly reflects the limitations of the method, but is also explained by increasing evidence that most cases of cerebral palsy follow an insult in the antenatal period and therefore will not be prevented by changes to the management of labour.

Intra-partum FHR monitoring may be undertaken by intermittent auscultation using a Pinard stethoscope or hand-held Doppler monitor, or by continuous electronic fetal monitoring to produce a CTG. This article focuses on the CTG, but this does not mean that it is superior to intermittent auscultation for most women. Trials comparing intermittent auscultation with continuous electronic fetal monitoring consistently show no reduction in perinatal death with electronic fetal monitoring. Electronic fetal monitoring is associated with a reduction in perinatal morbidity because it reduces the incidence of early neonatal seizures, however, this is not associated with any reduction in longer-term morbidity (e.g. cerebral palsy). An important drawback of electronic fetal monitoring is that it increases the number of instrumental vaginal deliveries and caesarean sections performed. This increases maternal morbidity and mortality for no improvement in long-term neonatal outcome.

Interpretation of the CTG: the CTG consists of parallel tracings of uterine activity and FHR. The physiological basis for monitoring FHR to detect developing acidosis is that FHR is under the control of the autonomic nervous system. As a fetus becomes hypoxic, and eventually acidotic, the autonomic nervous system is affected before the CNS develops permanent injury. Changes in the FHR may therefore be seen before permanent damage has occurred. The following elements are considered when interpreting the CTG:
- background risk to the pregnancy
- presence and frequency of contractions
- baseline rate (normal range 110–150 beats/minute at term)
- baseline variability (normal range 10–25 beats/minute)
- presence or absence of accelerations in the FHR
- presence or absence of decelerations in the FHR.

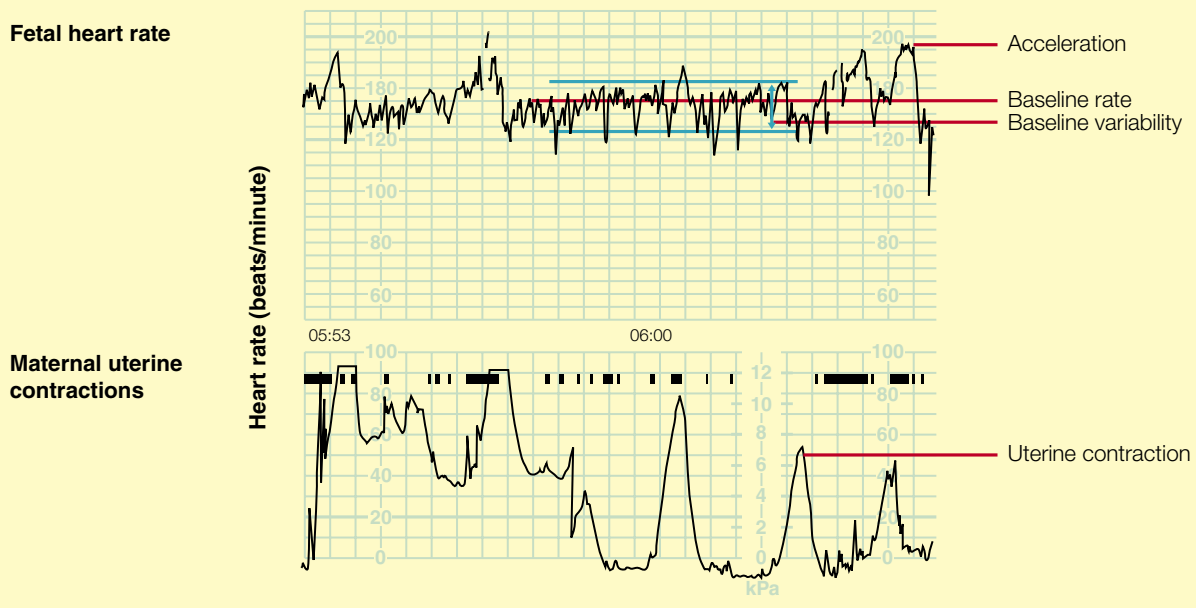
Figure 1 shows a normal CTG from a low-risk pregnancy illustrating the signs of fetal health. The baseline rate is 135 beats/minute and the baseline variability is 15–20 beats/minute. Accelerations in the FHR are present and there are no decelerations. Such a CTG is described as 'reactive' or 'reassuring' as it is a reliable indication that the fetus is not acidotic.

CTG changes that may indicate developing acidosis include:
- a rising baseline rate
- decrease in baseline variability
- lack of accelerations
- presence of decelerations.

Decelerations are classified as early, variable or late depending on their relationship to the timing of contractions and are of differing significance. Late decelerations start after the contractions begin, reach their nadir after the contraction peaks and recover after the contraction has finished. This type of deceleration is most strongly associated with fetal acidosis.

A CTG indicating possible acidosis may be described as 'abnormal' or 'non-reassuring'. There is a high false-positive rate for diagnosing acidosis from the CTG (over 50%) and the term 'fetal distress' should be avoided because it is emotive and a less accurate description of the information conveyed by the CTG than 'non-reassuring'.

A normal cardiotocograph from a low-risk pregnancy



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Fetal scalp blood sampling

The CTG should be regarded as a screening tool for fetal acidosis and a suspicious CTG requires further investigation or delivery if this is impossible. Once the cervix has dilated beyond 3 cm it is usually possible to obtain a sample of blood from the fetal scalp, which can be analysed for pH and base deficit. In the UK, a scalp pH less than 7.2 is an indication for delivery, though this is arbitrary. There is no significant increase in risk of neurological deficit in the neonate until the pH falls below 7.0 and the base deficit is above 16 mmol/litre, which indicates a metabolic acidaemia. The use of fetal scalp blood sampling has not been shown to improve fetal outcome but rather to reduce the rate of operative delivery and thus maternal morbidity by allowing identification of the numerous cases where the CTG is non-reassuring but the fetus is not acidotic.

Umbilical cord gases

After birth, blood can be taken from the arteries and vein of the umbilical cord and analysed for pH, base deficit and partial pressure of carbon dioxide, providing an indication of whether the fetus was acidotic *in utero* and, if so, whether this was respiratory or metabolic in origin. This is unnecessary if the neonate is vigorous and obviously healthy at birth but may provide useful information if the neonate shows signs of compromise. Good recovery from a respiratory acidosis is the rule but the risk of neurological deficit is raised in significant metabolic acidosis as described above.

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Ethical Issues in Obstetric Analgesia

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There has been a shift away from the paternalistic attitude that 'doctor knows best' to a more patient-focused view, respecting the patients' autonomy to make choices about the treatments they receive. This requires doctors to explain the various treatment options to patients as well as the risks involved, so that patients may make an informed choice. In obstetrics particularly, documents such as *Changing Childbirth* have stated that women should be encouraged to express their views and expectations regarding labour and treatments they would prefer in labour, and these should be met in most cases.

The obstetric anaesthetist is likely to be faced with numerous ethical dilemmas, revolving around the ability of a woman to give truly informed consent in labour, which is a period of intense discomfort and anxiety for some women. Additionally, women may have received opiates (e.g. pethidine) before having to make a choice, which could limit their ability to give truly informed consent to anaesthetic interventions in labour. A further ethical complication is the presence of the fetus, especially if there is conflict between the woman's wishes and the optimal outcome for her child. There are also ethical concerns about research on pregnant women. Nationally, anaesthetists may be involved in resource allocation and setting standards of care for women in labour, as well as being required to participate in the National Enquiries into Maternal Death, which may involve issues of confidentiality.

Consent issues in labour

Undertaking a procedure without consent constitutes battery under English law. It is difficult to obtain informed consent for epidural analgesia from the labouring parturient. Ideally, information about proposed anaesthetic interventions in labour should be given before labour begins, but this is not common practice in the UK. A recent study showed that recall of the risks of epidural analgesia was better in women who had attended antenatal education classes than in those who received the information in labour, though the overall recall of information was poor.

Birth plans

Difficulties may arise if a woman has made a birth plan before labour refusing epidural anaesthesia, particularly if there are disagreements between previously expressed wishes and currently expressed desires. Scott maintains that it would be unethical not to provide epidural anaesthesia in these circumstances. However, she cites a case in which an anaesthetist was threatened with physical violence by a woman's partner should an epidural be performed contrary to her prior expressed wishes. Some commentators have compared birth plans with advance directives made by patients in other circumstances (e.g. not to undergo cardiopulmonary resuscitation in certain circumstances). Legally, this situation has not been tested in the UK in pregnancy. In the USA, pregnant women are specifically excluded from the effectiveness of any such declarations while they are pregnant. Therefore, while a birth plan may be taken into account when deciding on epidural anaesthesia, a woman has the right to deviate from this plan at any stage of her labour and the prudent anaesthetist should obtain as valid a consent as applicable in the particular circumstances at that time.

Human Rights Act 1998

The introduction of the Human Rights Act may result in the definitions of informed consent and negligence being challenged. Obstetric anaesthetists should be familiar with the provisions of the Act. Informed consent will probably change to the model used in the USA in which patients are informed of every risk, no matter how minuscule.

Forced obstetric intervention

The way English Courts have regarded enforced caesarean section cases has developed from the highly paternalistic view taken in *Rochdale Healthcare (NHS) Trust v C* in which the judge held that a woman who was in labour was incompetent to make a decision if she was prepared to accept death rather than undergo a caesarean section. It is now recognized that a woman carrying a fetus is entitled to the same respect as any other woman and that 'refusal of medical treatment can be for any reason, rational or irrational, or for no reason at all.'

Under English law, a fetus has no legal status and this concept has been re-affirmed many times in various cases. There is no justification therefore in acting on behalf of the unborn child in these decisions. It is important that anaesthetists recognize that stringent conditions must be satisfied in order that an enforced caesarean section be undertaken, and that if they provide anaesthesia to a competent woman who is refusing an obstetric intervention, they may be accused of battery. An excellent summary of the law and ethics of enforced caesarean sections in the UK can be obtained from the Royal College of Obstetricians and Gynaecologists' website at *www.rcog.org.uk/guidelines/ethics/ethics.htm.*

Research on pregnant women

Anaesthetists involved in research on pregnant women must ensure that there are no unnecessary risks to the woman or the fetus. Some commentators have suggested that the standards for obtaining ethical committee approval for research involving pregnant women should be more stringent. A full explanation of the research aims should be provided and informed consent obtained from the women involved. Failure to do so may leave the anaesthetist open to charges of trespass and battery.

Analgesia for pregnant women

Resource allocation: anaesthetists should ensure that all women have equal access to the provision of safe analgesia and anaesthesia during labour. In the UK, the Obstetric Anaesthetists' Association and other national bodies have responsibility to ensure that training and anaesthetic service in labour wards are of a uniformly high standard. Some anaesthetists may be involved in resource allocation for their hospital or at a national level. Most healthcare service resource allocation is still provided by the medical profession, which is considered to have a largely male perspective in its approach to women's health issues. Resources should be distributed fairly, in a non-discriminatory manner.

Confidentiality must be maintained at all times. Anaesthetists may be required to submit data to various bodies, such as the National Enquiries into Maternal Death. The duty of confidentiality must be maintained after death and the anaesthetist should ensure that no aspects of the case could identify the woman or the hospital involved.

Analgesia for abortion: anaesthetists may be asked to provide analgesic services for women undergoing third-trimester abortions. Scott argues that it would be 'morally wrong to accept a post knowing that one could not possibly undertake all the duties implied in the job description.' The present author does not think that doctors should be compelled to provide services that go against their own beliefs. Senior anaesthetists involved in the provision of labour ward analgesia services should ensure that no anaesthetist is forced into a situation in which their own moral code may be violated. Alternative anaesthetists should be sought at an early stage to ensure that women receive analgesia without compromising any individual's beliefs. ◆

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Failed Intubation in Obstetrics

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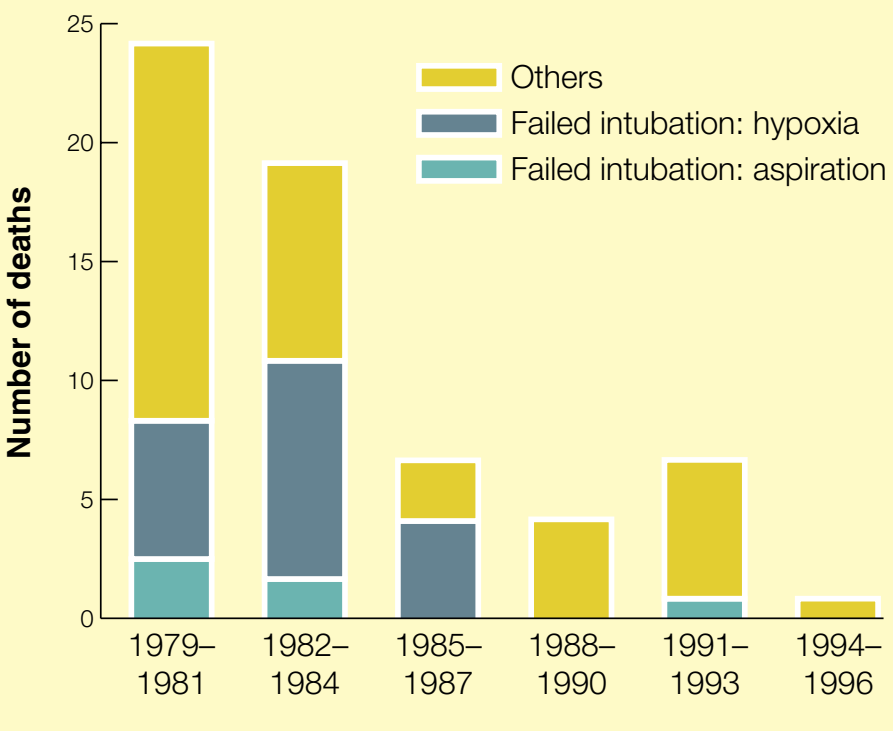
In the UK, between 1979 and 1987, failed intubation was a common cause of direct anaesthetic maternal deaths (Figure 1). In the past 20 years, anaesthetic practice has seen a rise in the use of regional anaesthesia, an increased number of caesarean sections, the routine use of pulse oximetry and capnography and the appointment of anaesthetists with a commitment to obstetrics. Parallel to these changes, anaesthetic maternal mortality has declined sharply.

In practice, the relative impact of the changes on the decrease in maternal deaths is speculative. An audit in the authors' teaching hospital from 1981 to 1999 showed that caesarean deliveries increased from about 400 to 900 per year. Over the same period, the number of general anaesthetics fell from 300 to 20 per year. In the UK, a survey of 31 obstetric units showed a doubling of emergency caesarean section rate since 1982, but the absolute number of general anaesthetics remained about the same. Increasingly, a general anaesthetic is chosen only for women at high risk and only if urgent anaesthesia is required. This suggests that the decrease in maternal deaths related to general anaesthesia is probably due to improved standards of practice rather than simply the increased use of regional techniques.

The incidence of failed intubation in obstetrics is about 1/130–300, which is eight times the rate reported for the general patient population. The obstetric population differs from the surgical population in that it includes young women, mostly with a full set of teeth. Pregnancy is accompanied by changes in physiology that can promote difficulties with intubation, increase the risk of aspiration and accelerate desaturation. Oedema of the larynx due to capillary engorgement and increased total body water in pregnancy is compounded by the venous distension of the head and neck that accompanies the strenuous effort of labour. Pethidine delays gastric emptying and mothers who have had opioids in labour are more likely to present with a full stomach in theatre. Many of these factors coincide, resulting in an urgent general anaesthetic occurring out of hours when organizational weaknesses will be exposed. A full list of contributory factors is given in Figure 2.

The way in which these factors come together can be seen in an imaginary scenario in which an anaesthetic trainee with 18 months' experience is asked to do an emergency caesarean section at night at short notice. The mother is distressed and communication is difficult because she speaks little English. To circumvent problems with communication the trainee elects to give a general anaesthetic. The theatre technician is unfamiliar to the anaesthetist and with the set-up in the obstetric theatre. Overconcern for fetal transmission of the drug leads to the administration of an inadequate dose of thiopental (thiopentone). Cricoid pressure is applied with enthusiasm resulting in a Cormack grade 4 view on laryngoscopy. Multiple attempts at intubation with intermittent pauses to oxygenate follow until more senior help arrives. Further attempts at laryngoscopy coincide with the lightening of anaesthesia and return of muscle tone and regurgitation occurs.

Direct deaths due to anaesthesia in the UK[1]



[1]Data compiled from six confidential inquiries showing a steady decline in maternal anaesthetic mortality. Most deaths are associated with general anaesthesia

1

Factors leading to failed intubation in pregnancy

Causes of increased difficulties of intubation
- Full dentition
- Large breasts due to engorgement and increased body fat
- Increased total body water causing pharyngeal and laryngeal oedema especially in women with pre-eclampsia
- Engorgement of capillary mucosa
- Left lateral tilt, or presence of badly placed wedge
- Poorly applied cricoid pressure

Causes of increased risk of aspiration
- Reduced oesophageal barrier pressure promoting reflux of oesophageal contents
- Opioid administration in labour leading to delayed gastric emptying

Factors leading to accelerated desaturation
- Reduced functional residual capacity which is compounded in the supine position
- Increased maternal oxygen consumption

Organizational issues
- Greater use of general anaesthesia out of hours and for sicker patients
- 24-hour service dependent on less experienced non-consultant staff

2

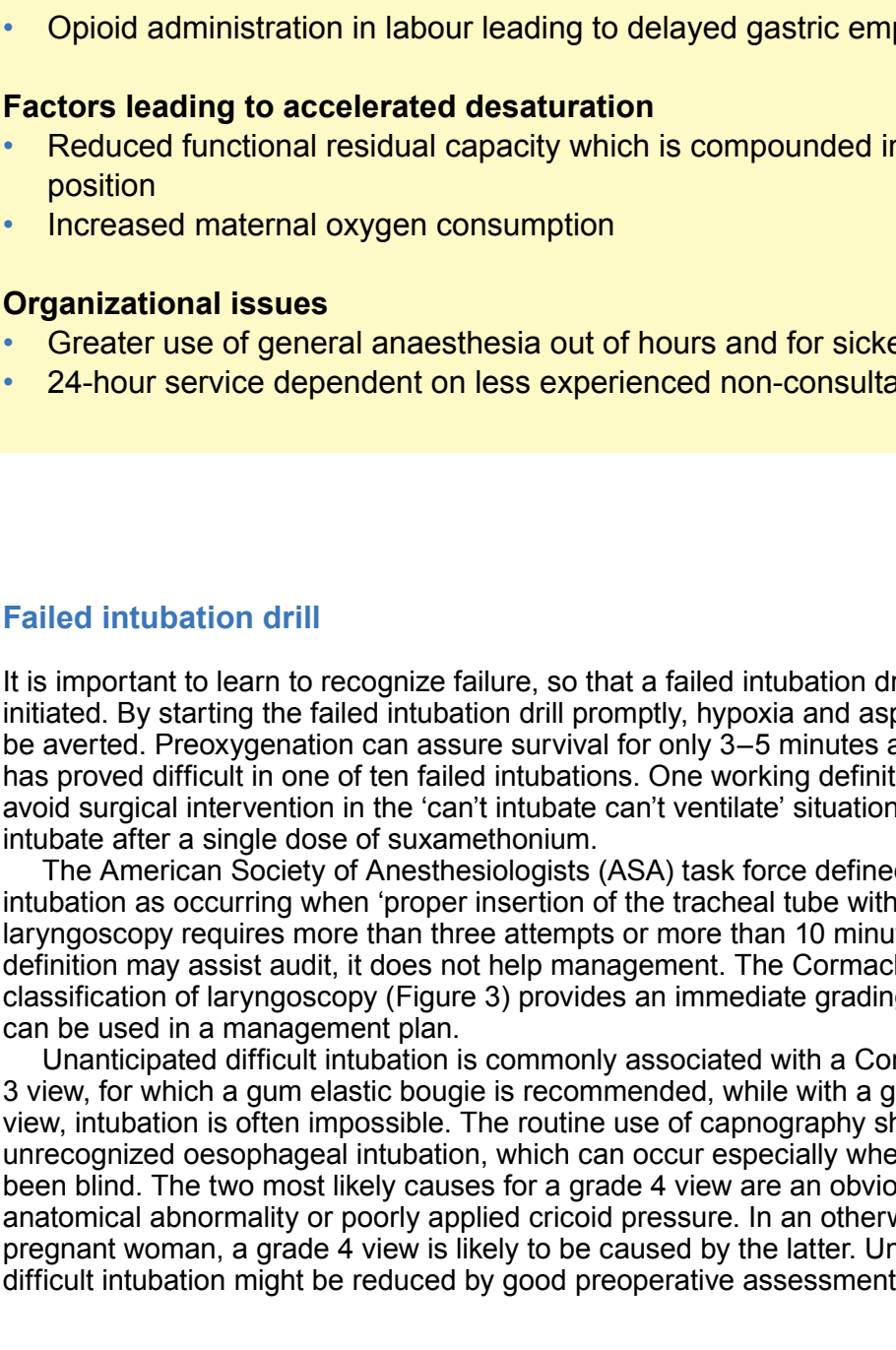
Failed intubation drill

It is important to learn to recognize failure, so that a failed intubation drill can be initiated. By starting the failed intubation drill promptly, hypoxia and aspiration may be averted. Preoxygenation can assure survival for only 3–5 minutes and ventilation has proved difficult in one of ten failed intubations. One working definition, intended to avoid surgical intervention in the 'can't intubate can't ventilate' situation is the inability to intubate after a single dose of suxamethonium.

The American Society of Anesthesiologists (ASA) task force defined difficult tracheal intubation as occurring when 'proper insertion of the tracheal tube with conventional laryngoscopy requires more than three attempts or more than 10 minutes'. While this definition may assist audit, it does not help management. The Cormack and Lehane classification of laryngoscopy (Figure 3) provides an immediate grading of difficulty that can be used in a management plan.

Unanticipated difficult intubation is commonly associated with a Cormack grade 3 view, for which a gum elastic bougie is recommended, while with a grade 4 view, intubation is often impossible. The routine use of capnography should prevent unrecognized oesophageal intubation, which can occur especially when intubation has been blind. The two most likely causes for a grade 4 view are an obvious gross anatomical abnormality or poorly applied cricoid pressure. In an otherwise healthy pregnant woman, a grade 4 view is likely to be caused by the latter. Unanticipated difficult intubation might be reduced by good preoperative assessment.

Difficult intubation algorithm based on view at laryngoscopy (adapted from Cormack and Lehane)



3

Airway assessment

Tests to assess the airway must be easy, rapid, accurate and performable at the bedside. As no test is 100% accurate, higher sensitivity and specificity can be achieved by combining several.

The three most commonly used predictors for difficult intubation are:
- inability to view the posterior pharyngeal wall when mouth is opened wide and tongue protruded
- a thyromental distance less than 7 cm when head is fully extended
- inability to protrude the jaw such that the lower incisors lie in front of the upper incisors.

Frerk predicted difficulty in 14 out of 244 patients in a non-pregnant population using the first two tests. At intubation, 11 proved difficult, of which 9 had been predicted, giving a sensitivity of 81% and specificity of 98%.

Mallampati's original three-tier grading of oropharyngeal view was modified to four by Samsoon and Young with grade 4 representing the most difficult. A significant correlation exists between the Mallampati score and the Cormack and Lehane laryngoscopy view. In 99% of the cases, grade 1 and grade 3–4 laryngoscopic views were associated with class 1 and class 4 airways, respectively. Inter-observer variability can be high, due to phonation, arching of the tongue, and performing the test in the supine position. Wilson's five factors take into consideration the patient's body weight, inter-incisor gap, buck teeth, neck movement and receding mandible. Similar to Mallampati's modified score, it showed a 50% chance of predicting difficult intubation but the inter-observer variability was lower. Other potential risk factors such as short neck and, missing, protruding or single maxillary incisors, have been reported to be significantly associated with difficult intubation.

An assessment that summates anatomical characteristics is more likely to predict problems accurately. If one test is abnormal it cautions the anaesthetist but if two or more are abnormal then appropriate preparation should be made and an awake intubation considered. The high false-positive values of these tests mean that the anaesthetist is often faced with an anticlimax. This is a benign consequence and should not deter clinicians from airway evaluation.

There is no preoperative test with 100% accuracy and the anaesthetist must be prepared for unanticipated difficult intubation. A range of intubation aids should be available. Particularly useful are a short-handled laryngoscope, McCoy laryngoscope and tracheal bougie.

Technique

Tunstall described the first failed intubation drill in 1976. He proposed that if delivery was not urgent, then general anaesthesia should be abandoned, the woman placed in the head-down, left lateral position, and allowed to wake up before proceeding to a regional technique. Urgent delivery proceeded only after stomach emptying with general anaesthesia, using trilene and face mask. Personal experience has taught us that stomach emptying in this situation is not easy and trilene has been replaced by more acceptable and more rapid agents. There are as many expert opinions in management as there are anaesthetists and many modifications of the drill now exist.

A general principle of any drill is that the time of greatest risk is not the time to perform previously unattempted practical procedures. The drill should consist of manoeuvres that are daily events for clinical anaesthetists. Management principles should be based on common sense with the aim of maintaining maternal oxygenation and survival.

Cricoid pressure: general anaesthesia should not be initiated without an anaesthetic assistant who is trained to apply cricoid pressure. Before induction, cricoid pressure is started and is increased firmly to a maximum of 30 Newtons or 3 kg force, which should be sufficient to prevent regurgitation even from a gastric pressure of 40 mm Hg. Forces greater than 40 Newtons, which can be easily misjudged even in trained hands, can lead to airway obstruction, a poor view at laryngoscopy, and difficulty in passing the tracheal tube. Before abandoning intubation it is worth releasing cricoid pressure momentarily to assess if visualization of the airway improves.

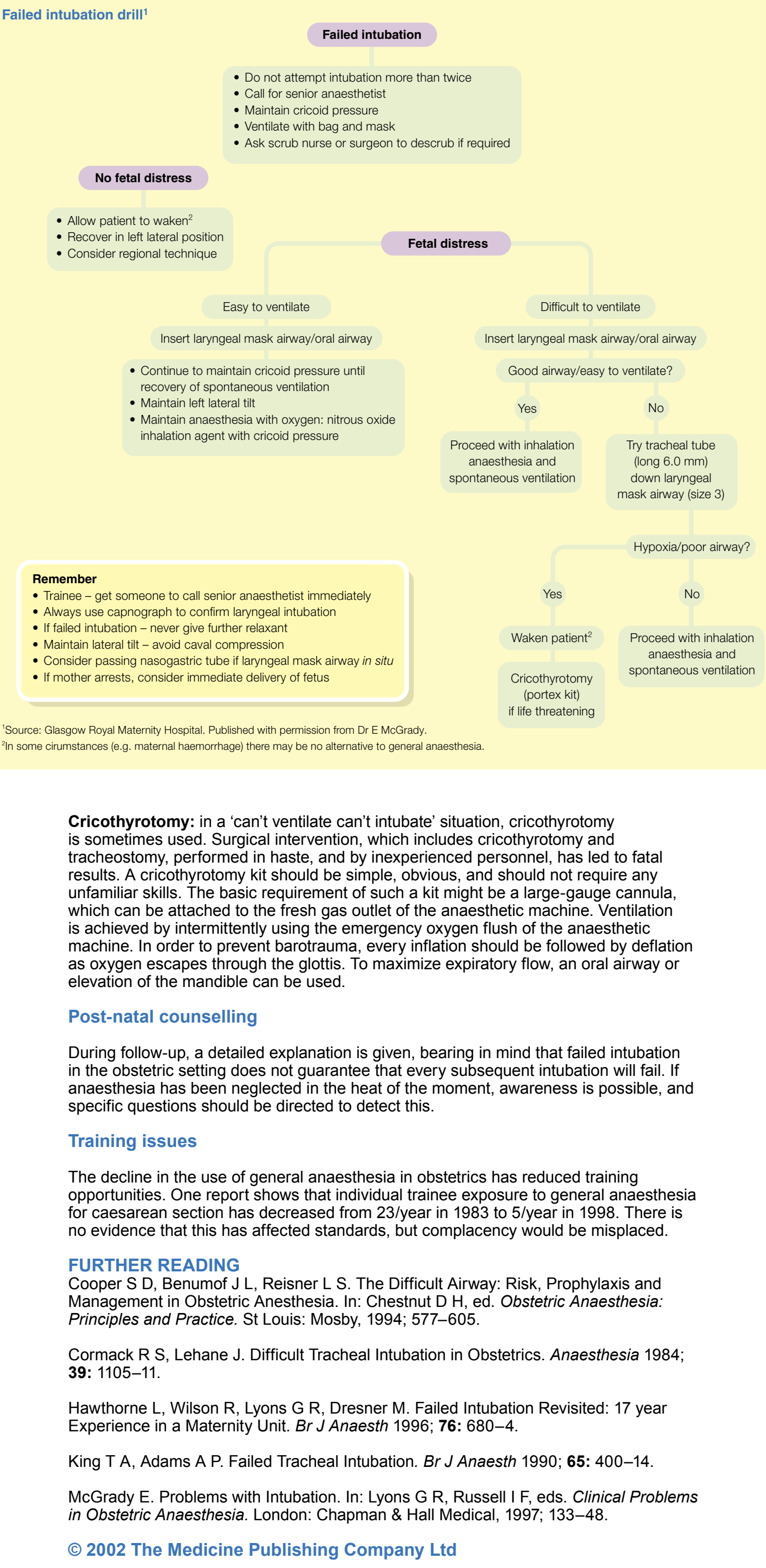
Left lateral position: the original drill advocated the left lateral position. When combined with the head-down position, the mouth is lower than the larynx and pharyngeal pooling will spill out of the mouth before aspiration can occur. If it does occur it is most likely that only one lung will be affected. Cricoid pressure is therefore unnecessary. Also the tongue falls forward resulting in a better airway. However, there are arguments against using the left lateral position.

- Hand ventilation of the patient is more difficult because the counter pressure at the occiput is lost.
- Cricoid pressure cannot be given adequately.
- Surgery or cricothyrotomy is impossible in this position.
- Moving a heavy patient can be difficult.

A balanced practice would be to use the left lateral position if the airway is controlled and a decision has been made to abandon general anaesthesia.

Laryngeal mask airway (LMA): though easy and atraumatic to insert, a LMA does not protect against aspiration, and continuous cricoid pressure interferes with insertion and placement. Without cricoid pressure, the LMA has been used routinely for elective and emergency caesarean section in 224 women with a success rate of 99%. There are reports of successful use of the LMA for failed intubation in caesarean section. On balance, it seems that the LMA should have a place in the drill. Much of the debate is based on arguments that are largely untested and founded either on opinion or anecdote. The only outcome study of failed intubation in relation to caesarean section used cricoid pressure and turned women on their side and head down, in the main without the LMA. All women made a complete recovery. It seems that the measures discussed above are unlikely to make a noticeable change to outcome, and use of any drill is more important than the constituent parts. One example of a failed intubation drill is shown in Figure 4.

Failed intubation drill[1]



[1]Source: Glasgow Royal Maternity Hospital. Published with permission from Dr E McGrady.

[2]In some cirumstances (e.g. maternal haemorrhage) there may be no alternative to general anaesthesia.

4

Cricothyrotomy: in a 'can't ventilate can't intubate' situation, cricothyrotomy is sometimes used. Surgical intervention, which includes cricothyrotomy and tracheostomy, performed in haste, and by inexperienced personnel, has led to fatal results. A cricothyrotomy kit should be simple, obvious, and should not require any unfamiliar skills. The basic requirement of such a kit might be a large-gauge cannula, which can be attached to the fresh gas outlet of the anaesthetic machine. Ventilation is achieved by intermittently using the emergency oxygen flush of the anaesthetic machine. In order to prevent barotrauma, every inflation should be followed by deflation as oxygen escapes through the glottis. To maximize expiratory flow, an oral airway or elevation of the mandible can be used.

Post-natal counselling

During follow-up, a detailed explanation is given, bearing in mind that failed intubation in the obstetric setting does not guarantee that every subsequent intubation will fail. If anaesthesia has been neglected in the heat of the moment, awareness is possible, and specific questions should be directed to detect this.

Training issues

The decline in the use of general anaesthesia in obstetrics has reduced training opportunities. One report shows that individual trainee exposure to general anaesthesia for caesarean section has decreased from 23/year in 1983 to 5/year in 1998. There is no evidence that this has affected standards, but complacency would be misplaced.

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Maternal Analgesia, Anaesthesia and the Fetus

Felicity Reynolds

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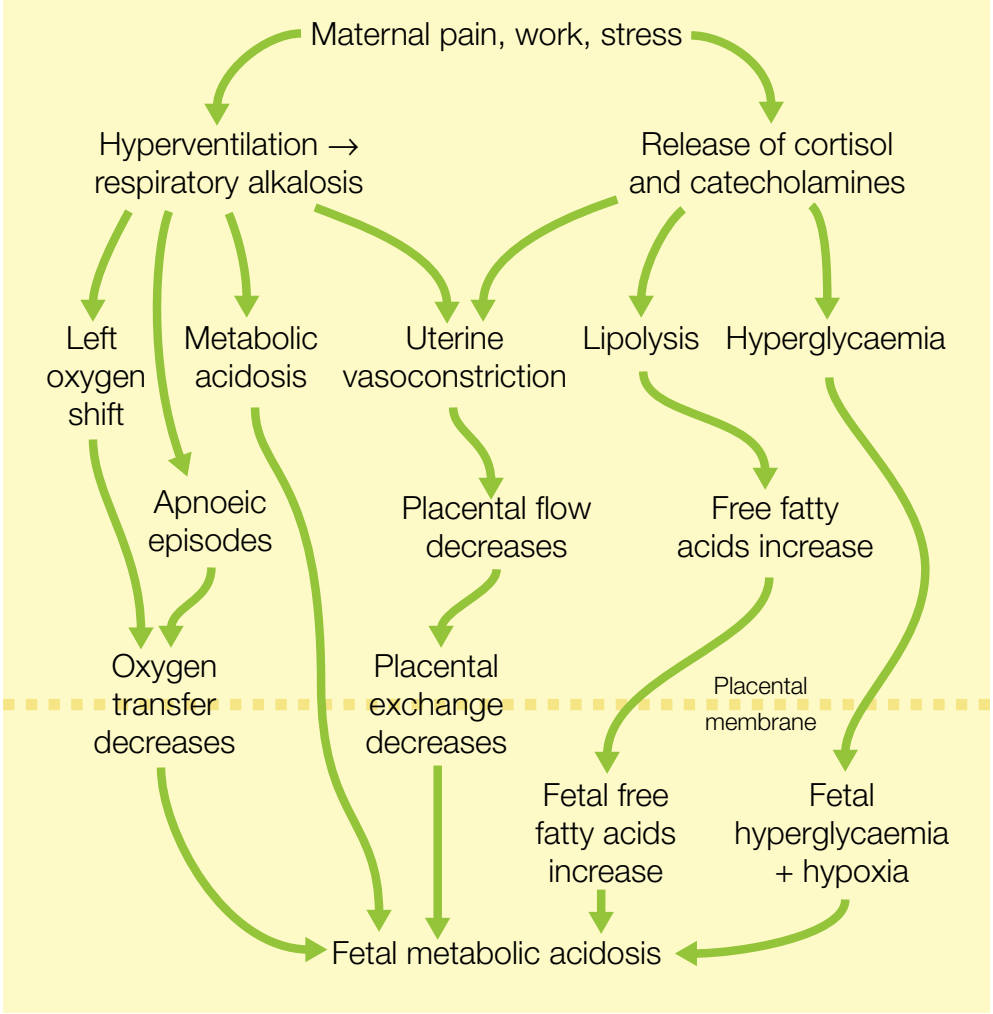
Although natural labour is painful, such pain has little value and is potentially detrimental to the fetus. Some mechanisms for this detriment are outlined in Figure 1. Reducing labour pain is therefore of potential benefit to the baby.

Drugs given to a parturient may have a direct effect on the baby after crossing the placenta, and an indirect effect via changes in maternal physiology and biochemistry. Systemic analgesia depends on an effective concentration of drug in the maternal blood. Since any compound that crosses the blood–brain barrier also crosses the placenta, such an approach is likely, given time, to affect the fetus as well as the parturient. Regional analgesia does not depend for its effect on the presence of analgesic drug in the maternal circulation, therefore a direct drug effect on the baby is less likely. However, regional analgesia may produce changes in maternal physiology or biochemistry that can affect the baby indirectly. It is seldom appreciated that regional analgesia, properly handled, is not only more effective than systemic analgesia, but also safer for the baby.

Potential adverse effects of maternal labour pain on the fetus



1

Placental drug transfer

Drugs used for anaesthesia and analgesia cross the placenta by passive diffusion. In this respect the placenta behaves like other lipid membranes, allowing lipophilic particles up to a molecular weight of 600–1000 (encompassing most drugs but not plasma proteins) and polar substances up to 60–100 to cross readily. Therefore, drugs used to provide systemic and regional analgesia cross the placenta readily in the unbound and non-ionized state, while hydrophilic substances such as neuromuscular blocking drugs, diffuse slowly and are unlikely to attain effective concentration in the fetus.

The transplacental distribution of lipophilic substances, whose unbound and non-ionized moiety equilibrates readily across the placental membrane, is influenced by the trans-placental gradient for pH and binding protein (Figure 2). As fetal plasma pH is lower than maternal, free base tends to concentrate on the fetal side due to ion trapping, the reverse being true for weak acids. This increases the exposure of the acidotic fetus to basic drugs such as opioid analgesics and local anaesthetics.

Acidic drugs are bound mainly to albumin, which shows little transplacental gradient. While a few basic drugs are also bound to albumin, the principal binding protein is α_1-acid glycoprotein, the concentration of which is variable, but always much lower in fetal than in maternal plasma. Figure 3 shows the physicochemical properties and characteristic equilibrium fetal:maternal ratios of some basic drugs, with antipyrine, which is neither ionized nor protein-bound, for comparison. For drugs mainly bound to α_1-acid glycoprotein, equilibrium fetal:maternal ratio is inversely related to binding. Figure 2 illustrates how such a ratio may be predicted. Although diffusion is no bar to the transfer of lipophilic drugs, the fetal compartment is deep, and equilibration takes longer in fetal than in maternal tissues. Fetal exposure is therefore dependent on blood flow on either side of the placenta (so-called flow-dependent transfer), equilibrium ratios and duration of maternal exposure.

Although the immediate effect of the drug is related to the concentration of the free moiety, a large albumin-bound component represents a storehouse for the newborn. Albumin binding, moreover, tends to decline in the first postnatal days, thereby exacerbating the many adverse effects of a drug such as diazepam.

Placental transfer of hydrophilic substances is slower, permeability-dependent and inversely related to molecular size. Thus, if given in normal doses during general anaesthesia for caesarean section, neuromuscular blocking drugs do not achieve effective concentrations in fetal plasma. Even if polar compounds are given to a mother over a long period, they never reach high concentration in fetal plasma because they are rapidly excreted by the kidney and accumulate instead in amniotic fluid.

Calculation showing how pH and binding protein gradient affect the fetal:maternal total drug concentration ratio illustrated using data for bupivacaine

Bupivacine pK_a 8.1

Mother	Fetus
Protein binding 95%	Protein binding 80%
pH 7.4	pH 7.25
pK_a – pH = + 0.7	pK_a – pH = + 0.85
Base [1] ⟷	Base [1]
↑↓	↑↓
Cation [5]	Cation [7]
Total free = [6]	Total free = [8]
(bound = 19 x free)	(bound = 4 x free)
Therefore: bound = 114	Therefore: bound = 32
Total = 120	Total = 40

Ratio of umbilical venous to maternal venous concentration (UV/MV) = 0.3

Only free base is assumed to diffuse readily. The Henderson–Hasselbalch equation is used to calculate the relative concentrations of cation and base on the two sides of the placenta

2

Physicochemical and pharmacokinetic characteristics of some basic drugs

	Molecular weight	pK_a[1]	Partition coefficient[2]	Adult protein binding (%)	Fetal:maternal ratio
Antipyrine	188	1.5	1.7	0	1.0
Pethidine	251	8.5	20	60[4]	→1→[3]
Lidocaine (lignocaine)	234	7.9	39	75[4]	0.55
Alfentanil	416	6.5	70	91[4]	0.3
Bupivacaine	288	8.1	250	94[4]	0.3
Diazepam	285	3.4	310	95[5]	2.0
Fentanyl	336	8.4	550	88[5]	1

[1]The higher the pK_a the stronger the base.
[2]Approximate oleyl alcohol/buffer partition coefficient.
[3]The fetal:maternal plasma ratio for pethidine rises with time to exceed unity in 3 hours or more.
[4]Principally bound to α_1-acid glycoprotein.
[5]Diazepam is bound principally to albumin and fentanyl to a mixture of plasma proteins.

3

Systemic opioid analgesia

Most studies of the fetal and neonatal effects of maternal systemic opioid analgesia relate to pethidine, which is the most widely used agent. It may cause loss of short-term variability in the fetal heart trace, and reduced muscular activity, aortic blood flow and oxygen saturation, largely via a direct effect. Pethidine exacerbates the episodes of maternal haemoglobin desaturation that normally occur during labour, which may contribute indirectly to its detrimental fetal effects.

Large doses of pethidine are associated with low Apgar scores, while minor degrees of neonatal depression from smaller doses may be undetected by this method of assessment. Nevertheless, even small doses depress neonatal respiration. Neurobehavioural scores are usually reduced while all neonatal effects are reversed by giving naloxone to the baby. Detrimental effects may last for 72 hours or more after delivery and are attributed principally to accumulation of norpethidine. Fetal:maternal ratios of pethidine rise with time after intra-muscular administration (Figure 3), and maximal fetal exposure occurs if pethidine is given to the mother 3–4 hours before delivery, while effects are barely discernible if it is given only within 1 hour of birth.

There are few important differences between pethidine and other opioid analgesics, though it has been claimed that meptazinol produces less neonatal depression. Morphine and diamorphine may not be as dangerous for the baby as was once supposed. Fentanyl, and more recently remifentanil, have been used systemically in labour with less neonatal detriment than is seen with pethidine.

It is probably logical to administer naloxone to every baby whose mother has received opioid analgesics during labour.

Nitrous oxide

Nitrous oxide is not only a slightly less ineffective analgesic in labour than pethidine, it is also less cumulative and less harmful to the baby, who can excrete it via the lungs once born. Nevertheless, in an attempt to obtain maximum analgesia from it, a parturient's natural tendency to hyperventilate during contractions may be encouraged, resulting in hypoventilation and consequent desaturation between contractions, thus potentially exacerbating the detrimental fetal effects outlined in Figure 1. When nitrous oxide is combined with 50% oxygen as *Entonox*, the oxygen may partly offset this effect, though if supplementary oxygen is needed to treat a distressed fetus, administration should be continuous rather than intermittent. Prolonged administration of nitrous oxide is associated with inhibition of the enzyme methionine synthase, a theoretical risk for the fetus.

Despite these theoretical disadvantages, maternal analgesia using 50:50 nitrous oxide and oxygen during labour has not been shown to produce any obvious neonatal detriment.

Adjuncts to nitrous oxide analgesia: to improve analgesia during labour, subanaesthetic concentrations of various volatile inhalational agents (trichloroethylene, methoxyflurane, enflurane and currently isoflurane) have been tried, alone or in conjunction with nitrous oxide. There is some gain in analgesic efficacy, with little obvious neonatal detriment, though higher concentrations have caused neonatal sedation.

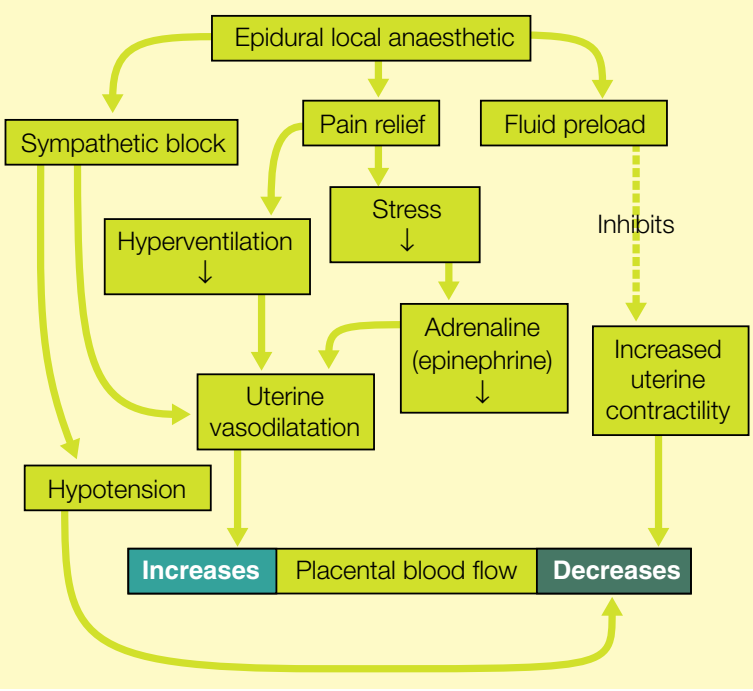
Regional analgesia

Direct effects
Adverse direct drug effects on a baby are likely to be observed only if maternal systemic effects reach a detectable threshold. Thus, when lidocaine (lignocaine) was used to provide continuous epidural analgesia, toxic effects were observed in both mother and baby. The longer action of correctly sited bupivacaine denotes slow absorption and thus favours a local over a systemic effect; the latter is usually observed only after accidental intravenous administration. Although opioids are well recognized to produce direct fetal and neonatal depression when used systemically, their potential to do so when used for regional analgesia is more debatable.

Indirect effects

Following regional analgesia, indirect effects are more likely to be clinically important. Regional blockade, as the only reliable form of labour analgesia, can block the detrimental fetal effects of pain shown in Figure 1. It does, however, have circulatory effects that may be beneficial or otherwise and are summarized in Figure 4. Provided maternal aortocaval compression and hypotension are avoided, the occurrence of a significant increase in maternal placental flow following epidural local anaesthetic is well documented, and is particularly consistent in the presence of pre-eclampsia. With correct management of the mother, adverse fetal effects are unlikely. Although regional analgesia may prolong labour, there is no evidence that this is harmful to the fetus.

Mechanisms by which central neural blockade with local anaesthetic may affect placental blood flow



4

Fetal heart rate

The value of continuous fetal heart rate monitoring in labour is often questioned, but cardiotocography is usually considered mandatory for mothers receiving regional analgesia. As a consequence, numerous fetal heart changes have been observed after the institution of epidural and intrathecal analgesia. Recently, loss of short-term variability, decelerations and major bradycardias have been reported following opioids, particularly given intrathecally. In randomized studies, however, such changes are no more common than after epidural bupivacaine, while meta-analysis of controlled trials shows that fetal heart abnormalities are no more common after epidural than after systemic opioid analgesia.

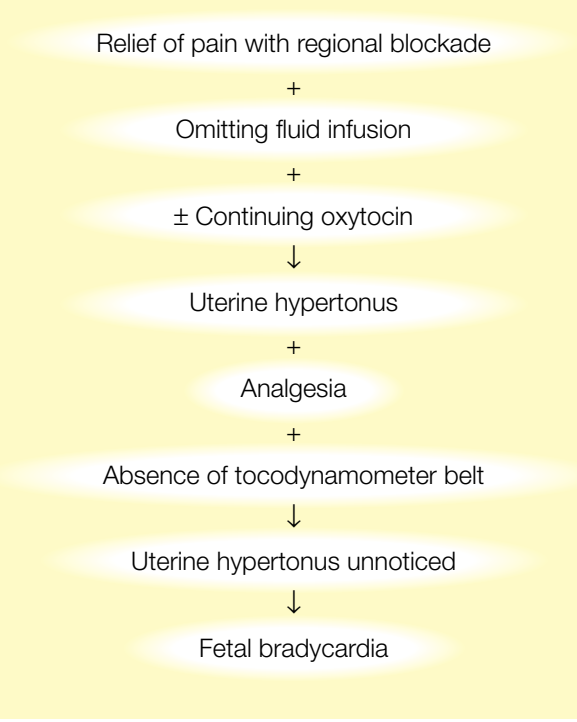
Fetal bradycardia has been associated with the rapid onset of analgesia, and various mechanisms have been considered to explain this, even though a causal relationship has not been established. Maternal placental flow ceases during a uterine contraction. At least some of the bradycardias in question are associated with uterine hypertonus, which is thought to result from a decline in the circulating adrenaline (epinephrine) concentration, itself a myometrial inhibitor (Figure 4). Direct fetal effects from the opioids (unlikely with intrathecal doses), plus maternal hypotension and hypoventilation are possible factors, though unlikely to be unnoticed.

Several points should be borne in mind.

- If local anaesthetic is omitted in the loading dose, and intrathecal opioid given alone, then there will be no sympathetic blockade to cause uterine vasodilatation (Figure 4).
- Fluid infusion before inducing regional analgesia has become less fashionable. A fluid preload has been shown to inhibit uterine contractions and to reduce the incidence of fetal heart decelerations. Uterine hypertonus is, therefore, theoretically more likely to occur in the absence of preload.
- Although a good midwife will continue to monitor the fetal heart, the external tocodynamometer belt is commonly removed before siting an epidural needle. Unless the belt is replaced quickly after the procedure, with the onset of analgesia uterine contractions will be undetected.
- There are occasions when the obstetrician is keen to continue the administration of oxytocin without a break. This should be resisted during epidural insertion in order to avoid the adverse situation outlined in Figure 5.

Whether such cardiotocographic changes are associated with adverse neonatal outcome is unsure, but at times decelerations have been so prolonged as to prompt caesarean section. Provided the changes are brief and do not reflect poor placental perfusion resulting from uterine hypertonus, maternal hypotension or aortocaval compression, their presence is probably irrelevant to fetal outcome.

Administration of oxytocin



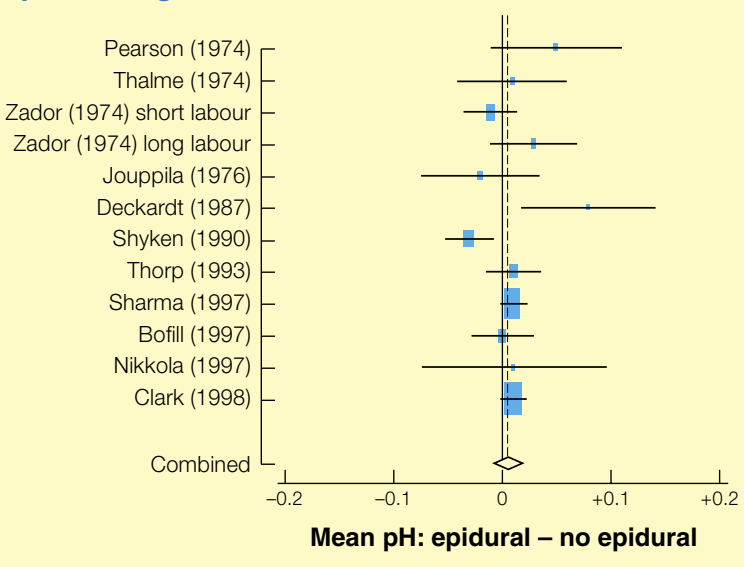
5

Fetal and neonatal acid–base status

Cord blood gas and acid–base balance reflect *in utero* status but give little indication of a newborn's ability to sustain adequate respiration and circulation. Umbilical vein values reflect placental exchange, while umbilical artery values indicate the status of fetal tissue more accurately, though the two are closely related.

Normal labour, associated as it is with maternal pain, stress and tension, may cause progressive maternal respiratory alkalosis and metabolic acidosis (Figure 1). These changes tend to be mirrored in the fetus, while any reduction in placental exchange may increase the transplacental gradient for oxygen, [H^+] and fixed acids. This gradient is also increased during the second stage, particularly with expulsive efforts. Alleviating pain, therefore, has a variable effect on fetal pH, but base excess is more consistently improved. This is confirmed by meta-analysis of trials comparing epidural with systemic opioid analgesia (Figure 6), which also suggest a protective effect of epidural analgesia in long labour.

Meta-analysis of urinary artery pH and base excess in controlled trials of epidural versus systemic opioid analgesia



Mean pH: epidural – no epidural

Uterine artery pH in 12 trials. There was no significant difference between the results of randomized and non-randomized trials, or between the two treatments.

Base excess: epidural – no epidural

Uterine artery base excess data from seven trials. There is a significant difference between the two treatment groups, favouring epidural analgesia.

Both meta-analyses conducted and figures constructed by Paul T Seed of the Department of Public Health Sciences, Guy's, King's and St Thomas' School of Medicine, King's College, London. Reproduced, with permission of the publishers, from: Reynolds F, Porter J. Neonatal Effects of Regional Analgesia. In: Reynolds F, ed. *Regional Analgesia in Obstetrics: A Millennium Update.* London: Springer, 2000: 237–52.

6

Apgar score

Apgar score is strongly influenced by the intrauterine environment and can be used only during the first 10 minutes of life, which is a highly stimulating time for the newborn, so subtle degrees of neonatal depression may be undetected. Nevertheless, meta-analysis of controlled trials showed that there were significantly fewer low Apgar scores at both 1 and 5 minutes with epidural than with systemic opioid analgesia.

Neurobehavioural assessments

Over the years, various tests have been developed to assess the newborn further into the postnatal period. The most popular with anaesthetists – the neurological and adaptive capacity score (NACS) – may not be the most sensitive or reliable. Studies have shown epidural local anaesthetic to be associated with neurobehavioural scores that are variously lower, similar or higher than systemic or no analgesia, while meta-analysis of randomized trials revealed no significant difference in NACS scores between epidural bupivacaine and systemic opioid analgesia, though slightly favouring babies in the epidural group.

Similarly variable results are seen when plain bupivacaine is compared with low-dose combinations of local anaesthetic and opioid. Dose-related effects have been demonstrated for epidural sufentanil and alfentanil, but not for fentanyl, though its use has been occasionally associated with slightly reduced NACS.

Neonatal respiration

Epidural analgesia using bupivacaine, unlike systemic pethidine, is not associated with any depression of neonatal respiration, but the question arises whether neuraxial opioids might reintroduce this danger. Painstaking studies of neonatal respiration have not revealed any obvious detriment from epidural fentanyl infusion, although unnecessarily large doses of neuraxial opioid by bolus or infusion should probably prompt neonatal naloxone administration.

Maternal anaesthesia

It is generally agreed that regional anaesthesia is not only safer than general anaesthesia for the mother but also preferable for the sake of the baby. This is largely true, although with carefully conducted anaesthesia there may be little to choose between them.

General anaesthesia

All general anaesthetic drugs, whether used for induction or maintenance, will accumulate in fetal tissues for about 20–40 minutes, thus if surgery is delayed or prolonged, the baby may be born sedated. This is of little importance, however, compared with asphyxia. It is therefore more important for the baby that the mother receiving general anaesthesia should be induced in a calm stress-free environment, with adequate doses of all agents. Awareness represents a further major stress – potentially far more damaging to the fetus than a little fully reversible anaesthesia.

Propofol is unsuitable for induction of anaesthesia before operative delivery. Too small a dose risks maternal awareness with all its attendant dangers, too big a dose depresses the fetus more than thiopental (thiopentone), and an intermediate dose risks both maternal awareness and neonatal depression.

Regional anaesthesia
Regional anaesthesia has been associated with higher Apgar scores and less neonatal acidosis than general anaesthesia after both elective and emergency caesarean section, but nowadays the difference may be slight. Interestingly, in most comparative studies, neonatal acidosis is more severe with spinal than with epidural anaesthesia. For epidural use, bupivacaine is likely to be safer for the baby than lidocaine (lignocaine), but details of anaesthetic technique may be of less importance to neonatal welfare than other factors.

Other factors in neonatal well-being
Other factors to be considered in neonatal well-being are:
- aortocaval compression – to avoid this a wedge may be better able to produce something approaching the prescribed 15° left tilt than tilting the table (most tables only reach 10° tilt)
- maternal circulatory status – prolonged maternal hypotension may result in fetal acidosis
- maternal oxygen and carbon dioxide tension
- maternal stress
- slow surgery – particularly uterine incision to delivery interval
- fetal status before starting the procedure.

FURTHER READING

Halpern S H, Leighton B L, Ohlsson A, Barrett J F R, Rice A. Effect of Epidural vs Parenteral Opioid Analgesia on the Progress of Labor. ***JAMA*** 1998; **280:** 2105–10.
Consider all these factors before allowing anaesthesia to be blamed for neonatal depression. A baby depressed by drugs is easily resuscitated.

Medical Diseases Complicating Pregnancy

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In the most recent Report on Confidential Enquiries into Maternal Deaths in the UK covering 1994−1996, the leading causes of direct maternal deaths are thromboembolic disease (46 patients), hypertension (20), early pregnancy loss (14), haemorrhage (12), amniotic fluid embolism (17), genital tract sepsis (14) and death from anaesthesia (1). This pattern shows little change from the previous triennium. Heart disease (28) is a major cause of indirect death. Other causes of indirect death include epilepsy (19) and asthma (3).

Thromboembolic disease

In the UK, thromboembolic disease remains the leading cause of maternal mortality, accounting for 36% of direct deaths. The rate was 2.1 deaths per 100,000 maternities in 1994−1996 and is increasing. Thromboembolic disease may occur at any gestation, and healthcare professionals should have a low threshold for investigating leg or chest symptoms in pregnant women.

A thromboembolic event occurs in 1/1500 pregnancies. Antenatal deep vein thrombosis (DVT) occurs in 0.06−0.09% of pregnancies, being twice as common in women over 35 years. In the puerperium DVT is also related to maternal age and mode of delivery. Pulmonary emboli are more common in the puerperium, especially following caesarean section.

Physiological changes of the coagulation system in pregnancy: the risk of thromboembolic disease is increased six-fold in pregnancy. There is an increase in coagulation factors I (fibrinogen), V, VII, VIII, IX, X, XII, von Willebrand factor antigen and ristocetin cofactor activity and a decrease in some endogenous anticoagulants (antithrombin, protein S and activated protein C ratio) which is most marked near term and following delivery. Fibrinolysis is impaired during pregnancy.

Peripheral vasodilatation occurs in normal pregnancy, resulting in a marked fall in velocity of blood flow. This fall is most marked in women undergoing caesarean section. It also occurs to a greater extent in the left femoral vein compared with the right. This is secondary to compression of the left iliac vein by the right iliac artery and the ovarian artery, which cross the vein only on the left side, leading to the predominance of left-sided (85%) DVTs in pregnancy.

Management

Ante-partum: every pregnant woman's risk of thromboembolic disease should be assessed at booking, by establishing whether she has a personal or family history. In addition, every pregnant woman who enters a high-risk situation should have her risk re-evaluated. Prophylactic treatment for thromboembolic disease should be offered to women at high risk. Women who have experienced a thrombosis during pregnancy should be closely followed up, preferably by a doctor with an interest in the management of thrombosis in pregnancy.

Previous thromboembolic event −women who have had a single previous thromboembolic event, have no family history and a negative thrombophilia screen should take aspirin, 75 mg/day, throughout pregnancy and low molecular weight heparin (LMWH) at a thromboprophylactic dose (e.g. dalteparin sodium, 5000 U/day subcutaneously) from the onset of labour until 6 weeks post-partum. Women who have had more than one thromboembolic event or who have had a single event but have a positive family history or thrombophilia screen should take prophylactic LMWH from early pregnancy until 6 weeks after delivery.

Positive thrombophilia screen − increasingly, women discover they have a thrombophilia when a family member is screened. The risk of thrombosis in the presence of thrombophilia is lower in those with a family rather than a personal history of thromboembolic disease. It may be appropriate to give low dose aspirin antenatally. Thromboprophylaxis should be determined on an individual basis, but these women require LMWH if they undergo caesarean section.

High-risk obstetric guidelines − in 1995, the Royal College of Obstetricians and Gynaecologists issued guidelines relating to thromboprophylaxis in pregnancy, including treatment following caesarean section (Figure 1). Each unit should have a locally agreed policy, based on these guidelines, which is strictly adhered to. Many hospitals give thromboprophylaxis to most, if not all, women undergoing caesarean section.

Acute episodes− it is essential to confirm or exclude a diagnosis of thrombosis with objective testing. Data from non-pregnant individuals suggest that 16% of patients with untreated DVT develop pulmonary embolus, and 13% of these die, though anticoagulation reduces the risk. Thus, a positive diagnosis of thrombosis requires immediate management, but because the treatment is not without risk, it is vital that the diagnosis is confirmed.

Chest radiography seldom diagnoses pulmonary embolism but may reveal other causes of dyspnoea or chest pain. It should not be withheld solely because of the pregnancy, and can be performed with the knowledge that the amount of radiation is negligible (Figure 2).

Arterial blood gas analysis should be performed in the sitting or left lateral position because in the supine position, inferior vena caval compression by the gravid uterus and functional reduction in pulmonary residual capacity and closing volume may give a false impression of hypoxia. In uncomplicated pregnancy, the partial pressure of oxygen is unchanged or increased, compared with the non-pregnant situation, but falls by about 2 kPa (17 mm Hg) when lying supine. The partial pressure of carbon dioxide in normal pregnancy falls from 5 kPa (35−40 mm Hg) to 4 kPa (30 mm Hg).

ECG lacks specificity, but shows a sinus tachycardia if pulmonary embolism is present. D dimers may be elevated in pregnancy as a result of the prothrombotic changes that occur and are therefore unreliable. There should be a low threshold for performing Doppler ultrasound of the femoral veins or lung ventilation and perfusion scanning (Figure 2).

If a DVT or pulmonary embolus is diagnosed (or strongly suspected), anticoagulation with heparin should be commenced. Warfarin should not be used in the first-line management of thromboembolic disease in pregnant women: it is teratogenic in the first trimester, increases the risk of miscarriage and stillbirth, anticoagulates the fetus and increases the risk of spontaneous haemorrhage (especially intracerebral) *in utero*. Both, heparin and warfarin are safe during lactation.

When an intravenous infusion of unfractionated heparin is used for acute treatment, chronic-phase treatment is commenced after 5−7 days. This is given traditionally as unfractionated heparin 10,000 U b.d. subcutaneously, because the standard non-pregnant dose of 5000 b.d. is insufficient. LMWH is effective and safe in pregnancy, and it is used for treatment and prophylaxis. If used for treatment, it is continued in therapeutic doses to complete 6−12 weeks of therapy depending on individual circumstances and local policy. It is then replaced by a once daily prophylactic dose of LMWH (e.g. enoxaparin, 40 mg, dalteparin sodium, 5000 U, tinzaparin, 50 U/kg) which is continued until 6 weeks postnatally. For pulmonary embolism or extensive iliofemoral DVT, intravenous unfractionated heparin may be used as first-line treatment in the acute phase until there is enough evidence for the efficacy of LMWH in pregnancy in these circumstances.

Thromboprophylaxis at caesarean section

Definition	Management
Low risk	
• Elective caesarean section • Uncomplicated pregnancy • No other risk factors	Early mobilization Good hydration
Moderate risk	
• Emergency caesarean section in labour • Age (> 35 years) • Obese (> 80 kg) • Gross varicose veins • Current infection • Pre-eclampsia • Immobilization before caesarean section for more than 4 days • Major current illness (e.g. heart or lung disease, inflammatory bowel disease, nephrotic syndrome, diabetes)	Prophylactic stockings for thromboembolic disease or subcutaneous heparin
High risk	
• Three or more moderate risk factors • Extended abdominal or pelvic surgery (e.g. caesarean hysterectomy) • Personal or family history of thromboembolic disease • Positive thrombophilia • Paralysis of lower limbs	Prophylactic stockings for thromboembolic disease plus subcutaneous heparin (commencing during caesarean section and continuing for 5 days)

Source: Royal College of Obstetricians and Gynaecologists. Report of the RCOG Working Party on Prophylaxis against Thromboembolism in Gynaecology and Obstetrics. London: Chameleon Press, 1995.

Estimated radiation to the fetus and increased risk of childhood cancer following common diagnostic procedures[1]

Investigation	Estimated radiation to the fetus (mGy)	Probability of fatal cancer to age 15 years
Conventional radiograph		
• Chest	0.01	< 1/1,000,000
• Pelvis	1.1	1/300,000
• Skull	0.01	< 1/1,000,000
• Spine	1.7	1/20,000
CT		
• Chest (including spiral CT)	0.06	1/560,000
• Pelvimetry	0.2	1/170,000
Nuclear medicine		
• Lung perfusion (technetium 99m)	0.2	1/170,000
• Lung ventilation (technetium 99m)	0.3	1/110,000

[1]The baseline UK national risk for cancer in the first 15 years of life is about 1/650, of which 50% is fatal.

Intra-partum: it is important to have a clear delivery plan including every possible emergency situation. The plan should be clearly documented in the patient's notes and agreed by the woman, obstetrician, anaesthetist and haematologist/obstetric physician.

Most obstetric anaesthetists are willing to perform a regional blockade 12 hours following the last LMWH dose. It is important to remember that removal of the epidural catheter has a higher incidence of LMWH-related complications than insertion and this should be delayed until at least 12 hours post LMWH dose. For women with antithrombin deficiency, depending on the titre in the weeks leading up to delivery, an antithrombin infusion may be required before and/or during labour.

Thrombolysis − in non-pregnant patients, there is no clear evidence that thrombolysis improves the clinical outcome of thromboembolic disease, and most physicians reserve its use for critically ill patients. Experience of thrombolytic treatment in pregnancy is even more limited. There is a significant risk of bleeding and it is recommended for use only in life-threatening circumstances.

Post-partum: for women who had thromboembolic disease during pregnancy, a thrombophilia screen should be performed after discontinuation of anticoagulation treatment at least 6 weeks postnatally to assess the risk of recurrence, and to plan management during future pregnancies. Warfarin does not pass into breast milk, therefore women injecting heparin may wish to change to warfarin after delivery, once the risk of post-partum haemorrhage has passed (up to day 5). However, they will have to attend regularly for measurement of their prothrombin time. Contraception should also be discussed. The oestrogen-containing combined oral contraceptive pill is contraindicated in women who have had a thrombosis, but other forms of contraception (hormonal and non-hormonal) are permissible.

Cardiac disease

In the UK, cardiac disease is the second most common cause of maternal death. The physiological haemodynamic adaptation to pregnancy and delivery may place the woman with cardiac disease at serious risk. In the most recent Report on Confidential Enquiries into Maternal Deaths, 29% of the indirect deaths were a result of cardiac disease, of which 26% were congenital, 21% ischaemic and 53% acquired. The incidence of congenital heart disease in pregnancy is increasing, reflecting advances in corrective surgery for severe defects. It is important to consider the woman's risk of ventricular failure (particularly when the right ventricle is acting as the systemic pumping chamber) and any residual pulmonary hypertension. Paradoxical embolism through a right-to-left shunt may cause cerebrovascular accidents in uncorrected Fallot's tetralogy and atrial septal defects. The incidence of rheumatic fever has declined, but rheumatic heart disease, most commonly mitral stenosis, may present for the first time in pregnancy, especially in immigrants.

Whatever the underlying cardiac problem, the ability to tolerate pregnancy and delivery is related to the presence of cyanosis and pulmonary hypertension, the haemodynamic significance of any lesion and the functional state (Figure 3). Cyanosis alone may not be as important in predicting poor outcome as the association of cyanosis with Eisenmenger's syndrome, poor functional class, or both. Poor pregnancy outcome is more likely if the woman is in a poor functional status (NYHA class III or IV) regardless of the specific lesion. Conversely, those in functional classes I or II are likely to do well in pregnancy. Each case must be assessed individually, but women with certain conditions must always be treated as high risk. These include pulmonary hypertension and Eisenmenger's syndrome, severe aortic or mitral stenosis, Marfan's syndrome or cyanotic congenital heart disease.

New York Heart Association (NYHA) functional classification

- Grade I — No breathlessness
- Grade II — Breathlessness on severe exertion
- Grade III — Breathlessness on mild exertion
- Grade IV — Breathlessness at rest

3

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Management
Ante-partum: women with cardiac disease should be assessed before pregnancy. Counselling regarding possible fetal and maternal risks and, in some women, the need to avoid pregnancy, may be appropriate. Detailed assessment by an obstetrician, cardiologist and obstetric anaesthetist with an agreed plan for delivery is crucial. Women with congenital heart disease should be referred for a detailed fetal cardiac ultrasound scan because the risk of a congenital heart defect (2–5%) is more than double that of the general population. Some women require elective admission for bed rest to maximize oxygen saturation. Maternal cyanosis and hypoxaemia may adversely affect the fetus increasing the risks of intrauterine growth restriction, miscarriage and spontaneous and iatrogenic prematurity. Serial assessment of fetal growth and well-being is appropriate. If antidysrhythmics are required there is most experience in pregnancy with digoxin and β-blockers. Verapamil, adenosine and DC cardioversion are safe, and flecainide is safe in the second and third trimesters.

Intra-partum: antibiotic prophylaxis to cover delivery is advocated for women with structural heart defects. The exceptions are those with a repaired patent ductus arteriosus, those with an isolated ostium secundum atrial septal defect, and those with mitral valve prolapse without regurgitation. Prophylaxis is mandatory for women with artificial heart valves and those who have had endocarditis.

Women should be nursed in the left or right lateral position. The supine and lithotomy positions should be avoided to minimize the risk of pulmonary oedema. If the mother has to be kept on her back, the pelvis should be rotated so that the uterus drops forward, and cardiac output as well as uteroplacental blood flow are optimized. Continuous ECG and oxygen saturation monitoring, and for certain patients, more invasive monitoring with central venous and arterial cannulation, is required. Full resuscitation facilities must be available.

Epidural anaesthesia and analgesia using incremental doses and with judicious pre-loading are well tolerated in most conditions. Nevertheless, extreme caution is needed in cases of limited stroke volume and left ventricular outflow tract obstruction (e.g. aortic stenosis, hypertrophic cardiomyopathy). If a pudendal block is required lidocaine (lignocaine) without adrenaline (epinephrine) should be used. Oxytocin without ergometrine is recommended for management of the third stage. If there are concerns regarding the need to avoid vasodilatation, this can be administered by small increments of a dilute solution. Women should sit up as soon as possible after delivery. Close and regular observation is required for at least 24 hours after delivery, and transfer to a high-dependency or intensive care ward may be appropriate.

Post-partum: if the mother is well, breast-feeding is not contraindicated. Contraception should be discussed together with the safety of future pregnancies.

Pulmonary hypertension
Pulmonary hypertension may be the result of lung disease (e.g. cystic fibrosis), primary pulmonary hypertension, pulmonary veno-occlusive disease, or Eisenmenger's syndrome. The fall in systemic vascular resistance in pregnancy combined with the fixed pulmonary vascular resistance (which usually falls in pregnancy) means that there is an increase in right-to-left shunting and these women cannot increase pulmonary blood flow to match the increased cardiac output.

Maternal mortality is 30−50% in Eisenmenger's syndrome, and pregnancy is contraindicated. If a woman with significant pulmonary hypertension becomes pregnant, termination should be offered. If this is declined, prophylactic heparin should be given and bed rest and oxygen therapy instituted if hypoxia develops. Any systemic hypotension or vasodilatation (such as intra-partum or post-partum haemorrhage or related to anaesthesia) may lead to shunt reversal or increased right-to-left shunting, and should be avoided by immediate volume replacement. Opinion varies as to whether these patients should be delivered by elective caesarean section and whether regional anaesthesia is safe. They should be managed in an ICU by anaesthetists, cardiologists and obstetricians with expertise in the care of complicated heart disease. Any drug given to reduce pulmonary artery pressure (other than inhaled nitric oxide) will also reduce systemic pressures and the temptation to manipulate pulmonary artery pressure with vasodilators should be resisted. For this reason, monitoring with arterial and central venous lines with attention to adequate filling is recommended in preference to Swan–Ganz catheterization. Most women with Eisenmenger's syndrome who die as a result of their pregnancy, do so after delivery.

Aortic stenosis
Aortic stenosis is unlikely to cause problems unless the gradient is severe (over 100 mm Hg in the non-pregnant state). The risks are angina, hypertension, heart failure and sudden death. Symptoms (e.g. angina, dyspnoea, syncope) as well as hypertension may be controlled with β-blockers, provided left ventricular function is good. The development of resting tachycardia may indicate a failing left ventricle, unable to maintain the increased stroke volume of pregnancy. Balloon valvotomy may allow relief of severe stenosis and continuation of the pregnancy in severe cases. During delivery, the main complications are pulmonary oedema secondary to left ventricular failure and low cardiac output from decreased venous return. Venocaval compression and hypovolaemia must therefore be avoided.

Mitral stenosis
The increased blood volume, heart rate, and cardiac output accompanying normal pregnancy increase left atrial pressure and may cause pulmonary congestion and pulmonary oedema. Tachycardia is particularly dangerous in mitral stenosis, because diastolic filling of the left ventricle (which is slowed in mitral stenosis) is further decreased, and there is a consequent fall in stroke volume and a rise in left atrial pressure, precipitating pulmonary oedema. Even if a woman is asymptomatic at the beginning of pregnancy, she may deteriorate rapidly and develop exertional dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea due to pulmonary oedema later in gestation. This may be precipitated by a rise in the resting heart rate as a result of a failure to increase stroke volume adequately. If tachycardia develops, β-blockers should be given to slow the heart rate and allow time for left atrial emptying. If atrial fibrillation occurs, this should be converted to sinus rhythm with digitalization, or DC cardioversion. The risk of pulmonary oedema is greatest immediately after delivery, owing to the increase in wedge pressure accompanying the rise in blood volume. For this reason, cautious reduction in pre-load is desirable before delivery. Generally, fluid restriction and the fluid losses accompanying labour are adequate to produce a wedge of 14 mm Hg or less. If the pre-load is decreased too much, cardiac output will fall. Decreases in systemic vascular resistance lead to tachycardia and should be avoided. Epidural anaesthesia is desirable for vaginal and abdominal delivery. Pulmonary oedema should be treated promptly if it occurs.

Marfan's syndrome
The cardiovascular features of Marfan's syndrome include mitral valve prolapse, mitral regurgitation, aortic root dilation and aortic incompetence. Marfan's syndrome is inherited as an autosomal dominant condition and those with cardiac lesions tend to have offspring with cardiac abnormalities. Women should be advised that pregnancy carries a significant risk if the aortic root diameter is greater than 4−4.5 cm, or if there has been a steady increase in the aortic root dimension over preceding visits. Pregnancy increases the risk of aortic dissection and aortic rupture, particularly in those with pre-existing aortic dilatation. This risk is related to the family history, and is increased if relatives with the syndrome have suffered aortic rupture. There is a significant risk even in the absence of preconceptual cardiovascular abnormality and though aortic root dilatation may be a predictor of risk, dissection may occur without significant dilatation or hypertension.

Regular echocardiography assessments should be performed throughout pregnancy. β-blockers have been shown to reduce the rate of aortic dilatation and the risk of complications. They should be continued or started in pregnant patients with aortic dilatation or hypertension. For women with stable aortic measurements less than 4 cm, a vaginal delivery under epidural anaesthesia is recommended, unless there are obstetric indications for caesarean section. Epidural anaesthesia helps to limit the rise in systolic and diastolic blood pressure occurring with the pain and anxiety accompanying uterine contraction. Elective caesarean section with regional anaesthesia is recommended for those with aortic root dimensions greater than 4 cm or with increases in aortic root diameter during pregnancy, in order to avoid the rise in cardiac output associated with labour.

Peri-partum cardiomyopathy
Peri-partum cardiomyopathy is a rare condition specific to pregnancy that usually presents peri-partum or in the first month after delivery. There is a dilated cardiomyopathy and congestive cardiac failure with markedly reduced left ventricular function. There is a significant risk of pulmonary, cerebral and systemic embolization. Peri-partum cardiomyopathy is more common in multiple pregnancy, pregnancy complicated by hypertension, and in multiparous and older women. Management includes anticoagulants and conventional treatment for heart failure including bed rest, diuretics, digoxin, after-load reduction and inotropes. Elective delivery should be undertaken if the condition presents antenatally. Thromboprophylaxis should be continued intra-partum and post-partum. Angiotensin-converting inhibitors may be used to treat cardiac failure after delivery. About 50% of patients make a spontaneous and full recovery. Women should be counselled regarding the high risk of recurrence in future pregnancies especially if cardiac size does not return to normal.

Ischaemic heart disease
The incidence of myocardial infarction in pregnancy is increasing as older women who smoke are becoming pregnant. The risk is highest in the third trimester and overall maternal mortality is about 20%. Myocardial infarction in pregnancy has been successfully managed with thrombolysis, balloon angioplasty and coronary artery bypass grafting. Low-dose aspirin, 75−150 mg/day, is safe in pregnancy and should be continued or commenced for primary and secondary prophylaxis or in the acute management of myocardial infarction. Anti-anginal medication including nitrates and heparin may also be used safely.

Asthma

The prevalence of asthma in women of childbearing age is increasing. Asthma is the most common pre-existing medical disorder encountered in pregnancy. Management during pregnancy should include reassurance regarding the safety of medications used to control asthma. The biggest danger to the mother and fetus comes from poorly controlled or undertreated disease.

Changes in respiratory function during pregnancy: normal pregnancy is associated with a 20% increase in oxygen consumption and a 15% increase in the maternal metabolic rate. This extra demand is achieved by a 40−50% increase in resting minute ventilation, resulting mainly from a rise in tidal volume rather than respiratory rate. This hyperventilation causes the partial pressure of oxygen in the arteries to increase and that of carbon dioxide to fall, with a compensatory fall in serum bicarbonate to 18−22 mmol/litre. A mild respiratory alkalosis is normal in pregnancy (arterial pH 7.44). Up to 75% of women experience a subjective feeling of breathlessness at some time during pregnancy, possibly because of an increased awareness of physiological hyperventilation. This is most common in the third trimester and may lead to diagnostic confusion. In late pregnancy, the diaphragmatic elevation caused by the enlarging uterus leads to a decrease in functional residual capacity (FRC), but diaphragm excursion is unaffected and therefore vital capacity is unchanged. There is no change in peak expiratory flow rate or forced expiratory volume in 1 second in pregnancy. However, the fall in FRC may exacerbate hypoxaemia because of premature airway closure when acute asthma complicates pregnancy.

The effect of pregnancy on asthma in an individual woman is unpredictable. Women with mild disease are unlikely to experience problems, whereas those with severe asthma are at greater risk of deterioration, particularly late in pregnancy. Physiological changes during pregnancy that may improve asthma include progesterone-mediated bronchodilation and increased serum free cortisol. Those that may explain deterioration include increased stress and increased gastro-oesophageal reflux. Many asthmatics experience worsening of their symptoms during pregnancy because they stop or reduce medication, due to unfounded fears (either their own or their medical advisers') about its safety.

The effect of asthma on pregnancy in most women is negligible. However, severe, poorly controlled asthma may have an adverse effect on fetal outcome as a result of chronic or intermittent maternal hypoxaemia. Some studies have suggested an increase in the risk of premature labour and low birth weight, though two prospective case-control studies have not confirmed these findings. Similarly, higher rates of pregnancy-induced hypertension or pre-eclampsia, and caesarean section have been reported, but this may be a consequence of increased surveillance of asthmatic pregnancies, rather than a result of maternal asthma. Corticosteroid use may act as a confounder. The magnitude of any adverse effect on perinatal outcome is small and related to the degree of control of the asthma.

Management

Management of asthma in pregnancy does not differ from management outside pregnancy. The priority should be effective control of the disease process, with the aim being total freedom from symptoms both day and night. The medications used to treat asthma are safe in pregnancy. Great attention must be given to reassuring women about the safety of the drugs used to treat asthma in pregnancy and during lactation. Asthma should be treated as aggressively in pregnant women as in non-pregnant women. Pregnancy, because of the increased contact with healthcare professionals, provides an ideal opportunity to optimize asthma management. The drug treatment of asthma requires a short-acting symptom reliever and a long-term daily medication to address the underlying inflammation. All the drugs commonly used to treat asthma, including short- and long-acting β_2-agonists, inhaled corticosteroids, and methyl xanthines are safe in pregnancy. Fluticasone may be used for those requiring high doses of inhaled corticosteroids.

Acute severe asthma is dangerous and should be vigorously managed in hospital. Treatment is no different from the emergency management of acute severe asthma outside pregnancy. Oxygen, nebulized β_2-agonists, nebulized ipratropium, oral or intravenous corticosteroids, and in severe cases intravenous aminophylline or intravenous β_2-agonists should be used as indicated. Provided abdominal shielding is used, a chest radiograph results in minimal exposure of the fetus to ionizing radiation, and if clinically indicated this investigation must never be withheld because the patient is pregnant.

Labour and delivery: acute attacks of asthma during labour and delivery are rare, and women should be reassured. Women may continue to use their regular inhalers throughout labour. Those taking oral corticosteroids (prednisolone, over 7.5 mg/day for more than 2 weeks) at the onset of labour or delivery should receive parenteral corticosteroids (hydrocortisone, 100 mg 6−8 hourly) during labour, and until they are able to restart their oral medication. Prostaglandin E_2 used to induce labour, to ripen the cervix, or for early termination of pregnancy is a bronchodilator and is safe. Prostaglandin F_{20}, indicated for severe post-partum haemorrhage should be used with caution because it may cause bronchospasm.

Asthmatic women may safely use all forms of pain relief in labour, including epidural analgesia and *Entonox*. In the unlikely event of an acute asthma attack, opiates should be avoided. If anaesthesia is required, women should be encouraged to have epidural rather than general anaesthesia because of the increased risk of chest infection and associated atelectasis. Ergometrine has been reported to cause bronchospasm, particularly in association with general anaesthesia, but this does not seem to be a practical problem when it is combined with oxytocin to prevent post-partum haemorrhage. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain relief following caesarean section. Women with asthma should be asked about any known aspirin or NSAID sensitivity before the use of these drugs.

Epilepsy

Epilepsy is the most common chronic neurological disorder to complicate pregnancy, affecting about 0.5% of pregnancies. Epilepsy is classified according to the clinical type of seizure, of which the most common are grand mal (tonic-clonic seizure), petit mal (absence seizure), and temporal lobe seizures (complex partial seizure). The term petit mal should be reserved for typical absences occurring almost exclusively in children and associated with 3 Hz spike and wave discharge on the EEG. Absence attacks occur in adulthood as a feature of partial seizures.

Most cases of epilepsy are idiopathic. Secondary epilepsy may be encountered in pregnancy in patients who have previously undergone surgery to the cerebral hemispheres or who have intracranial mass lesions. This should always be considered if the first fit occurs in pregnancy. Epilepsy may be a feature of antiphospholipid syndrome. Other causes of seizures in pregnancy include eclampsia, cerebral vein thrombosis, thrombotic thrombocytopenic purpura, cerebral infarction, drug and alcohol withdrawal and hypoglycaemia (complicating insulin-treated diabetes). Most women with epilepsy in pregnancy have already been diagnosed, but when a first fit occurs in pregnancy, having excluded pre-eclampsia, imaging with CT or MRI of the brain is appropriate.

Effect of pregnancy on epilepsy: in general, pregnancy does not affect the frequency of seizures. About 25% of women report improvement, and 10−30% experience an increased seizure frequency in pregnancy. Poorly controlled epileptics, especially those who fit more than once a month, are more likely to deteriorate in pregnancy. There is no relation to the seizure type or the course of epilepsy during previous pregnancies. Reasons for deterioration in seizure control during pregnancy are shown in Figure 4. There is no difference in the change of seizure frequency between trimesters, though the risk of seizures is greatest peri-partum (see below).

Ante-partum: folic acid should be continued throughout pregnancy because there is a small risk of folate deficiency anaemia. There is no need to change the anticonvulsant used in pregnancy if the woman is well controlled. Prenatal screening for congenital abnormalities with maternal serum screening or nuchal translucency and detailed ultrasound at 18−20 weeks should be offered. A repeat scan at 22 weeks is advisable if cardiac defects are suspected.

The altered pharmacokinetics (Figure 4) in pregnancy mean that drug levels are likely to change, and for most drugs, concentration of the free drug falls. This is because of the increased plasma volume and the enhanced renal and hepatic drug clearance. These effects are partially offset by decreased protein binding. In practice it is useful to have a baseline blood level early in pregnancy to confirm compliance, and to guide any necessary increases. If a woman is fit free there is no need to measure serial drug levels or adjust the dose. In women who have regular seizures, and who are dependent on critical drug levels, it is worth monitoring drug levels (preferably of the free drug) because they are likely to fall, and increasing doses of anticonvulsants should be guided by serum concentrations. The dose of anticonvulsant should be altered only on clinical grounds. Vitamin K, 10−20 mg orally, should be prescribed from 36 weeks' gestation because, in women taking hepatic enzyme-inducing drugs, vitamin K-dependent clotting factors in the fetus may be reduced, thus increasing the risk of haemorrhagic disease of the newborn.

Intra-partum: the risk of seizures increases around the time of delivery. 1−2% of women with epilepsy will have a seizure during labour, and 1−2% will fit in the first 24 hours post-partum. Caesarean section is required only for obstetric indications or if there are recurrent generalized seizures in labour.

Reasons for increase in seizures in pregnancy

- Poor drug compliance
- Nausea and vomiting
- Increased blood volume
- Changes in protein binding
- Increased drug clearance
- Lack of sleep
- Reduction of absorption of anticonvulsant drugs from the gastrointestinal tract during labour
- Hyperventilation during labour

Post-partum: epileptic patients require particular care in the immediate puerperium because of the increased risk of seizures. They should be supervised in the bath. Mothers with major seizures require advice regarding precautions such as bathing infants with somebody else around and changing nappies on the floor. The neonate should also receive vitamin K. All women with epilepsy should be encouraged to breast-feed.

Amniotic fluid embolism

Amniotic fluid embolism is rare but it is associated with a mortality rate of about 80%. Despite a low incidence of 1/80,000 deliveries, amniotic fluid embolism was responsible for 17 confirmed and suspected cases of maternal death in the 1994−1996 UK triennial report. The anaphylactic-like reaction occurs as a result of passage of amniotic fluid and particulate debris into the maternal circulation. Associated maternal factors include multiparity, caesarean section, uterine stimulation, uterine manipulation and increased age. Fetal factors include large baby, polyhydramnios, intrauterine death, placental abruption and rupture of membranes. All but one case in the triennial report had one or more of these complications.

There is a national register for suspected amniotic fluid embolism set up in the UK and the USA. The criteria for entry are detailed in Figure 5.

Management: death usually occurs as a result of cardio-respiratory collapse or disseminated intravascular coagulation. The treatment of amniotic fluid embolism remains supportive and includes adequate oxygenation and ventilation, maintenance of cardiac output and correction of coagulopathy. Current studies are focused on the possible role of leukotrienes, histamine, bradykinin, cytokines, prostaglandins and thromboxane.

Entry criteria for the amniotic fluid embolism register

- Acute hypotension or cardiac arrest
- Acute hypoxia (dyspnoea, cyanosis or respiratory arrest)
- Coagulopathy, disseminated intravascular coagulation or unexplained haemorrhage
- Onset during labour, caesarean section, uterine evacuation or within 30 minutes post-partum
- Absence of any other potential explanation of above symptoms and signs

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Medico-legal Aspects of Obstetric Anaesthesia

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This article is based on British law, but the principles can be extrapolated to most legislatures based on the British or North American legal systems.

The concept of negligence

In order for a patient to bring a successful case of negligence against a practitioner, she must be able to demonstrate that, on the balance of probabilities:

- there was a breach of duty of care
- damage arose as a direct result of that breach.

How good does the care provided by the anaesthetist have to be for him not to be in breach of duty? It is reassuring to know that the necessary standard is not particularly high. The anaesthetist does not have to achieve the level of care that is represented by the brightest and best in his specialty, but only to act 'in accordance with the practice accepted as proper by a reasonable body of medical men skilled in that particular art' (Bolam v Friern Hospital Management Committee (1957) 2 ALLER 118). This standard, known widely as the Bolam principle, implies that, as long as there is support for the individual's practice among his peers, then he has fulfilled his duty of care to the patient, even if another body of opinion would disagree. The Bolam principle has been clarified (some would say diluted) recently by a case in which the judge ruled that the final decision on whether a standard of care was acceptable was the Court's prerogative, and that the expert medical evidence was to be considered only as a guide (Bolitho v City and Hackney Health Authority (1993) 4 Med LR 117 (CA)).

The patient who has not suffered damage does not have a claim in negligence against her doctor, however poorly he may have performed in caring for her. Indeed, to be successful in proving negligence, the claimant must demonstrate not only that damage occurred, but that it was directly caused by the failure of duty of care.

Common features relating to negligence claims

Consent

Patients in the UK do not have to be given a full explanation of all the risks involved in a procedure, but it is important to provide them with enough facts to enable them to make an informed decision. There are no rules about how common an adverse event has to be before it should be mentioned to a patient, and the widely quoted cut-off point of 1% has no basis in UK law. The practitioner should bear in mind not only the probability but also the severity of an adverse event in deciding whether to mention it, and his explanation should relate to his own practice rather than that of the institution or the country as a whole. If in doubt, it is better to inform the patient.

Having told the patient of the risks, benefits and alternatives to what you intend to do, it is good practice to record a brief summary of the explanation.

Taking consent for obstetric analgesia may be difficult if the patient is in severe pain and under the influence of powerful drugs such as nitrous oxide and pethidine. A brief explanation may be the best that can be done in the circumstances, but the reasons for this should be recorded. Consent to continue a procedure should be sought regularly if it is proving difficult or if the patient is distressed.

Record-keeping

Poor record-keeping often makes negligence suits impossible to defend. A contemporaneous record of the level of block and the modality used to test it is essential if a defence is to be successful against a patient who claims to have felt pain during caesarean section. The key points of good record-keeping are detailed in Figure 1. A summary of good practice points is shown in Figure 2.

Good record-keeping

- Note details of risks and benefits explained when taking consent
- Record evidence of the success and extent of regional blockade
- Record reasons for deviating from standard or accepted practice
- Write legibly in black ink
- Always put the date and time
- Sign notes and print your name if your signature is illegible
- Put your specialty and status
- Avoid writing too close to the edges of the paper – words are often missed in photocopying
- It is acceptable to make notes when a crisis is over or to add corrections later, but they must be dated and timed and the previous notes must not be made illegible
- Ensure that all records are properly bound in the patient's folder – this particularly applies to operating or labour analgesia records, which are often loose

1

Avoiding negligence litigation

- Keep good records
- Note details of consent, including the risks and benefits discussed with the patient
- Be honest with the patient at all times
- Prepare good local guidelines and stick to them
- Establish an early referral system for potential problems
- Maintain close communication with other staff involved in the care of your patients
- Do not get overly focused on the technical aspects – maintain perspective
- Do not be reluctant to seek help or a second opinion
- If things go wrong, apologize – do not avoid the patient
- Be nice – nice doctors are less likely to be sued

2

Negligence claims relating to regional obstetric analgesia or anaesthesia

Pain during caesarean section

Pain felt during caesarean section under epidural or spinal anaesthesia is probably the most common successful medico-legal claim made against anaesthetists in the UK. One reason why these claims are difficult to defend is the subjective nature of pain. This, allied to the delay in getting these cases to court, makes it almost impossible for the defence to counter the claimant's description of what she felt at the time.

Pain-free caesarean section cannot be guaranteed, however effective the block. Consequently, the patient who feels pain during the operation is not necessarily the victim of negligence. However, for the anaesthetist to have a good defence, he must be able to demonstrate that he took reasonable steps to minimize the chance of pain and then to treat it when it occurred. These steps are summarized below.

- As part of the consent process, warn the patient about the risk of pain and the possibility of conversion to general anaesthesia. Make a record of the risks explained to the patient in case of later dispute.
- Use a technique that is recognized as acceptable.
- Test the extent of block and demonstrate its effectiveness. A block to touch to T5 has been shown to minimize the risk of pain, and this represents best practice, but the minimum acceptable standard is probably a bilateral block to pinprick to T6. A survey carried out in 1996 showed that only 4% of practitioners regard a T8 block as adequate for caesarean section.
- Treat pain when it occurs by use of epidural top-ups, intravenous or inhalational analgesia, or induction of general anaesthesia. Incidents of pain should be recorded, as should the efficacy of treatment. General anaesthesia should not be withheld without good reason if the patient is not coping with the procedure.
- Provide follow-up and support to the patient who feels pain.

Neurological damage after regional blockade

Neurological symptoms in the lower limbs can arise during childbirth whether or not a neuraxial block has been used. However, the woman who develops a persistent area of numbness or weakness after epidural analgesia is likely to link the two events. The key feature linking neurological damage to the regional technique is whether the patient experienced paraesthesia during the procedure. Persistent paraesthesia should always be a sign to withdraw and reorientate the needle. Failure to do so in a patient who subsequently develops lower limb neurological signs strongly indicates failure of duty of care and causation.

It is not medico-legally incumbent on the anaesthetist to warn the patient of the risk of nerve damage before embarking on the epidural (although it may be good practice). The rare incidence of this complication means that only 20% of anaesthetists would mention it when explaining the risks of epidural analgesia. Practitioners should avoid the temptation to focus on the minutiae of the technical procedure, and to lose the wider perspective. If an epidural is proving difficult and the patient is becoming restless, it is better to call a temporary halt to the proceedings. Consider whether the epidural is needed and whether it would be useful to ask a colleague for help.

Post-dural puncture headache (PDPH)

PDPH is a recognized complication of epidural analgesia and is not necessarily indicative of negligence. Some PDPH claims succeed, however, and this usually relates to delay in treatment, specifically in performing an epidural blood patch. Conservative measures are seldom successful, therefore a blood patch should be offered early and carried out by a senior member of staff. Meticulous follow-up is mandatory, and it should be remembered that PDPH can recur after the patient has returned home. Patients should be told to contact the hospital if they have a recurrence of symptoms, the GP should be informed and it is good practice to arrange a formal follow-up appointment after discharge. ◆

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Obstetric Emergencies

Diana Brighouse

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Amniotic fluid embolism and obstetric haemorrhage are significant causes of maternal death. In the report on Confidential Enquiries into Maternal Deaths in the UK (CEMD) 1994–1996 amniotic fluid embolism is the third cause of direct death after thromboembolism and hypertensive disorders of pregnancy; obstetric haemorrhage is the fourth. Of the 12 deaths resulting from haemorrhage, three were caused by placenta praevia, four by placental abruption and five by post-partum haemorrhage.

Placental abruption

Definition and diagnosis

Placental abruption is the premature separation of the placenta after the twentieth week of gestation. Its incidence is about 2%. It is associated with a high rate (up to 50%) of fetal mortality. The risk factors for placental abruption are:

- smoking
- external cephalic version
- polyhydramnios (following membrane rupture)
- previous abruption
- increasing multiparity
- multiple pregnancy
- blunt trauma
- cocaine ingestion.

Placental abruption is followed by concealed (20–35% cases) or revealed haemorrhage. A grading system has been proposed ranging from grade 0 in which retroplacental clot is found at placental examination after delivery in an asymptomatic woman, to grade 3 in which there is maternal shock, abdominal pain, uterine tetany and a dead fetus. Revealed haemorrhage is not invariable. A coagulopathy is present in 30% of women with grade 3 abruption.

It is important to realize that although this is the typical presentation of placental abruption there may be neither pain nor revealed bleeding. The 1994–1996 CEMD describes a woman presenting in the third trimester ‘feeling unwell’ and ‘pale and clammy’. There was no complaint of pain, and no cardiovascular compromise. The woman died 2 hours after admission to the Accident and Emergency Department, and at emergency caesarean section was found to have 2 litres of blood in the uterus. A high index of suspicion is required for any pregnant woman who is inexplicably unwell, especially if her symptoms are accompanied by any abnormal signs. The incidence of coagulopathy increases as time elapses following abruption, and in the presence of a dead fetus. The complications of placental abruption are:

- maternal hypovolaemia
- fetal distress
- intrauterine fetal death
- disseminated intravascular coagulation (DIC)
- post-partum haemorrhage from uterine atony
- acute renal failure.

Management

Venous access should be secured promptly, and an intravenous infusion of crystalloid begun. In the presence of major haemorrhage it may be necessary to administer group O rhesus negative blood, though group-specific blood is preferable and should be available within 15 minutes. Surgery should not be delayed until blood is available, because the condition of mother and fetus is increasingly jeopardized by a prolonged decision to delivery time.

If the mother is in the third trimester of pregnancy onset of labour usually follows the abruption. If the fetus is not compromised, vaginal delivery is possible. Vaginal delivery is also indicated in severe cases of abruption in which the fetus has died. If labour does not start spontaneously it is usually induced with prostaglandin pessaries.

If abruption occurs during the second trimester of pregnancy, or if there is fetal distress, delivery by caesarean section is necessary.

Anaesthesia and analgesia

Anaesthesia for operative delivery depends on the clinical presentation. Immediate delivery is indicated in the presence of severe fetal distress, or if the mother is hypovolaemic. Resuscitation with intravenous fluids and blood transfusion can be performed at the same time as preparation for operative delivery is made. In this situation, general anaesthesia is indicated. Oral sodium citrate is given before induction of anaesthesia, and many anaesthetists also administer intravenous ranitidine or omeprazole. The uterus is displaced off the vena cava and aorta either by tilting the operating table or by placing a wedge under the patient’s right hip.

The anaesthetist must be alert to the possibility of consumptive coagulopathy in any patient who appears to be bleeding abnormally. If DIC occurs it should be treated with appropriate blood products and the advice of a haematologist should be sought. The patient is at increased risk of postoperative haemorrhage due to failure of the uterus to contract.

In less urgent situations the mother’s condition can be stabilized, and results of haematological investigations awaited. In the absence of a platelet count below 80,000 or an abnormal coagulation screen, regional anaesthesia can be used. Spinal, combined spinal-epidural or epidural anaesthesia are all suitable; the final choice is made according to the anaesthetist’s preferred technique, though the flexibility of the combined spinal-epidural compared with single-shot spinal anaesthesia has led some anaesthetists to recommend it as the technique of choice.

If analgesia is required for labour the mother should be advised to accept epidural analgesia providing that there are no contraindications. Her chances of requiring emergency caesarean section in labour are high, and a functioning labour epidural can readily be extended for operative delivery.

Placenta praevia

Placenta praevia accounted for 25% deaths from obstetric haemorrhage in the 1994–1996 CEMD report. Placenta praevia is the persisting implantation of the placenta in the lower uterine segment. The placenta may partially or completely cover the cervical os and may be positioned anteriorly or posteriorly. Placenta praevia is graded I to IV.

- Grade I, the placenta encroaches on the lower uterine segment.
- Grade II reaches the internal os.
- Grade III asymmetrically covers the internal cervical os.
- Grade IV symmetrically covers the cervical os.

The main risk factors for placenta praevia are the presence of a uterine scar, increasing maternal age and increasing parity. Previous caesarean delivery is a major risk factor, with the risk rising from less than 0.3% in women with no previous caesarean delivery to over 10% in women who have had four previous caesarean sections.

There is a particularly high risk of placenta accreta – placental invasion of the myometrium – in women who have had previous caesarean deliveries. 24% of women with placenta praevia and one previous caesarean section are likely to have placenta accreta, and as many as 67% of women with placenta praevia and at least four previous caesarean deliveries. These women should be investigated with ultrasound scanning during the third trimester of pregnancy to ensure that the placenta is not adherent to the uterine scar. In severe cases of placenta accreta the placenta may invade through the myometrium and into the bladder, bowel or major blood vessels (placenta percreta).

A rare cause of bleeding is vasa praevia, in which an insertion of the umbilical cord encroaches on the cervical os.

Diagnosis

Placenta praevia classically presents as painless vaginal bleeding occurring at any time during the third trimester. It may not present before the onset of labour, when the onset of uterine contractions together with effacement of the cervix precipitates bleeding from the abnormally implanted placenta. Placenta praevia is differentiated from bleeding caused by abruption by the absence of pain, and the diagnosis is confirmed by ultrasound investigation. Placenta accreta, if not diagnosed preoperatively by ultrasound, may present as uncontrollable haemorrhage at caesarean section.

Vasa praevia is invariably accompanied by fetal distress because the blood loss occurs entirely from the fetus.

In the absence of fetal distress, the management of placenta praevia occurring before 37 weeks’ gestation is initially conservative. The diagnosis is confirmed by ultrasound scanning and blood is taken for cross-matching. Intravenous access is secured and the woman is admitted to the antenatal ward. Traditionally she then remains in hospital until delivery, with cross-matched blood being kept continually available. Recently, however, obstetricians have been prepared to allow women with lesser degrees of placenta praevia, especially those who have had only one bleed, to go home and attend the maternity unit regularly as outpatients. Placenta praevia may cause major antenatal haemorrhage, and the mother may present in hypovolaemic shock. If the mother is rhesus negative she should receive anti-D prophylaxis following a vaginal bleed.

Anaesthesia and analgesia

If the mother is bleeding heavily or is hypovolaemic she is almost certain to require operative delivery. This should not be delayed by waiting for cross-matched blood. Volume resuscitation should occur simultaneously with preparations for induction of general anaesthesia. Antacid prophylaxis is given as usual, and anaesthesia is induced with the mother in the wedged supine position to minimize aortocaval compression. The presence of a second anaesthetist is desirable to assist with resuscitation. Early insertion of central venous and arterial cannulas has been recommended in the hypovolaemic woman.

If there is a high suspicion of placenta accreta preoperatively it is mandatory for a senior anaesthetist to administer general anaesthesia, and for there to be a second anaesthetist present to assist. Two large-bore intravenous cannulas should be inserted before induction of anaesthesia, and cross-matched blood should be available immediately. There is a significant risk of proceeding to caesarean hysterectomy in cases of placenta accreta, and the mother should be warned of this (and appropriate consent obtained) preoperatively. Use of direct right atrial and intra-arterial pressure monitoring help to guide volume replacement. If the mother is scheduled for elective caesarean section and is haemodynamically stable many anaesthetists would consider using regional rather than general anaesthesia. It is important to investigate the mother for accurate ultrasound location of the placenta before initiating regional anaesthesia.

In hospitals with the facilities to perform radiological embolization of the uterine or iliac arteries, the possibility of performing a caesarean section in the Department of Radiology should be considered. The appropriate pelvic vessels can be cannulated prior to performing the caesarean section and embolization can be performed in the event of major haemorrhage.

If regional anaesthesia is chosen, epidural, combined spinal-epidural or single-shot spinal techniques can be used. There may be advantages in choosing an epidural or combined spinal-epidural technique that can be extended if surgery proves difficult. Some anaesthetists favour epidural rather than spinal anaesthesia on the assumption that it offers greater cardiovascular stability. Whichever technique is chosen it is advisable to secure intravenous access with two large-gauge cannulas before initiating anaesthesia. Use of direct intra-arterial monitoring may be helpful if this facility is readily available. Cross-matched blood should be available immediately.

A trial of vaginal delivery may be considered for women with minor degrees of placenta praevia. These women should be offered epidural analgesia and it is prudent to anticipate greater blood loss than usual at delivery.

In the absence of access to accurate ultrasonography the anaesthetist may be asked to assist with examination in theatre of a mother with suspected placenta praevia. In this situation, the woman is placed in the lithotomy position and a speculum vaginal examination is carried out. Two large-gauge intravenous cannulas should be inserted before the woman is examined, and if major placenta praevia is confirmed the mother is moved into the wedged supine position and rapid-sequence induction of general anaesthesia is performed.

An alternative technique is to induce regional anaesthesia before vaginal examination and then to proceed to caesarean section under regional anaesthesia. The disadvantages of this technique are that major haemorrhage may occur during surgery and induction of labour and vaginal delivery may be attempted. These considerations should be taken into account when deciding on a suitable anaesthetic approach. In the UK, most obstetric units have access to high-quality ultrasonography and most UK anaesthetists are unlikely to be faced with this dilemma.

Obstetric haemorrhage

The uterus receives 10–15% maternal cardiac output by term. Major haemorrhage can occur with frightening rapidity. The causes of obstetric haemorrhage are shown in Figure 1. Worldwide, obstetric haemorrhage remains a major cause of maternal death. The 1994–1996 CEMD report considered that the care given to eight out of the twelve mothers who died following obstetric haemorrhage was substandard. Failure to diagnose placenta praevia occurred in two cases. In the other six cases, the haemorrhage was recognized but was treated inadequately.

Causes of obstetric haemorrhage

Ante-partum
- Placental abruption
- Placenta praevia

Intra-partum
- Placental abruption
- Placenta praevia
- Uterine rupture

Post-partum
- Uterine atony
- Cervical, vaginal or perineal trauma
- Uterine inversion
- Retained products of conception

1

Ante-partum haemorrhage
Placental abruption and placenta praevia should be treated as discussed above.

Intra-partum haemorrhage
Placental abruption and placenta praevia may both present during labour. Management follows the guidelines outlined above.

Uterine rupture is a rare cause of intra-partum haemorrhage but is accompanied by high fetal mortality and potential maternal mortality. Uterine rupture is almost always associated with labour following previous caesarean section. The causes of uterine rupture are:
- previous caesarean section (especially if classical uterine incision)
- external cephalic version
- previous uterine rupture
- prostaglandins for mid-trimester termination of pregnancy
- obstructed labour (in the developing world).

Scar dehiscence may occur gradually and relatively painlessly, causing progressive fetal distress, and may not be diagnosed until caesarean section is performed. At the other extreme there may be rapid uterine rupture associated with fetal death, severe abdominal pain, maternal shock and cardiovascular collapse. Suspicion of uterine rupture should be raised when breakthrough pain occurs in women who have epidural analgesia for labour, when there is pain that persists between contractions or when there is a loss of beat-to-beat variability on the cardiotocograph.

Post-partum haemorrhage
Blood loss of more than 500 ml following vaginal delivery is classified as post-partum haemorrhage; massive obstetric haemorrhage is blood loss of at least 1500 ml. Primary post-partum haemorrhage occurs within 24 hours of delivery; secondary haemorrhage occurs between 24 hours and 6 weeks after delivery.

Uterine atony: failure of the uterus to contract after delivery of the placenta causes haemorrhage. Causes of uterine atony include:
- prolonged labour
- precipitate labour
- multiple pregnancy
- grand multiparity
- intrauterine infection
- β-sympathomimetic drugs
- magnesium
- volatile anaesthetic agents
- retained products of conception.

Genital tract trauma: blood loss from unrecognized genital tract trauma can be extensive and examination under general anaesthesia is often necessary once initial resuscitation is under way.

DIC may complicate major obstetric haemorrhage of any aetiology, and may also complicate amniotic fluid embolism. The common factor in DIC, regardless of cause, appears to be the release of tissue thromboplastin into the circulation, resulting in platelet aggregation, coagulation and fibrinolysis.

The platelet aggregation together with fibrin production leads to formation of microthrombi in small vessels which stimulate the release of plasminogen activator. Fibrinolysis releases fibrin degradation products into the circulation, which inhibit platelet aggregation and aggravate the bleeding tendency by causing thrombocytopenia. DIC is often diagnosed clinically, and the diagnosis is confirmed by the presence of thrombocytopenia, hypofibrinogenaemia plus elevated fibrin degradation products or D-dimer. Thrombin time is prolonged and antithrombin III activity is reduced.

Management
The principles of management of obstetric haemorrhage are the same regardless of cause (Figure 2). Previous CEMD reports have given clear guidelines for the management of obstetric haemorrhage. The extent of haemorrhage is often underestimated. Delay in treating obstetric haemorrhage aggressively may be fatal.

Management of obstetric haemorrhage

General principles

- Resuscitate the mother
- Give oxygen, intravenous fluids
- Deliver fetus and placenta
- Ensure uterus is empty
- Achieve uterine contraction
- Examine under general anaesthesia if bleeding continues
- Ligate uterine/internal iliac arteries
- Embolize uterine/internal iliac arteries
- Consider hysterectomy

Clinical management

- Call for help
  - obstetrician and anaesthetist
  - extra midwife
  - porters
- Alert haematologist, consultant obstetrician and anaesthetist
- Insert at least two large intravenous cannulas
- Consider CVP line
- Send blood for cross-match (minimum 6 units) and clotting screen
- Give oxygen
- Resuscitate with colloid/group O negative/type-specific blood until cross-matched blood available
- Use blood warmer and pressure infusion device
- Monitor blood pressure, ECG, urine output, blood gases, temperature
- Continue fluid resuscitation following haematological advice
- Consider examination in theatre
- Consider early transfer to ICU

2

Uterine rupture: treatment of uterine rupture is delivery of the fetus by caesarean section, followed by uterine repair or hysterectomy. General anaesthesia should be used for speed and because the mother is likely to be haemodynamically compromised. Women with a history of uterine rupture are usually delivered at 36 weeks' gestation by elective caesarean section.

Uterine atony: initial management should follow the guidelines outlined above. Intravenous access should be secured with two large cannulas and fluid resuscitation should be started. Any drugs likely to be contributing to uterine atony should be discontinued, and oxytocic drugs should be given. If a bolus of syntocinon is given this should not exceed 10 iu, and many anaesthetists would advise a maximum of 5 iu as a bolus, followed by an infusion of 50 iu in 500 ml saline, given over 2–4 hours.

Manual stimulation of uterine contraction may be successful. If haemorrhage continues a bolus of ergometrine is given (Figure 3). Ergometrine causes an increase in systemic arterial and intracranial pressure and provokes vomiting. It should be diluted to 10 ml and administered slowly. Its use is contraindicated in hypertensive women and those with intracranial pathology. If bleeding continues, prostaglandins may be administered; in the UK prostaglandin $F_{2\alpha}$ (*Carboprost, Hemabate*) is used in a dose of 0.25 mg i.m. or directly into the myometrium. There is a relatively high incidence of anaphylactoid reaction to systemic prostaglandins.

Drug treatment of uterine atony

- Stop tocolytics (salbutamol, magnesium)
- Stop volatile anaesthetic agents
- Give syntocinon, 5–10 iu i.v. bolus followed by infusion
- Give ergometrine, 0.25 mg i.v. slow bolus repeated once
- Give *Carboprost,* 0.25 mg i.m. or into myometrium; repeat if necessary at 15 minute intervals; maximum dose 2 mg

3

If bleeding continues the patient should be taken to theatre for exploration of the uterus under general anaesthesia. It is possible that undiagnosed retained products of conception are preventing uterine contraction.

Genital tract trauma: if post-partum blood loss continues despite the above measures it may be necessary to tie off the uterine or internal iliac arteries. If this fails, hysterectomy should be considered. A second anaesthetist should be present during these procedures because coagulopathy has often developed by this stage. Appropriate blood products including fresh frozen plasma, platelets and cryoprecipitate should be given following the advice of a haematologist. The patient should be transferred to the ICU postoperatively.

A small number of obstetric units have access to radiological embolization of the uterine and internal iliac arteries, and this is an alternative to surgical ligation. Although general anaesthesia is usually indicated for obstetric hysterectomy, there have been reported series of obstetric hysterectomies performed under epidural anaesthesia with no difference in complication rates. Regional anaesthesia can be considered only in the well- resuscitated and haemodynamically stable mother, in whom there is no evidence of coagulopathy.

DIC: primary treatment is removal of the triggering event, together with intravascular volume replacement. Replacement of blood products should be guided by a haematologist, and should include transfusion of blood, fresh frozen plasma and cryoprecipitate or fibrinogen. Platelet transfusion is usually indicated if the platelet count falls below 50 x 10^9/litre. The use of heparin, antithrombin III and aprotinin have all been reported in the treatment of DIC but their efficacy has not been evaluated.

Women who refuse blood transfusion: some women refuse blood transfusion either on religious grounds (Jehovah's Witnesses) or because of fear of contracting blood-borne diseases such as HIV. It is important to identify these women during the ante-natal period and to counsel them about the risks of refusing blood transfusion. Delivery should be arranged in a large obstetric unit that has facilities for the management of major obstetric haemorrhage. Management of these women is described in Figure 4.

Management of obstetric haemorrhage in women who refuse blood transfusion

- Ante-natal identification and counselling
- Maximize iron stores antenatally
- Deliver in large obstetric unit
- Secure intravenous access early
- Treat haemorrhage early and aggressively with crystalloid/ colloid
- Consider cell-saving techniques
- Administer oxygen
- Provide opportunity for the woman to change her mind (partner does not have right to consent or withhold consent)
- Consider hysterectomy early
- Consider hyperbaric oxygen if available
- Consider erythropoietin and parenteral iron
- Transfer to ICU
- Arrange counselling for staff if patient dies

4

Inversion of the uterus

Uterine inversion occurs in about 1/2000 deliveries, and is defined as complete or incomplete depending on whether the fundus of the uterus has passed through the cervix. Acute uterine inversion occurs within 24 hours of delivery; subacute and chronic uterine inversion may also occur. Risk factors for uterine inversion include primiparous labour, augmentation of labour with oxytocics, macrosomic fetus, and implantation of the placenta at the uterine fundus. Acute uterine inversion presents with pain, haemorrhage and shock disproportional to blood loss.

Management

Current obstetric opinion favours leaving the placenta undelivered until the uterus has been replaced. The mother should receive fluid resuscitation and an initial attempt at manual replacement is made under regional anaesthesia once the mother is haemodynamically stable. If immediate attempts at replacement are unsuccessful the mother may be given intravenous magnesium, 2 g by slow bolus injection, or a β-sympathomimetic (e.g. salbutamol) to facilitate uterine replacement. The use of volatile anaesthetic agents such as halothane is no longer advocated because of the risk of prolonged uterine atony and further haemorrhage.

If the mother remains haemodynamically unstable despite fluid resuscitation she should receive a general anaesthetic to facilitate uterine replacement.

Hydrostatic pressure is used to replace the uterus if this cannot be done manually, and if this technique fails, laparotomy and abdominal replacement of the uterus is required.

Amniotic fluid embolism

The incidence of amniotic fluid embolism is unknown; in the 1994–1996 CEMD report the UK mortality rate was 7.7/1 million maternities. In Australia between 1973 and 1990, the mortality was 65/1 million maternities. There is under-reporting of non-fatal cases, partly because of diagnostic confusion. The pathophysiology of amniotic fluid embolism is uncertain. Current theories favour the involvement of leukotrienes as a trigger in an anaphylactoid cascade that precipitates a systemic inflammatory response. Most of the traditionally cited risk factors have not been substantiated. An American review found no correlation with duration of labour, use of oxytocics, presence of intact membranes or hypertonic uterine activity. There may be an association with increasing maternal age.

Diagnosis

In the USA, diagnostic criteria for amniotic fluid embolism have been established (Figure 5). Shivering, sweating, dyspnoea or cyanosis may precede cardiovascular collapse. The woman may have convulsions, leading to misdiagnosis of eclampsia. DIC may be apparent soon after initial presentation. Diagnosis is supported by the finding of fetal material in the pulmonary arterial tree.

US criteria for diagnosis of amniotic fluid embolism

- Acute hypotension or cardiac arrest
- Acute hypoxia
- Coagulopathy or unexplained haemorrhage
- Onset of symptoms during dilatation and curettage, labour, caesarean section or within 30 minutes of delivery
- No other explanation for signs and symptoms

5

Management

The management of amniotic fluid embolism is entirely supportive and includes:

- tracheal intubation and ventilation with high inspired oxygen
- fluid resuscitation
- symptomatic treatment of coagulopathy
- aggressive management of haemorrhage
- delivery of fetus and placenta
- supportive use of inotropes.

Maternal resuscitation

Causes of collapse in the pregnant or recently delivered woman include:

- hypovolaemia
- embolism (pulmonary or amniotic)
- cardiac disease
- drug administration
  - anaphylaxis
  - high-spinal/epidural
  - drug abuse (cocaine, temazepam, opioids)
  - drug toxicity (magnesium, opioids, local anaesthetics)
- eclampsia
- intracranial event
- sepsis.

Initial resuscitation attempts must include displacement of the gravid uterus off the major vessels. A purpose-made resuscitation wedge can be used (this needs to be made of a non-compressible material, and to be of adequate length), or a second person can kneel on the floor and use their knees as a wedge. Early tracheal intubation reduces the chances of aspiration of gastric contents.

Use of adrenaline (epinephrine) and cardiac defibrillation should follow standard resuscitation guidelines for the non-pregnant patient. Sodium bicarbonate can precipitate fetal intracerebral bleeding, and reduce cerebral perfusion in the mother, and therefore should be given only in response to proof (from arterial blood gas analysis) of severe metabolic acidosis.

Cardiopulmonary resuscitation of the pregnant mother is unlikely to succeed while the mother remains undelivered, because aortocaval compression prevents an adequate cardiac output being obtained with cardiac massage. The standard ABC of resuscitation should be supplemented with D for delivery in women of more than 24 weeks' gestation. Vaginal delivery with vacuum extractor or forceps, or peri-mortem caesarean section should be performed if resuscitation has not been successful within 5 minutes of cardiac arrest.

North American guidelines suggest that if resuscitation has not been successful within 15 minutes open-chest cardiac massage should be considered. Use of cardiopulmonary bypass has been shown to be life saving in certain clinical situations but this is an option only in hospitals where the obstetric and cardiac units are in close proximity.

Local anaesthetic toxicity

Bupivacaine has a narrower safety margin between therapeutic and cardiotoxic dose than lidocaine (lignocaine). It also has a narrower margin between the dose that is neurotoxic and that which is cardiotoxic. Bupivacaine cardiotoxicity produces asystolic cardiac arrest, or ventricular fibrillation that is refractory to defibrillation. The drugs of choice for treatment of bupivacaine toxicity are atropine, maximum 2 mg, and isoprenaline. Cardiac pacing may be useful. If cardiac function is restored and is complicated by ventricular dysrhythmias these should be treated with bretylium and adrenaline (epinephrine). ◆

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Pain Relief in Labour: Alternative Techniques (Gaseous and Parenteral)

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Inhalational agents (Figure 1)

Agents of historical interest
Ether was the first inhalational agent described for analgesia in labour. Although effective, ether was irritant to the airways, slow in onset, and caused nausea and vomiting. Chloroform, introduced at the end of 1847 and famously administered to Queen Victoria by John Snow for the birth of Prince Leopold on 7 April 1853, was less irritant and quicker in onset. However, the dose administered was hard to control and loss of consciousness often occurred. Furthermore, chloroform reduced uterine contractility and readily crossed the placenta causing neonatal depression. Trichloroethylene (*Trilene*) and methoxyflurane have been used for analgesia in labour without any great benefit.

Inhalational agents used for pain relief in labour

Agent	Amount inspired for analgesia in labour (%)
Ether	Unmeasured
Chloroform	0.2–0.9/unmeasured
Trichloroethylene	0.35–0.5
Methoxyflurane	0.35
Nitrous oxide	50
Enflurane	0.25–1.25
Isoflurane	0.2–0.75
Desflurane	1–4.5
Sevoflurane	Not reported

Nitrous oxide
Entonox, a 50:50 mixture of nitrous oxide and oxygen, is the most widely used form of inhalational analgesia in modern obstetric practice. It has a rapid onset in sub-anaesthetic doses and is eliminated between contractions, so that there is minimal accumulation in mother or fetus. Despite promising early reports of analgesic efficacy, *Entonox* has produced poor results in placebo-controlled trials. However, *Entonox* compares favourably with other forms of non-regional analgesia, such as transcutaneous electrical nerve stimulation and pethidine.

To optimize analgesia, *Entonox* inhalation must begin at the start of the contraction in order to try to attain analgesic levels as the contraction peaks. As soon as the contraction starts to wane, inhalation should stop to minimize hangover between contractions. Supplementary, continuous, low-flow *Entonox* via nasal prongs between contractions may improve efficacy.

Side-effects include dizziness, loss of control, nausea and vomiting, but resolve rapidly once *Entonox* is withdrawn. During contractions, hyperventilation may cause hypocapnia that can decrease oxygen transfer across the placenta by causing vasoconstriction and increasing the affinity of maternal haemoglobin for oxygen. Between contractions, hypocapnia combined with the residual sedative effects of *Entonox* may increase the incidence of maternal hypoventilation and consequent arterial oxygen desaturation.

Entonox has no documented effect on the progress or outcome of labour. Comparison of Apgar scores and more complex neonatal outcome measures show no detrimental effects on the baby. The high inspired concentration of oxygen in *Entonox* may be of benefit, particularly when there is fetal distress.

Other agents
The newer volatile agents, desflurane and sevoflurane, offer rapid onset and elimination. Desflurane provides similar analgesia to *Entonox* but with an increased incidence of amnesia. However, the cost of desflurane, the complex vaporizer required for its delivery and its lack of significant therapeutic advantage makes widespread use unlikely. Sevoflurane has not been investigated in obstetric practice, but may become an alternative or adjunct to *Entonox*.

Parenteral analgesics (Figure 2)

History
Opioids have been used for analgesia in labour for hundreds of years, often as an incidental component of a complex potion. In 'twilight sleep', first described in 1902, a single dose of morphine was followed by intermittent doses of hyoscine. Side-effects were severe, analgesia was poor and the technique was abandoned at the end of the 1930s.

Parenteral drugs used for pain relief in labour

Drug	Dose
• Pethidine	50–100 mg i.m. 3–4 hourly; 25–50 mg i.v. 3–4 hourly; 10–25 mg i.v. PCA (lock-out 10 minutes)[1]
• Morphine	5–10 mg i.m. 3–4 hourly
• Diamorphine	2.5–5 mg i.m. 3–4 hourly
• Meptazinol	100–150 mg i.m. 2–4 hourly
• Pentazocine	40 mg i.m. 2–4 hourly
• Nalbuphine	10–20 mg i.m. 2–4 hourly
• Fentanyl	25–100 μg/hour i.v.; 12.5–25 μg i.v. PCA (lock-out 5 minutes)[1]
• Remifentanil	0.5–0.75 μg/kg i.v. PCA (lock-out 3 minutes)[1]
• Tramadol	50–100 mg i.m. 3–4 hourly

[1] PCA, patient-controlled analgesia.

Pethidine
Pethidine was introduced in the 1930s and has since become the most commonly used and widely investigated systemic opioid in labour. Widespread availability and ease of administration has resulted in the continued use of systemic pethidine in labour, despite overwhelming evidence that it is ineffective and has detrimental effects on both mother and baby.

Pethidine is usually given as an intramuscular injection, although intravenous boluses and infusions have been used in an attempt to improve the quality of analgesia. Better analgesia has been reported with intravenous boluses and infusions, but the side-effect profile remains unchanged. Improved efficacy has also been reported with patient-controlled analgesia (PCA), though pethidine consumption may be increased and neonatal depression more common.

A number of attempts have been made to improve the efficacy of pethidine by administering it in combination with other drugs. In general, such combinations have only increased sedation, amnesia and dysphoria, while having little impact on analgesia. When compared with epidural analgesia in randomized trials, pethidine invariably produces clinically inferior analgesia.

Effects on the mother: pethidine causes sedation and dysphoria. Pain relief during contractions is minimal, although some women report feeling less distressed. Respiratory alkalosis caused by hyperventilation associated with pain continues to occur during contractions. This causes a reduction in uterine blood flow and impairs placental gas exchange. Hypocapnia and sedation between contractions exacerbates maternal hypoventilation and hypoxia. Pethidine causes nausea, vomiting and delays gastric emptying.

Effect on the progress of labour: conflicting reports have suggested that pethidine might either slow or accelerate the progress of labour. Slowing of labour may be caused by an effect on maternal oxytocin and acceleration of labour by a number of mechanisms including: increasing the contractility of the body of the uterus; decreasing the contractility of the cervix; and stimulating the production of enzymes responsible for degrading cervical collagen and elastin. None of these changes has been shown to correlate with the duration of the active phase of labour and there continue to be no randomized, controlled trials to suggest that opioids in general, or pethidine in particular, have any effect on the progress of labour.

Effects on the baby: pethidine is a highly lipophilic molecule that is able to diffuse rapidly across the placenta. It is bound principally (30–60%) to α_1-acid glycoprotein. At term, levels of this protein tend to be higher in the maternal than in the fetal circulation and, in theory, favour distribution of pethidine into the maternal compartment. pH gradients across the placenta may be of greater importance. In the compromised fetus, acidosis may cause ion trapping, resulting in increased fetal pethidine levels and concomitant side-effects.

The neonatal side-effects of pethidine are compounded by production of its active metabolite norpethidine by both mother and fetus. Norpethidine is a considerably less potent analgesic than pethidine, but causes more respiratory depression and has pro-convulsant properties. The half-lives of pethidine and norpethidine in the mother are approximately 4 hours and 20 hours, respectively, but in the neonate are 13 hours and 62 hours, respectively. These prolonged half-lives probably explain why some of the behavioural changes observed in exposed neonates persist for several days after delivery.

Intrauterine effects *of pet*hidine include changes in fetal heart rate pattern (reduce**d variability), fetal br**eathing movements and muscular activity, fetal EEG activity and fetal scalp oxygen tension. Though these changes may not represent fetal distress per se, they may result in unnecessary obstetric intervention.

Early neonatal effects of pethidine include respiratory depression that is worst after a dose delivery interval of about 3 hours, and particularly after repeated maternal doses. This results in decreased Apgar scores, depressed oxygen saturations and increased arterial carbon dioxide tensions. Babies are sleepy, less able to develop suckling skills and take longer to establish breastfeeding. In large doses, pethidine can cause impaired thermoregulation in the newborn.

The effects of pethidine on the baby can be rapidly reversed immediately after delivery by administering n***aloxone,*** **a**n opioid antagonist, 60–100 μg/kg intramuscularly. At this dose, naloxone appears to have a clini***cal effect f***or up to 48 hours and reverses the neurobehavioural effects of pethidine without any apparent harm.

Other opioids
Morphine given via any systemic route confers no advantage and causes similar side-effects to pethidine.

Diamorphine is used enthusiastically in a small nu<u>m</u>**b*er of unit***s, but there is little information comparing it with other opioids. Increased lipid solubility suggests that it might reach the sites of action more quickly than morphine, but it is unlikely to offer any great improvement.

Meptazinol is a mixed opioid ***agonist/ant***agonist that enjoys popularity in a small number of units in which it is believed to be superior to pethidine. Though analgesia may be slightly improved, side-effects are similar apart from vomiting, which is more common.

Pentazocine is a mixed opioid agonist/antagonist that was deliberately synthes***ized to mi***nimize potential for abuse (large doses causing dysphoric side-effects). It causes sedation and is irritant on intramuscular or subcutaneous injection. There is no evidence that it provides superior analgesia to pethidi***ne.***

Nalbuphine is a mixed opioid agonist/antagonist similar to pentazocine. Sedation is common and it can cause dysphoria, though less so than pentazocine. There is little evidence that nalbuphine is more effective than pethidine.

Fentanyl is a highly lipid-soluble phenylpiperidine derivative that acts primarily on μ receptors. It is approximate***ly 80–100 ti***mes more potent than morphine. Information about systemic fentanyl in labour consists of unblinded studies and case reports. It is unlikely that fentanyl will provide significantly better analgesia by the systemic route.

Remifentanil is an ultra short-acting opioid analgesic agent. It produces rapid onset and offset of profound analgesia, but equally profound sedation and muscle rigidity. It was hoped that remifentanil might be suitable for intravenous PCA in labour. Unfortunately, although fast in onset, its peak effect does not occur until about 80 seconds after injection, when ***the inte***nsity of contraction pain is declining. Reports suggest that the dose required to provide effective analgesia during contractions can result in a high incidence of sedation, hypoventilation and hypoxia between contractions.

Tramadol is a weak μ agonist reported to have few of the detrimental side-effects associated with other opioids. Evidence concerning maternal and fetal side-effects is conflicting and tramadol has no clear advantages over pethidine.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Compared with pethidine, ketorolac is less effective, but causes fewer maternal and neonatal side-effects. It is unlikely that NSAIDs will gain popularity for analgesia in labour because of the perceived risk of adverse effects on the fetal circulation, in particular, vasoconstriction and premature closure of the ductus arteriosus.

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Pain Relief in Labour: Regional, Epidural and Patient-Controlled Epidural Analgesia

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Although many methods have been used to relieve the pain of labour, regional blockade is the most effective. In the last national UK survey of pain relief in labour conducted in 1990 by the National Birthday Trust, about 20% of women received epidural analgesia. This figure has recently increased to 24% with a range of 5–40% between units.

Indications for regional analgesia

Maternal

Maternal request – because labour causes many women severe pain, an increasing number of maternity units now provide a 24-hour on-demand epidural service.

Coexisting disease – effective pain relief reduces maternal stress and the associated neuroendocrine response which, in certain conditions such as pre-eclampsia, may benefit both mother and baby.

Potential problems with general anaesthesia – compared with regional anaesthesia, emergency general anaesthesia carries a greater risk for both mother and baby. Regional analgesia can be readily extended to provide anaesthesia for operative delivery, therefore regional block is recommended for women at risk of intervention in whom intubation is expected to be difficult or those with known anaesthetic problems. Regional analgesia is also advisable for obese women because they are at increased risk of requiring operative delivery. Although the procedure may be technically challenging, the hazards of emergency general anaesthesia are avoided.

Fetal

Impaired utero-placental flow – fetal well-being may be improved with epidural analgesia because vasodilatation on both maternal and fetal sides of the placenta improves blood flow. This is of benefit in pre-eclampsia, in the growth-restricted fetus and in those with poor cardiotography (CTG) traces or Doppler studies.

Multiple pregnancy – the risk of malpresentation, especially of a second twin, is increased in multiple pregnancy making intervention more likely. Epidural analgesia reduces the need for emergency general anaesthesia should operative delivery be necessary.

Breech presentation – although many breech babies are now delivered by caesarean section, regional analgesia allows a controlled vaginal delivery with a calm cooperative mother and, if emergency caesarean section becomes necessary, the block may be extended.

Intrauterine death – provided coagulation is normal, regional analgesia may be suitable for pain relief.

Labour

Induction or augmentation of labour results in more severe pain. In prolonged labour, epidural analgesia allows the mother to rest while minimizing fetal acidosis. Operative delivery is more likely and the use of regional analgesia reduces the need for emergency general anaesthesia.

Previous caesarean section – epidural analgesia may be beneficial, although it used to be contraindicated because of fear that the pain of scar dehiscence would be masked. Pain is not an invariable feature of scar rupture and CTG abnormalities are a more reliable indicator of rupture. Scar dehiscence or rupture should, however, be considered in women with a working epidural who develop pain.

Operative or instrumental delivery – any woman in whom intervention is thought likely should be advised to have an epidural so that general anaesthesia may be avoided.

Manual removal of the placenta – in the absence of hypovolaemia, regional block negates the need for emergency general anaesthesia.

Repair of third-degree tear – effective pain relief is needed and local infiltration may be inadequate.

Contraindications to regional anaesthesia

Maternal refusal – informed consent must be obtained and, though this may be difficult in advanced labour, every effort must be made to explain the procedure.

Lack of trained staff – despite the potential benefits of regional analgesia, suitably trained staff must be available to monitor the mother for the duration of the block.

Risk of spinal haematoma – vascular trauma during needle insertion or catheter manipulation in the presence of abnormal coagulation may lead to an expanding haematoma, with the risk of ischaemic damage to neural tissue.

Local or systemic infection – epidural abscess or meningitis may occur in the presence of local or systemic infection. Prophylactic antibiotics may help to reduce the risk.

Coexisting disease – in certain cardiovascular conditions, such as pulmonary hypertension, severe valvular stenosis and bi-directional shunts, regional blocks may produce haemodynamic instability.

Uncorrected hypovolaemia – sympathetic blockade in the presence of hypovolaemia results in a dramatic reduction in cardiac output.

Allergy – true allergy to local anaesthetics is rare. Alternative drugs (see below) may be used where true allergy exists.

Pharmacology

Local anaesthetics

Local anaesthetics have a nonselective action that blocks all nerve fibres. Bupivacaine is the most popular agent in obstetric analgesia having replaced the shorter-acting lidocaine (lignocaine). Unlike its predecessor, it causes less motor block, does not demonstrate tachyphylaxis and produces lower systemic levels in both mother and baby. There have, however, been concerns regarding its safety, especially following accidental intravenous injection when cardiac arrhythmias are more likely to occur in doses close to those producing convulsions.

Bupivacaine is a racemic compound composed of two stereoisomers, of which the levo form is less toxic. Although the danger of cardiotoxicity may be minimized by safe practice (catheter aspiration and slow injection while maintaining eye and verbal contact with the mother), a search for a safer local anaesthetic has led to the development of new agents.

Ropivacaine is a single levo isomer which, in addition to reduced toxicity, may produce less motor block than bupivacaine. This may be because it has only 60% of the potency of bupivacaine. Levobupivacaine, the levo isomer of bupivacaine, unlike ropivacaine, has a similar potency to racemic bupivacaine.

Opioids

Unlike local anaesthetics, opioids produce only selective block of nociceptive pathways. Opioid receptors are found in the substantia gelatinosa of the spinal cord. Epidural or intrathecal injection allows ready access to these receptors at a much higher concentration than that which results from systemic administration. Side-effects such as nausea, vomiting, pruritus, urinary retention and respiratory depression are dose dependent. The lipophilic opioids are preferable because the more polar agents (e.g. morphine) have a slow onset of action and greater potential for side-effects.

Fentanyl is the most widely used agent in the UK. On its own, it does not produce reliable analgesia throughout labour and therefore it is usually combined with low-dose bupivacaine. Sufentanil may be effective without additional local anaesthetic when given intrathecally, but it is not available in the UK.

Alfentanil has been used effectively in epidural infusions, though large doses (30 μg/kg/hour) have been associated with neonatal hypotonia.

Diamorphine has a much longer duration of action and, when given with a loading dose, reduces the subsequent need for bupivacaine.

Pethidine has some local anaesthetic effect, but its duration of action is short.

Other drugs

Adrenaline (epinephrine) and clonidine both augment other analgesics through their α_2-action. Adrenaline (epinephrine) also has an α_1-action producing vasoconstriction, which intensifies the action of bupivacaine, while prolonging that of lidocaine (lignocaine). The anticholinesterase neostigmine produces analgesia, but nausea and vomiting limit its clinical usefulness. Other agents currently under investigation include adenosine, ketamine and midazolam.

Effects and complications of regional analgesia

Accidental dural puncture should occur in less than 1% of cases. An epidural needle may breach both the dura and arachnoid leading to free flow of CSF or, alternatively, the dura alone may be punctured and a catheter placed in the subdural space. A subdural block is typically slow in onset, extends much higher than would be expected with an epidural, but spares the sacral roots. It is often patchy with minimal motor block. Where both dura and arachnoid are torn, epidural insertion may be attempted at another level or alternatively the catheter passed directly into the CSF producing spinal analgesia. With the latter, analgesia is not delayed, there is no risk of repeat dural puncture and, provided appropriate doses are used, there is less risk of a dangerously high block. Furthermore, the block may be safely and quickly extended for operative delivery. As the dose for epidural analgesia is ten times greater than that for spinal use, unrecognized spinal injection of an epidural dose of local anaesthetic results in a rapidly ascending block with hypotension and, ultimately, apnoea and unconsciousness – total spinal anaesthesia. If this occurs, the mother must be intubated, ventilated and circulatory support provided until the block wears off. Urgent delivery of the baby may be required.

Local anaesthetics

Effects on the mother

Sensory block – block of lower thoracic, upper lumbar and sacral nerve roots provides pain relief in labour.

Motor block – increasing motor block, which is dependent on cumulative dose, reduces maternal satisfaction.

Autonomic block – block of preganglionic autonomic B fibres produces vasodilatation, which may lead to venous pooling with a fall in maternal cardiac output. This is exacerbated by the supine position (supine hypotensive syndrome), which must be avoided in women receiving regional block.

Proprioception – increasing doses of local anaesthetics progressively impair dorsal column function making ambulation unsafe.

Stress response – increased cortisol and catecholamine levels resulting from painful labour are reduced. Impaired uterine contractility from β-receptor stimulation and reduced placental blood flow from α-receptor stimulation are prevented.

Temperature regulation – epidural analgesia is associated with a rise in maternal temperature. Both the mechanism and significance of this rise are uncertain, though no adverse effect on either mother or baby has been demonstrated. Similarly, the cause of shivering that is often observed after large epidural top-ups is not fully understood.

Bladder function – difficulty passing urine is not uncommon in labour, though it is more common in those receiving regional blocks.

Toxicity – systemic toxicity (see above) may follow accidental intravenous injection or, rarely, the administration of large epidural doses for caesarean section.

Effects on the baby

Direct effects – lipophilic drugs readily cross the placenta, but adverse effects are unlikely and observed only if the amount in the maternal systemic circulation reaches toxic levels.

Indirect effects – hypotension resulting from autonomic blockade (see above) may reduce placental blood flow and produce fetal acidosis. Hypotension should be treated immediately with intravenous fluids and vasoconstrictors.

Effects on the progress of labour: there remains a widespread belief that regional analgesia has an adverse effect on the progress of labour and mode of delivery. Retrospective analysis reveals increased duration of labour with more operative and instrumental deliveries. However, such methodology is flawed, because women do not choose analgesia at random, but depending on the nature of labour. Consequently, those experiencing prolonged labour, that is more likely to end in intervention, are more liable to request regional analgesia. Moreover, if intervention appears probable, such as in fetal distress, women are advised to have an epidural so that emergency general anaesthesia is avoided.

Randomized studies, in which regional analgesia is compared with systemic analgesia, have produced conflicting results. Some studies have shown an increase in intervention, while others have not. As these studies are not blind, observer bias cannot be eliminated. Impact studies, in which the effects of introducing a service or increasing the number of women receiving regional analgesia are observed, may be more helpful. Several authors have reported little or no change in delivery outcome despite large increases in the epidural rate. The use of historic controls may be criticized as change in practice is not accounted for, however, it may be that this change is necessary to prevent increased intervention.

Delay in siting an epidural before an arbitrary cervical dilatation has been reached is not to be encouraged because no randomized data to suggest a benefit are available. Excessive intravenous fluid loading is also unnecessary and may transiently impair uterine contractility.

Different regional techniques (see below) appear to offer little benefit in terms of labour outcome. However, reducing the local anaesthetic dose leads to more spontaneous deliveries. Appropriate management of the second stage is vital and delay in pushing, providing there is no evidence of fetal distress and analgesia is maintained, allows descent of the presenting part. Pushing should be continued so long as there is continued descent and intervention should occur only when definitively indicated. The judicious use of oxytocin reduces the number of instrumental deliveries in nulliparous women.

Opioids

Effects on the mother

Pain relief – see above.

Pruritus is common, but is seldom troublesome other than with morphine.

Nausea and vomiting are common in labour. The increased incidence with opioids is dose dependent.

Respiratory depression is unlikely if appropriate doses of lipophilic agents are used. The potential for respiratory depression is much greater with epidural morphine.

Hypoxia – minor degrees of maternal desaturation have been observed when opioids are added to epidural solutions, though no adverse effects on mother or baby have been demonstrated.

Bladder function – urinary retention may occur as a result of blocking pelvic parasympathetic outflow.

Gastrointestinal – systemic effects, such as delayed gastric emptying are seen with large or repeated doses.

Reactivation of herpes simplex virus has been reported following epidural morphine.

Effects on the baby: although adverse changes in fetal heart rate have been observed after intrathecal opioids, the significance of these findings has yet to be established. If used appropriately, epidural opioids are unlikely to have clinically important effects on the baby.

Other drugs

Concerns have been raised about the effects of epidural adrenaline (epinephrine) on uteroplacental flow. Most studies have suggested that, in healthy women, its use does not compromise intervillous blood flow, although it may be best avoided in pre-eclampsia, when vessels are more sensitive to catecholamines. The addition of adrenaline (epinephrine) increases motor block. Clonidine in doses much above 100 µg produces maternal sedation and hypotension, both of which are undesirable. Clonidine does not appear to have any adverse effect on the baby.

Techniques

Before siting a regional block, informed consent must be obtained. Wide-bore intravenous access is established, though the practice of routinely pre-loading a fixed volume to prevent hypotension has been questioned. The procedure is performed at the second or third lumbar interspace for epidural analgesia (the lower space is safer for combined spinal-epidural) using a meticulous aseptic technique. Multi-hole catheters provide more reliable analgesia and are best inserted 4–5 cm into the epidural space.

The advantages and disadvantages of different regional techniques are listed in Figure 1.

Advantages and disadvantages of regional analgesic techniques

Advantages	Disadvantages
Intermittent top-up	
• Simple	• Fluctuations in analgesia
• Familiar	• Increased risk of side-effects after bolus
Epidural infusion	
• Continuous	• ? Increased motor block
• Increased safety	• Equipment
• Decreased midwifery workload	• Decreased feedback
Patient-controlled epidural analgesia	
• Autonomy	• Equipment
• Satisfaction	• Decreased anaesthetic input
• Decreased bupivacaine dosage	
Combined spinal-epidural analgesia	
• Rapidity	• Failure
• Ambulation	• Opioid side-effects
• Improved sacral block	• ? Increased neurological problems
• Increased satisfaction	

1

Test dose

To detect intrathecal or intravenous catheter placement, a test dose is given. No more than 15 mg of bupivacaine is injected and the mother is observed for evidence of hypotension, and motor and sensory block (see loading dose below). After 5 minutes, further doses may be given, though it is wise to limit each to less than 15 mg. Intravascular catheter placement is more difficult to detect as small doses of local anaesthetic have little systemic effect. The addition of adrenaline (epinephrine) lacks sensitivity and specificity in labouring women. For increased safety, a multi-hole catheter should be used, and gently aspirated before each injection. Each dose should be injected slowly while maintaining eye and verbal contact with the mother to look for symptoms of local anaesthetic toxicity.

Loading dose

The use of low-dose bupivacaine (< 0.125%) with fentanyl, using volumes of 15–20 ml (i.e. bupivacaine, 10–20 mg) in divided doses where appropriate, to ensure adequate spread, is becoming increasingly popular. A test dose of a more concentrated solution is unnecessary in this situation. Reducing the local anaesthetic dose minimizes motor block thereby increasing maternal mobility. Maternal blood pressure and fetal heart rate should be monitored closely after the loading dose.

Intermittent top-ups

Top-ups are given by either a midwife or anaesthetist as soon as painful sensations return as each dose takes several minutes to become effective. However, levels of analgesia invariably fluctuate and, after each top-up, hypotension is possible. Maternal blood pressure should be checked after each top-up. Top-ups should not be withheld early in the second stage of labour because maternal distress is increased without improving the chance of spontaneous delivery.

Epidural infusions

Epidural infusions decrease the need for top-ups, and reduce variations in pain relief as well as the risk of hypotension. Infusions may also be preferable to top-ups, because intrathecal or intravenous catheter placement should produce gradually increasing symptoms allowing more time for recognition and treatment. The workload for midwifery staff is also reduced.

Although infusions may increase motor block and immobility compared with top-ups of a similar concentration, infusions of more dilute local anaesthetics may be used to maintain analgesia with ambulation still possible. This technique, however, requires infusion pumps and delivery tubing, both of which may be expensive. Feedback on the spread of sensory block is lost during an infusion and a careful check on block height must be maintained.

Bupivacaine, in concentrations of 0.1% or less, is the preferred agent combined with an opioid, usually fentanyl. An initial rate of 10–12 ml/hour may be changed depending on block height, which should be kept at T10. Block height should be checked hourly, and maternal pulse and blood pressure noted every 30 minutes. Mothers should pass urine every 4 hours, otherwise a catheter may be required. In the second stage, block height and perineal sensation should be assessed. If the block is above T10 and perineal sensation absent, the infusion rate should be decreased. If the block is at or below T10, decreasing the rate leads to the return of abdominal pain and is of little benefit. If the mother reports pain, it may be advisable to give a top-up and stop the infusion.

Patient-controlled epidural analgesia (PCEA)

PCEA uses small intermittent self-administered boluses. Compared with continuous infusions of similar concentration, bupivacaine utilization is reduced, as is the need for supplementation. Autonomy allows women greater control and leads to high levels of satisfaction. PCEA does, however, require sophisticated pumps and concerns have been raised regarding the level of anaesthetic input after the initial loading dose.

Solutions containing bupivacaine 0.125% or less with fentanyl, 2–3 µg/ml, are preferable. The local anaesthetic dose is usually bupivacaine, 2.5–5 mg, with fentanyl, 10–12.5 µg, in a bolus of 3–5 ml. Lock-out time is set to 10–15 minutes with an hourly maximum dose of bupivacaine, 15 mg, and fentanyl, 30 µg. Background infusion offers little advantage and is not recommended. Mothers should be monitored as with epidural infusions.

Combined spinal-epidural analgesia (CSEA)

A needle-through-needle technique is most commonly used for CSEA, though the use of separate needles in either the same or different interspaces has been described. Onset of analgesia is more rapid and the quality of sacral analgesia better than with epidural block. Motor block is usually minimal if small intrathecal doses of bupivacaine and fentanyl are used, and most women may ambulate safely following the first dose.

The failure rate of CSEA is up to 10% when administered by those inexperienced in the technique. Intrathecal administration of opioids increases side-effects, especially pruritus, nausea and vomiting. Concerns about threading the epidural catheter through the dural hole are overstated and the incidence of dural puncture headache does not appear to be significantly increased. The possible increase in neurological problems is perhaps of greater concern. Although several cases of meningitis have been described following CSEA, it is uncertain whether the technique increases this risk. The possibility of conus damage is increased if the procedure is performed above the third lumbar interspace.

Intrathecal loading is usually with bupivacaine, 2.5 mg, and fentanyl, up to 25 µg, although in North America sufentanil, 10 µg, is often preferred. Initial analgesia usually lasts for at least 1 hour, after which the epidural catheter must be tested and its position confirmed.

CSEA is used routinely in some units, but many prefer to reserve its use for advanced labour, multiparous women in whom delivery is imminent and for resiting an unsatisfactory block in a distressed woman.

Postnatal complications

Post-dural puncture headache: see **OBSTETRICS**

Neurological symptoms are often attributed to the use of regional analgesia, but are more likely to be due to labour itself. The estimated incidence of prolonged neurological problems is 1/10,000–15,000 after epidural analgesia and 1/5000–10,000 after spinal block.

Chronic backache has been linked to the use of epidural analgesia in labour in several retrospective surveys. However, no prospective study has demonstrated such an association.

Urinary dysfunction may occur postnatally if the bladder becomes over-distended during labour. Long-term bladder dysfunction has not been directly linked with the use of regional analgesia in labour.

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Physiology of Pregnancy

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Pregnancy initiates many alterations to body systems, some of them extreme. Many of these changes are initiated within the first few weeks of pregnancy and return to baseline values 6 weeks after pregnancy. Knowledge of these adaptations is essential for understanding the physiology of normal pregnancy and the pathophysiology of conditions arising in pregnant women. In addition, some pregnancy-induced changes result in considerable adjustments to the reference ranges for many laboratory criteria; a failure to appreciate these alterations could cause diagnostic error or therapeutic mistakes.

Cardiovascular system

The details of the physiological changes of the cardiovascular system in normal pregnancy are debated, in part because of the difficulties of performing reliable and safe measurements. Longitudinal studies of echocardiography with Doppler measurement of blood flow at the pulmonary, mitral and aortic valves and in the ascending aorta using the women as their own nonpregnant controls give the most accurate assessment of cardiovascular changes.

The placenta creates a low resistance circulation, vasodilatation occurs peripherally and circulating volume increases. Increased heart rate, myocardial contractility and preload, and reduced afterload all influence cardiac performance in pregnancy, by expanding cardiac output.

Heart rate: early in the first trimester, the heart rate increases from about 75 beats/minute to almost 90 beats/minute. Palpitations and premature atrial and ventricular beats are common and usually benign. Stroke volume increases significantly, from 65 to 85 ml in the first trimester, reaching a peak at 20 weeks' gestation, which is maintained until term. Cardiac output changes over a similar time from 5 to 7 litres/minute. This is also maintained until term, and does not decrease in the third trimester; early studies that suggested a fall at the end of pregnancy were inaccurate because they were confounded by use of the supine position, and by changes in pulmonary vasculature and aortic dilatation which older techniques could not account for. This increase in cardiac output is distributed to the uterus (400 ml/minute extra), kidneys (300 ml/minute), skin (300–500 ml/minute) and other sites such as breasts, gastrointestinal tract, and cardiac and respiratory muscles.

Peripheral vascular resistance falls by almost 50% in early pregnancy even before the low resistance placental circulation has a significant effect. The underlying aetiology is uncertain, but oestrogen, prostaglandins, nitric oxide, relaxin and calcitonin gene-related peptide have all been implicated. The reduced peripheral vascular resistance, combined with the obstructive effect of the gravid uterus, contributes to the development of varicose veins and haemorrhoids in pregnancy. It also accounts for the susceptibility of pregnant women to supine hypotension; a left lateral tilt should always be used when lying a pregnant woman on an operating table.

Increases in left atrial and left ventricular end diastolic volume (preload) occur in the second and third trimesters, reflecting the increase in venous return. This combination of increased venous return and reduced peripheral vascular resistance is achieved by a marked increase in blood volume, which reaches a peak of 50% by the third trimester, and a relatively smaller increase in RBC count (20–40%) such that there is a reduction in blood viscosity (this may be one mechanism offsetting the prothrombotic effects of pregnancy; see later). The subsequent physiological dilutional anaemia of pregnancy does not require treatment providing haemoglobin remains above 10.0–10.5 g/dl.

Cardiovascular examination in pregnancy

The cardiovascular changes of pregnancy that are most clinically apparent are listed below.

- Enlargement of the heart by 10–15% and rotation to the left in the frontal plane.
- Mild sinus tachycardia.
- Apex beat displaced to the left.
- Loud third heart sound caused by rapid ventricular filling.
- More pronounced splitting of the second heart sound, especially towards term.
- Ejection systolic murmur in more than 90% of women, caused by flow across the pulmonary or aortic valves.
- Mammary soufflé (a continuous murmur in the left or right second intercostal space, which is uncommon and can be modified by pressure with the chest piece of the stethoscope).
- ECG often reveals a Q wave and inverted T wave in lead III, which should not, for example, be misconstrued as suggesting pulmonary embolus.

Blood pressure measurement: diastolic, and to a lesser extent, systolic blood pressure fall during normal pregnancy. Blood pressure depends on the cardiac output and peripheral resistance. In pregnancy, the increase in cardiac output is less than the decrease in peripheral resistance, therefore overall blood pressure falls. The nadir is reached at 12–16 weeks' gestation; systolic blood pressure falls by 0–9 mm Hg and diastolic pressure by 12–17 mm Hg. In the late second and third trimesters, blood pressure increases towards levels found in the nonpregnant woman (Figure 1).

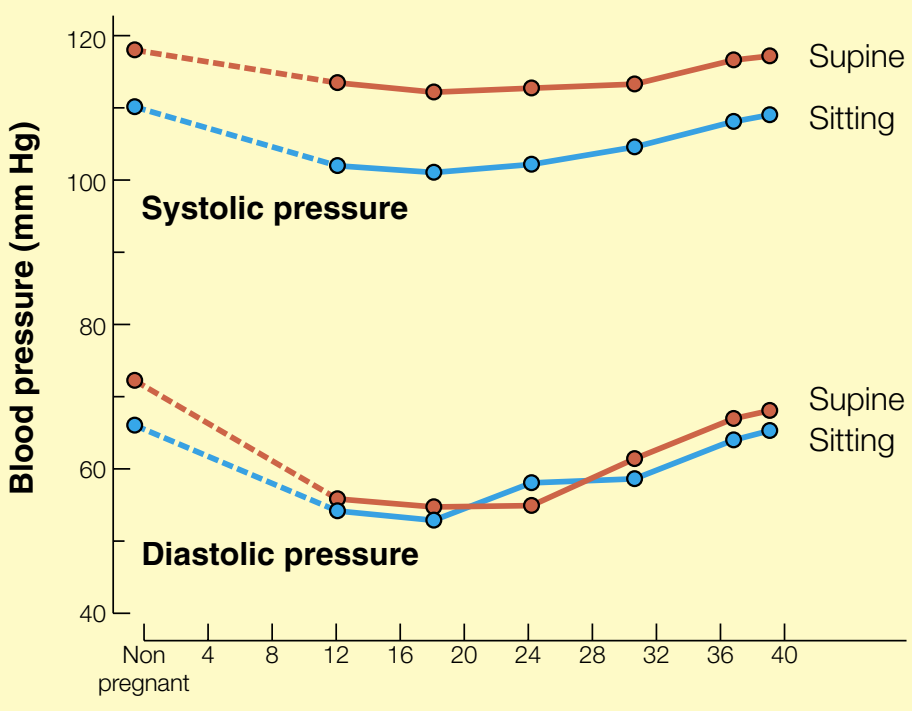
Although a blood pressure reading of 140/90 mm Hg is often considered to be part of the diagnostic criteria for pre-eclampsia, it is important that the measurement is interpreted in relation to gestation. At term, 20% of women have at least one measurement of 140/90 mm Hg or more; at 30 weeks' gestation this occurs in only 1% of pregnant women, and therefore is much more likely to reflect significant pathology.

Problems in measuring blood pressure in pregnancy include:

- compression of the inferior vena cava by the gravid uterus (pregnant women should not be supine when blood pressure is measured)
- white-coat hypertension
- observer error
- equipment inaccuracies
- uncertainty about which Korotkoff sound to use (evidence is now accumulating that Korotkoff sound 5 (K5) is more reproducible in pregnancy than sound 4 (K4); many now use K5 rather than K4, except in unusual cases when K5 falls to zero).

Automated devices – automated blood pressure devices significantly under-read diastolic pressure in a variable and unpredictable manner, by up to 25 mm Hg, particularly in women with pre-eclampsia. When an automated device is used in pregnancy, measurements should be checked against those obtained from a mercury sphygmomanometer or an aneroid device.

Changes in blood pressure with advancing gestation



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1

Obstetric haemorrhage

Obstetric haemorrhage (antenatal or postnatal) can be catastrophic and require aggressive management from a multidisciplinary team. The increased circulating volume of pregnancy provides some initial protection from the effects of haemorrhage. In general, pregnant women have a healthy reactive vasculature, and are able to compensate for blood loss by mounting a tachycardia; blood pressure falls late in the course of obstetric haemorrhage and is an ominous sign (Figure 2).

Blood loss and shock in pregnancy

Blood loss (ml)	Circulating volume lost (%)	Systolic blood pressure (mm Hg)	Symptoms/signs	Shock
500–1000	10–15	Normal	Palpitations, dizziness, tachycardia	Compensated
1000–1500	15–25	Slight fall	Weakness, sweating, vomiting	Mild
1500–2000	25–30	80	Restlessness, pallor, oliguria	Moderate
2000–3000	30–50	50–70	Collapse, air hunger, anuria	Severe

2

Peripheral oedema

Peripheral oedema of the legs and hands occurs in most normal pregnancies as a result of physiological changes:

- obstruction of venous return by the gravid uterus
- peripheral vasodilatation
- increased plasma volume
- decreased colloid osmotic pressure (due to haemodilution rather than altered protein production)
- increased vascular permeability.

The presence of peripheral oedema is seldom helpful in the assessment of pre-eclampsia, and it has been removed from most definitions of the condition.

Physiological changes in coagulation and thromboembolic risk

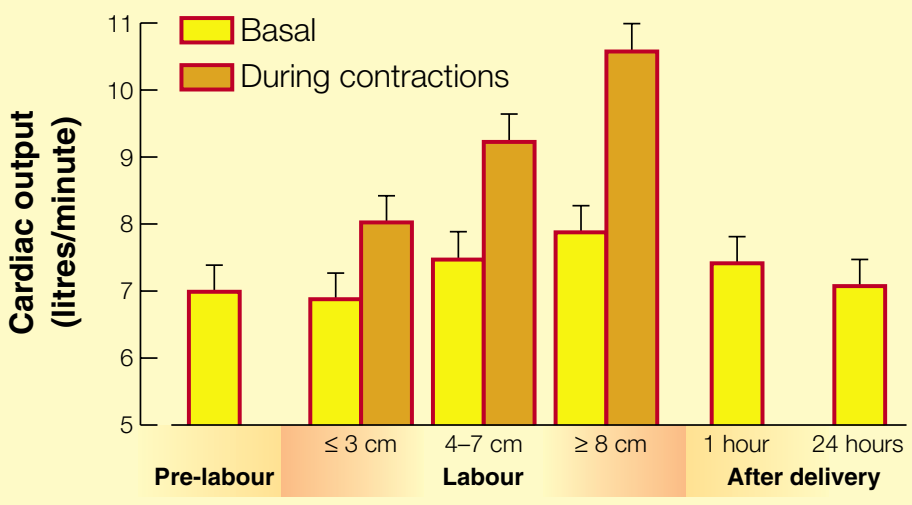
Physiological increases in coagulation factors I (fibrinogen), VII, VIII, IX, XII and a decrease in some endogenous anticoagulants (antithrombin, protein S, activated protein C resistance) occur during pregnancy, and are intended to reduce the risk of haemorrhage, especially at delivery. However, associated with the physiological vasodilatation of pregnancy, they contribute to a six-fold increase in risk of thromboembolism during pregnancy. Trauma to the pelvic veins at delivery, sometimes in association with dehydration or immobility, accounts for the additional thromboembolic risk in the puerperium. In the UK, thromboembolic disease is the leading cause of maternal mortality. Prevention entails assessment of thromboembolic risk in every pregnant woman, and in particular at delivery. Caesarean section is a major risk factor for thrombosis, and the Royal College of Obstetricians and Gynaecologists has issued guidelines for thromboprophylaxis.

The diagnosis of acute thromboembolism should be considered in a pregnant woman with relevant leg or chest symptoms, and care taken in the correct interpretation of investigations. D-dimer measurement is unhelpful because it is elevated in normal pregnancy. Duplex Doppler assessment of the femoral veins is used to diagnose deep vein thrombosis. The amount of radiation involved in ventilation perfusion scanning is negligible in the face of the risks to maternal and fetal well-being of an incorrectly diagnosed pulmonary embolus.

Cardiovascular changes in labour

During labour additional physiological changes occur. Cardiac output increases by a further 15–20%, in part because of 'autotransfusion' from the contracting uterus (Figure 3). At delivery, a further 500 ml or more of blood may be autotransfused as the placenta is delivered; in a small group of women with volume-dependent cardiac disease (e.g. pulmonary or mitral valve stenosis), the postnatal period may therefore be particularly dangerous. Sympathetic nervous system stimulation through maternal pain or anxiety results in a further increase in heart rate and possibly an increase in blood pressure. Regional anaesthetic techniques can play an important role in assisting blood pressure control during labour, both by providing analgesia and as a direct result of sympathetic blockade.

Changes in cardiac output during labour



Changes in cardiac output in 15 women during labour measured using cross-sectional and Doppler echocardiography in the left lateral position. Figures are mean (± SE).

Source: Robson S C, Dunlop W, Boys R J, Hunter S. Cardiac Output during Labour. *BMJ* 1987; **296:** 1169–72. With permission from the BMJ Publishing Group.

3

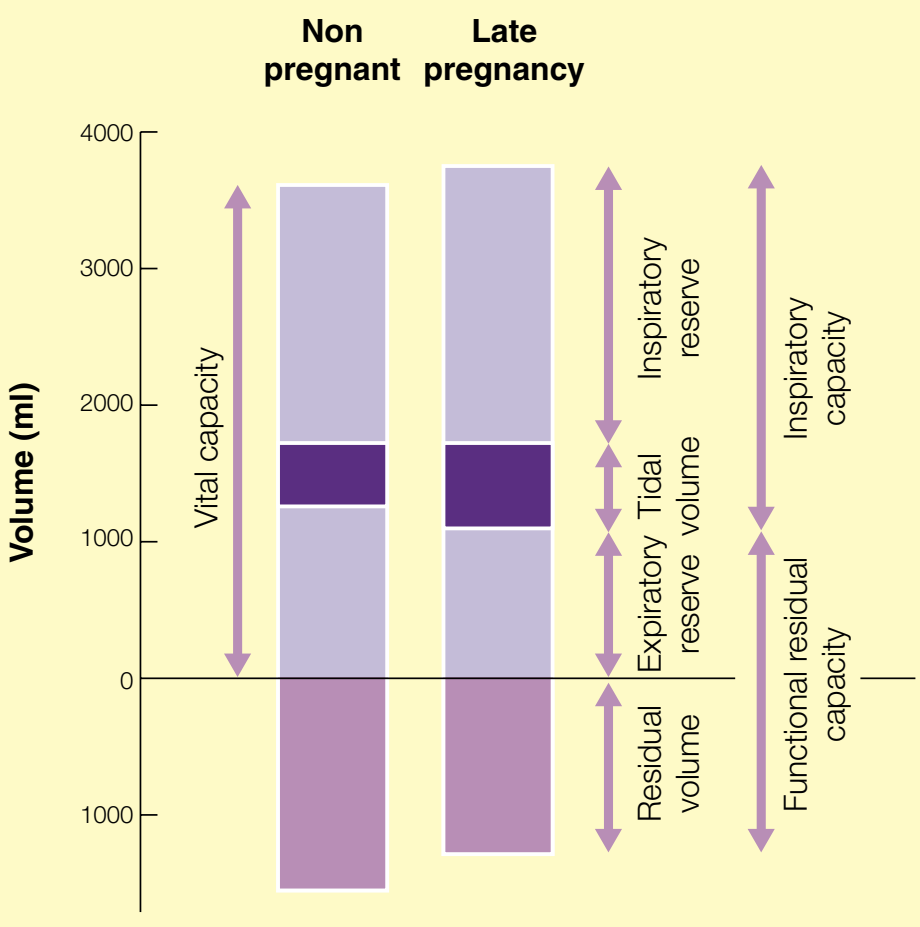
Respiratory system

In nonpregnant women, oxygen consumption is 250 ml/minute at rest. During pregnancy, this increases by 15–20% to about 300 ml/minute. The increase is mainly to maintain the additional metabolic requirements of pregnancy; the uteroplacental circulation and the additional 'work' of the maternal circulation. However, ventilation increases by 40%, such that the partial pressure of oxygen is unchanged (i.e. more oxygen is consumed but more is acquired), remaining at about 13 kPa (100 mm Hg). The partial pressure of carbon dioxide is considerably reduced by this increase in ventilation, falling from 5 kPa (35–40 mm Hg), to about 4 kPa (30 mm Hg); thus in, for example, the assessment of severe asthma, an apparently normal partial pressure of carbon dioxide may represent carbon dioxide retention. Arterial blood gas assessment should never be performed in the supine position during pregnancy because inferior vena caval compression by the gravid uterus and functional reduction in pulmonary residual capacity and closing volume may give a false impression of hypoxia; the partial pressure of oxygen falls by 2 kPa to about 11 kPa (83 mm Hg).

This increase in ventilation is achieved by increasing the tidal volume (the volume of air moved during a normal inspiration or expiration) from 500 to 700 ml. The 'driving force' is progesterone, which stimulates the respiratory centre directly and increases sensitivity to carbon dioxide. This is achieved at the expense of the inspiratory and expiratory reserve volumes, but the vital capacity (the volume that can be inhaled from forced expiration) is unchanged. The expanding uterus decreases the residual volume (the volume of air remaining in the lungs at the end of forced expiration) and, therefore, the total lung capacity, thereby reducing the 'dilution' effect of inspired air and further improving ventilation in the alveoli (Figure 4).

There is no change in the respiratory rate, peak expiratory flow rate or the forced expiratory volume in 1 second. Transfer factor falls early in pregnancy, which may account for the deterioration of some cases of severe fibrotic lung disease during pregnancy. However, many pregnant women have a subjective sensation of shortness of breath. It may be related to the extra work resulting from the increased ventilation of pregnancy or to a change in the shape of the thorax as the ribs become more horizontal and therefore at a potential mechanical disadvantage.

Changes in lung volumes during pregnancy



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4

Renal tract

During pregnancy, the kidneys increase in length by 1 cm, and the renal calyces, renal pelvis and ureter dilate. This is more marked on the right than the left side, because of the uterine tendency to dextrorotation, but is mostly under the smooth muscle relaxing effect of factors such as progesterone.

Renal blood flow increases in pregnancy. One consequence of this is a 50% increase in glomerular filtration by the end of the first trimester. The filtered load therefore increases, which is paralleled by increments in tubular reabsorption. The increase in glomerular filtration rate (GFR) is reflected in clinical practice by a rise in creatinine clearance; this also occurs in transplanted kidneys and often in diseased kidneys. As a consequence, serum creatinine begins to fall early in the first trimester, reaching a nadir in the second trimester and then increasing slightly towards term. Therefore, in pregnancy, a serum creatinine level greater than 85 µmol/litre is usually the result of renal impairment; care must be taken to interpret renal function blood results correctly in pregnancy.

Glycosuria is common in pregnancy and does not warrant further investigation unless persistent and severe. It is usually a consequence of the increased GFR; the increased amount of glucose passing into the urine may saturate the active transport system of the proximal tubule which 'retrieves' glucose. This is particularly likely if there has been a significant carbohydrate load.

Uric acid is freely filtered by the glomerulus and actively reabsorbed by the proximal tubule, the net consequence in pregnancy being a 25% fall in the circulating levels. As pregnancy progresses, tubular function changes, net excretion by the tubules falls, and consequently plasma levels increase towards their nonpregnant values in the third trimester. In general, the urate concentration rises in parallel with the number of weeks of pregnancy (< 300 µmol/litre at 30 weeks, < 350 µmol/litre at 35 weeks). In pre-eclampsia, urate levels are increased compared with normal pregnancy. This often occurs early in the course of the disease, and is the result of impaired tubular function. Later in pre-eclampsia, glomerular function may be altered, resulting in an increase in creatinine; interpretation of the result in relation to normal values for pregnancy is critical.

Proteinuria: in normal circumstances, there is virtually no protein in urine. During normal pregnancy there is an increment in proteinuria, the upper limit of normal being 300 mg/ 24 hours. This may reflect the increased GFR, changes in the glomerular basement membrane or altered tubular function. In pre-eclampsia, proteinuria may be marked, with values commonly reaching more than 3 g/24 hours. This is due to (temporary) glomerular damage by pre-eclampsia and usually occurs after an increase in uric acid.

Gastrointestinal tract

The causes of the extensive physiological changes in the gastrointestinal tract in pregnancy are debated. Hormonal effects, including smooth muscle relaxation, and pressure effects from the gravid uterus are likely to be important.

Changes in oestrogen and progesterone result in a fall in pressure at the lower oesophageal sphincter. This combined with slowing of peristaltic waves in the lower oesophagus makes it 'easier' for stomach contents to reflux into the oesophagus. Early in pregnancy, there is also a small increase in intragastric pressure and 80% of pregnant women experience heartburn. The pH of gastric contents and the production of gastric acid are unchanged in pregnancy. The contractile response to exogenous stimuli is impaired, for example protein-rich foods stimulate less production of gastrin, resulting in decreased gastric emptying. This is marked during labour and is exacerbated by the use of parenteral opioids. This is one of the reasons why general anaesthesia should be avoided during labour.

Hormonal relaxation of large bowel smooth muscle contributes to the reduced frequency of defecation in pregnancy.

Physiological effects of human chorionic gonadotrophin

Hyperemesis gravidarum is a potentially serious complication of the first half of pregnancy. Vomiting can be of sufficient severity to cause dehydration, weight loss or both, and the woman is likely to be dependent on anti-emetics and intravenous fluids; thiamine supplementation is essential to prevent Wernicke's encephalopathy. In at least 25% of such pregnancies, abnormal liver or thyroid function may occur, and these are markers of disease severity; biochemical abnormalities resolve as hyperemesis gravidarum abates. The aetiology of the liver abnormality is likely to be a direct toxic effect of the dehydration and starvation. The thyroid abnormality is a result of human chorionic gonadotrophin (hCG). The α subunit of hCG is identical to the α subunit of thyroid stimulating hormone (TSH), and as a consequence hCG has weak TSH-like activity. In some women with hyperemesis gravidarum, hCG subtypes with increased TSH-like activity are produced. This results in a biochemical picture of thyrotoxicosis, which resolves when hCG returns to normal. It does not require treatment with antithyroid agents.

Liver

During pregnancy, the absolute blood flow to the liver is unchanged. Oestrogen influences the metabolism of a number of hormone-binding proteins produced by the liver; for example, the half-life of thyroxine binding globulin (TBG) is extended from 15 minutes to 3 days. This results in increased circulating concentrations of TBG, and therefore of total thyroxine (T4) and tri-iodothyronine (T3). Free T4 and T3 concentrations are essentially unchanged in iodine-replete areas, until the third trimester when they both fall. Pregnancy-specific reference ranges must be applied, and only free T4, free T3 and TSH should be used. Other markers of liver function fall during pregnancy, probably because of the haemodilutional effects of pregnancy (albumin, transaminases, γ-glutamyltransferase and bilirubin fall by about 20%). However, alkaline phosphatase increases; the upper limit of normal for pregnancy is three times greater than the nonpregnant reference range. This is because of placental production of a heat-stable isomer. In cases of clinical uncertainty, heating the blood to 60°C for 10 minutes results in destruction of the heat-labile liver isomer, and reanalysis of the sample allows the source of the excess to be determined. Spider naevi and palmar erythema are common physiological changes in the skin during pregnancy, probably as a result of high oestrogen concentrations. They do not imply liver disease.

Pruritus may occur in normal pregnancy and is probably benign. It must be distinguished from the itching of obstetric cholestasis by the finding of liver function tests outside the normal range for pregnancy, because this condition has a 2% risk of stillbirth.

Post-dural Puncture Headache in Obstetrics

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Post-dural puncture headache (PDPH) is a well-known complication of spinal or epidural anaesthesia and diagnostic lumbar puncture. First described by August Bier in 1898, it represents the most common potentially serious complication of obstetric regional analgesia and anaesthesia. The reported incidence of accidental dural puncture during epidural analgesia is 0.19–4.2% in the UK, and 4–6% in the USA.

Aetiology

The precise aetiology of PDPH is unknown, though it probably involves leakage of CSF through the dural hole. This reduces the physical buffering provided by CSF within the skull. In the upright position, the intracranial structures 'settle', exerting traction on pain-sensitive fibres attached to venous sinuses, dura and other structures. This explanation fits with the observation that the bigger the dural hole, the greater the incidence and severity of PDPH. There is evidence of intracranial vasodilatation associated with PDPH, raising the possibility of similarities between PDPH and migraine, in which cerebral vascular reactivity is also implicated.

Contributory factors

Several factors may increase the risk of PDPH following accidental dural puncture (Figure 1). Many investigators have shown that the incidence of PDPH decreases with increasing age. Previous studies have demonstrated increased susceptibility to PDPH in females though recent investigations have found no relationship; the general belief that gender affects PDPH may relate to the inclusion of young parturients in the older studies.

Leakage of CSF through a dural tear is influenced by the size of the spinal needle and the design of the needle tip. In obstetrics, the incidence of PDPH ranges from under 1% with 27 G pencil-point needles to 14% with 20 G cutting needles. Sharp-point spinal needles (e.g. Quincke) cut dural tissues and allow dural tears to persist. Non-cutting atraumatic needles (e.g. Whitacre, Sprotte) are believed to spread dural fibres and allow rebound closure after their withdrawal (see *Anaesthesia and Intensive Care Medicine* **2:3:** 106 Figure 5). The incidence of PDPH following accidental dural puncture with a 16 G epidural needle is 70–85%. Insertion of the epidural needle with the bevel orientated parallel to the longitudinal dural fibres is associated with reduced incidence of PDPH should accidental puncture occur, compared with insertion with the bevel perpendicular to the dural fibres. Dural fibres are thought to close round a longitudinal hole more efficiently than round a transverse hole.

The effect of pushing in the second stage of labour on PDPH is contentious. It was previously common that any woman suffering accidental dural puncture was given an instrumental delivery to avoid pushing, but this practice became unpopular in the 1990s because any neonatal injury arising from the delivery could be traced to the accidental dural puncture. However, a recent retrospective study found that the incidence of PDPH and requirement for epidural blood patch were higher in women who actively pushed in the second stage following a well-documented single accidental dural puncture, compared with parturients who underwent caesarean section without pushing.

Predisposing factors for post-dural puncture headache

Patients' characteristics
- Younger age
- ?Female sex
- Pregnancy

Characteristics of dural hole
- Large size
- Made with cutting, as opposed to pencil-point, needle
- Bevel of needle oriented transverse to dural fibres

Subsequent management of patients
- ?Allowing mothers to push in second stage of labour

1

Presentation and diagnosis

Typically, PDPH presents 1–3 days after accidental dural puncture. It may be severe and is usually occipital or frontal. Neck pain may be a primary feature or secondary to muscle spasm. The headache may be accompanied by dizziness, vomiting and visual or auditory symptoms. Characteristically, the headache is absent or markedly reduced when supine and worse when upright. Following a slow CSF leak (e.g. after spinal anaesthesia with a pencil-point 27 G needle) headache may develop 15–30 minutes after adopting the upright position.

There are many causes of headache post-partum (Figure 2), therefore it is important to confirm the diagnosis. A history of definite accidental dural puncture and a clear postural component to the headache make the diagnosis almost certain, with two caveats. First, it is possible for more than one aetiology to coexist, which may confuse the clinical picture. Second, post-partum presentation of an incidental brain tumour is a rare but well-recognized event, so the fundi should always be examined. In difficult cases, a useful manoeuvre, described by Gutshe in 1990, is to ask the mother to sit up, wait until the headache returns and compress her right upper abdominal quadrant (remembering this may be painful after caesarean section), asking her to comment on the headache's severity. A PDPH will ease, presumably as a result of epidural venous congestion secondary to hepatic compression.

It may be possible to diagnose a dural tear using imaging techniques (e.g. MRI) and estimations of CSF volume, but this is not widely available. The diagnosis in most cases remains clinical.

Causes of headache in the early post-partum period

- Post-dural puncture headache
- Non-specific headache
- Migraine
- Pre-eclampsia
- Meningitis
- Cerebral tumour
- Subarachnoid haemorrhage
- Subdural haematoma
- Cerebral vein thrombosis

2

Management

Left untreated, most headaches resolve over 5–7 days, though PDPH lasting for several months or even years has been reported. Rarely, serious neurological sequelae may follow PDPH, including subdural haematoma and seizures. Deaths from subdural haematoma or coning have been described following accidental dural puncture, diagnostic lumbar puncture and spinal anaesthesia in patients without raised intracranial pressure or other risk factors. Subdural haematoma is presumed to be caused by shearing forces on delicate subdural vessels resulting from intracranial hypotension in the upright position. It is thus considered important to treat PDPH in order to prevent these serious late sequelae, though it is unknown whether symptomatic treatment of PDPH reduces their incidence.

Few treatments of PDPH have been shown to be effective in randomized clinical trials, though several have been described anecdotally (Figure 3).

Treatment for post-dural puncture headache[1]

Supportive
- Avoidance of dehydration
- Emotional support

Drugs
- Simple analgesics
- Caffeine
- Sumatriptan
- Adrenocorticotrophic hormone
- Ergotamine

Interventional procedures
- Epidural blood patch

[1]Most treatments are supported only by weak, if any, evidence.

3

Supportive management
Traditional supportive management of PDPH includes bed rest and hydration. Bed rest may temporarily alleviate symptoms but does not prevent the onset of PDPH and there is no evidence that hydration (rather than avoidance of dehydration) helps. It is important to offer emotional support because the headache may be incapacitating and prevent the mother from caring for her baby.

Drug treatment
Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used as first-line treatment; while paracetamol may help, NSAIDs are often ineffective (personal observation). Paracetamol–opioid combinations have not been shown to be more effective than paracetamol alone.

Caffeine has been found to provide relief, albeit sometimes transient, in randomized controlled trials. It may also reduce the incidence of moderate or severe headache if given prophylactically following spinal anaesthesia. Its mechanism of action is uncertain but may be related to its ability to increase cerebral vascular resistance and decrease cerebral blood flow and volume. A suitable oral dose is 150–300 mg every 6–8 hours. Side-effects include nausea, convulsions and neonatal irritability.

5-HT, a cerebral vasoconstrictor, is important in the pathophysiology of migraine. Sumatriptan, a 5-HT_{1D} receptor agonist, is effective against migraine, and anecdotal reports (but not randomized controlled trials) suggest that 6 mg subcutaneously, repeated if necessary, may be useful in PDPH. Side-effects include pain at the injection site and transient chest tightness; 5-HT_{1} agonists are contraindicated in ischaemic heart disease.

Use of adrenocorticotrophic hormone (ACTH), 1.5 μg/kg i.v., or its synthetic analogue tetracosactide (tetracosactrin), 1 mg i.m., repeated 24 hours later if necessary, has been described but without validated trials. A mechanism of action has not been proposed.

Another drug that has been used is ergotamine. A combination of caffeine, 100 mg, and ergotamine tartrate, 1 mg, has been successful anecdotally but a definitive report has not been published. In addition, ergotamine is contraindicated in pregnancy and breast-feeding.

Epidural blood patch

Epidural blood patch is generally considered the definitive treatment for PDPH and its effectiveness is well established. Blood is taken aseptically from the patient's arm and slowly injected into the epidural space. First reported by Gormley in 1960 using 2–3 ml blood, more recent evidence suggests larger volumes are more effective; 15–20 ml is usually used as a target though injection may be limited by back pain or discomfort. Success rates of over 90% have been quoted, with complete and instantaneous resolution of symptoms. However, recent reports suggest success rates of 61–75% though over 90% of patients may experience initial relief. There is some evidence that 2 hours or more spent lying flat following epidural blood patch may increase the chance of success. A second blood patch may occasionally be required.

Contraindications to an epidural blood patch are related to placement of the epidural needle (patient's refusal, coagulopathy or infection at the puncture site) or to injection of autologous blood, primarily the potential for epidural injection of infected blood. Pyrexia may reflect concurrent bacteraemia and, despite limited data, many authorities advocate delaying epidural blood patch until the patient becomes afebrile.

Anecdotal evidence suggests that epidural injections of solutions other than blood may be effective in treating established PDPH. Dextran 40, 20–30 ml, has been used with encouraging results, albeit in uncontrolled trials. Fibrin glue, a preparation of pooled human plasma used to treat CSF leak in neurosurgery, has been injected into the epidural space and reported to be effective. Saline has been used to provide temporary relief and as a diagnostic measure before epidural blood patch in difficult cases.

Prevention

Approaches to minimizing PDPH include reducing the incidence of accidental dural puncture and reducing its severity should it occur. The first strategy involves adequate training and supervision, because accidental dural puncture rates are higher in units with a large number of relatively inexperienced trainees. The minimum number of procedures required for trainees to achieve competence is unclear but attempts to define this have been made. Other possibly preventative factors (although evidence is weak) include the use of saline instead of air for loss of resistance and the paramedian approach to the epidural space. There are no published prospective, randomized controlled trials of adequate size comparing air and saline for loss of resistance. There are, however, numerous case reports of complications associated with the use of air, including pneumocephalus, spinal cord and nerve root compression and venous air embolus.

Several methods for reducing the severity of PDPH after accidental dural puncture have been proposed. Subarachnoid insertion of the epidural catheter after recognized accidental dural puncture is an alternative to traditional management (removing the needle and resiting the epidural at an adjacent interspace). The catheter is then used to provide analgesia during labour. A potential benefit of this approach is suggested largely by retrospective studies. The catheter may 'plug' the dural tear during labour and reduce the efflux of CSF; increased formation of fibrin around the catheter has been described experimentally and this may also contribute if the catheter is left *in situ* for 24 hours. Accidental intrathecal injection of epidural doses of drugs must be avoided by labelling the catheter and informing all relevant staff.

There is consistent evidence that prophylactic epidural saline decreases the incidence and severity of headache after accidental dural puncture. Epidural saline is administered either by bolus, 60 ml at 0 and 24 hours, or by continuous infusion, 500–1000 ml over 24 hours. The saline is thought to tamponade the intrathecal space and prevent efflux of CSF.

Prophylactic blood patch (i.e. via the epidural catheter before its removal) has been used in an attempt to reduce the incidence and severity of PDPH, but this is controversial, with poor success rates described by some authors. A possible reason for its failure is the property of local anaesthetics to inhibit coagulation of blood.

Finally, use of neuraxial opioids has been suggested as reducing PDPH after accidental dural puncture but the evidence is weak. A putative mechanism is unknown.

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Postoperative Pain Management in Obstetrics

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This article concentrates on pain management after caesarean section, because this operation makes up the bulk of obstetric anaesthetic cases. However, issues unique to pregnancy arise in the first trimester and continue into the post-partum period. In the UK, many drugs are not licensed for use in pregnant women. The licence for a particular indication, or in a certain group of patients, is gained when the manufacturer provides positive evidence of safety. Most pregnant women are healthy, therefore there is little financial reward for pharmaceutical companies in seeking a licence for drugs in this group of patients (with the exception of local anaesthetic drugs). Sometimes there is no drug for a given indication that has a licence for use in pregnancy. When presented with such a situation, it is sensible to use an 'old' drug wherever possible because there will be a body of evidence to support its use if problems arise.

During organogenesis, early in the first trimester of pregnancy, there is the possibility that a drug may cause teratogenesis (the production of a structural malformation in the fetus). No established analgesic or anti-emetic drugs that are used perioperatively are known to have this effect. A recent paper has suggested that use of non-steroidal anti-inflammatory drugs (NSAIDs) during early pregnancy is associated with an increased risk of miscarriage.

Later in pregnancy, there is the possibility that analgesic drugs given to the mother perioperatively have pharmacological effects on the fetus. There is a theoretical possibility that long-term use of NSAIDs might cause closure of the ductus arteriosus *in utero*, though this has not been found to be a problem when high-dose NSAIDs have been used in the short term for the treatment of preterm labour. Long-term use of NSAIDs is also associated with oligohydramnios.

It can be assumed that all drugs are transferred into breast milk, though many in trace concentrations only. The amounts that a breast-fed neonate ingests would not have pharmacological effects. However, many anaesthetists stopped using aspirin for routine post-caesarean section analgesia after the Committee on Safety of Medicines stated that it should not be used in children because of a suspected link with Reye's syndrome.

Caesarean section

In non-obstetric practice it is common to use multimodal analgesia at the time of operation, often given before skin incision to gain the benefit of a possible 'pre-emptive' effect. This is not used for caesarean section to avoid transplacental exposure of the fetus to different drugs, especially potentially sedative analgesics.

Guidelines for the use of analgesia in patients undergoing caesarean section are given in Figure 1.

Analgesia guidelines for caesarean section

General anaesthesia
- Peroperative: morphine at least 20 mg (or morphine and other opioid)
- Postoperative: morphine 1 mg (1 ml) dose given by patient-controlled analgesia, 5 minute lockout

Regional anaesthesia
- Spinal: elective diamorphine, 0.3 mg; very urgent case fentanyl, 25 μg
- Epidural top-up for caesarean during labour: ± fentanyl, up to 100 μg
- Postoperative: intramuscular morphine (up to) 1 hourly as needed – first dose not before 2 hours after spinal or epidural opioid

All cases
- Diclofenac 100 mg suppository at end of operation (contraindicated in cases of haemorrhage or pre-eclampsia)
- Regular paracetamol and diclofenac for first 3 days

Source: St Michael's Hospital, Bristol, UK.

General anaesthesia
In general, strong opioid drugs are not given systemically before delivery by caesarean section because of their depressant effect on the neonate. The use of remifentanil to provide analgesia until delivery, with no neonatal effects, has recently been described. This approach is potentially of major importance in a few cases in which cardiovascular stability is crucial, but its role in routine practice remains to be defined.

Large doses of fentanyl or morphine (e.g. at least 20 mg) given after delivery are tolerated and indeed are required. After the patient wakes, increments of morphine or diamorphine are given intravenously until she has been made comfortable (moderate pain or less), and then patient-controlled analgesia (PCA) is started.

Maternal deaths have occurred after general anaesthesia for caesarean section when hypotensive or shocked patients had several doses of intramuscular or subcutaneous morphine close together. There was a suggestion that excessive blood levels of morphine were produced when muscle blood flow started to return to normal. It is important to be aware of this possibility when the intramuscular route is used, especially as recovery facilities in obstetric units may be of an inferior standard to those in general operating theatres.

Ilio-inguinal blocks have been tried but do not confer much advantage.

Regional anaesthesia
When a regional anaesthetic is used for caesarean section, the analgesic options become more flexible and more effective. The local anaesthetic block provides pre-emptive analgesia. Opioids may be given before delivery, because the doses are lower than those required for systemic analgesia. The ratio of the dose used neuraxially (i.e. epidural or spinal (intrathecal)) compared with the systemic dose depends on two factors. Spinal doses are smaller than epidural doses, and drugs that are less lipid-soluble are used in smaller doses than those with greater solubility. The dose of spinal morphine, which has the lowest lipid solubility of clinically used opioids, is about one-hundredth of the systemic dose.

When there is an option of using either the spinal or epidural route, the spinal option may be preferable because equipotent analgesia is possibly associated with fewer minor side-effects. The serious complication of delayed respiratory depression may also be less likely with the spinal route. The epidural space may act as a 'depot' for delayed absorption, whereas a lipophilic opioid placed into the CSF is rapidly cleared into tissues. These include neural tissues, and thus lipophilic drugs given spinally also have a rapid onset of action.

Worldwide, morphine is the most commonly used spinal opioid. Doses of 0.1–0.15 mg produce prolonged analgesia. It has a good safety record in obstetric practice. However, because of slow absorption from the CSF, the drug is unlikely to have an effect during or immediately after the operation. Thus fentanyl, 10–25 μg, is often combined with morphine for its intraoperative effect.

A simpler answer is to use diamorphine. This has a rapid onset that supplements intraoperative anaesthesia and anal-gesia. It gives postoperative analgesia of comparable duration to morphine but with less central side-effects of itch and drowsiness. The author currently uses diamorphine, 0.3 mg, as the best compromise between analgesia and side-effects, but further studies may alter this. The maternal position in which the spinal block is inserted may influence the duration of analgesia. There is evidence that when insertion is in the sitting position, doses larger than 0.3 mg are needed to produce a comparable effect to 0.3 mg administered while the woman is in the lateral position.

Analgesic considerations are similar when comparing an epidural or combined spinal-epidural, though an epidural opioid is more likely to be required before delivery to supplement the anaesthesia produced by an epidural block on its own. When anaesthesia is provided with local anaesthetic only in the spinal during combined spinal-epidural anaesthesia, it is common to give a dose of opioid through the epidural catheter after delivery of the fetus. Morphine is usually given as a single dose only, whereas diamorphine may be repeated on several occasions.

In a small number of sick mothers, such as those with severe pre-eclampsia, an optimum postoperative analgesic technique may promote cardiovascular stability and therefore aid overall management. The author favours continuous infusion of a low concentration mix of opioid and local anaesthetic, which provides analgesia and possibly a reduction of plasma catecholamines, while avoiding the fluctuations of effect seen with bolus doses. However, this technique is labour intensive and many units would be unable to provide this for routine post-natal cases.

There are a number of units in which all women who have had neuraxial opioids perioperatively are managed in a high dependency unit. Readers should check their own local policies.

Other analgesics
The use of non-opioid analgesics is similar after general and regional anaesthesia. NSAIDs are effective and should be used in most cases, but are contraindicated in pre-eclampsia and if there are concerns about recent or impending haemorrhage and hypovolaemia. It is preferable that oral analgesics (NSAIDs and paracetamol) are prescribed on a regular basis rather than just given when requested.

Other operations

The author adapts the approach given above for other surgical procedures. Postoperative pain may not be a feature of some procedures (retained placenta or insertion of cervical cerclage), but can be severe after repair of episiotomies or large perineal tears. The author uses spinal fentanyl or diamorphine in the latter cases when spinal anaesthesia is used for surgery.

Pain management after vaginal delivery may also be greatly improved by applying a systematic approach to analgesia similar to that used for postoperative patients.

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Pre-eclampsia and the HELLP Syndrome

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Pre-eclampsia is a multisystem disorder of endothelial dysfunction, characterized by widespread vasoconstriction and increased capillary permeability. About 10% of pregnant women develop pre-eclampsia, generally leading to reduced placental perfusion. Pre-eclampsia has a variable clinical presentation (Figure 1) and there are no internationally agreed diagnostic criteria. It is traditionally denoted by hypertension, proteinuria and oedema. However, many cases present with one or more of the complications of pre-eclampsia (Figure 2) before hypertension or proteinuria are apparent. Therefore, it is important to consider pre-eclampsia in patients with any of these conditions even if hypertension or proteinuria has not been noted – in some patients these are late (or absent) manifestations of the pre-eclamptic syndrome. It is important not to overlook the presence of upper abdominal pain and vomiting in women in the third trimester, because these are symptoms of hepatic involvement and fulminant disease, and hepatic rupture is an infrequent but dramatic cause of death in pre-eclampsia.

Recognition of pre-eclampsia

- Pregnancy-induced hypertension
- Proteinuria
- Generalized oedema
- Excessive weight gain (> 1.0 kg/week)
- Ascites
- Upper abdominal pain
- Vomiting
- Decreased platelets
  - Increased packed cell volume
  - Increased haemoglobin
  - Increased plasma urate/uric acid
  - Increased plasma von Willebrand factor
  - Increased plasma cellular fibronectin
- Decreased plasma antithrombin III
- Fetal compromise
  - Intrauterine growth factor
  - Intrauterine hypoxaemia

Adapted from: Redman C W G, Roberts J M. Management of Pre-eclampsia. Lancet 1993; 341: 1451–4.

1

Complications of pre-eclampsia

- Cerebral haemorrhage
- Cerebral oedema
- Subcapsular hepatic haematoma/rupture
- HELLP syndrome
- Eclampsia
- Acute renal failure (cortical or tubular necrosis)
- Disseminated intravascular coagulopathy
- Airway oedema
- Pulmonary oedema
- Retinal detachment
- Placental abruption
- Impaired feto-placental perfusion
  - Intrauterine growth factor
  - Fetal distress
  - Fetal demise

Adapted from: Redman C W G, Roberts J M. Management of Pre-eclampsia. Lancet 1993; 341: 1451–4.

2

The relationship between essential (chronic) hypertension, pregnancy-induced hypertension and the pre-eclampsia–eclampsia syndrome are unclear, and often muddled. Oedema is usually omitted from the diagnostic criteria, because it is common in normal pregnancy and difficult to quantify. However, clinical experience suggests that obviously worsening oedema in a patient with pre-eclampsia is a significant clinical marker of leaky capillaries and fulminant disease. Obstetricians often use the plasma urate level as a marker of the progress of the condition. Rule of thumb for singleton pregnancy: plasma urate > 0.xx mmol/litre denotes advancing pre-eclampsia (where xx is the gestation in weeks).

Management of the woman with pre-eclampsia and associated conditions is based on expedited delivery of the placenta (and the baby), and the provision of end-organ protection and support for the mother. Contrary to expectation, pre-eclampsia does not always improve after delivery of the placenta. When pre-eclampsia develops in the preterm mother it is important to balance extra days of fetal maturity against the risks of advancing pre-eclampsia to mother and baby. In general, the more preterm the mother when pre-eclampsia is diagnosed, the more fulminant the condition is likely to be, and the greater the need for expedited delivery.

Mortality
Since 1950, pre-eclampsia has been one of the two most common direct causes of pregnancy-related death in the UK, being second to pulmonary embolism in the 1994–1996 data. Similar findings pertain in other parts of the developed world. For many years most deaths from pre-eclampsia were caused by cerebral haemorrhage, but since the mid-1980s pulmonary oedema (a poorly differentiated mix of iatrogenic fluid overload and adult respiratory distress syndrome) has become the main cause of death.

Pre-eclampsia protocol
To minimize mortality and morbidity a multi-disciplinary approach is essential with open communication between obstetric, midwifery and anaesthetic teams. Establishing a joint labour ward pre-eclampsia protocol may be useful in guiding anaesthetic and obstetric management, particularly for staff in smaller units less experienced with pre-eclampsia, and at points where conservative management may require more invasive action. Suggested guidelines to be included in the pre-eclampsia protocol are shown in Figure 3. The protocol written by Robson *et al.* (see Further Reading) has been used as the basis for local guidelines in many units in the UK. Early referral of severe cases to Regional Advisory Centres has been advocated though transfer of unstable critically ill patients should not be undertaken lightly.

Pre-eclampsia protocol

Guidelines are required for the following

- Control of blood pressure
- Fluid management
- Anti-convulsant prophylaxis
- Acute management of eclampsia
- Pain relief in labour (including management of epidural analgesia)
- Anaesthesia for caesarean section
- Management of oliguria
- Indications for invasive monitoring

3

Haemodynamics
Women with pre-eclampsia have an elevated systemic vascular resistance and a reduced blood volume. Most women with pre-eclampsia have a normal or high cardiac output with a hyperdynamic left ventricle, but a few have a low cardiac output owing to a range of causes.

Pulmonary oedema is a particular hazard owing to the combined effects of low plasma oncotic pressure and increased permeability of pulmonary alveolar capillaries. Other predisposing factors include impaired ventricular function, elevated pulmonary artery occlusion pressure (PAOP) and the poor correlation between central venous pressure (CVP) and PAOP that is seen in some patients, which may encourage iatrogenic fluid overload.

The CVP is usually low in early pre-eclampsia. When it is low, the CVP largely reflects left atrial filling pressures. However, when it rises (above 6 cm H_2O) it often underestimates the left atrial filling pressures, and pulmonary oedema becomes more likely. A high-normal CVP in pre-eclampsia is a warning sign of fluid overload or myocardial dysfunction, and provides an indication for the insertion of a pulmonary artery catheter.

Management includes the combination of controlled vasodilatation (e.g. with hydralazine) with limited colloid intravenous loading, a technique that improves cardiac function and reduces vascular resistance better than using either alone.

Hypertension
In the UK, the three drugs commonly used for the acute control of hypertension in pre-eclampsia are hydralazine, labetolol and nifedipine. Nifedipine should be used by the oral route only, not sublingually owing to the risk of dramatic and uncontrolled hypotension with consequent fetal and maternal compromise, particularly when used as a second-line drug. There is little evidence that any agent or combination is to be preferred, providing adequate reduction in blood pressure is achieved in a controlled manner. In patients with an aggressive form of pre-eclampsia, refractory hypertension may respond only to nitric oxide donors (i.e. nitroglycerine, nitroprusside); these patients require invasive monitoring in an ICU.

Coagulopathy
Pregnancy and early pre-eclampsia are pro-coagulant states, but a few women with pre-eclampsia develop coagulation disorders that put them at increased risk of spinal haematoma formation following epidural puncture. However, the relationship between platelet count, platelet activity and the risk of epidural haematoma following epidural puncture is unknown. There is no evidence of increased epidural bleeding caused by the use of low-dose aspirin in pregnancy. Thrombocytopenia is common in pre-eclampsia, but bleeding time is probably not a useful test. Other coagulation defects seldom occur in pre-eclampsia in the absence of thrombocytopenia, therefore platelet count alone has been proposed as a screening test. Elevations of the partial thromboplastin time (PTTK) in the presence of a normal platelet count are more likely to suggest other conditions (e.g. lupus anticoagulant).

Trends may be more significant than absolute numbers. The thromboelastogram and a new platelet function analyser (PFA 100) are being evaluated, though neither has been validated in pre-eclampsia. The findings have been inconsistent, though data from the thromboelastogram suggest that platelet function is largely retained with platelet counts above 75 x 10^9/litre. For many women with pre-eclampsia the benefits of epidural analgesia outweigh the small (but potentially serious) risk of epidural haematoma formation.

HELLP syndrome
The HELLP syndrome (Figure 4) is marked by **H**aemolysis (often presumed rather than detected), **E**levated **L**iver enzymes and **L**ow **P**latelets. Subcapsular hepatic haematoma formation may be a particular problem. As with pre-eclampsia, not all elements of the syndrome may be apparent simultaneously, and there are no universal diagnostic criteria. Although usually considered a complication of pre-eclampsia, it has been questioned whether HELLP is a distinct entity. Patients with HELLP syndrome show a marked increase in maternal morbidity (including pulmonary oedema, disseminated intravascular coagulation, abruption and renal failure) and risk of death. There is also a significant increase in perinatal morbidity and mortality.

Diagnostic features of HELLP syndrome

Haemolysis
- Red cell fragmentation on blood film
- Plasma bilirubin > 1.2 mg/dl

Elevated liver enzymes
- Aspartate aminotransferase > 70 U/litre
- Lactate dehydrogenase > 600 U/litre

Low platelets
- Platelets < 100 x 10^9/litre

Adapted from: Sibai B M. The HELLP Syndrome (Hemolysis, Elevated Liver Enzymes, and Low Platelets): Much Ado About Nothing? *Am J Obstet Gynecol* 1990; **162:** 311–16.

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Management remains delivery of the placenta and aggressive supportive therapy. Corticosteroid therapy may reduce the degree of thrombocytopenia, though expert opinion is divided.

Labour analgesia
The benefits of well-controlled epidural analgesia in labour are well recognized, producing excellent analgesia, a marked reduction in maternal plasma catecholamine levels, a useful fall in blood pressure, and optimizing feto-placental perfusion. Early studies from Finland showed that epidural anaesthesia improves the blood flow to the fetus in pre-eclampsia, and more recent Doppler studies suggest that epidurals produce useful vasodilatation on both the maternal and fetal side of the placenta, optimizing feto-placental blood flow. Therefore, the early use of epidural analgesia is recommended. Most epidural studies in pre-eclampsia have used strong epidural solutions and studies of weak local anaesthetic and opioid mixtures are needed.

The block should be established gently to minimize hypotension (e.g. a solution of 0.1% bupivacaine plus fentanyl, 2 μg/ml) and limited colloid preloading is recommended (though it is unclear whether preloading is desirable or necessary). The addition of adrenaline (epinephrine) to the local anaesthetic solution remains controversial, it has little clinical advantage, particularly when epidural opioids are used, and has several potential disadvantages in the pre-eclamptic woman who may be exquisitely sensitive to exogenous catecholamines. Adrenaline (epinephrine) should therefore be avoided in epidural solutions in pre-eclampsia. Ephedrine remains the vasoconstrictor of choice.

Anaesthesia for caesarean section
Women with pre-eclampsia are at increased risk for caesarean section. Careful assessment of the relative risks of general and regional anaesthesia must be made. Regional anaesthesia is usually considered safer, though patients must be assessed on an individual basis, and their coagulation status considered. Some authors consider fulminant pre-eclampsia or eclampsia (and the risk of an eclamptic seizure occurring during surgery) a contraindication to regional block. However, most obstetric anaesthetists would still choose a regional technique (if there are no signs of coagulopathy), believing that even women who have had an eclamptic convulsion may benefit from a regional technique, provided they are alert enough to protect their own airway, and are receiving magnesium sulphate.

Epidural anaesthesia is the preferred technique for caesarean section, and is associated with much lower maternal plasma catecholamine and blood pressure levels compared with general anaesthesia. If a working epidural is already present (i.e. for labour analgesia) this should be extended for surgery.

Spinal anaesthesia is controversial; because of the potential risks of pulmonary oedema, profound cardiovascular instability and fall in cardiac output, and the consequent recourse to intravenous fluids and vasoconstrictors, it is not generally recommended in pre-eclampsia. However, several recent studies suggest that most women with pre-eclampsia who received spinal anaesthesia do not develop catastrophic hypotension (Figure 5), and there is a growing suspicion that women with pre-eclampsia may behave contrary to expectation following spinal anaesthesia. There are insufficient published data to support the general use of spinal anaesthesia in pre-eclampsia, though in individual patients with unstable or fulminant disease, and a difficult, oedematous airway, it may be a safer technique than emergency general anaesthesia. Scrupulous attention to detail is probably a key factor in success. Sequential combined spinal-epidural (low-dose spinal, then epidural top-ups) may prove useful in experienced hands.

Published studies of the use of spinal anaesthesia in pre-eclamptic women

Author	Date	Country	Anaesthetic technique			Study design	Comments
			Spinal	Epidural	General		
Clark (Abstract only)	2000	UK	20			Prospective randomized	Pre-eclampsia patients required less ephedrine than normal controls
Wood	1999	USA	103	35		Case note review	? Selection bias, unequal group size
Sharwood-Smith	1999	UK	11	10		Prospective randomized	Study stopped prematurely owing to poor quality epidural
Ahmed	1999	India	17	16		Case note review	Some in labour
Van Bogaert	1998	S Africa	24			Case note review	
Rout	1998	S Africa	49	49		Case note review	Some in labour
Karinen	1996	Finland	12			Prospective observational	Mixed severity (6/12 severe pre-eclampsia) 2/12 became hypotensive, 2/12 had increased UA PI
Wallace	1995	USA	27	27	26	Prospective randomized	Some in labour, severity unknown. Combined spinal-epidural supplementation in some
Assali	1950	USA	15			Prospective observational	Full supine position procaine 0.2% or 1.0% spinals

The added risks associated with general anaesthesia include airway difficulties resulting from oedema (often aggravated by tracheal intubation), and the pressor response to laryngoscopy and extubation. If general anaesthesia is chosen, care should be taken to obtund the pressor response to laryngoscopy. Several techniques have been described to abolish this, including β-blockers, opioids and/or intravenous lidocaine (lignocaine), but none is completely reliable. A bolus of magnesium sulphate may be the most effective technique. Extubation may be hazardous because the trauma of intubation is likely to aggravate laryngeal and airway oedema. Attention should be paid to the degree of airway oedema at intubation, and if it is significant, consideration should be given to the possible benefit of keeping the tracheal tube in place postoperatively and transferring the patient, intubated and ventilated, to the ICU for stabilization. Residual neuromuscular blockade is another problem in patients receiving magnesium sulphate, because they are sensitive to the effects of non-depolarizing muscle relaxants, and behave similarly to myasthenics. Very small doses should be used with peripheral nerve stimulator monitoring.

Whatever anaesthetic technique is used for caesarean section, adequate recovery facilities are mandatory, and these patients require high dependency nursing for at least 24 hours.

Oliguria
Most workers agree that, despite the presence of oedema, pre-eclampsia is characterized by a vasoconstricted, hypovolaemic circulation. Moderate fluid preloading before vasodilator therapy minimizes hypotension and improves cardiac output, and is usual practice. Oliguria (often considered as < 0.5 ml/kg/hour) is common but generally responds to moderate fluid load and delivery. Renal function should be checked by regular urinary electrolyte or osmolality analysis.

Moderate oliguria in the presence of normal plasma urea and creatinine (remembering that the values in pregnancy are usually lower than in the non-pregnant state) and high urinary osmolality suggest appropriate renal function: conservative management is appropriate. Other causes of oliguria include pre-renal or parenchymal renal failure and glomerular endotheliosis. However, while renal failure in the absence of obstetric haemorrhage is rare in pre-eclampsia, excessive fluid administration may easily precipitate life-threatening pulmonary oedema, aggravated by the underlying pulmonary capillary leak and low albumin levels. Oliguria generally resolves when the pre-eclamptic process improves, therefore the author considers that these patients are best run ‘on the dry side’ and that over-aggressive fluid loading in an attempt to increase urine output should be avoided.

Resistant oliguria occasionally requires the use of furosemide (frusemide), dopamine and CVP or pulmonary artery catheter monitoring, but these should not be used routinely. An agreed pre-eclampsia protocol may be useful to guide fluid administration and the management of oliguria.

Central haemodynamic monitoring
Most patients with pre-eclampsia do not require invasive monitoring, and the indications for CVP or pulmonary artery catheter insertion are controversial. For some years, the use of the pulmonary artery catheter has been strongly advocated in North America and whether the recent challenges to the use of the pulmonary artery catheter will alter this remains to be seen.

Arterial line insertion should be associated with few complications, but the risks of insertion of CVP and pulmonary artery catheter lines in a woman who is probably hypovolaemic and with an actual or incipient coagulopathy should not be underestimated. Some authors recommend avoiding the neck and using peripheral sites for the CVP line. Other problems include the misinterpretation of data obtained from these lines, and inappropriate management decisions based on the data (particularly with respect to fluid management).

In pre-eclampsia, the CVP may underestimate the left atrial pressure once it has risen to high-normal values (6 cm H_2O or above), but it may be useful for dynamic fluid challenges. In the presence of a high CVP or pulmonary oedema, a pulmonary artery catheter is indicated.

Eclampsia
In the UK, eclampsia occurs in about 1/2000 pregnancies. The onset of eclamptic convulsions may be unexpected, may occur before other markers of pre-eclampsia are apparent, and, particularly in the developing world, is associated with increased maternal and neonatal mortality. Airway reflexes may be lost, and pulmonary aspiration and hypoxia may ensue rapidly. Intravenous diazepam may be used for terminating seizures, but an intravenous bolus of magnesium sulphate, 4 g over 5–10 minutes, is recommended.

Magnesium sulphate is the drug of choice in eclampsia, because it is more effective than diazepam or phenytoin in preventing further fits and minimizing maternal morbidity. All eclamptic women should receive magnesium sulphate, though the best dosing regimen remains controversial (4 or 6 g initial bolus, followed by infusion at a rate of 1–2 g/hour). All labour ward staff should be trained in the basic ABC of resuscitation, and must appreciate the importance of turning the convulsing or unconscious patient rapidly on to her side into the recovery position.

The role of anticonvulsant prophylaxis in pre-eclampsia is controversial. For anticonvulsant prophylaxis, phenytoin is ineffective, and older sedative treatments with chlormethiazole and diazepam, which risk respiratory depression and pulmonary aspiration, have largely been eradicated in the UK. Opinion on the use of magnesium sulphate in pre-eclampsia is divided, but a rational argument suggests that if it works in eclampsia by reversing cerebral vasospasm, a condition known to occur in pre-eclampsia, then it seems appropriate to use it in patients with severe pre-eclampsia before they develop eclamptic convulsions. The use of magnesium sulphate in pre-eclampsia and eclampsia has increased markedly in the UK over the past decade.

Pre-eclamptic women are at high risk and should receive regular antacid prophylaxis during labour or delivery (e.g. oral ranitidine, 150 mg 6 hourly) to minimize the risks of pulmonary aspiration during an eclamptic convulsion or at general anaesthesia. ◆

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Regional Anaesthesia, Anticoagulation and Antithrombosis

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Physiological changes during pregnancy induce a hypercoagulable state presumably as a means of minimizing blood loss during childbirth. Venous stasis, increased procoagulant activity (elevated levels of factors II, VII, VIII, X and XI and fibrinogen) and reduced anticoagulant activity (increased plasminogen activator inhibitors and reduced protein C) contribute to an approximate incidence of thromboembolism of 1/1000. Obstetric haemorrhage causes maternal mortality in all countries, but in Australia (1991–1993) and the UK (1994–1996), pulmonary embolism was the leading cause of direct maternal death. In the UK, the rate of fatal pulmonary embolism (deaths/million maternities) appears to be rising, from 14.6–15.1 (1985–1993) to 21.8 (1994–1996).

Anticoagulation and antithrombosis

Anticoagulation is commonly instituted during pregnancy. Awareness of thromboembolic risk and concern were heightened by the findings and recommendations of the recent Confidential Enquiries into Maternal Deaths in the UK. Additionally, more patients at risk are now diagnosed and the incidence of operative delivery (a risk factor) remains high. Some units routinely use prophylaxis for thromboembolism following caesarean section, while others base policies on risk-stratification (increased risk with advanced maternal age, high parity, obesity and pre-eclampsia). Prophylaxis against thromboembolism is also initiated for many other parturients (Figure 1). It is now appreciated that hereditary thrombophilias are not uncommon; for example deficiencies of antithrombin, protein C or protein S; activated protein C resistance; or the factor V Leiden mutation. The latter has a 4% prevalence and is detected in 20% of those presenting with a thromboembolic event during pregnancy. The antiphospholipid syndromes and systemic lupus erythematosus are important thrombotic disorders. Many women with serious cardiac disease now achieve reproductive status and continuous anticoagulation may be warranted (Figure 1).

Peri-partum thromboembolism and some other situations demand urgent anticoagulation (Figure 1). This is usually initiated with intravenous unfractionated heparin or a therapeutic dose of low molecular weight heparin (LMWH) subcutaneously for 5–10 days, followed by maintenance with therapeutic LMWH for 3 months. Thereafter, either prophylactic or therapeutic anticoagulation is continued throughout pregnancy and 6 weeks into the puerperium. Despite a relative contraindication because of placental abruption and post-partum haemorrhage, antifibrinolytic drugs (e.g. streptokinase, tissue plasminogen activator) are occasionally used for massive pulmonary embolism.

Warfarin and the vitamin K antagonists are also usually avoided during pregnancy and reserved for anticoagulation after delivery. During organogenesis, fetal embryopathy and cerebral haemorrhage may occur and warfarin given in the second and third trimester may cause fetal CNS abnormalities, haemorrhage and stillbirth.

Antithrombotic and potent antiplatelet drug therapy is rare, though low-dose aspirin therapy is used for prophylaxis against severe pre-eclampsia in certain subgroups and for medical management after myocardial infarction and cerebrovascular disease.

Indications for anticoagulation during pregnancy

Prophylactic therapy
- Postoperative
- History of thromboembolism
- Low-risk thrombophilic disorder
- Antiphospholipid syndromes
- Systemic lupus erythematosus
- Cyanotic heart disease, some corrected congenital disorders, cardiomyopathy, atrial fibrillation, severe mitral stenosis
- Critical illness

Therapeutic therapy
- Mechanical cardiac valve
- Acute thromboembolism
- High-risk thrombophilic disorder
- Arterial thrombosis

Heparin
Heparin is the anticoagulant of choice during pregnancy.

Unfractionated heparin has a long history of safe use, but evidence supporting specific regimens in obstetric patients is lacking. Heparin does not cross the placenta, owing to its high molecular weight (mean 15–40 kDa). Maternal effects (other than bleeding or under-coagulation) include thrombocytopenia (early, mild, transient platelet aggregation or severe IgG antiplatelet antibody-induced). Although thrombocytopenia is uncommon (3% after therapeutic and 0.3% after prophylactic dosing in non-pregnancy after 14 days), the platelet count should be checked after 5–14 days. Following prolonged heparinization, subclinical maternal osteopenia occurs in 20% of women, though fractures are rare. Only the pentasaccharide fraction of unfractionated heparin activates antithrombin III (with subsequent inactivation of factors IIa, Xa and IXa), therefore variability in heparin effect is wide. The pharmacokinetics of unfractionated heparin are altered in pregnancy by placental heparinase, increased plasma volume, renal clearance and heparin-binding proteins. Consequently, requirements increase 1.5–2.5 times after early pregnancy, though they may fall at term with placental ageing. Many obstetric units currently use standard (non-pregnant) prophylactic doses that are inadequate. For example, therapeutic doses of 20,000 units t.d.s. subcutaneously or prophylactic doses of 7,500–10,000 units b.d. subcutaneously, often fail to achieve appropriate levels.

Low molecular weight heparins (LMWH) of 4–5 kDa are alternatives that also do not cross the placenta (Figure 2). In non-pregnant women, LMWH is as effective as, or more effective than unfractionated heparin for acute thromboembolism. Therefore, despite a lack of good evidence, LMWH is currently considered the agent of choice in pregnant women at high risk for thromboembolism. Higher doses (e.g. enoxaparin, 40 mg rather than 20 mg daily) may be required during pregnancy and the puerperium, probably because of increased renal clearance.

Advantages of low molecular weight heparin compared with unfractionated heparin

- Longer half-life
- More predictable and non-dose-dependent bioavailability
- Monitoring (anti-Xa activity) not usually required
- Heparin-induced thrombocytopenia rare
- Heparin-induced osteopenia less common

Regional anaesthesia and analgesia

The increasing use of regional techniques for caesarean section and labour analgesia has meant that many obstetric patients taking anticoagulants present as candidates for central neuraxial block. This poses a dilemma for the obstetric anaesthetist, who, in each case, must balance the relative advantages of central neuraxial block (reduced mortality, reduced thromboembolism or cardiac morbidity, benefits in pre-eclampsia) against the risks (e.g. intraspinal haematoma). The use of regional techniques in anticoagulated patients has been extensively reviewed (see Further Reading), though points pertinent to obstetric anaesthesia were not addressed. It is essential that all pregnant women taking anticoagulants are seen before delivery and a multidisciplinary management plan prepared. Spinal rather than epidural techniques, and intravenous or inhalational labour analgesia may be prudent. General anaesthesia for operative delivery will need to be considered, despite its association with a higher risk of postoperative thromboembolism in high-risk non-obstetric settings.

Intraspinal haematoma is rare (only seven reports in obstetric patients), suggesting that traditional guidelines have been successful in minimizing its incidence. Both the timing of needle insertion and catheter removal are relevant to haematoma formation. Central neuraxial block is generally contraindicated if an antifibrinolytic has been administered within 7–10 days, but is only relatively contraindicated following warfarin which acts for 4–6 days until vitamin K dependent factors II and X are replenished. Retrospective and prospective series report no haematoma formation after central neuraxial block among hundreds of non-pregnant patients on subtherapeutic doses of warfarin. In contrast, warfarin has been implicated in a large proportion of haematomas after lumbar puncture and in several case reports after epidural techniques. Reversal of warfarin using vitamin K (which takes several hours to work) or fresh frozen plasma is seldom used except for the management of uncontrolled obstetric haemorrhage or before urgent surgery. Ideally, aspirin should be stopped at least 3 days before a central neuraxial block. However, in the absence of other risk factors, aspirin does not exclude regional techniques.

The short duration of unfractionated heparin generally assists the organization of obstetric anaesthesia when labour ensues or operative delivery is required. Prophylactic subcutaneous unfractionated heparin peaks at 3 hours and may elevate the APTT (therapeutic doses may do so for up to 24 hours) so testing is advisable. Two large reviews of intraspinal haematoma (see Further Reading) suggest prophylactic unfractionated heparin is seldom implicated and clinical experience is reassuring. A regional technique or removal of an epidural catheter is generally considered safe 4–6 hours after conventional prophylactic doses (5,000 units b.d.), though even this may be conservative practice. In contrast to experience with unfractionated heparin, unfavourable experience with central neuraxial block in the presence of LMWH (though not in obstetric patients) has generated concern in the USA. LMWH has weak fibrinolytic activity and it seems appropriate to apply current general recommendations to obstetrics (Figure 3). Local policies need to be developed, because the window of opportunity for central neuraxial block, when anti-Xa activity is at its lowest, is brief.

Recommendations for low molecular weight heparins (LMWH) and central neuraxial block

- Avoid central neuraxial block for at least 24 hours if therapeutically anticoagulated with LMWH
- Avoid central neuraxial block for at least 12 hours after prophylactic LMWH
- Discuss the timing of prophylactic LMWH preoperatively, or before induction of labour, with the obstetrician
- In patients not at high risk, or if needle insertion is traumatic, begin prophylactic LMWH at least 12 (preferably 24) hours postoperatively
- Remove the epidural catheter when activity is lowest (at least 12 hours after the last dose)
- To avoid clot disruption, do not administer LMWH until 2–4 hours after central neuraxial block or catheter removal
- Avoid concurrent non-steroidal anti-inflammatory drugs, antiplatelet drugs (e.g. aspirin, dextran) and anticoagulants

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Social Problems in Pregnancy

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Social factors directly and indirectly affect the health of pregnant women and their unborn babies and should be addressed in obstetric management. Drug use is not the foremost route of blood-borne virus infection in the UK, but because both have a social dimension that can affect pregnancy and both illustrate management of social problems in pregnancy they are jointly discussed here.

Problem drug use

There has been a marked increase in drug use among women of childbearing age and consequently during pregnancy. Problem drug use with significant medical and social consequences is closely associated with socioeconomic deprivation, which is associated with poor health and ineffective service use and both are exacerbated by problem drug use. Therefore, pregnant drug-using women have potentially high-risk pregnancies but may receive less maternity care. The design, delivery and content of obstetric care are all important in the management of drug use and associated problems in pregnancy.

In the UK, the most commonly used drugs are opiates/opioids (including heroin, methadone and dihydrocodeine), amphetamines and benzodiazepines. The use of cocaine is also significant. Drugs can affect pregnancy directly and indirectly by their effect on maternal lifestyle and general health. Injecting use carries additional risks.

Opiates/opioids: heroin is a short-acting opiate and withdrawal carries a risk of preterm labour and reduced intrauterine growth. Therapy with longer acting methadone reduces the risk of preterm labour. Opiate/opioid detoxification during pregnancy is dangerous in theory, but not in practice, and can be undertaken at any stage of pregnancy, at any speed, but only if likely to be successful. Management usually involves a combination of detoxification/reduction and maintenance therapy with the aim of achieving the lowest drug dose compatible with reasonable stability. Unlike detoxification, reversal of opiate/opioid effects with naloxone can precipitate severe fetal distress antenatally and postnatally and should be used cautiously and only if necessary. All opiates and opioids can cause withdrawal symptoms in the neonate.

Benzodiazepines: apart from a reported association with cleft palate, benzodiazepine use does not directly affect pregnancy. The most important consequence of benzodiazepine use is social instability, which has implications for delivery of care and parenting. There is no evidence of benefit from benzodiazepine sub-stitution therapy in pregnancy but sudden withdrawal can cause maternal convulsions. Short-term substitution (up to 7 days) to cover withdrawal is recommended. Benzodiazepine use also causes neonatal withdrawal symptoms.

Amphetamines: chaotic injecting use carries risks for maternal health and can be socially destabilizing. However, amphetamines *per se* seldom affect pregnancy outcome, do not cause withdrawals in the neonate and there is no evidence of benefit from substitute prescribing in pregnancy.

Cocaine use is increasing in the UK, but use of crack cocaine is less prevalent than in the USA. In pregnancy, the vasoconstrictor action of cocaine has been reported to cause underdevelopment of organs including limbs and gut as well as reduced brain growth, increased rates of placental abruption, preterm rupture of membranes and fetal death. However, there is evidence of a publication bias in favour of studies with adverse outcomes, which seem to be largely restricted to heavy, chaotic, injecting use. Cocaine does not cause withdrawal symptoms in the neonate and substitution is neither feasible nor beneficial.

Neonatal withdrawal symptoms

Neonatal withdrawal symptoms (neonatal abstinence syndrome) occur with maternal use of opiate/opioids and benzodiazepines. Their severity is largely dose related but the many other relevant co-factors (e.g. intra-partum hypoxia, infection or other illness in the baby) make it impossible to predict outcome for an individual baby. A combination of opiates/opioid and benzodiazepine use is particularly problematic. Breast-feeding reduces the severity of neonatal withdrawals and is especially beneficial in this vulnerable group of babies. While the mother's drug use should be reasonably stable, successful establishment of breast-feeding is in itself sufficient proof of stability. Babies should be gradually weaned because sudden discontinuation of breast-feeding could precipitate withdrawals in the baby.

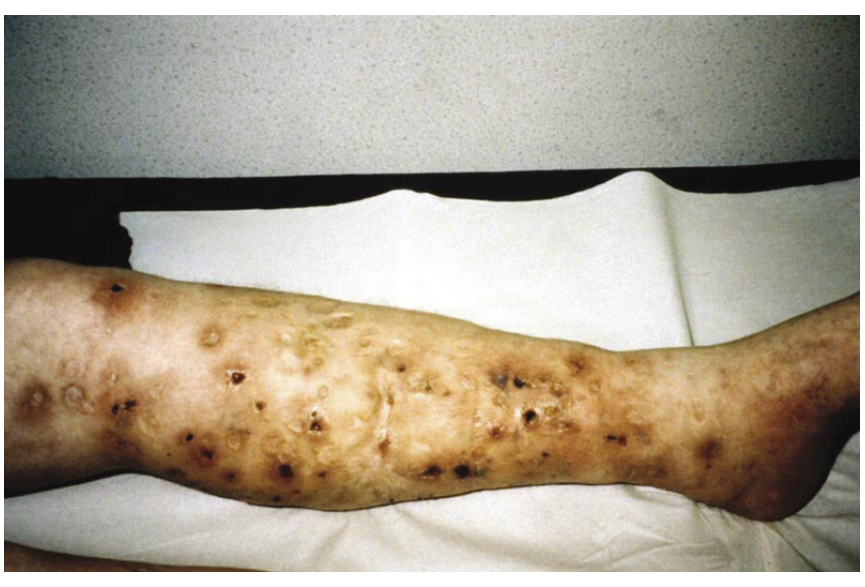
Obstetric management

Use of opiates/opioids or benzodiazepines can reduce fetal heart rate variability and make it difficult to interpret antenatal or intra-partum cardiotocographs. Reversal of maternal opiate/opioid intoxication or neonatal sedation with naloxone can be dangerous.

Methadone medication should be continued in labour if due. Opiate analgesia can also be given and while, in theory, larger doses may be required this is often not the case in practice. Epidural analgesia is often appropriate but venous access can be difficult, which can also cause problems if immediate delivery by caesarean section is required.

Associated medical problems

Injecting drugs causes vascular damage and infection can lead to endocarditis and valvular damage necessitating use of prophylactic antibiotics during labour and other procedures likely to cause bacteraemia (Figure 1). Blood-borne virus infection is also a risk.



1 Scarring of leg caused by injecting drug use. © Mary Hepburn

Poor diet and poor oral hygiene make dental caries common. These are often associated with bacteraemia and should be dealt with during pregnancy under antibiotic cover.

Injecting into veins or arteries carries the risk of thrombo-embolic disease and women with current or past episodes of thrombosis with or without embolism require therapeutic or prophylactic anticoagulation.

Blood-borne virus infection

Women should be offered antenatal screening because they are pregnant and not because they are perceived as likely to be infected. Testing should be offered in their interests, not for infection control and should always be offered without pressure to accept.

HIV infection

Known HIV-positive women should be offered interventions to reduce the risk of vertical transmission. Antiretroviral therapy, if already started, is usually continued throughout pregnancy but is otherwise offered during the third trimester. The aim is to reduce maternal viral load, ideally to an undetectable level. Treatment of the baby for the first month of life is also advocated. Elective caesarean section reduces vertical transmission but may not carry significant additional benefit for women with undetectable viral load. If aiming for vaginal delivery, early rupture of the membranes and use of fetal scalp electrodes should be avoided if possible. Breast-feeding increases the risk of vertical transmission and should be avoided.

Hepatitis B infection

Perinatal transmission of hepatitis B can be prevented by immun-ization of the baby at birth. Babies of Ag positive mothers require active and passive immunization while babies of Ag negative mothers require active immunization. Both groups can safely breast-feed. Hepatitis B immunization is recommended for all injecting drug users and for women infected with hepatitis C. A complete course can be safely administered during pregnancy using an accelerated regimen.

Hepatitis C infection

There is no effective immunization against hepatitis C nor any intervention that significantly reduces perinatal transmission. However, maternal screening allows infected mothers to access specialist care and identifies babies who require follow-up. The available evidence suggests breast-feeding does not increase the risk of vertical transmission of hepatitis C.

Outcome of pregnancy among drug-using women

Neonatal abstinence syndrome can be a major management problem but there is no reliable evidence to suggest that it causes permanent damage. However, low birthweight, which may be associated with preterm delivery or fetal compromise has long-term health implications. There is also an increased risk of sudden infant death syndrome (SIDS). Both low birthweight and SIDS are multifactorial in origin and socioeconomic deprivation and associated problems (including smoking) are other aetiological factors.

Design and delivery of care

Management of maternal drug use should be provided within multidisciplinary maternity care. Although unsuitable for midwifery-only care these women can receive much of their care from midwives in the community. The multiple social problems associated with drug use can tax parenting skills especially if the baby is sick. Consequently, drug-using women often require considerable support with childcare. Careful antenatal and post-partum assessment is essential with early introduction of support services.

Effective multidisciplinary collaboration is essential to provide integrated care that addresses the medical and social problems. This provides the best chance of delivery of a healthy baby that can go home with and be adequately cared for by its mother.
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Ophthalmology

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Anaesthesia for Eye Surgery in Paediatrics

Jonathan Lord

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Children present for ophthalmic surgery from the neonatal period onwards. Neonates and infants generally present for cataract extraction and treatment for congenital glaucoma whereas older children more often have strabismus, lacrimal, vitreo-retinal or ocular plastic surgery. Many children present for repeated procedures and skilled anaesthesia contributes to a successful result. The problems of anaesthesia are essentially the same as those of paediatric anaesthesia in any field, however, there are some areas that require particular attention.

General considerations

Airway: although not strictly a 'shared airway', most ophthalmic operations involve draping the head and thus abolish or at least reduce access to the airway.

Intraocular pressure (IOP): normal IOP is 10–22 mm Hg. The factors that affect IOP are essentially the same as those that affect intracranial pressure. The control of IOP is an important part of the anaesthetic management of intraocular surgery. Any sudden increase in IOP with an open eye leads to loss of ocular contents and/or an expulsive haemorrhage. The likely outcome of such an event is loss of vision. The main factors involved in the regulation of IOP are the choroidal, aqueous and vitreous volumes together with external pressure.

Choroidal volume can be affected by venous pressure, arterial pressure and arterial partial pressure of carbon dioxide.

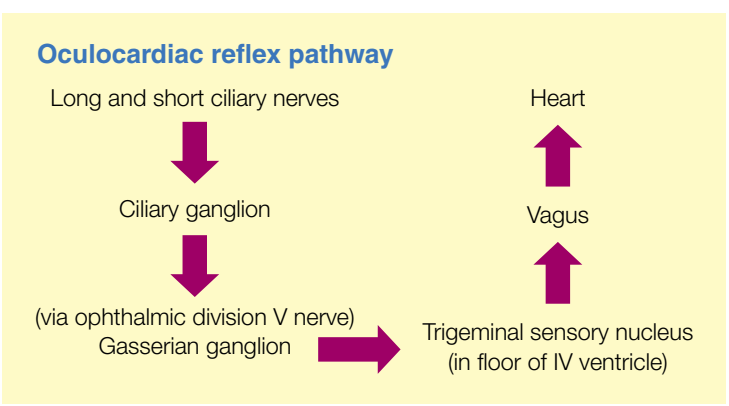
- Venous drainage from the eye is valveless and therefore any changes in venous pressure produce an immediate change in ocular pressure by altering the volume of blood within the choroid. Raised venous pressure also impedes aqueous drainage via the canal of Schlemm and causes a secondary rise in IOP. Coughing, straining and retching all increase venous pressure. A 15° head-up tilt reduces IOP.
- Mean arterial pressure has little effect on IOP but sudden increases in mean arterial pressure produce a rapid and unpredictable rise in IOP.
- Alterations in arterial partial pressure of carbon dioxide have a linear effect on IOP. A reduction causes a fall in choroidal volume and thus in IOP and vice versa.

Aqueous volume – although alteration of aqueous volume is the mainstay of glaucoma therapy it is of limited importance during anaesthesia because without direct drainage the volume alters slowly. Acetazolamide reduces aqueous production and reduces IOP.

Vitreous volume is of limited importance during anaesthesia. Osmotic diuretics (e.g. mannitol) can dehydrate the vitreous and reduce its volume.

External pressure – direct pressure on the eye, for example with a mask, must be avoided. Increase in tone of the extraocular muscles increases IOP, thus depolarizing muscle relaxants (e.g. suxamethonium) cause an increase in IOP. The rise produced by suxamethonium is maximal at 2 minutes and lasts for 5 minutes. Pre-treatment with non-depolarizing muscle relaxants to prevent this has been advocated but is of unproven value.

Oculocardiac reflex is potent in children. The afferent and efferent pathways are shown in Figure 1. It can be triggered by increases in IOP, traction on the extraocular muscles, trauma or pain. It usually produces a bradycardia but asystole quickly ensues in children if left untreated. Other arrhythmias such as nodal rhythms and ventricular fibrillation can also occur. Without any preventive treatment the reported incidence varies from 30 to 90%. Pre-treatment with a vagolytic is protective. Oral atropine can be given as part of the premedication, and intravenous atropine or glycopyrrolate can be given peroperatively. Infiltration around the extraocular muscles with local anaesthesia also reduces the reflex. It is important that a pulse monitor with an audible bleep is used peroperatively so that both the anaesthetist and the surgeon can hear if a bradycardia occurs.



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Acute ocular trauma: the question of how to deal with acute ocular trauma in an unstarved child is often discussed. Many centres avoid the problem by avoiding emergency surgery because there is no evidence that waiting for the child to be starved influences the outcome of surgery. However, 6 hours' starvation in a traumatized child does not mean that the stomach will be empty and consideration must to be given to this. Prokinetics (e.g. metoclopramide) together with H_2-blockers (e.g. ranitidine) to increase stomach pH can be given. The management of the anaesthetic is controversial but the need to avoid suxamethonium if the eye is open is paramount because loss of contents can occur from the rise in IOP. The author's opinion is that induction of anaesthesia should be either intravenous with a fast-acting non-depolarizing muscle relaxant (e.g. rocuronium) or inhalational. Intubation is preferable to protect the airway. The child should then be extubated awake.

Postoperative nausea and vomiting (PONV): ocular procedures in general are emetic and if consideration is not given to this a high proportion of children will have PONV. It is produced as a result of the manipulation of the extraocular muscles, by alterations in the IOP or by volume expansion within the orbit. Any child with persistent vomiting following an intraocular procedure must be checked by the surgeon to exclude raised IOP as the cause. As always, prevention is better than cure and suggested drug treatments are shown in Figure 2.

Associated syndromes: eye abnormalities in children are often manifestations of multisystem disorders. Many of these syndromes have anaesthetic significance and any anaesthetist involved in paediatric ophthalmology should look out for any associated problems. Some of the common syndromes are given in Figure 3.

Anti-emetic drugs for postoperative nausea and vomiting

Drug	Dose	Comments
Ondansetron	0.1–0.15 mg/kg (maximum 8 mg)	Excellent anti-emetic; low side-effect profile
Cyclizine	1 mg/kg (maximum 50 mg)	Effective but sedative
Dexamethasone	200–300 μg/kg (maximum 8 mg)	Very effective, particularly for orbital implants

2

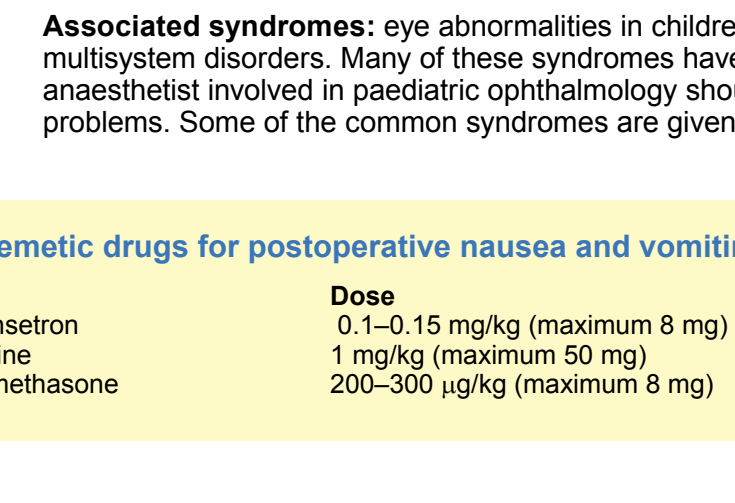
Congenital syndromes

Syndrome	Ocular manifestation	Anaesthetic significance
Down's	Strabismus, cataract	Cardiac problems, hypothyroidism, blood dyscrasias
Goldenhar's	Ptosis	Difficult intubation
Homocystinuria	Lens dislocation	Thromboembolism, hyperinsulinaemia
Marfan's	Lens dislocation, retinal detachment	Heart valve defects, thoracic aneurysms
Sickle haemoglobinopathies	Retinopathy	Sickle crises
Stickler's	Retinal detachment	None
Sturge–Weber	Secondary glaucoma	Epilepsy

3

Malignant hyperthermia is more common in ophthalmic, and in particular strabismus, surgery. Temperature should therefore always be monitored. All anaesthetic departments should ensure that personnel are aware of the recommendations for treatment of malignant hyperthermia as well as the location of the necessary drugs within the department.

Analgesia: most ophthalmic operations are not particularly painful and simple analgesia in the form of paracetamol or other non-steroidal anti-inflammatory drugs (NSAIDs) is all that is required. The main exceptions are strabismus surgery in which the muscle necrosis following suturing can cause marked pain, detachment surgery where an encircling band is used and larger procedures such as tumour resection or eviscerations. Postoperative analgesia should be considered as part of the overall plan of anaesthesia. A multimodal approach using local anaesthesia, paracetamol, NSAIDs and opioids is logical. A suggested regimen is given in Figure 4. Local anaesthesia can take the form of topical local anaesthetic drops or formal local blocks. Sub-Tenon anaesthesia is particularly useful in strabismus and detachment surgery.



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Specific problems

Measurement of IOP: glaucoma can be defined as a progressive optic neuropathy and if left unchecked eventually results in blindness. The effective management of children with glaucoma includes the accurate measurement of their IOP. In those under 5 years, this usually requires an anaesthetic. All currently available anaesthetic agents, with the exception of ketamine, reduce IOP. The extent of this reduction is unknown and not repro-ducible even in the same individual. This can lead to misleading IOP readings and have a detrimental effect on treatment.

Ketamine is the drug of choice for IOP surveillance. It is a phencyclidine derivative that produces dissociative anaesthesia via its action at the N-methyl-D-aspartate (NMDA) receptors. It produces either no change or a transitory rise in IOP through a combination of its sympathomimetic effects and extraocular muscle contraction. Studies suggest, that this rise is not seen if the child is premedicated with a benzodiazepine. A suggested technique for ketamine anaesthesia is shown in Figure 5.

It is unnecessary to secure the airway and the child should be allowed to breathe spontaneously in air. Supplemental oxygen is occasionally required. Premedication with a benzodiazepine is essential because it causes amnesia (which is useful in repeated anaesthetics in children), 'ketamine sparing' (allowing the dose of ketamine to be reduced) and reduces emergence phenomena. Ketamine causes excessive salivation and should always be used in conjunction with an anticholinergic to reduce the risk of laryngeal spasm. Ketamine is emetic and routine administration of an anti-emetic is required. Children having multiple frequent ketamine anaesthetics can develop an unpredictable resistance to ketamine, necessitating escalating doses. This resistance resolves if ketamine is avoided for a few weeks.

Anaesthetic technique for measuring intraocular pressure

Premedication

- Oral atropine, 30 mg/kg 1 hour preoperatively
- Oral midazolam, 0.5 mg/kg 1 hour preoperatively
- Ametop over convenient vein

Induction

- Intravenous ketamine (50 mg/ml strength) 1–2 mg/kg
- Onset 30 seconds
- Duration 5–10 minutes

  or
- Intramuscular ketamine (100 mg/ml strength) 10 mg/kg
- Onset 2–8 minutes
- Duration 10–20 minutes
- Intravenous access after induction

  or
- Inhalational induction
- Oxygen and sevoflurane up to 8%
- Intravenous access
- Intravenous ketamine as above
- After inhalational induction it is advisable to wait 5 minutes before measuring intraocular pressure to allow sevoflurane washout

Intraocular surgery: the key to successful intraocular surgery is a balanced general anaesthetic with intermittent positive pressure ventilation. Two suitable schemes are shown in Figure 6. The anaesthetic should be planned to try to avoid any of the factors previously described that may increase IOP.

Extraocular surgery is mainly strabismus and lacrimal duct surgery. In general, these are best performed with a straightforward anaesthetic allowing spontaneous breathing. In strabismus surgery, consideration must be given to analgesia, avoidance of the oculocardiac reflex and anti-emesis. A suggested technique is shown in Figure 7.

Anaesthesia for intraocular surgery

Premedication
Midazolam, 0.5 mg/kg orally if required
Ametop to a suitable vein

Induction

Intravenous access	Inhalational – oxygen + sevoflurane
Remifentanil, 1 µg/kg	Intravenous access
Propofol, 2–3 mg/kg	Rocuronium 0.6–0.9 mg/kg

Laryngeal mask airway or tracheal tube

Maintenance

Intermittent positive-pressure ventilation with oxygen + air	Intermittent positive pressure ventilation with nitrous oxide + oxygen + sevoflurane
Remifentanil intravenous infusion 0.3–0.5 µg/kg/minute	

Propofol intravenous infusion 4–8 mg/kg/hour

Analgesia
Diclofenac 1–2 mg/kg p.r.
and/or paracetamol, 20–30 mg/kg p.r.

Reversal

Nil required	Neostigmine, 50 µg/kg + glycopyrrolate, 10 µg/kg

6

Anaesthesia for strabismus surgery

Premedication
- Midazolam, 0.5 mg/kg orally if required
- Atropine, 30 µg/kg orally
- Ametop to a suitable vein

Induction
- Inhalational or intravenous as required
- Laryngeal mask airway

Maintenance
- Spontaneous ventilation with nitrous oxide + oxygen + sevoflurane

Analgesia
- Diclofenac, 1–2 mg/kg p.r.
  And/or
- Paracetamol 20–30 mg/kg p.r.
  And/or
- Codeine phosphate, 1 mg/kg i.m. or p.r.

Anti-emetic
- Ondansetron, 0.15 mg/kg i.v.

7

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Care of the Eye during Anaesthesia

Emert White

Emert White is Consultant Anaesthetist at Warwick Hospital, Warwick, UK. He qualified from Birmingham University and trained in anaesthesia in Nottingham and Southampton. He has a special interest in ocular physiology and anaesthesia.

Perioperative eye injuries and blindness are rare but important complications of anaesthesia. Eye injuries account for 3% of claims against anaesthetists. A better understanding by anaesthetists of orbital anatomy and ocular physiology and the mechanisms of ocular injury may help to reduce injuries.

Arterial supply to the optic nerve and retina

The ophthalmic artery enters the orbit through the optic canal enclosed within the dural sheath of the optic nerve and its first branch within the orbit, the central retinal artery, runs along the inferior aspect of the optic nerve, exiting from the dural sheath of the optic nerve about 10 mm behind the globe. The vascular supply to this posterior part of the optic nerve is from pial branches of the ophthalmic artery and the central retinal artery.

The central retinal artery divides into four major vessels at the optic disc each supplying one quadrant of the retina. The retinal vessels are distributed within the inner two-thirds of the retina, while the choroidal circulation supplies the outer layers of the retina.

Two to three posterior ciliary arteries arise from the ophthalmic artery, each of which divides into one long and 8–10 short posterior ciliary arteries. The short posterior ciliary arteries pierce the sclera and form the choriocapillaris, which supplies the anterior part of the optic nerve, the lamina cribosa and the choroid posterior to the equator.

The choriocapillaris is composed of small lobules supplied by a terminal arteriole. Each lobule has draining venules at the periphery.

The long posterior ciliary arteries travel forward in the suprachoroidal space to the ciliary body where they combine with the anterior ciliary arteries to form the major arterial arcade. Recurrent branches of the long posterior ciliary arteries supply the choroid anterior to the equator and anastomose with the short posterior ciliary arteries.

Watershed zones occur between the:

- choroidal and retinal circulation
- long posterior ciliary arteries
- short posterior ciliary arteries
- long posterior ciliary arteries and the anterior ciliary arteries
- choriocapillaris lobules.

Thus, in the event of ischaemia, the pattern of visual disturbance is variable.

Ocular blood flow and perfusion

Ocular blood flow (OBF) is determined by the pressure difference between mean arterial pressure (Pa) and mean venous pressure (Pv) and the resistance to that flow (R).

$$OBF = \frac{Pa - Pv}{R}$$

Retinal blood flow is about 170 ml/100 g/minute. The choroid receives 65% of the total ocular blood flow, while the retinal circulation receives 2%.

In the upright position, the pressure within the artery entering the eye is 60–70 mm Hg, while the intraocular pressure is 10–15 mm Hg, which under normal conditions provides a perfusion pressure of about 50 mm Hg. The episcleral venous pressure is about 3–7 mm Hg (7–8 mm Hg lower than the intraocular pressure) and increases by 3–4 mm Hg in the supine position. When intraocular pressure increases above 15 mm Hg, the episcleral venous pressure rises in direct proportion to the intraocular pressure thus reducing perfusion pressure. Retinal blood flow is maintained by autoregulation over a wide range of perfusion pressures. Autoregulation does not occur in the choroidal vascular system and increases in intraocular pressure reduce choroidal blood flow.

Ischaemic optic neuropathy

When intraocular pressure increases, retinal blood flow remains constant until the intraocular pressure reaches about 40 mm Hg. At an intraocular pressure of about 60 mm Hg, blood flow to the optic nerve at the disc ceases, but flow is maintained in the choroidal and retinal circulation. In humans there is little correlation between occlusion time and visual outcome, but in other primates irreversible damage occurs if ocular ischaemia exceeds 100 minutes.

Ischaemia of the optic nerve is caused by:

- arterial hypotension (hypotensive anaesthesia, haemorrhage)
- elevated venous or intraocular pressure
- increased resistance to flow (seen in atherosclerosis, diabetes mellitus, hypertension, thromboembolism)
- decreased oxygen delivery (anaemia).

Ischaemia of the optic nerve is classified as anterior or posterior ischaemic optic neuropathy.

- Anterior ischaemic optic neuropathy is characterized by infarction at the watershed zones listed above, a visual field defect, a pale oedematous optic disc and oedema of the optic nerve in the posterior scleral foramen.
- Posterior ischaemic optic neuropathy occurs when the pial branches of the ophthalmic artery become occluded. Blood flow in the posterior part of the optic nerve is significantly less than that in the anterior part. These pial vessels are incapable of autoregulatory control and therefore this part of the optic nerve is more vulnerable to ischaemia in the event of a fall in perfusion pressure or anaemia. Posterior ischaemic optic neuropathy is characterized by a slower onset of visual field defect and mild optic disc oedema.

The incidence of ischaemic optic neuropathy varies between 1/30,000 and 1/60,000 operations. High-risk procedures are spinal surgery, cardiopulmonary bypass and bilateral neck dissection. The primary mechanism of ocular ischaemia following bilateral radical neck dissection is the reduction of the ocular perfusion pressure caused by the increase in venous pressure when the normally adequate venous collateral circulation is sacrificed to ensure adequate tumour clearance.

During spinal surgery, patients may be placed prone with the head in a dependent position thereby elevating venous pressure and reducing perfusion pressure. In the prone position, venous pressure may be further increased by abdominal compression with resultant upward shift of the diaphragm. During spinal surgery, direct pressure on the eye as a result of patient malposition has caused ischaemic optic neuropathy. Stigmata of orbital compression are:

- intraoperative bradyarrhythmias
- hyperaemic conjunctiva
- periorbital numbness
- periorbital abrasions
- periorbital oedema.

Major blood loss resulting in anaemia, intraoperative hypotension and long operative times in combination with the above factors appears to be the cause of ischaemic optic neuropathy following spinal surgery. It is recommended that the haemoglobin level should be maintained above 8 g/dl and the systolic arterial blood pressure at a level greater than 60% of its preoperative recording. Cases of ischaemic optic neuropathy have occurred above these recommended levels.

Ischaemic optic neuropathy should be suspected when a patient complains of painless visual loss (with macular sparing) on emergence from anaesthesia. An urgent referral to an ophthal-mologist for advice on diagnosis and treatment should be sought. The aims of treatment are to reduce optic nerve fibre oedema as it passes through the posterior scleral foramen with cortico-steroids or osmotic diuretics and to optimize oxygen delivery by maintaining normal arterial blood pressure and haemoglobin. Vision seldom improves after ischaemic optic neuropathy.

Anaesthetists need to be aware that reductions in ocular blood flow are multifactorial, which cumulatively can put the eye at risk. Hypotension associated with increases in venous pressure, raised intraocular pressure and poor positioning when prone can jeopardize the eye especially in patients at high risk (e.g. those with hypertension, diabetes, atherosclerosis).

Central retinal artery occlusion

Central retinal artery occlusion is often caused by emboli. It may occur in conjunction with perioperative ischaemic optic neuropathy. It presents with a painless visual defect. Ophthalmic examination shows a pale retina with a cherry-red spot. An urgent ophthalmic opinion is required because treatment often improves the visual defect. Treatment options are:

- vasodilator therapy; inhalation of oxygen/carbon dioxide, calcium channel blockers, nitrates
- removal of obstruction
- increasing perfusion pressure; paracentesis, carbonic anhydrase inhibitor
- thrombolysis
- reducing blood viscosity
- reducing RBC rigidity – pentoxifylline (oxpentifylline)
- corticosteroids.

If the cause of central retinal artery occlusion is embolic, a cardiac or carotid source should be sought.

Aetiology of perioperative corneal abrasions

The most common complication is corneal abrasion. The incidence is 0.03–0.17% depending on the method of reporting. It is most commonly caused by exposure keratopathy, chemical injury or direct trauma.

Anaesthesia reduces the tonic contraction of the orbicularis oculi muscle, which may cause lagophthalmus. If the anaesthetist does not ensure that the eyes are fully closed, exposure keratopathy may occur. Anaesthesia inhibits the protective mechanism afforded by Bell's phenomena, and decreases tear production and tear film stability, which may lead to corneal epithelial drying and lysosomal protection.

Chemical injury can result from cleaning materials on the face mask and inadvertent spillage of antiseptic skin preparations on to the eye. The only antiseptic skin preparation that is not toxic to the cornea is povidone–iodine 10% in aqueous solution. It is the agent of choice when antimicrobial skin preparation of the face is required. Antiseptic solutions with detergent readily penetrate the corneal epithelium causing damage to the underlying iris, ciliary body, lens and blood vessels leading to ischaemia. Chlorhexidine, cetrimide and alcoholic antiseptic solutions cause oedema and de-epithelialization of the cornea. Trauma to the eyes can occur at any time during the perioperative period. During induction of anaesthesia it can be caused by ill-fitting face masks, the laryngoscope, or the anaesthetist's fingers, watchstrap, identification badge or stethoscope. After induction of anaesthesia, trauma to the eyes by surgical drapes, surgical instruments and during patient repositioning have all been reported. In the recovery room, the patient's fingers, pulse oximeter probe, pillow or Hudson mask may injure the eye.

Methods to prevent perioperative corneal injuries include:

- manual closure of the eyelids
- taping the eyelids closed
- using protective goggles
- suture tarsorrhaphy
- bio-occlusive dressings
- contact lenses
- installation of ointment, methylcellulose or viscous gels.

No method is 100% effective and the various protective strategies themselves may be associated with morbidity. Vigilance regarding the perioperative care of the eye is required to reduce these rare but potentially devastating complications.

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Eye Signs in Anaesthesia and Intensive Care

Rahul Bajekal

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The eyes are commonly used as clinical monitors in anaesthesia because they are easy for anaesthetists to access, and generally give well-defined responses to interventions. Most eye signs involve motor responses or reflexes related to different parts of the eye (Figure 1).

Eye signs in anaesthesia

Sign	Implications
Local anaesthesia	
• Horner's syndrome	• Cervical sympathetic block
• VI nerve palsy, dilated pupils	• Spinal anaesthesia
Sedation	
• Saccades	• Depth of sedation
General anaesthesia	
• Guedel's signs	• Ether anaesthesia
• Nystagmus	• Ketamine
• Pupillary size	• Opioids
Intensive care	
• Glasgow Coma Score	• Head injury
• Vestibulo-ocular, oculocephalic, corneal, pupillary reflexes	• Brain stem death
• Sustained unreactive pupils	• Poor recovery following cardiopulmonary resuscitation

1

Eye signs in local anaesthesia

The success of a retro- or peribulbar local anaesthetic block of the eye may be gauged from the degree to which it achieves an anaesthetic, immobile globe.

Horner's syndrome: ocular signs as part of Horner's syndrome have been used to monitor cervical sympathetic blockade. Ptosis, miosis and enophthalmos may be indicators of a successful stellate ganglion block. These signs may also herald possible complications, for example if seen with brachial plexus blockade.

Spinal anaesthesia: eye signs have been reported with spinal anaesthesia though not commonly. Abducens nerve (lateral rectus muscle of the eye) palsy has been observed as a complication, sometimes in the absence of a typical post-spinal headache; most cases eventually resolve without intervention. Dilated pupils seen with a high spinal block are associated with other features including cardiovascular and respiratory effects and loss of consciousness. The presence of non-reactive dilated pupils should not delay or interfere with attempts at resuscitation.

Eye signs in sedation
Traditionally, simple eye signs have been used to guide the depth of sedation. Drooping of the eyelid (Verrill's sign) was used by some clinicians while administering diazepam. Loss of eyelid and eyelash reflexes was also used to assess adequacy of sedation. These signs are inconsistent and almost always result in unacceptably deep levels of sedation. Verbal contact with the patient is preferred rather than relying on ocular signs.

Saccades: a recent review has evaluated the role of saccadic eye movements as biophysical monitors of anaesthetic sedation. Saccades have been described as rapid, semi-voluntary, conjugate, gaze-shifting movements designed to centre a target of interest on to the fovea. They may be monitored using electro-oculography or infrared oculometry. Peak saccadic velocity is useful for monitoring benzodiazepine-induced sedation but other parameters and application to other anaesthetic agents is debatable.

Eye signs in general anaesthesia

Guedel's signs: ocular signs used to be taught as part of the clinical assessment of anaesthetic depth. What are commonly known as Guedel's signs or stages of anaesthesia were a continuum of observations extending from analgesia to overdose. Eye signs progressed from loss of the eyelash reflex to successive abolition of the eyelid, conjunctival and corneal reflexes. The positions of the eyeball, eye movements and pupil size were also used to assess the depth of inhalational anaesthesia.

The advent of relaxant and intravenous techniques combined with the increasing popularity of opioids made Guedel's signs obsolete. Pupillary signs were masked by opioids, and other signs were inconsistent with newer inhalational and intravenous agents.

During intravenous induction, anaesthetists commonly test the eyelash reflex. This probably indicates deep sedation though it does not predict general anaesthesia reliably.

Nystagmus is commonly associated with ketamine anaesthesia. Some clinicians have used this with movement and phonation to titrate intermittent boluses of intravenous ketamine. However, isolated eye signs are not useful.

Pupillary size has been used to monitor the depth of anaesthesia and opioid overdosage. Though various studies have used pupillometry to describe the effect of single drugs, applicability to anaesthesia is limited. Opioids generally cause miosis and a decrease in the velocity of the pupillary light reflex. In equianalgesic doses, there is little difference between the various opioids. Mydriasis has been described with pethidine intoxication.

Tears have been used as part of scoring systems for adequacy of level of anaesthesia. Used in conjunction with other signs, they may signify light anaesthesia, but alone they are inadequate markers.

Eye signs in intensive care

Various eye signs have been described with concurrent medical conditions. Diseases such as myasthenia may manifest with ptosis; though pure eye signs are inadequate in diagnosis, the constricted pupil may help differentiate a cholinergic from a myasthenic crisis.

The effect of various drugs on the pupils may help to diagnose certain cases of poisoning. The presence of pallor, icterus or oedema of the conjunctiva and periorbital haematomas all aid in diagnosing underlying conditions.

The Glasgow Coma Score (GCS) uses eye signs as one of its three components. Observations range from no eye response to spontaneous eye opening; the score for this parameter ranges from 1 to 4. The GCS is easy to use and standardized. It does not describe pupil size or responses.

Dilated, non-reactive pupils: the presence of a dilated pupil unreactive to light is sometimes used as an indicator of poor prognosis after cardiopulmonary resuscitation (CPR). During the acute phase of CPR, the administration of drugs including anticholinergics may mask underlying pupillary responses. Complete recovery has been seen in patients who were noted to have so-called 'fixed dilated' pupils. The presence of unreactive and dilated pupils in the days following resuscitation suggests a poor prognosis. Current guidelines for CPR do not recommend cessation of resuscitative efforts in the presence of dilated non-reactive pupils.

Brain stem death: eye signs remain a diagnostic test for brain stem death. The neural pathways for ocular reflexes involve the brain stem and their absence, along with other criteria, is used to confirm the absence of brain stem activity. Tests include a fixed pupil, unreactive to light regardless of pupillary diameter along with the absence of corneal, oculocephalic and vestibulo-ocular (to caloric testing) reflexes.

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General Anaesthesia for Ophthalmic Surgery

Nicholas C B Pritchard

Nicholas C B Pritchard is Consultant Anaesthetist at Moorfields Eye Hospital, London, UK. He qualified from St Mary's Hospital, London, and trained in anaesthesia in London. His special interests are oculoplastic, paediatric and intravenous anaesthesia.

The use of local anaesthesia for eye surgery is increasing but general anaesthesia will always have a place (Figure 1). Eye conditions are seldom immediately life threatening and it is nearly always possible to wait for the stomach to empty before giving general anaesthesia.

Eye operations are relatively painless procedures; however, patients are often anxious and at the extremes of age. Coexistent disease is common. Most patients are treated on a day-care basis or require an overnight stay only. There are multiple ophthalmic subspecialties. Good cooperation between anaesthetist and surgeon is important and the surgeon requires a 'soft', motionless eye on which to operate. Clinical strategies to ensure immobility are also vital. An analysis of closed insurance claims by the American Society of Anesthesiologists found that 30% of claims for eye injuries associated with anaesthesia were related to patient movement during surgery.

Patient selection for general anaesthesia

Absolute

- Patient preference
- Young children
- Uncooperative patient (e.g. mental retardation)
- Patient unable to keep still (e.g. Parkinson's disease, dystonia, arthritis, nystagmus, tremor, cough, dyspnoea, vertigo)
- Patient unable to lie flat for duration of operation
- Long procedure
- Allergy to local anaesthesia

Relative

- Surgery to the patient's only functioning eye
- Claustrophobia
- Communication problems (e.g. deaf patient, poor language comprehension)
- Bleeding disorder

1

Preparation of patients

Coexistent disease is common in ophthalmic patients and preoperative optimization of medical conditions is required. Investigations can be arranged through the anaesthetic clinic and liaison with appropriate specialists (e.g. cardiologists, neurologists) organized. Eye hospitals are sometimes remote from hospital backup services such as intensive care and CT scanners.

Blood coagulation control: the maximum acceptable inter-national normalized ratio (INR) for a patient taking warfarin depends on the operation (e.g. cataract < 3.5, eyelid procedures < 2). Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin should not be stopped for cataract surgery but should be stopped at least 10 days before surgery for eyelid procedures.

Starvation: the patient should be starved of solids for 6 hours before surgery and of clear fluids for 2 hours.

Prophylaxis for deep vein thrombosis: mechanical devices such as compression stockings, calf compressors and ankle elevators are useful. Heparin is usually avoided unless the patient is at high risk, especially for retinal and oculoplastic procedures.

Diabetic control: patients with diabetes should be given local anaesthesia if possible. If they have to be given general anaesthesia, their operation should be scheduled for early on the operating list and their morning hypoglycaemic tablet omitted. It is usually possible for patients to eat and drink soon after surgery, therefore it may be necessary for patients to omit only their morning insulin dose.

Drug treatment should be continued in most patients, especially cardiac drugs, antihypertensives, bronchodilators and cortico-steroids. It should be borne in mind that eyedrops and other ophthalmic drugs have systemic effects (Figure 2).

Systemic effects of ophthalmic drugs

Drug	Effect
β-blockers	Hypotension, bradycardia, bronchoconstriction
Phenylephrine	Hypertension
Acetazolamide	Hypokalaemia
Ecothiopate	Prolonged action of neuromuscular junction blockers broken down by pseudo-cholinesterases

2

Premedication may be required. Give the patient anti-emetics if they have a history of postoperative nausea or vomiting (PONV) or if they are having an emetogenic operation. Antihistamines (H_2-blockers) should be considered if gastric acidity or oesophageal reflux are problems, particularly if a laryngeal mask airway (LMA) is to be used. Anxiolytics may be given if needed, but should be avoided for day case surgery. Antimuscarinics should be given to children having ketamine for glaucoma screening. Topical anaesthetic cream should be used for children and patients with needle phobia.

Marking the side: the surgeon must mark the correct side for surgery before the patient leaves the ward. This is rechecked on arrival in the theatre suite and again in the anaesthetic room before induction. The eye that does not require surgery is taped closed after induction. The surgeon and scrub nurse should check which eye requires surgery for a final time just before cleaning the eye in the theatre.

Induction and maintenance of anaesthesia

Airway control

A mask is required for brief procedures only and avoids airway stimulation. The LMA is the ideal airway for most ocular procedures. Insertion and removal of a tracheal tube causes more cardiovascular stimulation than an LMA. Breath-holding, laryngospasm, bronchospasm and coughing are all less likely using an LMA. However, access to the airway during surgery is not easy without serious disturbance to the surgical field, therefore the LMA must be well positioned and stable before surgery starts. If there is any doubt about the reliability of the LMA position, it is safest to intubate the trachea.

Tracheal intubation is required in:

- the obese
- long procedures
- potential airway soiling – nasal bleeding from lacrimal surgery and mucous membrane graft material harvesting from inside the mouth (lower lip or palate)
- LMA failure
- infants having medium to long operations
- low chest compliance with high airway inflation pressures.

A preformed caudally directed, or an armoured flexible, tracheal tube taped away from the eyes, is ideal.

Intraocular surgery requires intermittent positive-pressure ventilation (IPPV). It allows accurate control of expired carbon dioxide and therefore intraocular blood volume and, to a lesser extent, intraocular pressure. Muscle relaxants are not usually required with the LMA if total intravenous anaesthesia is used. Some patients undergoing total intravenous anaesthesia do not maintain their eyes in the neutral position, they either look up or have a divergent squint. This can happen despite adequate depth of anaesthesia with total intravenous anaesthesia and sometimes a small dose of non-depolarizing muscle relaxant (rocuronium, 10–20 mg, in an adult) is required to correct it and allow surgery. If muscle relaxants must be avoided the surgeon can use a traction suture to return the eye to a neutral position.

Intravenous fluids

Provided there is little if any blood loss there is no need for intra-operative fluids other than maintenance crystalloid solutions. A full bladder causes hypertension and elevates intraocular pressure.

Anaesthetic maintenance drugs

Most standard methods of maintaining anaesthesia are possible. Either of the following work well for almost any combination of ocular operation and patient:

- LMA – remifentanil (Figure 3) + propofol / oxygen / air
- tracheal tube – remifentanil + sevoflurane / oxygen / air ± muscle relaxant for intubation.

The relatively unstimulating nature of most ophthalmic surgery can cause problems during general anaesthesia. Patients often become hypotensive, and sympathomimetics (e.g. ephedrine, methoxamine) should be used to maintain blood pressure and heart rate. On the other hand, awareness and patient movement are hazards if a proper level of anaesthesia is not maintained. In particular, accidental movement of the tracheal tube by the surgeon can cause coughing. The use of a peripheral nerve stimulator can be more of a stimulus than the operation (particularly anterior segment procedures) and can induce movement or coughing.

The benefits of using remifentanil for ocular surgery

- Produces stable, low and controllable blood pressure and heart rate and therefore intraocular pressure
- Rapidly titratable to patient needs
- Avoids need for maintenance muscle relaxants
- Rapid and unique recovery profile with no residual effects
- Dose and duration of infusion have almost no effect on recovery – ideal for long operations
- Low incidence of nausea – particularly with propofol
- Avoids use of nitrous oxide in vitrectomy with gas injection
- Well tolerated in patients with renal and hepatic disease

3

Monitoring

Spirometry is useful to identify changes in the position of an LMA during surgery. Increased peak airway pressure, decreased compliance, reduced tidal volumes and a difference between inspired and expired tidal volume should be sought. Invasive arterial pressure monitoring is useful if profound induced hypotension is required. Central venous pressure monitoring is seldom required. There is an association between malignant hyperpyrexia and oculomuscular abnormalities, however, the usual problem is hypothermia, which may cause shivering postoperatively. Postoperative shivering is most common after long procedures in young fit males having total intravenous anaesthesia. Intravenous pethidine is useful to abolish shivering. It is important to monitor the skin or nasopharyngeal temperature. Warming mattresses, warm air blowing devices and circle breathing systems may be used to maintain body temperature. There is seldom any need to expose the body below the neck, therefore patients can often be kept warm with blankets.

Postoperative management

Pain: NSAIDs and paracetamol/codeine mixtures are usually adequate to control pain. The surgeon can perform a sub-Tenon's local anaesthetic infiltration towards the endof surgery to provide good postoperative analgesia. Severe pain and nausea may result from raised intraocular pressure. This may be caused by a specific surgical complication and the patient should be examined by the operating surgeon rather than be treated for the symptoms. Intraocular pressure can be reduced in the short term by acetazolamide, 500 mg intravenously over 5 minutes, or mannitol, 1 g/kg intravenously over 30 minutes.be treated for the symptoms. Intraocular pressure can be reduced in the short term by acetazolamide, 500 mg intravenously over 5 minutes, or mannitol, 1 g/kg intravenously over 30 minutes.

Extubation is probably best performed deep with spontaneous breathing. It is important that the patient avoids coughing and straining on the tracheal tube.

Posture: after vitrectomy with injection of intraocular gas, the patient will have to posture as soon as they are conscious. A face-down position or with 'one cheek to pillow' is usual. Following oculoplastic surgery, patients are usually nursed in a sitting position.

Specific considerations for surgical subspecialties

Vitreo-retinal
Scleral buckle with or without cryotherapy:pain, PONV, and oculocardiac reflex are often marked, especially in young adults.

Vitrectomy: (the type of gas injected after vitrectomy, to provide retinal tamponade, depends on the required duration of action: Figure 4.) The patient will have to posture postoperatively so that the gas bubble lies over the appropriate area of the retina. Since the introduction of heavy perfluorocarbon liquids in vitreo-retinal surgery, the need for intraoperative posturing (including turning the patient prone) has been eliminated. Patients must not travel by aeroplane nor be exposed to nitrous oxide while the gas bubble is present. Nitrous oxide is 34 times more soluble in blood than nitrogen. Administered nitrous oxide rapidly diffuses into the intraocular gas bubble leading to a large increase in bubble volume and intraocular pressure, which may cause central retinal artery occlusion and blindness. If nitrous oxide is used during the anaesthetic for vitrectomy it must be discontinued at least 15 minutes before gas bubble injection.

Gases used for retinal tamponade

Gases used (all non-expansile)		Time in eye until bubble clears
Air		2–3 days
SF_6	20% (with air)	2–3 weeks
C_3F_8	14% (with air)	55 days (± 15)

Oculoplastics
Oculoplastic operations are often undergone by the elderly, or children with syndromes such as Goldenhar's. Antiplatelet drugs must be stopped for 10 days before these procedures, particularly eyelid surgery.

Orbital
Blood loss is possible during major orbital surgery, such as three wall orbital decompression procedures for thyrotoxic exophthalmos, and tumour resections. Transfusion of blood is seldom required, but induced hypotension with head-up positioning and maintenance of low to normal arterial carbon dioxide tensions all help to improve the surgical field and reduce bleeding. Retrobulbar or sub-Tenon's local anaesthetic infiltration is useful during enucleation surgery to reduce postoperative pain.

Glaucoma
In patients with glaucoma, reduction of the intraocular pressure is desirable. All anaesthetic agents except ketamine and suxamethonium reduce intraocular pressure. Local anaesthetic injection can further compromise optic nerve function and retinal perfusion by increasing intraocular pressure in patients with advanced glaucoma. Intubation (and extubation) of the trachea, can cause rises in intraocular pressure of up to 50 mm Hg. LMA insertion is much less stimulating and should be used if possible.

Cataract
Cataract operations are short and the surgical stimulus is low, therefore they are usually carried out under local anaesthesia. The use of LMA and total intravenous anaesthesia is good for anterior segment surgery.

Commonly mentioned topics

The oculo-cardiac reflex
Operations associated with the oculo-cardiac reflex include:
• squint
• scleral buckle retinal repair
• orbital implant
• evisceration
• enucleation.

The oculo-cardiac reflex is mediated via the trigeminal afferent with vagal efferent. It manifests as a slowing in the sinus rate, which may become irregular. Sinus arrest with asystole can occur but recovers when the precipitating cause (usually a surgeon pulling on the muscle) is abolished. Other arrhythmias that may be seen include atrioventricular junctional rhythms, wandering pacemakers, extrasystole and bigeminy.

Prophylactic antimuscarinic drugs (glycopyrrolate, 3–5 μg/kg, or atropine, 10 μg/kg) should be given after induction before the operations listed above, particularly if the patient is having total intravenous anaesthesia or other drugs that increase vagal tone. This pretreatment will reduce the chance of bradycardia not abolish it. Further doses may be required.

Local anaesthetic infiltration around the muscles abolishes the afferent pathway. Non-depolarizing muscle relaxants also reduce the incidence of the reflex by reducing extraocular muscle tone. There is a decrease in incidence with increasing age.

The 'open eye'
In an open eye the intraocular pressure is the same as atmospheric pressure. The danger is of expulsion of ocular contents. It is seldom necessary to operate as an emergency. Penetration of the eye by copper fragments may be an exception, but even then a delay for stomach emptying is usually possible. Do not try to empty the stomach with a nasogastric tube. An LMA can be used for open eye surgery, subject to the restrictions mentioned above.
• Avoid ketamine and suxamethonium, which increase intraocular pressure.
• Aim for a smooth, rapid induction. Rocuronium, 1 mg/kg, is suitable for muscle relaxation.
• Some degree of head-up tilt may be maintained during induction.
• Avoid mask pressure directly on the eye.
• Do not rush intubation. Wait for the induction drugs to have full effect.
• Coughing, straining or gagging during premature intubation attempts can lead to loss of ocular contents.

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Local Anaesthesia for Ocular Surgery

Caroline Carr

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Most surgery of the eye and its surrounding structures can be performed under local anaesthesia. General anaesthesia is reserved for those unable to cooperate (e.g. children), for bilateral surgery, and for extensive or lengthy procedures. Routine cataract surgery is usually performed under local anaesthesia and efforts have been concentrated on finding methods that have few serious complications. Traditionally, the surgeon administered the ocular anaesthesia as operator–anaesthetist. Recognition of occasional serious systemic complications of ophthalmic local anaesthesia, especially in medically compromised patients, led to involvement of the anaesthetist. The Joint Working Party report on Anaesthesia in Ophthalmic Surgery recommended the involvement of the anaesthetist, including performing the local anaesthetic.

Anatomy

With any local anaesthetic technique a detailed knowledge of anatomy is essential; that is beyond the scope of this article but the relevant areas are mentioned below.

The orbit may be visualized as a quadrilateral pyramid lying on its side. The open base forms the orbital rim at the front of the skull and the apex lies at a depth of 40 mm. The optic canal and superior orbital fissure open into the apex and admit the nerves and blood vessels of the orbit. The tip of the 40 mm needles used in traditional retrobulbar blocks could reach those vital structures at the orbital apex.

The globe is roughly spherical, with an average diameter of 24 mm and is suspended in the orbit by connective tissue. It is displaced towards the orbital roof and to the temporal side and projects anteriorly beyond the orbital rim. Needles placed medially and inferiorly in the orbit are less likely to penetrate the globe. The optic nerve pierces the globe medially to the posterior pole. The equator is midway between the two poles.

The extraocular muscles: the four rectus muscles originate at the apex of the orbit and insert into the globe behind the limbus, forming a cone within the orbit. The superior oblique muscle originates at the orbital apex and passes through the trochlear pulley on the medial side of the orbital roof behind the rim before passing back to insert on the globe. Needles should be avoided in this area to prevent trochlear damage. The inferior oblique muscle originates at the front of the orbit, on the medial side of the floor, and passes back and up between the lateral rectus and the globe before inserting. Inferomedial needle placement should be avoided to prevent muscle damage.

Orbital connective tissue: Tenon's capsule is a thin membrane of elastic fibres enveloping the globe from limbus to optic nerve. It adheres closely to the sclera with fine bridging fibres. All structures that attach to or pierce the globe cross the sub-Tenon's space including the long and short ciliary nerves. Local anaesthetic placed in this space provides globe anaesthesia. The globe is supported anteriorly by connective tissue slings passing from Tenon's capsule to the orbital wall. Posteriorly it is supported by a diffuse matrix of connective tissue from the sheaths of the extraocular muscles. All the connective tissue is embedded in fat. The connective tissue system allows local anaesthetic solution placed in the orbit to diffuse throughout the contents to provide anaesthesia of sensory and motor nerves.

The orbital blood vessels: the ophthalmic artery is a branch of the internal carotid and supplies the globe, orbital contents and neighbouring structures of the nose and forehead. It enters the orbit through the optic canal, crosses over the optic nerve to run medially in the orbit as it sends out branches to the contents. Venous plexuses on the medial wall and floor of the orbit drain via the superior and inferior ophthalmic veins through the superior orbital fissure into the cavernous sinus. Needles must be placed with care in the medial side of the orbit to avoid these vessels.

The nerve supply to the orbit: motor innervation is from cranial nerves III, IV, VI and VII (Figure 1). Sensory innervation is via the ophthalmic and maxillary divisions of cranial nerve V (Figure 2). Parasympathetic innervation is through fibres in cranial nerves III and VII. Sympathetic innervation is from the superior cervical ganglion. The optic nerve is cranial nerve II.

Motor innervation of the eye

Muscle	Nerve supply
Inferior oblique	Oculomotor (III)
Superior rectus	Oculomotor (III)
Inferior rectus	Oculomotor (III)
Medial rectus	Oculomotor (III)
Levator palpebrae superioris	Oculomotor (III)
Superior oblique	Trochlear (IV)
Lateral rectus	Abducens (VI)
Orbicularis oculi	Facial (VII) temporal and zygomatic branches

1

Sensory innervation of the eye

Structures	Nerve supply
Sclera, cornea, iris and ciliary body	Short ciliary nerves Long ciliary nerves
Conjunctiva – superior	Supraorbital nerve Supratrochlear nerve Infratrochlear nerve
Conjunctiva – inferior	Infraorbital nerve
Conjunctiva – lateral	Lacrimal nerve
Conjunctiva – limbal	Long ciliary nerve
Periorbital skin	Supraorbital nerve Supratrochlear nerve Infraorbital nerve Lacrimal nerve

2

The eyelids: the orbicularis oculi muscle is a flat elliptical muscle surrounding the orbital margin, which closes the eyelids. The levator palpebrae muscle opens the upper eyelid. It originates at the orbital apex and passes forward between the orbital roof and superior rectus to fan out to insert into the upper eyelid.

Methods of local anaesthesia

Topical
Topical anaesthesia provides good surface anaesthesia of the globe without the complications of a regional block. The patient retains full eye movement. Commonly used for superficial surgery of the conjunctiva and cornea, including removal of sutures and small foreign bodies, topical anaesthesia alone is now often used for cataract surgery. With the newer surgical techniques, akinesia and reduction of intraocular pressure are not of such importance. Patients experience discomfort owing to sensation from the iris and ciliary body but this can be abolished by intracameral preservative-free 1% lidocaine (lignocaine), up to 1 ml.

Infiltration
Local infiltration of the skin with anaesthetic is used for eyelid surgery in adults. For anaesthesia of deeper structures, the supraorbital and infraorbital branches of the trigeminal nerve are blocked where they emerge from the supraorbital notch and infraorbital foramen. 0.5% bupivacaine, 1–2 ml, with adrenaline (epinephrine) 1:200,000 are injected subcutaneously at each site. To avoid subcutaneous haemorrhage:

- aspirin should be stopped 2 weeks preoperatively
- warfarin should be stopped 3 days preoperatively
- avoid injection into deeper tissues
- use adrenaline (epinephrine) 1:200,000 as a vasoconstrictor in the local anaesthetic solution.

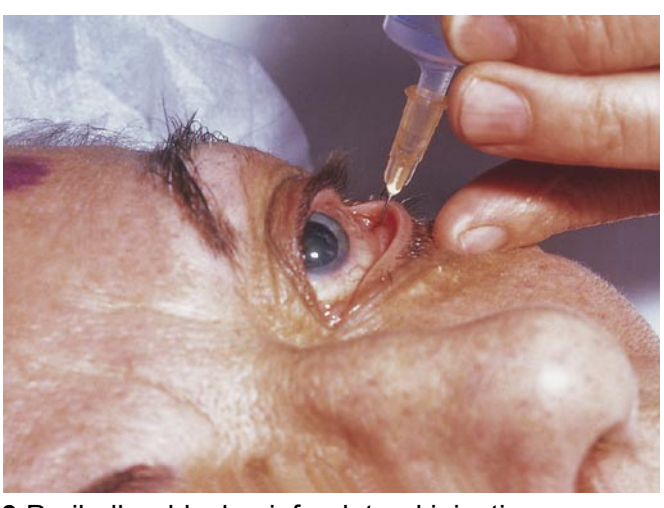
Retrobulbar block
The classical technique of retrobulbar block provided good akinesia and anaesthesia and was usually supplemented with a facial nerve block to paralyse orbicularis oculi. The principle of the technique was to deposit a small volume (2–3 ml) of anaesthetic solution in the muscle cone at the apex of the orbit using a 40 mm long needle. Rare, but serious, complications occurred with these blocks, including retrobulbar haemorrhage, globe perforation, damage to the optic nerve or ophthalmic artery and spread of the anaesthetic to the brain stem along the optic nerve dural sheath.

Peribulbar block
Peribulbar anaesthesia was introduced in 1986 to avoid the complications of retrobulbar block. A shorter needle is used and places larger volumes of anaesthetic solution outside the muscle cone with the needle tip no further back than the equator. The anaesthetic spreads throughout the orbit and provides satisfactory operating conditions. The technique usually consists of two injections of local anaesthetic, one inferior and one medial to the globe. These sites are selected to avoid vital structures within the orbit. The volume used is usually enough to block the nerves to orbicularis oculi directly. More recent adaptations of the technique have been to direct the lateral injection up into the muscle cone just behind the globe. This produces a more rapid and reliable onset of block with a smaller volume of anaesthetic solution, and often the medial injection is omitted. This is the 'modern retrobulbar' technique. However there is still a risk of globe perforation.

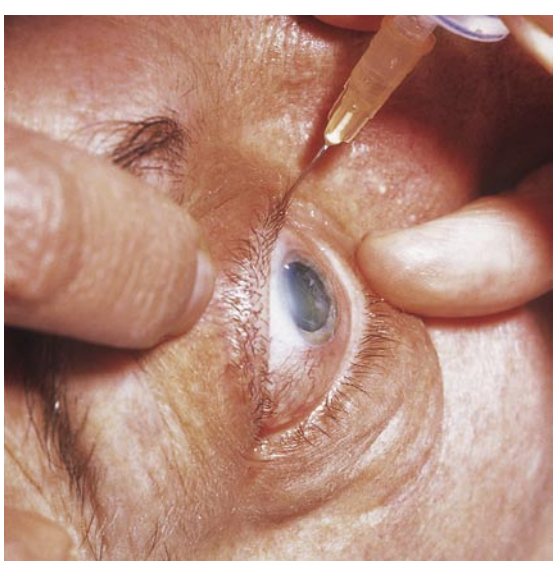
Technique of peribulbar block (Figures 3 and 4)

- The patient lies supine with his head on a pillow.
- The eyes are in neutral gaze.
- A few drops of topical anaesthetic are applied to the conjunctiva (0.4% oxybuprocaine).
- The inferotemporal injection is given first, using a 25 G 25 mm sharp needle and 5 ml of anaesthetic solution.
- Insert the needle through the conjunctiva, 2 mm away from the globe, midway between the lateral canthus and the lateral limbus.
- Keep the needle tangential to the globe and advance posteriorly and medially to a depth of 15 mm. Keep the needle tip lateral to the sagittal plane of the lateral limbus.
- Following test aspiration, slowly inject 2–5 ml of anaesthetic. Assess orbital tension digitally.
- Withdraw the needle, close the patient's eye and maintain gentle pressure for 2 minutes.
- Give the medial injection using a 25 G 12 mm needle.
- Insert the needle medial to the medial caruncle, with the needle bevel facing medially.
- Advance posteriorly at 90° to the face to the depth of the needle hub.
- Initial resistance may be felt at the medial check ligament.
- Following aspiration, slowly inject 2–5 ml of anaesthetic, assessing orbital tension.
- Withdraw the needle, close the patient's eye and maintain gentle pressure for 5–10 minutes.
- Assess the block and for hypotony for intraocular surgery apply an oculopressor device for 10 minutes.

Any technique using a blindly placed sharp needle may result in serious complications threatening sight, including globe perforation. The more recently described technique of sub-Tenon's block is now commonly used for most surgery on the globe.



3 Peribulbar block – inferolateral injection.

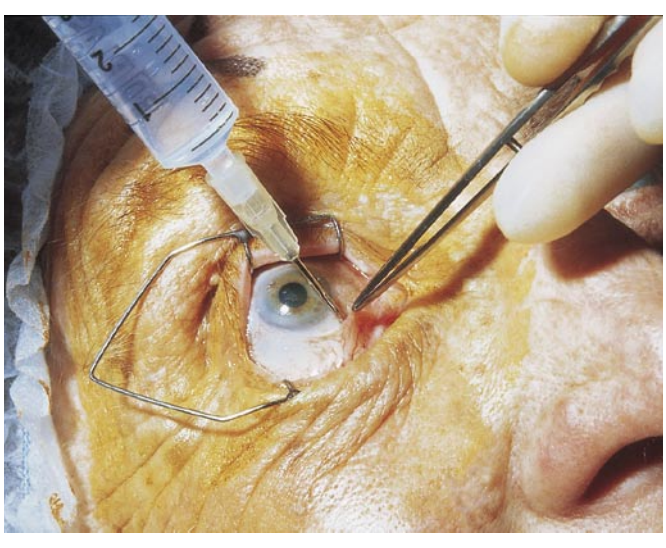


4 Peribulbar block – medial injection.

Sub-Tenon's block
Local anaesthetic is introduced to the sub-Tenon's space through a small incision in the inferior nasal quadrant of the eye. Posterior diffusion of the anaesthetic blocks sensation from the eye by direct action on the ciliary nerves as they pass through the sub-Tenon's space. If a suitable volume of anaesthetic is used, complete akinesia is obtained as it diffuses into the muscle cone from the sub-Tenon's space.

Technique of sub-Tenon's block (Figure 5)
- The patient lies supine with his head on a pillow.
- A few drops of topical anaesthetic are placed on the conjunctiva.
- A few drops of 5% aqueous iodine are placed on the conjunctiva.
- A small speculum is inserted to hold the eyelids apart.
- The patient looks up and laterally.
- The conjunctiva and Tenon's capsule are pinched firmly with non-toothed forceps 5–7 mm from the limbus in the inferonasal quadrant.
- With round-ended spring scissors a small snip is made through both layers.
- The closed scissor tips are passed through the hole and the blades opened while gently withdrawing them to form a short tunnel.
- A blunt curved 19 G 25 mm sub-Tenon's cannula is passed into the sub-Tenon's space and allowed to slide round the globe, over the sclera to a depth of 15–20 mm in the inferonasal quadrant.
- Up to 5 ml of local anaesthetic is injected slowly.
- The cannula is withdrawn and slight pressure maintained over the closed eye for 2 minutes, when complete akinesia and anaesthesia are seen.
- Sub-conjunctival haemorrhage is kept to a minimum by using topical adrenaline (epinephrine) 1:10,000, avoiding cutting conjunctival vessels, avoiding extensive dissection and using gentle direct pressure.

Globe perforation has not been reported with this technique and it is often used as the technique of choice in the long myopic eye. One case of retrobulbar haemorrhage has been reported and the anaesthetist must always be aware of this risk with any needle or cannula technique of ocular block.



5 Sub-Tenon's block.

The local anaesthetic mixture
The characteristics of a block depend on the anaesthetic solution used as well as the technique. 2% lidocaine (lignocaine) is effective within 5 minutes and gives 30–40 minutes of surgical anaesthesia. 0.5% bupivacaine has a slower onset of action but longer duration of surgical anaesthesia (up to 4 hours). The newer local anaesthetic ropivacaine has been used successfully in peribulbar blocks but has little advantage over bupivacaine in the small volumes needed in eye blocks. Mixtures of lidocaine (lignocaine) and bupivacaine are often used to provide rapid onset with delayed offset but are of no practical advantage. Addition of 1:200,000 adrenaline (epinephrine) reduces haemorrhage in skin infiltration techniques but is not used in orbital blocks because the vasoconstriction may compromise retinal blood flow. The enzyme hyaluronidase in concentrations of 5–30 iu/ml enhances spread of anaesthetic and speed of onset.

Patient management

Preoperative assessment is performed as for any anaesthetic. The patient's concomitant medical conditions should be controlled before surgery. Contraindications to ocular local anaesthesia are patient refusal, being unable to lie flat and still for the surgery, and allergy to local anaesthetic. The technique to be used should be explained carefully and supplemented with leaflets and other patients' experiences. Preoperative starvation is unnecessary unless the patient is at high risk. Anticoagulated patients must maintain their international normalized ratio (INR) within therapeutic limits (2–3) for ocular surgery under topical, peribulbar or sub-Tenon's anaesthesia. During surgery the patient should have intravenous access and pulse oximeter, ECG and non-invasive blood pressure monitoring should be available if required. Trained staff should monitor the patient and the anaesthetist should be available for resuscitation or sedation – this is a controversial point because of manpower implications.

Sedation
Most patients readily tolerate ocular surgery under local anaesthesia with careful explanation, gentle handling and a sympathetic approach. Occasionally, an anxious patient may require sedation. An anaesthetist provides this with the appropriate monitoring. Various techniques may be used. A small dose of intravenous midazolam, 0.5–1.5 mg, before the anaesthetic provides amnesia while allowing verbal communication.

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Ophthalmology and Anaesthesia

Luke Herbert

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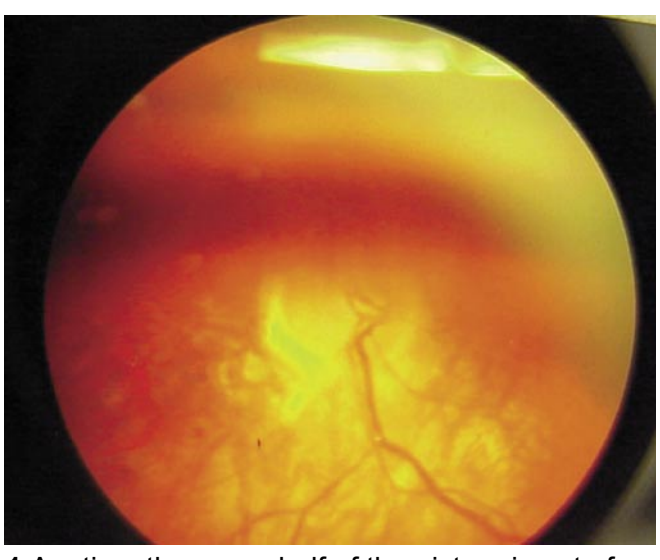
Possible eye problems in theatre

Intraocular gas
As part of the management of retinal detachment and some other retinal conditions, long-acting gas is injected into the vitreous cavity (Figure 1). The surface tension of the gas/fluid interface is used to close holes in the retina. However, the gas bubble has to be positioned correctly and lying on the back is usually contraindicated.

The wrong management of patients with gas-filled eyes can cause blindness. Several different gases can be used, the most persistent of which, C_3F_8, can remain in the eye for 3 months. The gases are poorly soluble and remain in the vitreous cavity, in equilibrium with, mainly, nitrogen. However, if a very soluble gas (e.g. nitrous oxide) is inhaled, there is a massive influx of gas into the eye. This can cause the intraocular pressure to rise rapidly, which can lead to blindness. Patients with gas in the eye must never be given nitrous oxide as part of anaesthesia. A typical situation in which this might occur is when the patient has ophthalmic surgery with long-acting gas injection and after discharge from the eye unit, develops an acute surgical problem such as acute retention of urine. The patient is then anaesthetized with nitrous oxide at a different unit, and wakes up blind.

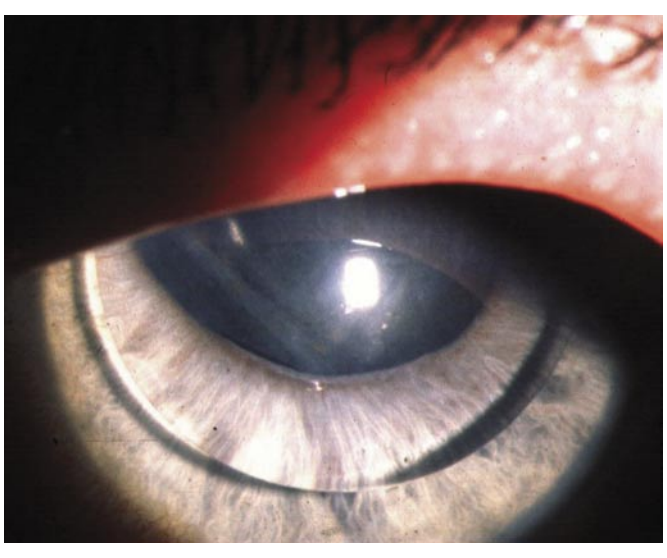
Some surgeons are also concerned about the use of nitrous oxide in the primary surgery. If an eye is filled with gas, which the surgeon expects to be say, 16% C_3F_8 in air, but the patient is anaesthetized with nitrous oxide, a large portion of the volume will be taken up by the volume of the nitrous oxide. When the patient resumes breathing room air the nitrous oxide rapidly leaves the eye, leaving the globe soft and vulnerable to minor trauma, and reducing the amount of gas in the eye thus reducing the duration of gas fill.

The total volume of gases in the eye tends to increase in the early postoperative period as nitrogen diffuses in to the eye but C_3F_8 (which is poorly soluble) diffuses out slowly. This can lead to raised intraocular pressure. It is important not to ignore pain as a symptom of high pressure after surgery.



1 A retina: the upper half of the picture is out of focus because there is a bubble of gas in the eye.

Silicone oil
In some patients, silicone oil is used instead of gas to plug holes in the retina. Silicone oil floats in the eye. If the patient lies flat on their back, oil can float into the anterior chamber of the eye (Figure 2), which can cause severe long- and short-term problems.



2 Oil has come into the anterior part of the eye and forms a round globule in front of the iris and lens.

Odd-looking eyes
A patient waking with a fixed dilated pupil, a divergent squint and a glassy appearance to the eye may have a prosthetic eye. Ask the patient about this before anaesthesia – it is not always easy to recognize a glass or plastic eye. Prosthetic eyes and their sockets are unsterile, and organisms colonizing prosthetic sockets have infected remote surgical sites.

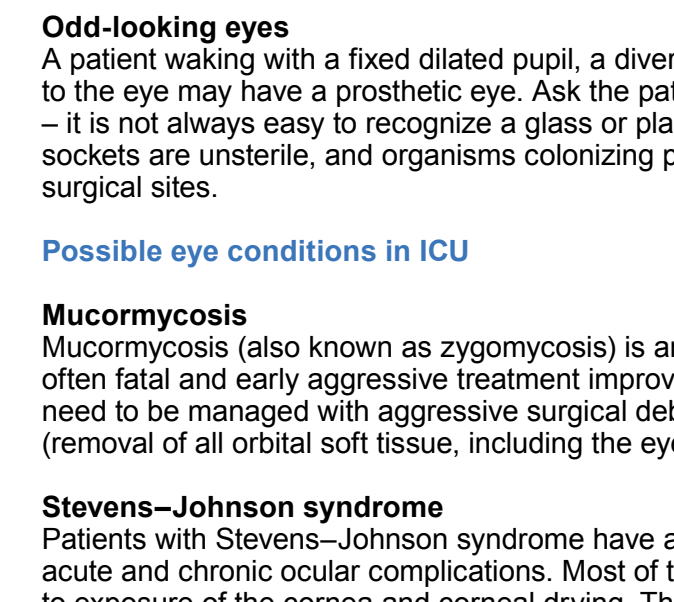
Possible eye conditions in ICU

Mucormycosis
Mucormycosis (also known as zygomycosis) is an uncommon fungal disease. It is often fatal and early aggressive treatment improves outcome. Orbital involvement may need to be managed with aggressive surgical debridement including orbital exenteration (removal of all orbital soft tissue, including the eye).

Stevens–Johnson syndrome
Patients with Stevens–Johnson syndrome have acute conjunctivitis that can lead to acute and chronic ocular complications. Most of the acute complications are related to exposure of the cornea and corneal drying. These can be prevented with physical barriers such as simple eye ointment, used copiously every 3–4 hours, or frequent use of lubricating drops (e.g. hypromellose 0.3% or normal saline, given every 30–60 minutes). Drops given so frequently are best used unpreserved to prevent local toxicity caused by preservatives. These drops may not be available in general hospitals in which case normal saline for intravenous use can be used. The solution should be kept cool, and discarded every day.

Chronic complications include scarring of the conjunctival surface. Previously, lysis of nascent scars was encouraged in the acute phase, breaking down conjunctival adhesions with a glass rod, but there is little evidence that this is of benefit. Many ophthalmologists prescribe corticosteroid drops in the acute phase, but there is little evidence of long-term benefit. Occasionally, the noninfected conjunctivitis can become secondarily infected with a sudden increase in the purulence of the secretions; this requires urgent ophthalmic attention.

Fungal endophthalmitis
Systemic fungal infections, typically with *Candida albicans* and occasionally *Aspergillus* spp. can metastasize to the choroid and vitreous cavity causing a fungal endophthalmitis (Figure 3). Patients with long-term intravenous line placement are at particular risk of fungal endophthalmitis. They present with pain, decreased vision and floaters. Many patients with systemic fungal infections do not develop endophthalmitis, and many patients with endophthalmitis show no other signs of infection, especially those who are transiently immunocompromised. *Candida* infections may resolve with systemic treatment alone, usually with oral fluconazole. In patients with advanced involvement of the vitreous, vitrectomy should be carried out to debulk the fungal load and remove the vitreous, which acts as a substrate for further fungal growth. An extended course of treatment is required. With appropriate management, most patients with *Candida* endophthalmitis will maintain some vision. The prognosis is not as good in *Aspergillus* endophthalmitis.



3 Fungal endophthalmitis; the fluffy white lesions are balls of fungus growing within the vitreous cavity.

Ophthalmic complications related to ICU care

Conjunctival oedema (chemosis)
Patients with low plasma oncotic pressure who lie on their back tend to accumulate fluid around the face. This can lead to profound swelling of the looser facial tissues, particularly around the eyes. The conjunctiva is bound to the underlying sclera by a weak meshwork of fibres. This potential space easily fills with tissue fluid causing the conjunctiva to balloon out. This is called chemosis and can be very striking, even preventing the eyelids from closing properly. Treatment is by raising the head of the bed. If the eyelids cannot close, the cornea should be protected with copious amounts of simple eye ointment to prevent drying and corneal exposure.

Corneal exposure
The cornea depends on tears, and the redistribution of tears and resurfacing of the tear film by blinking is essential. The production of tears is reduced when the patient is asleep or unconscious. When asleep, the eyelids can remain partly open, but in most people the Bell's phenomenon in which the eyes roll superiorly helps to protect the cornea from drying. In the anaesthetized, paralysed patient the cornea is vulnerable to drying, because tear production is low, the eyelids can open and the eyes remain in the primary position.

The corneal epithelium and even the conjunctival epithelium cannot survive dry for long. The cornea soon develops small dry spots of dead or dying epithelial cells, known as exposure keratitis. With continued dryness or other insults, these areas lose their epithelium to become corneal erosions, also called abrasions (Figure 4). Once the epithelium is lost the cornea is vulnerable to infection (the conjunctival sac is never sterile) and frank corneal ulcers can develop. This can be a problem in the high-dependency setting where the author has seen febrile, unconscious patients with fans thoughtfully placed to remove the last drops of moisture from the eye. The cornea should be protected with ointment and taping.

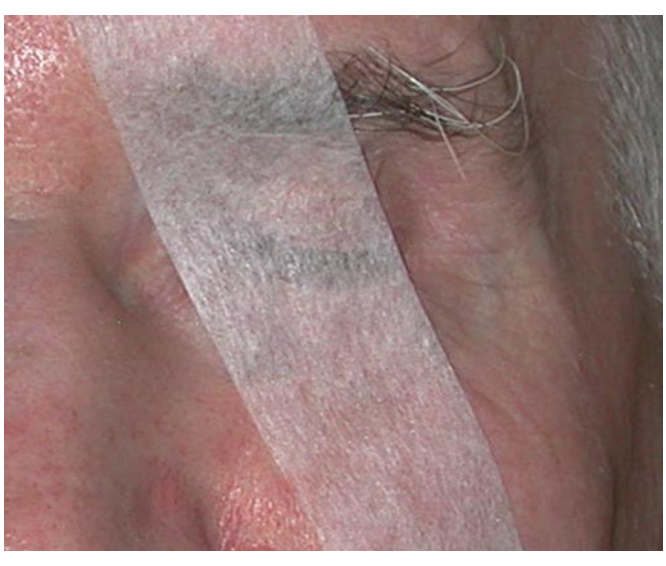
This chronically exposed eye has developed a corneal ulcer (**a**). The edges of the corneal ulcer are stained bright yellow (**b**) with fluorescein dye.

4

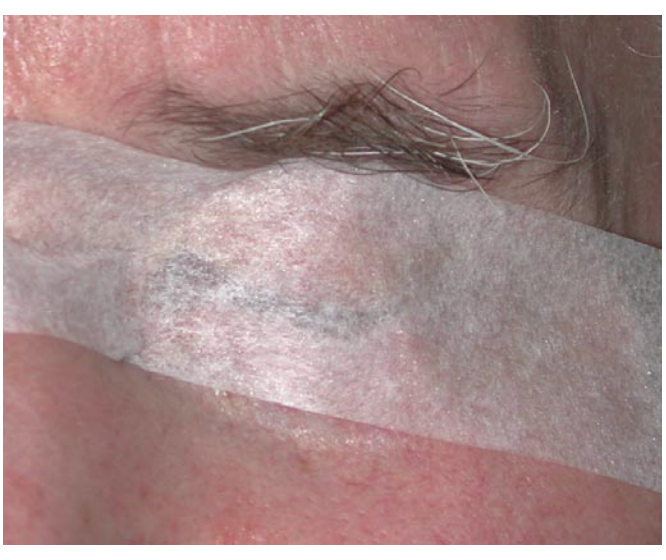
Corneal abrasion
The anaesthetist has to help protect the patient's cornea from drying and trauma otherwise a corneal abrasion may develop. Abrasions are exquisitely painful; the eye is usually red and the vision may be slightly blurred. However, they heal rapidly, and the pain should reduce within the first day of treatment.

Taping the eye: one way to protect the cornea is to tape the eyelid shut. Taping vertically across the eyelid is unhelpful, because the eyelid can open under the tape and the cornea can rub on the tape (Figure 5). The correct way to tape is from corner to corner (Figure 6).

Venturi masks, if they are badly placed**,** can cause corneal abrasions and corneal infection in debilitated patients. It is common on chronic wards to see the Venturi mask pushed off so that an edge rubs on the eye (Figure 7).



5 The wrong way to tape an eyelid shut.



6 The right way to tape an eyelid shut.

7 Venturi mask pushed off allowing an edge to rub the eye (this picture was posed, but this does happen).

Acute angle closure glaucoma
Anticholinergic agents allow the pupil to dilate and in susceptible patients this can lead to acute angle closure glaucoma. This is more common in older patients who have not had cataract surgery. The signs are of a mid-dilated pupil that does not react (direct or consensual) to light, a slightly dull sheen to the cornea and, in conscious patients, severe pain that can cause confusion and vomiting. Acute glaucoma is not related to chronic glaucoma. If a patient is already receiving treatment for glaucoma it is unlikely that they will suffer an attack because susceptible patients identified in an eye clinic usually have immediate prophylactic laser treatment or surgery.

Systemic problems caused by ophthalmic treatment

Eye drops
Most patients do not regard eye drops as medication and it is common for patients taking two or three eye drops to deny that they take any medication. Almost all eye drops have some systemic side-effects, and the most important are described below.

β-blockers: some topical β-blockers are relatively cardio-selective. All topical β-blockers precipitate asthma attacks in susceptible patients. All β-blockers reduce exercise tolerance and can precipitate heart failure. Most β-blockers are well know, the exception is *Cosopt*, which contains timolol 0.5% maleate.

α-agonists: adrenaline (epinephrine) used to be used as an antiglaucoma medication. It can precipitate angina and hypertensive episodes. Adrenaline (epinephrine) and its pro-drug, dipivefrine, are less fashionable now, but the new selective α_2-adrenoceptor agonists, brimonidine and apraclonidine, can act as systemic hypotensive agents in the same way as clonidine.

Pilocarpine is less commonly used now, but it used to be the mainstay of glaucoma therapy. It constricts the pupils, making assessment of pupillary function impossible. Pilocarpine worsens asthma in some individuals and is best not used in patients with severe reversible airway obstruction.

Latanoprost is a prostaglandin analogue used in glaucoma treatment. It can precipitate an attack in poorly controlled or brittle asthma.

Atropine is the prototype agent for the mydriatics, including homatropine, cyclopentolate and tropicamide. It is the agent most likely to cause problems in the ICU because of its long duration of action in the eye. Atropine is used for painful blind eyes, to ease ciliary spasm, to reduce pain in the postoperative period and to facilitate examination by keeping the pupil dilated. This fixed dilated pupil can be most disconcerting in an acute ICU setting because the dilating effects can take a week to wear off, particularly in darker eyes.

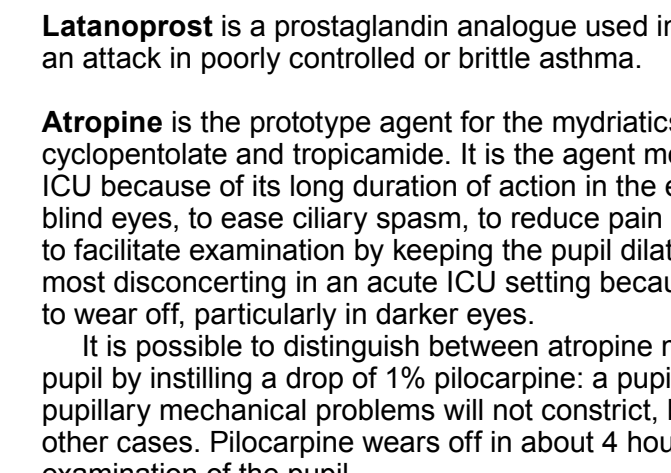
It is possible to distinguish between atropine mydriasis and a pathologically dilated pupil by instilling a drop of 1% pilocarpine: a pupil affected by atropine or by local pupillary mechanical problems will not constrict, but the pupil will constrict in all other cases. Pilocarpine wears off in about 4 hours, so it should not prevent further examination of the pupil.

Systemic medication
Corticosteroids: ophthalmologists do not use systemic corticosteroids often, but when they do, they tend to use high doses, particularly in temporal arteritis. Prednisolone, 80–100 mg/day, is prescribed, even in elderly patients, with all the usual corticosteroid side-effects.

Acetazolamide: some ophthalmologists routinely give the carbonic anhydrase inhibitor acetazolamide at the end of intraocular procedures as prophylaxis against intraocular pressure spikes. It is also used in some patients with chronic glaucoma refractory to treatment. The use of acetazolamide, even for a few days, causes hypokalaemia and a metabolic acidosis.

Posture
Long gone are the days when patients were immobilized for 2 weeks after cataract surgery. However, patients who have had retinal detachment surgery with gas injection or who have had macular hole surgery are often asked to posture for 50 minutes every hour.

These positions are often awkward (Figure 8) and this, combined with prolonged immobility after surgery, increases the risk of deep vein thrombosis. Ophthalmologists are very bad at considering the systemic effects of their surgery, and a little encouragement from anaesthetists might be useful.



8 Ophthalmologists can ask their patients to adopt this posture for up to 2 weeks

Orthopaedics

Anaesthesia
and intensive care medicine
on CD-ROM

Anaesthesia for Joint Replacement Surgery

Rachael Craven
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Joint replacement surgery is a common and effective procedure for the relief of disability due to severe joint pain and loss of function. The most common joints replaced are the hip, knee and shoulder, but with advances in technology and surgical techniques the range of joints that may be replaced is increasing. Most patients for joint replacement surgery have degenerative joint disease, commonly osteoarthritis. Other conditions necessitating joint replacement surgery include:

- rheumatoid arthritis
- osteoporosis and fracture
- metastatic lesions and pathological fractures
- avascular necrosis of the femoral head.

Most patients are elderly, and commonly have associated problems such as hypertension, ischaemic heart disease, chronic obstructive pulmonary disease (COPD) or renal disease. Younger people presenting for joint replacement surgery often suffer from rheumatoid arthritis, severe osteoporosis or obesity. Presentation for revision of previous replacement surgery is increasingly common.

Preoperative assessment

Problems in multiple systems are common because most patients are elderly. The problems of disease processes associated with orthopaedic conditions should also be considered; the most common is rheumatoid arthritis (Figure 1).

Problems associated with rheumatoid arthritis

Skeletal
- Instability of odontoid peg and atlanto-axial subluxation
- Restricted mouth opening due to temporomandibular joint involvement

Respiratory
- Rheumatoid lung nodules
- Pleural effusions
- Pulmonary fibrosis

Drugs
- Corticosteroids, non-steroidal anti-inflammatory drugs, gold and methotrexate may have significant systemic effects

Other
- Anaemia of chronic disease, pericarditis and amyloid deposits causing renal dysfunction

1

Assessment of co-morbidities

Cardiopulmonary reserve is most commonly estimated by assessment of exercise tolerance. However, this may be impossible or inaccurate because joint disease may limit exercise. In these circumstances the following may be used:

- lung function tests, arterial blood gases and oxygen saturation in air
- resting ECG for silent ischaemia or previous myocardial infarction
- echocardiography for left ventricular function, wall movement and valvular abnormality.

These tests are of limited relevance because they provide information only about the function of rested, rather than stressed, cardiopulmonary systems. Dobutamine stress tests provide information about cardiac function under stress but they are not readily available and have associated risks.

Renal function may be impaired owing to age, hypertension or chronic use of non-steroidal anti-inflammatory drugs (NSAIDs).

Musculoskeletal – other joint involvement is common. The range of limb and neck movements should be noted. Obesity may be a cause or consequence of degenerative joint disease. Assessment for positioning on the table and for regional blockade should be made. In patients with metastatic disease, the bone scan should be checked to ensure there are no spinal deposits that may interfere with regional anaesthesia.

Hip and knee replacement

Preoperative preparation

- Preoperative assessment should be carried out as above.
- Optimization of co-morbidities is required.
- Cross-matched blood must be available.
- Deep vein thrombosis (DVT) prophylaxis is required. If a regional technique is planned, ensure appropriate timing of low-molecular-weight heparin.
- Antibiotic prophylaxis (usually cephalosporin or aminoglycoside) is required.
- Invasive monitoring is seldom indicated unless there is significant cardiac disease or large blood loss is anticipated.
- Large bore intravenous access is required (sited in the non-dependent arm for laterally positioned patients).

Anaesthetic technique

Regional anaesthesia is probably the technique of choice because it:

- reduces blood loss, leading to a decreased need for bank blood and associated transfusion risks
- decreases bleeding at the operative site, improves cement bonding and decreases surgical time
- decreases the incidence of DVT and pulmonary embolus in hip and knee arthroplasty.

The reduction in blood loss seen with spinal anaesthesia, compared with general anaesthesia, is thought to be due to a combination of perioperative hypotension and a comparatively lower haematocrit level. There is a perception that regional anaesthesia reduces the incidence of postoperative confusion and cognitive dysfunction compared with general anaesthesia, but studies have failed to demonstrate this.

The decision to use neuraxial opiates usually depends on the presence of a resident anaesthetist, owing to the potential risk of delayed respiratory depression postoperatively.

Sedation is often desirable because of the duration of the operation, intraoperative noise and patient request. Patients positioned laterally for hip replacement may become restless and uncomfortable because of pain arising from the dependent shoulder. Intermittent midazolam, titrated in 1 mg increments, may be used but often causes intraoperative disorientation and confusion, resulting in patient movement. Increasingly popular is a target-controlled infusion of propofol, 0.5–2 μg/ml, which gives smoother, more titratable sedation. Oxygen should be administered throughout the operative period.

As sedation deepens, airway obstruction or snoring may occur. This is seldom a problem in the lateral position, but some supine patients may require a nasopharyngeal airway.

General anaesthesia: if general anaesthesia is indicated, bleeding may be reduced by modest hypotension in carefully selected patients, using volatile agents. Unless there is a risk of aspiration, spontaneous ventilation with a laryngeal mask airway is usually appropriate.

For hip arthroplasty, analgesia may be supplemented by the use of a 3-in-1 (femoral/obturator/lateral cutaneous of thigh) block. Some anaesthetists favour a lumbar plexus block because this also blocks the sciatic nerve, which has a component supplying the hip. For knee replacement a 3-in-1 block combined with a sciatic nerve block can be effective.

Intraoperative problems

Patient position: in the lateral position, there is a risk of excessive lateral neck flexion and pressure on the dependent limbs.

Hypothermia: orthopaedic theatres are often colder than other theatres, with a higher velocity airflow leading to more rapid patient cooling. Hypothermia may cause poor wound healing, infection, coagulopathy and cardiovascular dysfunction. Some surgeons are opposed to hot air warming devices because of the theoretical risk of increased wound infection, and a discussion of the balance of risks may be indicated. Fluid warmers, blankets and patient hats should be used routinely.

Blood loss: average blood loss in total hip replacement ranges from 300 to 1500 ml and may double in the first 24 hours post-operatively. During knee replacement surgery with an intra-operative tourniquet, most blood loss occurs in the recovery area. Careful fluid balance is essential because compensation for hypovolaemia is poor in the elderly. Provided normovolaemia has been maintained a haemocue can be used to guide blood transfusion requirements.

Cement reactions: prostheses may be cemented in place. At the time of cementing, a drop in blood pressure and oxygen sat-uration is often seen. This was originally thought to be caused by a directly toxic effect of the methyl methacrylate monomer component of the cement, but it is now known to be caused by a shower of microemboli of blood, fat or platelets forced into the circulation by high intramedullary pressure during cement packing and prosthesis insertion. Subsequent embolization to the lungs produces a raised pulmonary vascular resistance and reduction in left ventricular return, resulting in hypotension. The microemboli are toxic to the lung parenchyma causing haemorrhage, alveolar collapse and hypoxia. This may be severe enough to cause cardiovascular collapse, cardiac arrest and death. Reactions are more common and more severe in bilateral joint replacements and also in under-resuscitated patients; therefore it is vital to ensure that the patient is not hypovolaemic before cementing. Fractional inspired oxygen concentration may have to be increased. Cement reactions tend to be less common in knee replacement.

Thromboembolism is common after joint replacement. DVTs are more common following knee replacements than hip replacements. Following knee replacement, most DVTs are distal calf thromboses with a low risk of pulmonary embolus. In hip replacement surgery, extremes of movement at the hip and kinking of vessels lead to endothelial damage and blood stagnation. These thromboses tend to be of proximal veins with a higher risk of pulmonary embolus.

The use of a regional technique, low-molecular-weight heparin, graduated compression stockings or pneumatic compression boots decreases the risk of DVT. Intraoperative low-dose intravenous heparin reduces the incidence of DVT without increased bleeding but is not commonly used. A combination of the above techniques provides the best protection and the anaesthetist should ensure that the local thromboprophylaxis protocol has been followed.

Tourniquet: in some patients with cardiac disease the increase in systemic vascular resistance when the tourniquet is inflated has precipitated left ventricular failure. However, more of a problem occurs on releasing the tourniquet, when the acidic byproducts of metabolism are washed out of the limb causing hypotension secondary to vasodilatation and the effects of acidosis on cardiac contractility. In knee replacement surgery, as the duration of the operation increases, tourniquet pain can become a problem. Additional analgesia or epidural top-up may be required.

Postoperative management

Analgesia

Epidural analgesia is excellent, particularly in reducing quadriceps muscle spasm following knee replacements. However, there is an increased risk of urinary retention and the resulting catheterization may cause a bacteraemia, increasing the risk of prosthesis infection.

Patient-controlled analgesia is the choice in many institutions. Intramuscular opiates may also be considered.

Regular paracetamol, 1 g/6 hours, should be given orally or rectally.

NSAIDs should be used with caution especially in the elderly owing to the increased risk of renal impairment.

Midazolam infusions or baclofen are sometimes required to ease quadriceps muscle spasm.

Fluid balance: stringent fluid balance monitoring is mandatory because blood loss may double in the first 24 hours. Nausea may reduce the patient's oral intake.

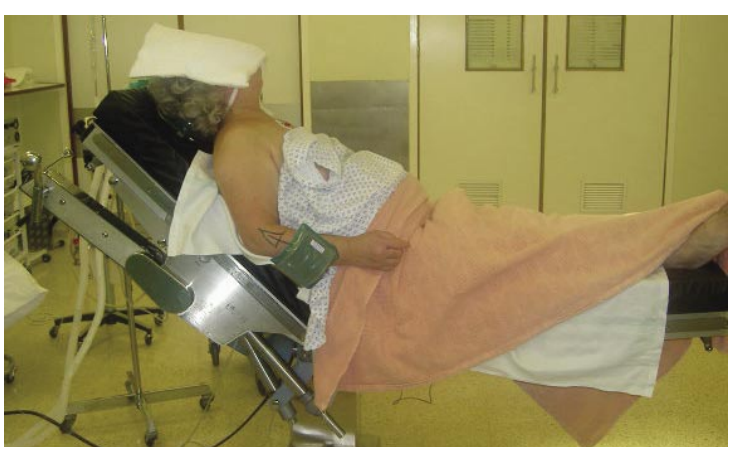
Oxygen: perioperative ischaemia is common and generally silent. Oxygen should be given for the first 72 hours postoperatively.

Shoulder replacement

Monitoring and intravenous access
Standard full patient monitoring is required. Large bore intravenous access is made on the non-operative side. Non-invasive blood pressure monitoring is instituted either on the non-operative side with a non-return valve on the intravenous line, or on the lower leg.

Anaesthetic technique
The most common technique is general anaesthesia using an armoured tracheal tube and positive-pressure ventilation. Selected patients may be managed satisfactorily using a spontaneous ventilation technique through an armoured laryngeal mask. Access to the patient's head intra-operatively is extremely restricted. The interscalene approach to brachial plexus blockade provides excellent intraoperative and postoperative analgesia and improves the operative conditions with decreased blood loss and good muscle relaxation. It commonly gives a unilateral phrenic nerve palsy, but this seldom causes alveolar hypoventilation even in spontaneously ventilating patients.

Patient position
The patient is placed in a sitting position, with a bolster behind the shoulder blades to improve surgical access (Figure 2). Care should be taken to ensure there is no excess strain on the lumbar spine. The torso should be securely strapped. Many tables are specially adapted with a built-in extension for the head ring, the height and angle of which may be adjusted.



2 The sitting position.

The head must be securely fastened because there will be considerable pull and movement at the shoulder. Access to the airway intra-operatively is difficult owing to the sitting position and the presence of surgical drapes; the tracheal tube must therefore be securely taped in place. The eyes should be taped and well padded.

Intraoperative problems
Elderly patients often have poor cardiovascular compensatory mechanisms while under general anaesthesia. At the start of the operation, while positioning the patient, a large drop in blood pressure may accompany the change from supine to sitting and vasopressors and a temporary return to a flatter position may be required. Patients are at risk of air embolism from open veins at the operative site.

Postoperative management
Shoulder replacements are extremely painful and, if possible, interscalene block should be used, supplemented with patient-controlled opiate analgesia. Regular paracetamol and NSAIDs (in those in whom they are not contraindicated) should also be prescribed.

Revision arthroplasty
As the number of active elderly people increases, more patients are returning for revision of earlier replacements. As well as the problems of hip or knee replacement, revision arthroplasties have added complications associated with prolonged surgery and high blood loss.

Preoperative preparation
Discuss the anticipated blood loss with the surgeon; this depends on the type of previous prosthesis and the number of components being revised. Pre-donation of autologous blood with acute normovolaemic haemodilution and the use of a cell saver should be considered. Platelets (often not immediately available) and clotting factors may be required.

Monitoring and intravenous access
Invasive blood pressure and central venous pressure monitoring should be considered in view of the long duration of surgery and the likelihood of significant blood loss. A urinary catheter should be inserted with the facility for hourly urine output measurements.

Anaesthetic technique
The technique of choice is probably general anaesthesia, combined with insertion of a lumbar epidural catheter and positive-pressure ventilation. An epidural reduces intraoperative blood loss and improves operating conditions as well as reducing the risk of DVT. Spinal anaesthesia is generally unsuitable because the length of the operation outlasts its effects.

Intraoperative problems
Temperature: it can be difficult to prevent perioperative hypothermia. These operations are long and considerable volumes of intravenous fluid are transfused. Fluid warmers, hot air blowers, humidification systems and patient hats are important because intraoperative hypothermia can contribute significantly to coagulopathy and perioperative blood loss.

Blood loss is often considerable. Pre-donation of 1 unit of blood in the anaesthetic room, using acute normovolaemic haemodilution, is useful if the patient has an adequate starting haemoglobin. Intraoperative use of a cell saver can reduce the need for bank blood and reduce the associated transfusion risks, but once cement is in use, cell salvage must stop. The use of a cell saver is contraindicated in patients in whom joint replacement is for metastatic disease or infection. Platelets and fresh frozen plasma are often required. Transfusion of pre-donated blood should wait until surgical haemostasis is obtained. Fluid balance should be guided by surgical blood loss, central venous pressure trends (where available), pulse, blood pressure and urine output, with the aim of maintaining normovolaemia. The haemoglobin concentration should be assessed often, either from blood gases or by using a haemocue device.

Postoperative management
Should be in a high dependency unit. Oxygen should be prescribed for at least 72 hours. Analgesia should be provided by epidural infusion with regular enteral paracetamol. Close control of fluid balance is aided by the use of central venous pressure monitoring and hourly urine output measurement. Coagulopathies should be treated, but the threshold to transfuse red cells depends, in part, on the presence of co-morbid medical conditions, especially ischaemic heart disease. ◆

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Anaesthesia for Spinal Surgery

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Clinical features of spinal disorders

Intervertebral disc lesions

Prolapsed discs: lumbar backache is one of the most common causes of chronic debility in Western society. Acute lumbar disc prolapse or chronic degeneration with disc-space narrowing at L4/5 or L5/S1 are the most common pathologies. In acute prolapse, the disc may bulge beneath the posterior longitudinal ligament in the mid line (central disc) or posterolaterally with consequent distortion of the spinal canal or nerve-root compression. Local oedema may exacerbate the problem. Symptoms result from distortion of the posterior longitudinal ligament (chronic pain), pressure on the nerve-root sheath (sciatica) and compression of the nerve itself (muscle weakness, numbness and paraesthesia). Cauda equina compression may cause urinary retention, but is relatively uncommon. Management may include rest, analgesia and physiotherapy, but the prolapsed disc can be treated effectively only by bed rest, disc reduction (including epidural injection or chemonucleolysis) or surgical discectomy.

Cervical disc prolapse may be precipitated by sudden unexpected flexion or rotational movements. In most cases, there is probably a pre-existing disc abnormality. The most common levels for prolapse are C5/6 and C6/7, and symptoms are similar to those of lumbar disc prolapse. Treatment of the prolapse may be effected by rest, reduction using bed rest and traction, or surgical removal, if the symptoms are severe.

Spondylosis: lumbar disc degeneration may occur following recurrent disc prolapse or for other reasons. This results in flattening of the disc, facet-joint displacement, and a degree of instability with limited and painful movement (spondylosis). Conservative treatment for lumbar spondylosis is appropriate in less severe cases. However, if the pain cannot be controlled, spinal fusion is indicated.

Spondylosis is the most common disorder of the cervical spine. In addition to disc flattening, bony spurs may grow at the margins of the vertebral bodies, impinging on nerve roots and producing symptoms. Physiotherapy is the mainstay of treatment, but in severe or refractory cases anterior spinal fusion may be the definitive option.

Spondylolisthesis

If intervertebral facet joints become affected by osteoarthritic changes, dysplasia or fractures, one vertebral body may slip forwards on the other (spondylolisthesis). The most common levels for this to occur are L4/5 and L5/S1. Stabilization is achieved by spinal fusion and may be necessary for symptomatic relief.

Spinal stenosis

The spinal canal may be congenitally small or narrowed by the presence of a spondylolisthesis. Further narrowing consequent on disc degeneration and osteoarthrosis may produce neurological symptoms, which may be unilateral (root canal stenosis). Spinal decompression is indicated if symptoms are severe.

Rheumatoid disease

Rheumatoid arthritis affects about 1% of the world's population. The disease causes destruction of synovial joints, tendons and bursae, and 75% of sufferers have extra-articular symptoms. The spine is commonly affected, most often the upper cervical region. Erosion of the odontoid peg or cruciate ligament may result in atlanto-axial subluxation, with the risk of cord compression. 'Vertical subluxation' may result from erosion of the lateral masses of the axis, causing the odontoid peg to approach or enter the foramen magnum. Of relevance to the anaesthetist is that the disease may involve the temporomandibular and arytenoid joints.

Assessment of atlanto-axial subluxation may be made by measuring the distance between the anterior arch of the atlas and the odontoid peg on lateral cervical spine radiographs. However, neither this 'anterior atlanto-dental interval' nor the posterior equivalent correlates well with the severity of neurological symptoms. Stabilization procedures or surgical decompression may be undertaken to relieve neurological symptoms, but they are hazardous, with equivocal benefit.

Spinal curvature

Scoliosis is a lateral curvature of the spine, often with a rotational element. The deformity usually arises in late childhood and may be postural or structural. Postural scoliosis arises as a compensatory mechanism for problems outside the spine, such as a shortened leg or abnormal pelvic tilt. Structural scoliosis is a fixed deformity and is always accompanied by bony abnormalities. Adolescent idiopathic scoliosis is the most common form, presenting in the 10–15 year age group. Operative treatment for scoliosis is indicated for curvatures over 40°, the surgery being potentially complex and challenging.

Kyphosis: 'structural kyphosis' is a fixed, excessive dorsal curvature of the thoracic spine. It may occur in osteoporosis and ankylosing spondylitis. In Scheuermann's disease (adolescent kyphosis), the vertebral bodies become wedge-shaped as they grow. If the curvature exceeds 60°, surgery, which carries a high risk of neurological damage, may be indicated.

Infection

Tubercle bacilli or staphylococci may cause abscess formation within vertebral bodies. Tubercle infection may spread to adjacent vertebrae with caseation and cold abscess formation, resulting in vertebral collapse with a high risk of spinal cord damage. Antibiotic therapy is the mainstay of treatment for both infections. However, abscess drainage or spinal fusion for progressive deformity may be necessary.

Surgical procedures

Lumbar laminotomy and laminectomy: laminotomy (partial removal of vertebral lamina) or laminectomy (complete removal) are performed to decompress the spinal cord and/or nerve roots via a posterior approach with the patient lying prone. Should a discectomy also be necessary, the dura is retracted to one side and the disc removed piecemeal. During these procedures there is a risk of damage to both the dura and retroperitoneal structures (e.g. major vessels). The extent of the procedure depends on the underlying problem and may vary from simple laminotomy for single nerve-root compression to decompression over several segments for spinal canal narrowing. In such cases, a stabilization or fusion procedure (e.g. plate and screws) may also be required.

Microdiscectomy can be performed to decompress nerve roots affected by simple pathology; bone is not usually removed. The patient is placed prone or kneeling and the appropriate spinal level is identified using radiographic control. A small incision is made over the appropriate interspace and an operating microscope is used to retract the nerve-root to allow disc material to be excised.

Thoracic laminectomy and costotransversectomy: thoracic laminectomy involves midline removal of the vertebral lamina to decompress the thoracic spinal canal. Costotransversectomy (removal of transverse process and rib-head) is performed for nerve root compression. Both procedures require the patient to be prone and involve the use of an operating microscope.

Cervical laminotomy, foramenectomy and laminectomy are used to decompress the spinal cord or nerve roots in the cervical region. As with the lumbar and thoracic regions, the nature and extent of the surgery depends on the underlying pathology. The patient may be positioned prone or sitting.

Anterior cervical discectomy is a common neurosurgical procedure performed for disc herniation or degeneration with neurological symptoms. It is often augmented by vertebral fusion with a bone graft.

Other cervical procedures

Vertebral corpectomy is essentially an enlarged version of an anterior discectomy and is performed as an anterior decompression procedure. If access is required above the level of C3, a transoral approach may be used, which may involve a mandibular split and division of the tongue.

Cervical or craniocervical fusion is indicated for spinal instability. The fusion usually involves several adjacent vertebrae and may include fusing the occiput to the upper cervical spine. A posterior approach is used with the patient lying prone.

Spinal reconstruction procedures: significant kyphoscoliotic deformities may benefit from reconstructive surgery and, regardless of the underlying condition responsible for the deformity, the surgical approach to the anterior spine is similar. Surgery to the upper thoracic spine is achieved via a modified and extended anterior cervical exposure, often involving resection of a clavicle, part of the manubrium and first rib. Mid-thoracic spinal surgery is more easily performed via a thoracotomy with rib resection. One-lung ventilation may be required. Once the vertebrae or discs are removed, the spinal cord is at risk of damage, the degree of risk depending on the extent of the vertebral disease and the extent of reconstruction required.

A transdiaphragmatic approach involving detachment of the diaphragm is required for lower thoracic procedures. The lumbosacral spine is approached via a flank incision and retroperitoneal dissection. Often the 11th or 12th ribs are resected, risking damage to the great vessels, ureters, sympathetic chain and presacral plexus. A posterior fusion is also often undertaken with the above procedures.

Anaesthetic considerations

Thoracolumbar procedures (excluding corrective surgery)

Preoperative: surgical procedures on the lumbar spine for disc problems are common. Any preoperative neurological deficit should be recorded in the patient's notes, especially if a regional technique is considered. Generally, these patients are otherwise healthy and no special investigations are normally required.

Intraoperative: it is possible to perform simple lumbar pro-cedures under local or regional (spinal or epidural) anaesthesia. However, this is seldom done in practice because of medico-legal concerns that any new postoperative neurological deficit may be blamed on the anaesthetic technique. A general anaesthetic technique involving intubation and mechanical ventilation is more usual. For all posterior spinal procedures the patient is placed prone or in the knee–elbow position. It is therefore advisable to use an armoured tracheal tube to minimize the risk of kinking and to ensure that the tube is well secured before and after turning the patient. Potential problems with the prone position are summarized in Figure 1. Thoracoscopy is being increasingly used for procedures on isolated regions of the thoracic spine. This requires a double-lumen tracheal tube and for the ipsilateral lung to be deflated.

Problems with the prone position

Potential problem	Comments
Eyes	
• Corneal abrasion	Ensure eyes taped shut
• Optic neuropathy	Increased intraocular pressure leads to decreased perfusion pressure Reduce risk by avoiding compression to the eyes, hypotension, low haematocrit
• Retinal artery occlusion	Avoid pressure on the eyes
Head and neck	
• Venous and lymphatic obstruction	Careful positioning to minimize venous obstruction
• Skull fixation	Insertion of pins into skull can result in a hypertensive response that is difficult to control
Abdominal compression	
• Impaired ventilation	Avoid abdominal compression as far as possible
• Decreased cardiac output	Bean-bag mattress or pillows are better than supportive frames or knee–chest position
Damage to major vessels	
• Aorta or inferior vena cava	Accidental damage following perforation of anterior longitudinal ligament Produces major bleeding into wound, and presents with acute reduction in blood pressure and electromechanical dissociation arrest High mortality
• Iliac vessels	Less acute presentation. High index of suspicion to avoid delayed diagnosis

Any standard maintenance regimen is acceptable. However, blood pressure control is important, balancing the need to ensure spinal cord perfusion with the requirement to produce a bloodless surgical field. Sodium nitroprusside and esmolol infusions have been widely used for this purpose, though remifentanil is becoming popular. Blood loss is usually minimal from simple procedures, though if extensive laminectomies and fusions are performed, cross-matched blood should be available.

Standard monitoring is appropriate for simpler procedures. However, invasive blood pressure monitoring, a central venous pressure line and a urinary catheter should be considered if deliberate hypotension is used or if the procedure is likely to be prolonged and involve large fluid shifts.

Postoperative: most spinal surgery is painful and good postoperative analgesia is important. Local anaesthetic and opioid drugs can be instilled into the epidural space before closing. More usually, however, a regimen including patient-controlled analgesia (PCA) combined with regular oral/rectal analgesics is successful. Postoperative complications include persistent hypotension, haemorrhage, urinary retention, nerve root damage and cauda equina syndrome (urinary/faecal incontinence, perineal sensory loss and lower-limb motor weakness).

Cervical procedures

Preoperative: cervical spine fractures may cause acute spinal cord trauma and result in acute ventilatory failure requiring emergency tracheal intubation. Cervical spine stabilization during intubation is essential. The acute injury may additionally produce dysfunction of the sympathetic nervous system, resulting in hypotension and bradycardia. Simple treatment with fluids and atropine usually suffices, though vasopressors (e.g. ephedrine) may be necessary.

Neurological signs and symptoms may be present. Nerve root compression produces pain in the neck and arm, often associated with weakness and sensory loss. Acute cord lesions above T1 produce paraplegia and if the lesion is above C5 the patient will be quadriplegic.

Careful airway assessment is vital in all patients requiring cervical spine surgery. Difficult intubation may be anticipated if there is reduced movement, swelling or deformity. Up to 40% of patients requiring cervical spine surgery for rheumatoid disease fall into this group. The patient may need to be prepared for an awake fibre-optic intubation and appropriate equipment and skilled staff made available. In certain circumstances (e.g. surgery involving maxillotomy or mandibulotomy), an elective tracheostomy may be necessary for postoperative airway management.

Intraoperative: general anaesthesia with tracheal intubation and ventilation is required; standard maintenance techniques are appropriate. For anterior cervical procedures, the patient is placed supine with the neck extended and supported. For posterior approaches, the patient is usually prone. However, the seated position is preferred by some surgeons, because surgical access may be easier and blood loss reduced. This position is associated with a high incidence of air embolism (25–45%). If a patent foramen ovale is present (20% of the population), paradoxical embolism may occur, resulting in air entering the cerebral or coronary circulations. Standard monitoring may be used for straightforward cases, but arterial and central venous pressure catheters are useful for more prolonged procedures. Additionally, spinal cord monitoring may be required (see below).

Extubation may be problematical and is best performed with the patient awake and able to support their own airway. If the risk of reintubation is high, a tracheal tube exchange catheter (e.g. Cook catheter) may be useful. The catheter can be introduced into the tracheal tube and left *in situ* when the patient is extubated. Should urgent reintubation be necessary, the new tracheal tube can be rapidly railroaded over the exchange catheter. However, prolonged sedation and ventilation should be avoided because this may mask postoperative neurological deterioration.

Postoperative: possible complications include airway obstruction post extubation, which is potentially life-threatening if the patient has had a spinal fusion and is encased in a stabilization device. Airway compromise may result from haematoma formation or neurological deficit. Pneumothorax is an occasional cause of postoperative respiratory distress.

Spinal reconstruction and fusion

Preoperative: spinal reconstruction is indicated for correction of kyphoscoliotic deformities and for stabilization following trauma, infection (e.g. tuberculosis) or metastatic carcinoma. Patients presenting for this type of major surgery require careful preoperative assessment, because complex and chronic problems are common (Figure 2). Preoperative management should include lung function tests (e.g. forced vital capacity, peak expiratory flow rate), arterial blood gas analysis and review by a cardiologist if cardiac abnormalities are suspected.

Preoperative considerations for patients undergoing major reconstructive spinal surgery

Problem	Comment
Respiratory	
• Reduction in total lung capacity and vital capacity	Reduction worse with increasing deformity. If vital capacity < 40% predicted postoperative ventilation likely. NB A further decrease in vital capacity of up to 40% may occur postoperatively; recovery may take up to 2 months
• Increasing V/Q mismatch	Hypoxaemia more likely
Cardiovascular	
• Increase in pulmonary vascular resistance	Independent of severity of scoliosis
• Increasing incidence of congenital heart disease and mitral valve regurgitation	High index of suspicion
Neurological	
• Variable preoperative deficit	Careful preoperative documentation
Musculoskeletal	
• Muscular dystrophy relaxants	Abnormal response to muscle
• Respiratory impairment required	Postoperative ventilation may be
Nutrition	
• Malnourishment	Likely in patients with metastatic carcinoma

2

Intraoperative: intubation with a double-lumen tube may be necessary. Standard maintenance techniques are applicable, although this may have to be modified (e.g. no muscle relaxants) depending on surgical technique and spinal cord monitoring (see below).

Major blood loss is not uncommon and suitable intravenous access should be secured. Intraoperative blood loss may be dramatically reduced by careful patient positioning, the use of controlled hypotension (mean arterial pressure 60–70 mm Hg) and mild haemodilution to a haematocrit of 25–28%.

Intraoperative monitoring should include invasive blood pressure, central venous pressure, and urine output measurement. Evoked potentials are used to monitor spinal cord function (see below). If there is any indication of spinal cord ischaemia during surgery, normal blood pressure should be restored immediately and any traction on the cord relaxed. Strenuous efforts should be made to maintain normothermia.

Early extubation is desirable and good postoperative pain relief is essential. Epidural analgesia is considered by many to be the gold standard. An epidural catheter can be inserted before surgery or by the surgeon during the operation. Some patients require planned ICU admission for elective post-operative ventilation.

Postoperative complications include the risk of respiratory failure increased by thoracotomy, diaphragmatic injury and fat embolism. Great care should be exercised when moving and transferring patients to prevent dislodgement of spinal fix-ation. Careful documentation of neurological status is important because postoperative neurological deterioration is a major concern.

Spinal cord damage

Neurological damage during surgery and anaesthesia is not limited to the site of surgery. Paraplegia and quadriplegia have been reported as a result of poor patient positioning. There are reports of patients with spinal disease who have suffered neurological damage either at levels remote from the site of surgery or during surgery unconnected with their spinal disease. However, neurological damage is more likely at or near the site of surgery on the spine. Risk factors and methods for minimizing them are listed in Figure 3.

Risks of spinal cord damage

Risk related to:
- length and type of surgical procedure
- spinal cord perfusion pressure
- underlying spinal pathology
- pressure on neural tissue during surgery

Risk minimized by:
- careful positioning
- maintaining SCPP
  - SCPP = MAP – CSFP
  - CSFP can be reduced by CSF drainage
  - MAP manipulated by anaesthetist
  - ? keep systolic blood pressure > 90 mm Hg
- drugs
  - methylprednisolone given less than 8 hours after insult
  - NMDA antagonists (ketamine, magnesium)
- prevention of haematoma formation
  - careful haemostasis
  - stop anti-platelet medication preoperatively
  - withhold heparin immediately postoperatively

CSFP, cerebrospinal fluid pressure; MAP, mean arterial pressure; NMDA, N-methyl-D-aspartate; SCPP, spinal cord perfusion pressure

3

Spinal cord monitoring

The ‘wake-up test’ involves lightening anaesthesia at an appropriate point during the procedure and observing the patient’s ability to move to command. The technique requires practice and adds to the duration of surgery. In addition, it provides information at the time of the wake-up only and misses damage occurring at other times.

Neurophysiological monitoring using somatosensory evoked potentials (SEPs) provides a continuous picture and offers a more sophisticated approach. Electrical stimuli are applied to the lower limbs and appropriately placed electrodes can record cortical (SCEP) or spinal (SSEP) evoked potentials. The resulting trace can be analysed for wave amplitude and latency with respect to a reference ‘time zero’. SCEPs are affected by anaesthetic induction and inhalational agents, opioids and local anaesthetic drugs, and interpretation requires care and experience. Nevertheless, a decrease in amplitude or latency unrelated to drug administration of 35–50% is thought to be significant and indicate possible cord damage. However, even in skilled hands, interpretation can be difficult and a ‘wake-up test’ may still be required.

SSEPs can be recorded from electrodes placed into the epidural space either percutaneously or during surgery. SSEPs are affected less by inhalational agents, but are sensitive to temperature changes and local anaesthetic drugs. Their stability during anaesthesia allows them to be used with more confidence during surgery than SCEPs.

Motor evoked potentials can be obtained by stimulating the motor cortex with a transcranial electrode and eliciting a response from the distal spinal cord, peripheral nerves or muscle. They have not been used extensively for spinal cord monitoring because they are more difficult to achieve and are sensitive to inhalational anaesthetic agents. ◆

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Preoperative Assessment in the Elderly

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An increasing elderly population and advances in surgical technology are challenging anaesthetists to provide safe, effective anaesthesia. The mean age of the population continues to rise and half of all patients over 65 years will undergo surgery before they die. Osteoarthritis is almost universal and many of these patients will require joint replacement surgery. This article concentrates on elderly and arthritic patients and their associated problems.

Increased age and pre-existing illness both increase the incidence of complications. A successful outcome depends on meticulous attention to preoperative assessment and an intelligent choice of suitable anaesthetic techniques. An understanding of the limitations of physiological function in the elderly and rheumatic patient enables an accurate assessment of the likely response to the stress of surgery and therefore the final outcome to be made. The anaesthetic technique used and the choice of perioperative monitoring often makes the difference between success and failure. Similarly, the opportunity to improve physiological function preoperatively, where applicable, should never be missed.

Elderly patients often present with a baffling array of pathologies. Most are chronic effects of the ageing process and the residual effects of past illnesses. Signs and symptoms are often masked by limitation of movement and lack of exercise because of the pain of arthritis. This enforced immobility often leads to weight gain and obesity, making pre-existing pathology in other systems worse and adding to the risks of anaesthesia and surgery.

The elderly and ageing

Old age is not a disease. The elderly undergo physiological and anatomical changes that evoke different responses to stress and anaesthesia. In 1982, the United Nations recognized this: 'Support to the aged people must be provided by practitioners who are knowledgeable in the subject of ageing, are interested in ageing people and their families and are skilled in working with them as well as being concerned about the quality of care given'.

The process of ageing is one of continuous biological change. The number of parenchymal cells decreases, with a concomitant increase in inactive interstitial cells, triggering a progressive decline in physiological function. Gross morphological changes occur with contraction of vertebral bodies and discs. Kyphosis occurs and flexion of hips and knees. The long bones of the legs bow, but the arms remain unchanged in length. This reverses the height:span ratio. Muscle size and bulk decrease rapidly with advancing age, together with alterations in fat distribution. Skin becomes thinner and more fragile.

Cardiovascular system

In the heart, myofibrils enlarge but become less numerous. Collagen and fat replace a substantial volume of the muscle mass. Deposits of amyloid and subendocardial calcification impair conduction in the ventricle. This, combined with a reduction in pacemaker cells, makes the elderly prone to arrhythmias.

Progressive coronary arterial sclerosis leads to a reduction in maximal coronary artery blood flow. While the oxygen delivery is within the demand of the resting state, relatively small increases in cardiac work index or heart rate result in ischaemia. There is reduction in vasomotor tone; both vagal and sympathetic influences are minimized.

These changes make the heart less compliant. Stroke volume decreases; systole time is prolonged; and with a decrease in ventricular contractility, cardiac output and its reserve decline. Despite this, the average arterial pressure rises, with an increase in the systolic and a slight drop in the diastolic pressures, except in obesity. The mean arterial pressure remains unchanged. Peripheral vascular resistance increases progressively. Vessel walls become less compliant as smooth muscle is reduced and collagen replaces elastin. Major vessels become stretched and distended, damaging the endothelium and baroreceptors, making blood pressures labile. Importantly, any increase in intrathoracic pressure, passively or actively, causes greater decreases in blood pressure with little or no rebound elevation. Degenerative vasomotor control precipitates syncope in the presence of decreased cardiac output or peripheral resistance. Postural hypotension can be spontaneous or an effect of drugs.

Respiratory system

Dorsal kyphosis and curvature of the thorax alter the position of the ribs, forming a 'barrel chest'. There is associated weakness of intercostal muscles and chest wall rigidity. This increases the work, and reduces the efficiency, of breathing. Cellular changes also occur in the lung parenchyma. Elastic recoil of the lungs is reduced, increasing the lung volume at end-expiration, thus increasing the residual volume. There is a parallel decrease in the vital capacity. Widening of the airways increases the anatomical dead space, together with increase in the size of the alveolar ducts. Reduction in elastic fibres in these ducts may explain why airway closure occurs at resting functional residual capacity. This premature closure of the airways further contributes to increases in residual volume.

Loss of recoil, increasing dependence on the diaphragm and abdominal muscles and reduced vital capacity all produce an uneven distribution of ventilation, without change in tidal volume at rest. The alveolar–arterial oxygen tension difference increases causing a decrease in the partial pressure of oxygen in arterial blood (PaO_2). The $PaCO_2$ remains unchanged. However, a greater contribution to progressive reduction in arterial oxygen-ation comes from reduced perfusion. Fibrous replacement of the muscular arterial media and reduction in the number of capillaries increases the pulmonary vascular resistance and shunting. Maximal pulmonary blood flow, and therefore perfusion, is lowered. The additional oxygen demand caused by increased activity induces increased ventilation in the presence of a diminished maximum breathing capacity. This leads to dyspnoea in the absence of underlying pulmonary disease.

Progressive weakness of intercostal and accessory muscles reduces the ability to cough forcibly. The bronchial mucosa degenerate because of impaired blood supply and the cilia are not always able to keep the small airways clean. Suppressed glottic reflexes make pulmonary infections common.

Circulation

In addition to reduced haemoglobin and haematocrit, older people have reduced marrow iron stores and can suffer anaemia following small haemorrhages. The temptation to transfuse red cells immediately should be resisted. One large retrospective observational study showed no increase in mortality provided the haemoglobin concentration was kept above 8 g/dl, even in the elderly. It recommended that an indication for transfusion is haemoglobin below 7 g/dl. However, if elderly patients do not respond to treatment of anaemia other causes should be sought, such as occult malignancy, chronic infection or poor nutrition.

Other haematological changes include reduced cellular immune response because of thymic atrophy and reduction in the number of T cells. Lymphocytosis within the marrow results in susceptibility to proliferative disorders and infections.

Renal function

The nephron mass in the kidney can decline by 30% between 60 and 70 years of age. This is reflected in changes in lean body mass and basal metabolic rate as a result of loss of functioning tissue. Vascular changes may initiate this deterioration. As renal blood flow is reduced, glomerular filtration and concentrating ability decline linearly at 1% per annum from 30 to 80 years. Large acid or alkali loads can overwhelm the ability of the kidney to maintain acid–base homeostasis. The serum creatinine level can be misleading because it does not necessarily increase in response to declining creatinine clearance rates, but reflects muscle turnover when muscle mass is reduced.

Nervous system

Changes in cognitive function are multifactorial. 20% of octogen-arians have some degree of dementia, but this diagnosis should be made only when other causes have been excluded. Organic causes of dementia include hypoxia, infection, drugs, hypoperfusion, hypothyroidism, constipation and impaired sight or hearing.

Temperature regulation, together with heat and cold homeo-stasis, is impaired in the elderly; they do not often shiver. Hypothalamic hunger and thirst centres are down-regulated and antidiuretic hormone is less effective, leaving these people vulnerable to dehydration and malnutrition. The peripheral nervous system declines in a similar manner. Nerve conduction velocity decreases and appreciation of pain reduces; the elderly complain less of pain.

Care must be taken to ensure nerves are not compressed or stretched, particularly in the neck. Many elderly patients have a reduced cerebral blood supply as a result of atheroma or sclerosis. Vertebrobasilar insufficiency is not uncommon. Flexion or extension of the neck can compromise cerebral oxygen delivery. Osteoporosis and laxity of ligaments is common in old age. Care should be taken in moving the neck lest dislocation or fracture occurs in the cervical vertebrae.

Rheumatoid arthritis

Rheumatoid arthritis is an inflammatory proliferative disease of synovium with a familial association with the DRW 4 allogen. 70% of sufferers are female and 85% show anti IgG or IgM antibodies. It is thought to be caused by defective cell-mediated immunity, characterized by lymphocytic proliferation involving macrophages and complement activation on joint surfaces giving rise to symmetrical polyarthritis with a centrifugal distribution. Clinical features include insidious or sudden onset of pain, swelling and stiffness in peripheral joints. Weakening of the joint capsules leads to subluxation and permanent deformity. It is associated with tenosinovitis and muscle wasting.

Anaesthetic implications: advance of rheumatoid arthritis affects most systems. The airway is often compromised and involvement of the temporomandibular joint restricts mouth opening. Atlanto-occipital instability is not uncommon and 25% of patients admitted to hospital with rheumatoid disease have subluxation of that joint.

Hyperflexion of the neck may induce vertebrobasilar insufficiency or paraesthesia. Crico-arytenoid involvement may present with stridor. Associated lung conditions include fibrosing alveolitis, pleural effusion and Caplan's syndrome. Pericarditis can be associated with pericardial effusions. Valvular nodules cause aortic or mitral stenosis. These nodules are sometimes due to amyloid, which also causes nephrotic syndrome. Renal failure can occur through vasculitis or as a result of the drugs used to treat rheumatoid arthritis (e.g. penicillamine, non-steroidal anti-inflammatory drugs). Usually, these patients suffer anaemia, which may be haemolytic, chronic normochromic or iron-deficient. They may also have pancytopenia and hypersplenism (Felty's syndrome). Fragile skin and veins are also associated with this condition together with a predisposition to carpal tunnel syndrome, polyneuritis and neuropathy. Special care is needed when positioning these patients for surgery.

History

Obtaining a clear history may prove difficult in elderly patients. Sensory perception is impaired and misunderstandings occur because of failure to hear. Sight may be compromised, distorting perception of surroundings. There may also be age-related generalized neurological degeneration. Recall of past events is usually clear but recall of recent episodes of illness and their significance can be hazy. Relatives often fill in important gaps and reference to medical notes and letters is invaluable. The history should include:

- previous anaesthetics, especially any problems
- previous medical history, especially heart, lungs, kidneys, blood pressure, oesophageal reflux
- allergies
- current medicines
- social habits (e.g. smoking, alcohol intake)
- dentition.

The medical history and current medication provide important clues about the patient's underlying state of health.

Examination

The patient should be sufficiently exposed to enable accurate observation, palpation, percussion and auscultation, while ensuring warmth, comfort and dignity. Palpation of the pulses cannot be over-emphasized; it often reveals clear indications of severe cardiovascular disease. Thorough examination of the cardiovascular and respiratory systems is often rewarded by eliciting signs absent in younger patients. Cardiac murmurs should be carefully classified according to site heard loudest, pitch, length and timing in the cardiac cycle. Irregularities of the pulse should be noted as well as abnormalities of the jugular venous pulsation.

Tests of respiratory function include the ability to count to 10 in one breath, breathlessness on dressing and ability to walk up a flight of stairs. Palpation of chest expansion, percussion and auscultation should be performed on anterior and posterior aspects of the chest. Unexpected signs are often found, which prove important in future management decisions. A hyper-dynamic pulse may sometimes indicate hypercarbia.

Although cognitive function is not usually directly related to anaesthetic processes, postoperative confusion and delirium are not uncommon. A simple mental test score such as that given in Figure 1 can be a useful marker and may highlight patients at special risk.

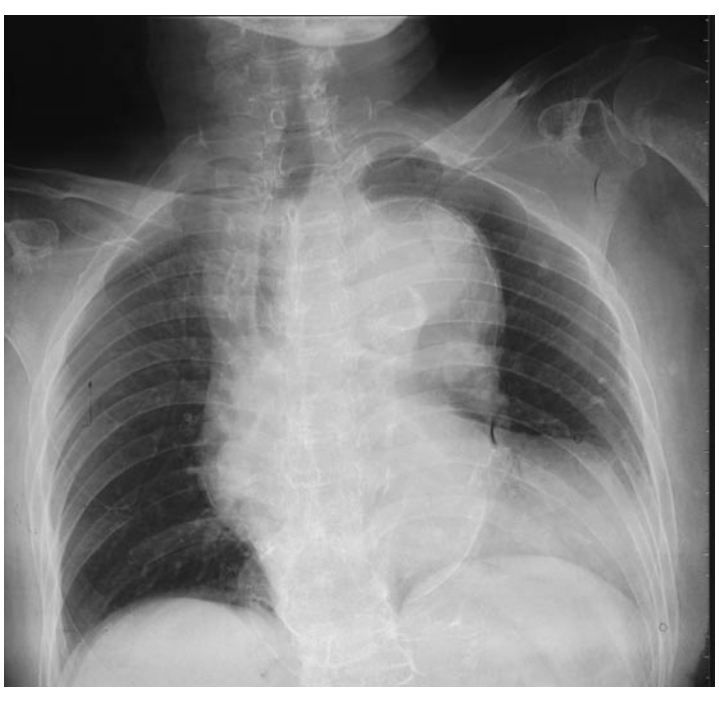
Mini-Mental State Examination

Section	Score	Task
Orientation	5	What is the date: year, season, date, day, month
	5	Where are we: country, county, town, hospital, floor
Registration	3	Name three objects – 1 second to say each, then ask the patient to recall all three. Repeat until the patient has learnt all three. Count and record trials
	5	Serial 7s – one point for each correct. Stop after 5 correct. Alternatively spell 'world' backwards
	3	Ask for the 3 objects repeated above – Give an example of each
Language	2	Name a pencil and watch
	1	Repeat the following 'no ifs, ands or buts'
	3	Follow a 3-stage command: 'take a piece of paper in your right hand, fold it in half and put it on the floor'
	3	Read and obey the following: 'close your eyes', 'write a sentence', 'copy a design'
Total score	30	
Score results:		30–29, normal 28–26, borderline cognitive dysfunction 25–18, marked cognitive dysfunction; dementia may be diagnosed < 17, severe dysfunction; severe dementia

From: Folstein M F, Folstein S E, McHugh P R. A Practical Method for Grading the Cognitive State of Patients for the Clinician. *J Psychiatr Res* 1975; **12:** 189–98.

Investigations

Together with haematology and biochemistry blood assays, a recent ECG should be available. Chest radiography may help to evaluate degrees of cardiac and respiratory disease. Occasionally surprise findings may occur (Figure 2).



2 Chest radiograph of a 71-year-old Chinese woman with a calcified dissected thoracic aortic aneurysm and aortic valve secondary to syphilis.

The value of 2D echocardiography is limited but can be useful in valvular heart disease in determining degrees of incompetence or stenosis. Assessment of hypokinetic ventricular damage in ischaemic heart disease is also possible. Ejection fractions are often not repeatable and can be misleading. If an estimation of ventricular function is required a multigated scintigraph scan (MUGA) may give a more reliable figure. Peak flow measurement can be easily performed. This simple test gives good quantitative estimates of pulmonary function, and in this context, is often as valuable as formal pulmonary function testing. ◆

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Procedures under Tourniquet

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Applying a pressurized pneumatic cuff to a limb can be used to prevent the central spread of local anaesthetic during intravenous regional anaesthesia. It may also be used to reduce bleeding and improve the surgical field when operating on an exsanguinated limb. Using a tourniquet can induce significant physiological changes depending on the duration of inflation and the general status of the patient.

Tourniquet application

Maintaining a bloodless field during limb surgery

The cuff should be wider than half the limb diameter and should be applied over smooth padding. The edges of the cuff must overlap to ensure it exerts even pressure all round the limb. Ideally, the overlap should be on the opposite side of the limb to the main neurovascular bundle. The limb is then exsanguinated either by elevation for 1 minute or by the application of Esmarch bandaging or a Rhys-Davies exsanguinator. (In the presence of infection or tumour, exsanguination by methods other than elevation is usually contraindicated.) When applied to the leg, the tourniquet is usually inflated to a pressure 100 mm Hg above systolic arterial blood pressure; on the arm it is inflated to 50 mm Hg above systolic arterial blood pressure. The pressure required depends on the size of the muscle mass to be compressed. During preparation of the surgical field, skin cleaning solutions should not come into contact with the tourniquet padding. If alcohol or iodine-based cleaning solutions soak into the padding they can cause skin irritation. Diathermy burns have also resulted from pooling of liquid around the tourniquet.

Intravenous regional anaesthesia

A machine equipped with two tourniquets is optimal for intravenous regional anaesthesia. Intravenous access is obtained in the limb before application of the tourniquet. Great care must be exercised during exsanguination to avoid dislodging the intra-venous cannula. After exsanguination, the proximal tourniquet cuff is inflated and local anaesthetic is introduced into the limb. (If the cuff were to fail at this stage the local anaesthetic would spread centrally resulting in a potentially toxic plasma concentration of local anaesthetic agent.) After a few minutes, the distal cuff is inflated and then the proximal cuff can be let down. The result is a tourniquet compressing a section of limb that has itself been rendered insensitive by intravenous regional anaesthesia. This is an attempt to reduce tourniquet-related pain (see below).
The tourniquet must remain inflated for a minimum of 20 minutes to allow the local anaesthetic time to bind to tissues. Deflation before 20 minutes may precipitate systemic local anaesthetic toxicity.

Physiological changes

Figure 1 summarizes the physiological changes that occur during inflation and deflation of a tourniquet.

Physiological changes

During inflation
- Rising volaemia and systemic vascular resistance lead to increased blood pressure, central venous pressure and heart rate
- Temperature reduction in non-perfused limb
- Anaerobic metabolites being produced

After deflation
- Reperfusion of limb
  – Reduction in volaemia and systemic vascular resistance lead to decreased blood pressure, central venous pressure and heart rate
  – Core temperature falls
  – Mixed acidosis, decrease in pO_2 and pH while pCO_2, K^+ and free radicals increase
- Reactive hyper-reperfusion

1

Cardiovascular

Increases in systemic blood pressure, central venous pressure and heart rate have been reported immediately after tourniquet inflation. These changes are related to the sudden increase in blood volume (up to 15%) combined with a reduction in the capacitance of the vascular bed. Reciprocal haemodynamic changes may be expected following tourniquet deflation due to a decrease in systemic vascular resistance and venous return while the limb is reperfusing. The magnitude of the haemo-dynamic changes can be reduced by the use of regional anaesthesia. Preoperative ketamine, 0.25 mg/kg, moderates the rise in blood pressure after tourniquet inflation. In some patients, who have been otherwise cardiovascularly stable, a sudden marked rise in arterial pressure may occur about 1 hour after tourniquet inflation. In these patients, the arterial pressure may continue to rise, despite increasing the depth of anaesthesia, and only resolves when the tourniquet is deflated. Severe hypertension and/or concerns about possible ischaemic limb damage are the two factors that most commonly limit the duration of tourniquet inflation. The exact physiological mechanisms involved in this late arterial pressure rise are unclear.

Generalized muscle perfusion remains above normal for up to 15 minutes after tourniquet deflation. This is caused by the release of anaerobic metabolites triggering reactive vasodilatation in capillary beds within the muscle fibres.

Temperature

While the tourniquet remains inflated, the temperature of the non-perfused limb falls. This has some protective effect against ischaemic damage. However, during reperfusion, blood is exposed to cold tissues and on deflation there can be a reduction in core temperature of up to 0.6°C for each hour the tourniquet was used.

Metabolic changes

Leaving the tourniquet on for more than 30 minutes produces anaerobic metabolism, resulting in a mixed acidosis with hypoxaemia, hypercapnia, hyperkalaemia and formation of free radicals. These changes are normally well tolerated by healthy individuals but may be detrimental to patients with poor cardio-pulmonary reserve. The acidosis can be partly corrected by a short period of hyperventilation immediately after tourniquet deflation. Maintaining anaesthesia with a propofol infusion rather than a volatile agent may significantly reduce the formation of free radicals. Nevertheless, caution is advised when bilateral tourniquets are required and, whenever possible, simultaneous inflation should be avoided.

Complications

The incidence of complications is related to the inflation pressure and the duration of inflation.

Limb ischaemia is the most serious complication. Current recommendations regarding the upper limit for the duration of inflation vary between 30 minutes and 4 hours (30 minutes is the time taken for the onset of anaerobic metabolism). Nevertheless, after 1 hour of ischaemia, electron microscopy can detect depletion of glycogen granules in the sarcoplasm of muscle fibres. After 2 hours, lesions associated with acidosis (e.g. mitochondrial swelling), myelin degeneration and Z-line lysis can be identified. These changes are reversible with reperfusion and it may be that intermittent reperfusion–exsanguination during surgery prolongs the safe limit of tourniquet application by preventing excessive anaerobic metabolism. This may, however, be at the expense of supplying more substrate for the production of free radicals.

Local anaesthetic toxicity: if the cuff is being used for intra-venous regional anaesthesia it must remain inflated for at least 20 minutes after local anaesthetic has been injected, if local anaesthetic toxicity is to be avoided. The risk of local anaesthetic toxicity is reduced if agents with low systemic toxicity are used. For prolonged procedures, the cuff can be deflated at intervals to prevent ischaemic damage and, if intravenous access in the operated limb has to be retained, further, smaller doses of local anaesthetic can be given.

Pressure-related nerve damage can be caused by a tourniquet with possible rupture of the Schwann cell membrane. This may lead to neuralgia paraesthetica, which usually resolves within a few weeks or months.

Excessive pressure can also damage underlying vessels, increasing the incidence of microemboli formation in the exsanguinated limb. This increases the risk of pulmonary microvascular injury (small pulmonary emboli). Prolonged tourniquet times have been related to respiratory failure requiring postoperative ventilation, especially in trauma. In a properly exsanguinated healthy limb, alterations in blood clotting physiology are usually minimal and theoretically should have no clinical impact. The incidence of deep vein thrombosis (DVT) may be higher when a tourniquet is used, but this has not been substantiated in arthroscopic knee surgery. Thromboprophylaxis must be considered in all patients aged over 40 years who have surgery performed under tourniquet (except for arthroscopic knee surgery), especially if there are other risk factors for DVT formation.

Tourniquet pain can occur 45–60 minutes after tourniquet inflation. Patients undergoing surgery under regional anaesthesia initially experience a dull ache in the exsanguinated limb after about 30 minutes of tourniquet application. This may occur even when a second cuff is inflated on an anaesthetized section of limb. As the pain worsens, patients may become restless and eventually the pain may become unbearable despite the presence of an otherwise satisfactory block. The pain may be transmitted through C fibres (slow, persistent, poorly localized pain), which are more resistant to local anaesthetic than Aδ fibres (sharp, fast pricking pain). At the onset of neural blockade, when the concentration of local anaesthetic is high, both are inhibited. As the local anaesthetic is metabolized, the concentration becomes insufficient to block C fibres despite continuing to anaesthetize Aδ fibres. This theory is supported by the observations that longer-acting local anaesthetic agents reduce the incidence of tourniquet pain and that its onset is delayed if a larger dose of local anaesthetic is used. There is also a reduction in the incidence of pain if clonidine is added to the local anaesthetic solution. Once tourniquet pain has developed it is difficult to treat, other than by releasing the tourniquet. General anaesthesia may need to be used if the surgery is continuing. Opiates alone are disappointing and tend to cause side-effects from excessive dose once the tourniquet is released and the afferent stimulus ceases.

Hypertension: patients undergoing general anaesthesia with a tourniquet *in situ* can develop signs of hypertension and tachy-cardia that mimic those seen during painful surgical stimulation. The reasons for the development of hypertension under these circumstances are unclear and it has been traditionally ascribed to the development of limb ischaemia, nerve compression or the development of tissue acidosis. Hypertension developing in these circumstances is often resistant to opiates and is relieved only when the tourniquet is deflated.

Treatment: Figure 2 lists treatments for complications. ◆

Treatment of complications

Easing the metabolic hurdle
- Whenever possible use a regional technique, even combined with general anaesthesia
- Preoperative ketamine, 0.25 mg/kg, prevents hypertensive response to tourniquet
- Total intravenous anaesthesia with propofol helps to scavenge the free radicals produced
- Hyperventilate after tourniquet deflation to reduce acidosis
- Caution with simultaneous tourniquets

Easing the tourniquet pain
- Reduce tourniquet time as much as possible
- Whenever possible use a regional technique, even combined with general anaesthesia
- Use longer-acting local anaesthetics to reduce incidence
- Use clonidine mixed with local anaesthetic
- Intrathecal opiates reduce incidence of pain
- If unbearable and patient awake, convert to general anaesthesia
- Caution with adjuvant systemic opiates in awake patient, they may lead to delayed respiratory depression

2

FURTHER READING

Barash, Cullen, Stoelting. *Clinical Anaesthesia.* 2nd ed. Philadelphia:Lippincott, 1992.

Rogers, Tinller, Covino, Louguedler. *Principles and Practice of Anaesthesiology.* New York: Mosby, 1993.

Local Anaesthetic Blocks in Ambulatory Orthopaedic Surgery

Patrick M Clarke

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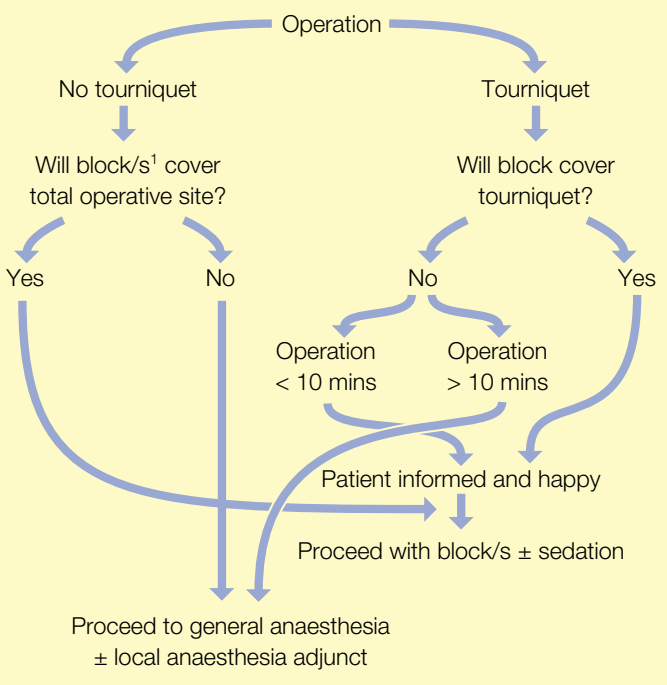
More surgery is now being performed in an outpatient setting. The growing complexity of surgical procedures challenges the anaesthetist's ability to provide postoperative analgesia. Inadequate analgesia is a cause of delayed discharge and unexpected hospital admission. In a large prospective study, 16% of ambulatory orthopaedic patients had severe postoperative pain. Opi-oids are associated with nausea, vomiting and urinary retention, causing delayed discharge. Local anaesthetic techniques used as the primary anaesthetic or as an adjuvant to general anaesthesia can provide a safe and effective alternative to opioid analgesia.

Selection of local anaesthetic technique – orthopaedic surgery lends itself to peripheral and central neural blockade. Several questions need to be answered before deciding on a local anaesthetic technique (Figure 1).

- Can the block be used as the primary anaesthetic?
- Is sedation required as well?
- Can the block be used to supplement a general anaesthetic?
- Is the patient happy with a local technique?

Block decision algorithm



[1]If bone graft is being harvested from non-blocked site general anaesthesia is usually necessary (e.g. iliac crest graft).
If several blocks are being considered is this acceptable to the patient or is sedation required (e.g. ankle block)?

1

Selection of a particular block depends on surgical procedure, use of a tourniquet, patient acceptability and operator experience.

Sedation

Sedation is useful for block placement and intraoperative sedation. Some blocks take time to site successfully and patients may become irritable and anxious and lose confidence in the anaesthetist; sedation minimizes these problems. For block placement the patient should be relaxed but conscious enough to report any paraesthesia. In a paraesthesia-seeking technique less sedation should be administered than when using a nerve stimulator to obtain motor stimulation. When a nerve stimulator is used the patient may receive more sedation but must be conscious enough to report major paraesthesia, which may indicate intraneural injection. Suitable sedation for block placement may be achieved using a combination of a short-acting benzodiazepine such as midazolam, 0.025–0.05 mg/kg, and fentanyl, 0.5–1.0 μg/kg (i.e. midazolam, 2 mg, and fentanyl, 50 μg, for a 80 kg patient).

Intraoperative sedation may be achieved with a variety of pharmacological agents ranging from intermittent boluses of benzodiazepine/opioid combinations to an infusional drug such as target-controlled propofol. In an ambulatory setting success is easily achieved using bolus techniques owing to the short duration of surgery. There is a fine balance between patient relaxation and disinhibition. It is better to have a less sedated cooperative patient than one who is over-sedated and confused.

Patient information

Informed consent is paramount for local anaesthetic techniques used as the primary anaesthetic or adjuvant to a general anaesthetic. To gain the patient's confidence and minimize anxiety it is important to explain the sequence of events that will take place on arrival in the anaesthetic room or operating theatre.

Side-effects must be discussed when obtaining consent. Pain at the site of injection occurs in about 30% of patients. 10% may experience tingling or numbness for up to 48 hours. Patients must be advised not to go near hot or cold objects and to beware of trauma to a numb extremity for up to 48 hours. Rare complications such as infection and bleeding should also be mentioned. Complications specific to individual blocks should be discussed. For example, in interscalene block, hoarseness, Horner's syndrome or difficulty with coughing (secondary to phrenic nerve paralysis) should be outlined.

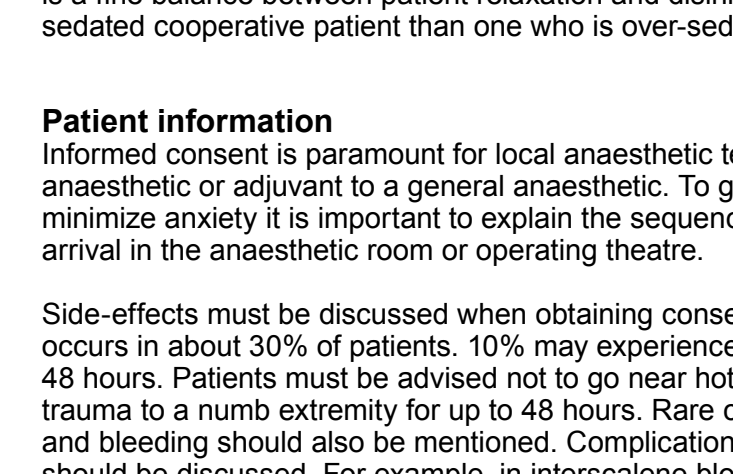
Patients must be told that even with a limb blocked satisfact-orily for surgery some sensation of movement and touch may occur otherwise they may panic when they feel touch during surgery. The sensation can be likened to that felt following dental local anaesthesia. "Touch may be felt but pinching is not painful".

Explain to the patient that pain will occur when the block wears off and give them advice about pre-emptive analgesia.

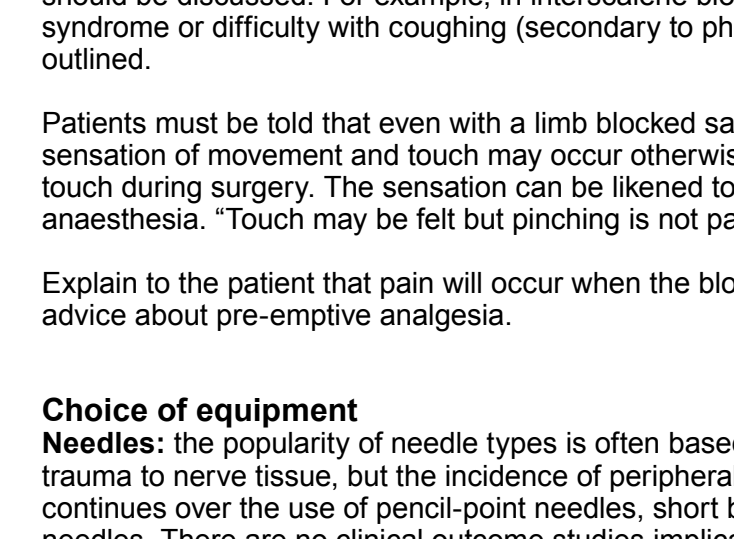
Choice of equipment

Needles: the popularity of needle types is often based on their likelihood of causing trauma to nerve tissue, but the incidence of peripheral nerve injury is small. Debate continues over the use of pencil-point needles, short bevelled needles or sharp needles. There are no clinical outcome studies implicating bevel design as a consistent factor in nerve injury. Evidence suggests that sharp needles cause less nerve damage, which is more rapidly repaired. Using a short bevelled block needle gives a better 'feel' of deeper tissue planes. Over-zealous seeking of paraesthesia should not take place.

When used in conjunction with a nerve stimulator in a conscious, relaxed patient, a carefully performed nerve block is unlikely to cause significant nerve injury. For single-shot techniques with needle and nerve stimulator, the Stimuplex short bevelled needle is excellent (Figure 2). It is available in various lengths, is well made and easy to hold. For a continuous catheter technique the combined Braun sheathed Tuohy needle, with side injection port and catheter is useful and well made (Figure 3). It is particularly useful following surgery when a continuous physiotherapy machine is required (e.g. post shoulder release).

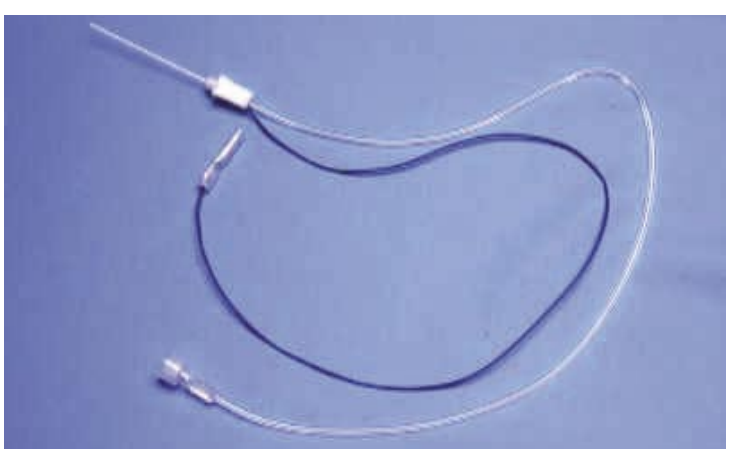


2 The Stimuplex short bevelled needle.



3 Braun catheter.

Nerve stimulator: there is little evidence that postoperative nerve injury is reduced by the use of nerve stimulators. There are also few studies to verify improved success of blocks. Ultrasound-guided block needles improve success in block placement. It is mandatory to use a nerve stimulator in some approaches to the brachial plexus (e.g. interscalene block because of proximity of the major blood vessels and CSF). The negative lead of the nerve stimulator should be attached to the needle and the positive lead attached to an ECG sticker at least 10 cm away from the limb to be anaesthetized (Figure 4). A current of 1 mA is used initially. Once the needle tip approaches the nerve/s to be blocked the current should be reduced to about 0.4 mA. Muscle twitching in the appropriate muscle group at this current indicates close proximity of the needle tip to the nerve. Muscle twitching at lower currents may indicate intraneural placement of the needle, though the patient will usually let you know if this occurs!



4 Patient attached to nerve stimulator.

Useful blocks in the ambulatory setting

Upper limb blocks: ambulatory orthopaedic surgery lends itself to the use of nerve blocks as both primary anaesthetic and as an adjunct to general anaesthesia (Figure 5). The main limiting factor for use as a primary anaesthetic is the use of tourniquets. The tourniquet must be placed on an anaesthetized part of the limb. With brachial plexus block this is easily accomplished, but with isolated nerve blocks the use of a tourniquet rules out blocks as the primary anaesthetic. If surgery takes less than 10 minutes a tourniquet may be tolerated, particularly with the use of sedation (e.g. carpal tunnel decompression under local infiltration).

For proximal upper limb surgery, the block of choice is the interscalene brachial plexus block. Shoulder arthroscopy, manipulation and arthroscopic rotator cuff repair may be extremely painful postoperatively. Interscalene anaesthesia is ideal. It is relatively easily performed using a nerve stimulator, the plexus usually being superficial at this level.

Most ambulatory orthopaedic surgery is performed on the distal part of the arm. In the forearm, removal of internal fixation devices is a commonly performed procedure. For forearm surgery the axillary approach to the brachial plexus is reliable and effective and may be used as the primary anaesthetic. Hand surgery is easily performed under axillary brachial plexus blockade.

The axillary approach is safe and reliable. Occasionally ab-duction at the shoulder joint is difficult, making an axillary approach impossible. In this situation, supraclavicular, infraclavicular or subcoracoid approaches to the brachial plexus may be used. Both supra- and infraclavicular approaches carry the risk of pleural puncture; the subcoracoid approach does not. In conjunction with a nerve stimulator the plexus is easily identified and block may be successfully achieved.

Nerve blocks at the elbow may be used to supplement brachial plexus blockade. Occasionally a nerve may be 'missed', requiring further block at the elbow. However, some anaesthetists consider that the likelihood of nerve damage is increased by attempting to block a 'partially' anaesthetized nerve because paraesthesia is decreased. The nerves at the elbow are superficial and paraesthesia must not be sought over-zealously.

Upper limb block

Block site		Primary anaesthesia	Adjunct to general anaesthesia	Advantages	Disadvantages	Volume of local anaesthetic
Plexus blocks	Interscalene Supraclavicular Infraclavicular Subcoracoid Axillary	Yes	Yes	Broad coverage	Variable block until experienced	20–40 ml
Block at elbow	Median Ulnar Radial	Possibly	Yes	Add on to brachial block if patchy	Does not cover tourniquet	5 ml/nerve
Block at wrist	Median Ulnar Radial	Possibly	Yes	Easy	Does not cover tourniquet	3–5 ml/nerve
Distal block	Ring block	Yes	Yes	Easy	None	5 ml
Other	Bier's block	Yes	No	Easy	Bloodless field not obtained	30–40 ml
	Local infiltration	Yes	Yes			

Distal nerve blockade at the wrist is usually used only as an adjunct to general anaesthesia due to use of a tourniquet. Surgery on the finger may be performed under ring block. A bloodless field is achievable using a finger tourniquet applied by the surgical team following block.

Bier's block is useful for simple forearm manipulations. Most surgeons do not use it for open procedures (e.g. excision of Dupuytren's contracture) because anaesthetic may ooze into the operative field.

Local infiltration is a useful anaesthetic tool. It may be used with a tourniquet for short procedures. It is valuable as an adjunct to general anaesthesia and for postoperative analgesia.

Lower limb blocks (Figure 6) are under-used. They are most appropriate when used with a general anaesthetic. Proximal lower limb surgery is unusual other than for removal of internal fixation devices (seldom performed in the ambulatory setting). Removal of small screws usually benefits from simple local infiltration by the surgeon. Most lower limb ambulatory orthopaedic surgery is distal. Commonly performed distal lower limb orthopaedic operations include bunion and bunionette excision, Zadek's procedure, removal of metalwork from distal tibia and fibula, excision of soft tissue lesions (e.g. Morton neuroma). Owing to the use of proximal tourniquets local anaesthetic techniques are not commonly used as the primary anaesthetic. However, local blocks are an excellent adjunct to general anaesthesia. ◆

Lower limb blocks

Block site		Primary anaesthesia	Adjunct to general anaesthesia	Advantages	Disadvantages	Volume of local anaesthetic
Proximal blocks	Femoral	Yes	Yes	Useful in avoiding central blockade	None	20 ml
	Sciatic	No	Yes		Experience required	20 ml
	Lateral cutaneous					
	3-in-1 block[1]	Yes	Yes		None	30 ml
At knee	Sciatic	No	Yes	Useful analgesia	Sometimes patchy	15 ml
	Saphenous	No	Yes			10 ml
	C.peroneal	No	Yes			10 ml
At ankle	5 nerves SSSPP[2]	Possibly	Yes	In sick patients	5 injections	20–30 ml
Distal	Ring	Yes	Yes	Easy	None	5 ml
Other	Bier's block	Yes	No	Easy	No bloodless field	30–40 ml
	Local infiltration	Yes	Yes			

[1]Femoral, obturator, lateral cutaneous nerve of thigh; [2]Saphenous, sural, superficial peroneal, deep peroneal, posterior tibial.

Paediatrics

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on CD-ROM

Acute and Chronic Airway Obstruction

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A baby has a large tongue in relation to the oral cavity and the larynx lies higher than in an adult. Both features bring the tongue closer to the palate, predisposing to obstruction. Obstruction in a baby or child due to trauma from intubation is most likely to occur at the subglottic region because this is the narrowest part of the airway, has a complete ring of cartilage (the cricoid) and loose mucosa (making it particularly susceptible to oedema). Oedema can cause dramatic increases in airway resistance and the work of breathing (for laminar flow, a 50% reduction in airway radius causes a 16-fold increase in airway resistance – from Poiseuille's law). Uncuffed tracheal tubes are less likely to cause trauma and are therefore preferred.

Physiological factors

Babies less than 5 months of age are obligate nose breathers. Obstruction of both nasal passages (e.g. because of secretions or choanal atresia) can cause asphyxia. Babies, especially, have a limited ability to cope with an obstructed airway because:

- the chest wall, trachea and bronchi are pliable and easily deformed
- the diaphragm and intercostal muscles have fewer 'fatigue resistant' type I fibres and tire easily
- oxygen reserves are lower because of a smaller functional residual capacity (FRC) and higher oxygen consumption (4–6 ml/kg/minute compared with 2–4 ml/kg/minute in adults).

If the work of breathing increases, respiratory failure and hypoxaemia can develop quickly.

Acute airway obstruction

The site of airway obstruction determines the clinical features. Agitation and crying worsen airway obstruction by causing turbulent airflow and by worsening dynamic compression.

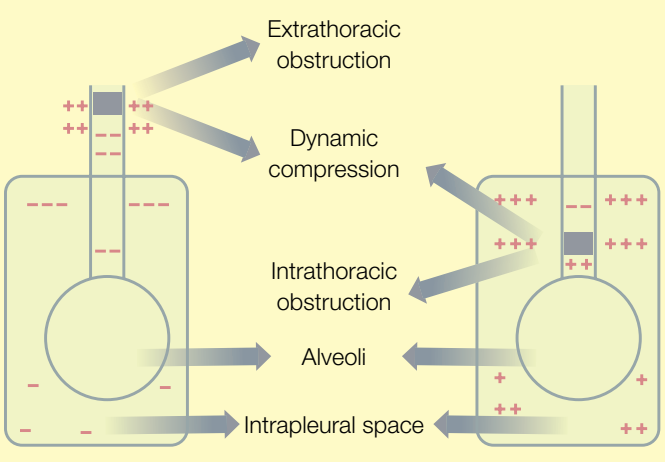
Extrathoracic obstruction – the calibre of the extrathoracic airways depends on the balance between the intraluminal and atmospheric pressures. Inspiratory efforts to overcome an extrathoracic obstruction generate large negative intrapleural pressures, which are transmitted to the extrathoracic airway as negative intraluminal pressure. The atmospheric pressure then exceeds the intraluminal pressure causing dynamic compression of the airway during inspiration (Figure 1a). Extrathoracic obstructions, therefore, cause inspiratory stridor, which may be improved by giving continuous positive airway pressure (CPAP) to help splint the airway open.

Intrathoracic obstruction – the patency of the intrathoracic airway depends on the balance of intraluminal and intrapleural pressures. Large positive intrapleural pressures generated during active expiration cause dynamic compression of the airways downstream of the obstruction (Figure 1b). Intrathoracic obstructions tend to cause expiratory stridor.

Sites of airway obstruction

a Extrathoracic obstruction causes dynamic obstruction during inspiration

b Intrathoracic obstruction causes dynamic obstruction during expiration



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Figures 2–4 list the causes, clinical features and severity of acute airway obstruction.

Causes of acute airway obstruction

Congenital	Acquired
• Choanal atresia (congenital blockage of nasal passages)	• Epiglottitis[1]
• Laryngomalacia[2]	• Laryngotracheobronchitis[2]
• Subglottic stenosis	• Bacterial tracheitis
• Subglottic haemangioma	• Subglottic stenosis
• Webs	• Burns
• Cysts	• Peritonsillar abscess
• Tracheal stenosis	• Foreign body
• Vascular rings or slings	• Angioneurotic oedema
• Bilateral vocal cord paralysis	• Nerve palsies
	• Mediastinal masses

[1]Uncommon [2]Common

2

Clinical features of acute airway obstruction

Features	Implication
• Stridor (noisy breathing caused by turbulent air flow)	Airway obstruction
• Inspiratory stridor	Supraglottic obstruction
• Expiratory stridor	Infraglottic obstruction
• Biphasic stridor	Glottic obstruction
• Stridor when crying or feeding	Moderate airway obstruction
• Stridor at rest	Severe airway obstruction
• Wheeze	Small airways obstruction
• Muffled cry	Supraglottic obstruction
• Hoarse cry	Laryngeal obstruction
• Unable to cry	Severe obstruction
• Dysphagia	Supraglottic obstruction
• Nasal flaring • Sternal, intercostal, subcostal retractions • Paradoxical respiration • Head bobbing	Increased work of breathing
• Tachypnoea • Tachycardia • Agitation	Hypoxaemia
• Sitting up and unable to lie supine	Severe airway obstruction
• Cyanosis	Severe hypoxaemia
• Sweating	Hypercarbia and fatigue
• Altered consciousness	Severe hypoxaemia
• Bradycardia or arrhythmias	Collapse imminent

3

Dos and don'ts in stridor

Do	Don't
• Give oxygen	• Examine the pharynx
• Observe closely	• Sedate the child
• Minimize stress to the child	• Send for radiography
• Ask for experienced help	• Attempt intravenous access until help is present and anaesthesia induced
• Maintain spontaneous respiration	• Use muscle relaxants until the airway is secure

4

Airway management

The primary goal of management is to secure the airway safely, which requires general anaesthesia. The child should be kept calm, allowed to adopt a comfortable position and given oxygen to breathe (unless this upsets them). Oxygen saturation (SpO_2) should be monitored continuously. Heliox (oxygen in helium) decreases airway resistance during turbulent flow because of its lower density, and can be useful.

Parents should accompany the child to the induction room to avoid the distress of separation. Appropriate equipment for emergency cricothyroidotomy or tracheostomy, a range of tracheal tubes (including sizes smaller than that calculated) and an experienced surgeon should be available.

An unhurried inhalational induction using either sevoflurane or halothane in oxygen is started. Induction can be slow because of the effects of airway obstruction and V–Q mismatch caused by atelectasis. Standard monitoring is established and intra-venous access secured once anaesthesia has been induced. Spontaneous breathing should be preserved throughout induction (CPAP helps to keep the airway open by combating dynamic compression and preventing atelectasis) and laryngoscopy attempted only when the child is deeply anaesthetized. Muscle relaxants can be given safely only when the airway is secure. The important management points are given in Figure 4.

Treating the common causes

Viral croup (viral laryngotracheobronchitis) is usually caused by either the parainfluenza, influenza or respiratory syncitial virus. It affects children from 6 months to 6 years of age and occurs in epidemics in late autumn and early spring. Croup is usually preceded by several days of coryza. Respiratory obstruction develops gradually producing stridor, which is typically worse at night (Figure 5). The child presents with a low-grade temperature, a brassy cough and hoarse voice. About 2% of affected children are admitted to hospital but less than 2% need tracheal intubation. Most respond to oxygen and nebulized adrenaline (epinephrine), 5 ml of 1:1000, repeated as required. Corticosteroids (dexamethasone or nebulized budesonide) reduce the need for intubation. Dexamethasone, 0.6 mg/kg oral or i.v., is usually given as a single dose but can be repeated (0.15 mg/kg). Nebulized budesonide, 2 mg, is given as a single dose; it may be repeated but a single dose has been shown to improve outcome. The duration of intubation varies but is on average 3–5 days. There is no evidence to support the use of steam tents (which can also limit clinical observation).

Assessment of croup severity

Moderate	Severe	Life threatening
Alert	Quiet or agitated	Depressed consciousness
Stridor present	Stridor present	Stridor may be absent
Mild recession	Severe recession	Limited chest movement
No fatigue	Increasing fatigue	Exhaustion
Oxygen saturation > 92% in air	Oxygen saturation < 92% in air	Oxygen saturation < 92% in oxygen
Steady respiratory rate	Increasing respiratory rate	Periods of apnoea
Steady heart rate	Increasing heart rate	Bradycardia

5

Epiglottitis (supraglottitis) is a bacterial infection caused by *Haemophilus influenzae* type B (HiB), which generally affects children of 2–6 years. The recent introduction of universal vaccination against HiB has made this condition rare. The symptoms progress rapidly and affected children look toxic (pale, pyrexial and shivery), have a high temperature and inspiratory stridor. They usually sit up, leaning forward, with their mouths open and tongue protruding, drooling saliva. They are reluctant to swallow or speak. On laryngoscopy, the epiglottis and aryepiglottic folds appear inflamed and swollen. Often, the only clue to the glottic opening is a small mucous bubble. After securing the airway and obtaining blood for culture, intravenous cefotaxime, 30 mg/kg/dose 8 hourly i.v., is given (contacts are treated with rifampicin). Airway oedema resolves in 48–72 hours. A leak around the tracheal tube (appropriate for the child's age) is a reliable guide to timing extubation.

Bacterial tracheitis (membranous laryngotracheobronchitis) is caused by *Staphylococcus aureus*. Affected children look toxic and have a brassy cough. Respiratory obstruction can progress rapidly. On laryngoscopy, thick purulent secretions resembling a membrane are seen covering the subglottic mucosa. Nebulized adrenaline (epinephrine) is of little use. Anti-staphylococcal antibiotics (e.g. flucloxacillin, 25–50 mg/kg/dose 6 hourly) should be administered. Toxic shock syndrome is a rare complication.

Inhaled foreign bodies may lodge in the larynx, trachea, main bronchi or smaller airways. A previously well child presenting with paroxysmal cough and respiratory distress should arouse suspicion of foreign body aspiration. Peanuts are the most common inhaled organic objects. They absorb water, swell up, and become soft and friable. They also cause chemical irritation of the airway and should be removed urgently. Severe obstruction is life threatening and urgent management of the airway a priority (Figure 6). Rigid bronchoscopy under general anaesthesia is required for removal of a foreign body (see below). A child with a small foreign body in the larynx may present with hoarseness or stridor. A foreign body in the lower airway may present with persistent cough, unilateral collapse or unilateral wheeze on auscultation. Expiratory chest radiographs are indicated in less urgent cases to locate the position of a radio-opaque body and identify other features typical of an inhaled foreign body. There are three characteristic patterns.

Management of choking

If a child is breathing and talking do not intervene because this could worsen the situation

If obstruction is complete, action depends on age

< 1 year
- Position child face down on rescuer's lap or forearm and administer four back blows between scapulae
- If obstruction persists place supine and give 4 rapid chest thrusts
- If unsuccessful attempt mouth-to-mouth resuscitation

Small child
- Administer 6–10 abdominal thrusts with child supine and rescuer at victim's feet. Place heel of hand above umbilicus in midline and below xiphoid process

Larger child
- Treat as adult; administer Heimlich manoeuvre

If obstruction persists and medical staff are available attempt cricothyroidotomy

6

A 'stop valve' obstruction completely obstructs a smaller airway. A chest radiograph shows collapse of the affected lung, mediastinal shift (towards the affected side) and upward movement of the ipsilateral diaphragm.

A 'ball valve' obstruction permits air entry during inspiration but stops air leaving during expiration. This causes hyper-inflation on the affected side, pushing the mediastinum towards the opposite side and the ipsilateral diaphragm down.

A 'bypass valve' obstruction allows ingress and egress of air and causes no radiological changes.

Airway burns may accompany facial burns or occur in a victim burned in a confined space. Clinical clues include soot deposits in the mouth or nose. Other clues include stridor, facial burns or circumferential burns of the neck and oedema of the pharynx. When airway burns are suspected, the trachea should be intubated without delay because facial, oral and airway oedema can occur rapidly, making intubation difficult or impossible. It is wise to use an uncut tube to allow room for facial swelling, which may occur later.

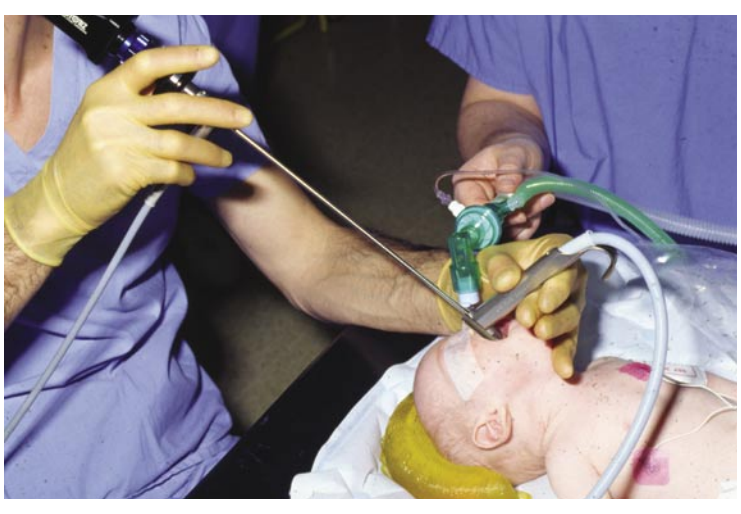
Laryngomalacia is a congenital laryngeal anomaly and the most common cause of stridor in early infancy (it generally develops within a few days of birth). Obstruction is caused by either a floppy tubular epiglottis or flabby supraglottic structures prolapsing into the glottis, causing inspiratory stridor. Symptoms worsen during feeding, crying or with respiratory infections, but disappear when the baby lies prone. The condition improves with growth, usually resolving spontaneously by 1 year of age. Occasionally, laser aryepiglottoplasty is used to treat severe obstruction but tracheostomy is rarely indicated.

Laryngoscopy and tracheobronchoscopy

The diagnosis and evaluation of airway obstruction and removal of a foreign body involves laryngoscopy and tracheobronch-oscopy, usually under general anaesthesia. Preoperative imaging (CT or MR) may be required to ascertain the nature and extent of the obstruction. Sedative premedication is avoided because of the risk of compromising the airway further. Both laryngoscopy and tracheobronchoscopy involve sharing the airway with the endoscopist. Spontaneous breathing is required to evaluate a dynamic obstruction (e.g. laryngomalacia, tracheomalacia) and is safer during removal of a foreign body.

Induction can be performed with sevoflurane or halothane (Figure 7). Sevoflurane has a better cardiovascular profile but halothane is useful in the obstructed airway where deepening anaesthesia is difficult. Preventing undesirable responses to instrumentation of the airway, such as laryngospasm, breath-holding or coughing, requires a deep plane of anaesthesia. The incidence of these problems can be reduced further by topical anaesthesia with lidocaine (lignocaine), maximum of 3 mg/kg, to the cords (by the anaesthetist) or carina (by the endoscopist). Anticholinergic agents (glycopyrollate, 10 μg/kg, or atropine, 20 μg/kg), given intravenously at induction, may reduce secretions and prevent bradycardia (especially if using halothane).

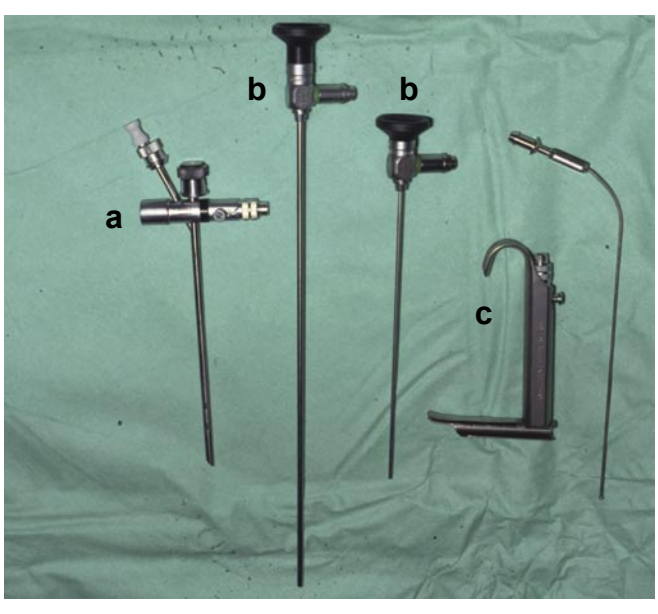
Maintaining the airway: inserting a tube into the trachea obscures the surgeon's view and impairs the movement of laryngeal structures during breathing. There are no specific microlaryngoscopy tubes for children, but if a tube is necessary, a size or two smaller is selected. A common alternative is to flood the pharynx with oxygen and a volatile agent delivered through a T-piece attached through a face mask (allowing flexible bronchoscopy through a modified angle piece) or nasopharygeal airway inserted into a nostril, while maintaining spontaneous breathing(Figure 7). Correct placement of the nasopharyngeal airway (usually a softened cut-down tracheal tube) can be verified by occluding the mouth and observing unobstructed breathing or during bronchoscopy. Delivering anaesthesia through a nasopharyngeal airway allows easy access by the surgeon to examine the supraglottic structures or introduce a flexible or rigid bronchoscope through the mouth and into the trachea. Vasoconstrictor nasal drops are useful to prevent traumatic bleeding (e.g. otrivine paediatric nasal drops or spray which contains xylometazoline 0.05%).



7 An infant maintained on oxygen and halothane via a nasopharyngeal airway while undergoing rigid bronchoscopy.

Monitoring: close observation, including movement of the chest and reservoir bag (once the breathing system is attached to the rigid bronchoscope) and SpO_2 monitoring are essential during the procedure to ensure adequate ventilation and oxygenation. The patency of the airway and movement of the cords can also be assessed by watching the endoscopic image on the screen. Leak of gases from the mouth makes end-tidal CO_2 monitoring less reliable.

The bronchoscope: the T-piece can be directly connected to the side arm of the Storz bronchoscope (Figure 8), allowing the bronchoscope to function effectively as a tracheal tube once passed through the cords. Positive-pressure ventilation or assisted breathing can also be delivered if the lesion is fixed. However, other rigid bronchoscopes do not permit ventilation (e.g. the Hopkins rod). Anaesthesia is maintained with a nasopharyngeal airway delivering oxygen and a volatile gas.



8 Rigid bronchoscope showing: **a** the Storz ventilating bronchoscope; **b** the Hopkins rod; and **c** the Storz laryngoscope.

During removal of foreign bodies from smaller airways, inadequate ventilation and hypoxia can occur. The surgeon should withdraw the bronchoscope to the trachea to improve ventilation.

Chronic airway obstruction

Causes of chronic airway obstruction are given in Figure 9. Obstructive sleep apnoea syndrome may complicate chronic airway obstruction. The features include:
- snoring
- apnoea
- fragmented sleep
- daytime somnolence
- failure to thrive
- recurrent respiratory infections.

Causes of chronic airway obstruction

Adenotonsillar hypertrophy
Macroglossia
Down's syndrome
Beckwith-Wiedemann syndrome
Hypothyroidism
Glycogen storage disorders
Mucopolysaccharidoses

Neuromuscular disorders
Duchenne muscular dystrophy
Cerebral palsy
Syringobulbia
Arnold-Chiari malformation

Laryngomalacia

Micrognathia/retrognathia
Pierre Robin syndrome
Treacher-Collins syndrome
Goldenhar's syndrome
Moebius syndrome
Hallermann-Streiff syndrome

Obesity
Praeder-Willi syndrome

Maxillary hypoplasia
Apert's syndrome
Crouzon's disease

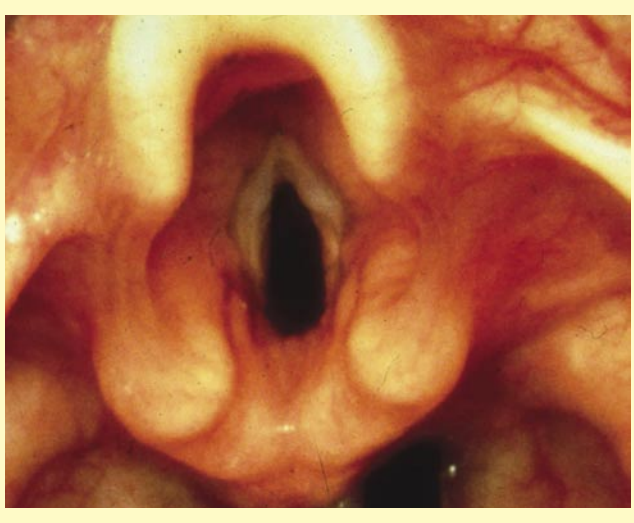
Laryngeal papillomatosis
(Figure 10)

9

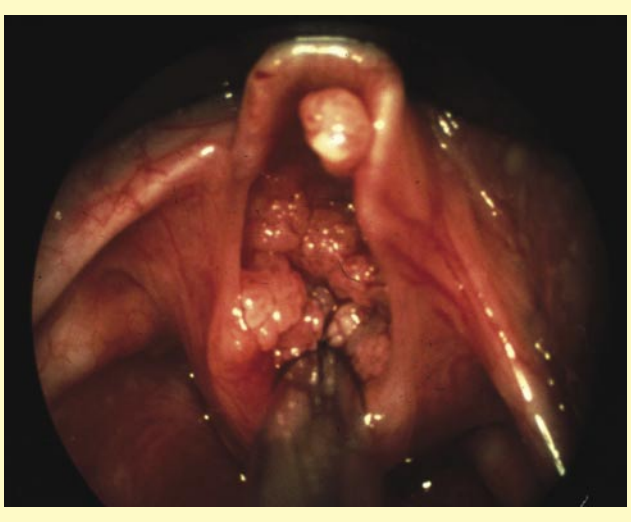
Right heart failure may occur in severe obstructive apnoea, the pathophysiology of which is given in Figure 11.

If obstructive sleep apnoea is suspected, the ECG should be examined for signs of right ventricular hypertrophy. Echocardiography helps to assess right ventricular hypertrophy and pulmonary pressures and detect tricuspid regurgitation. If heart failure is present, preoperative nasal CPAP and diuretics may optimize the child's condition.

Surgery should be deferred, if possible, in the presence of respiratory infections. Sedative premedication should be avoided because of the risks of oversedation and airway obstruction.



a The normal infant larynx.



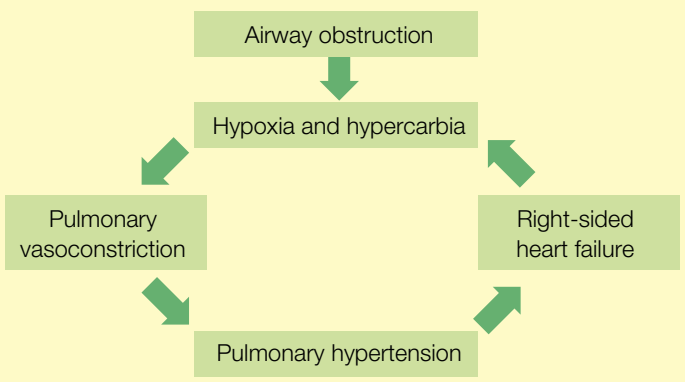
b Laryngeal papillomatosis.

10

Airway laser surgery

Laser beams are used to vaporize papillomata (see Figure 10b), and occasionally other pathology, but is associated with scarring. To enable the surgeon to aim the laser with precision, the target area should be still. Although neuromuscular blockade and tracheal intubation can ensure this, a laser beam can set fire to a normal polyvinyl chloride tube. Special metal-coated, laser-resistant tubes are expensive and their external diameter (ED) exceeds that of ordinary tracheal tubes of the same internal diameter (ID). The smallest laser tube has an ID of 3.0 mm and an ED of 5.2 mm (compared with 3.0 mm and 4.2 mm for a standard tube) and is suitable only for children over 1 year of age. Narrowing of the airways further limits their use. The dangers of airway laser surgery are discussed elsewhere.

Pathophysiology of right heart failure in obstructive sleep apnoea



11

Alternative anaesthetic techniques

Jet ventilation down the bronchoscope or operating laryngoscope, combined with total intravenous anaesthesia and muscle relaxants. The flow generated decreases with smaller injector needles. A 16G needle is commonly used in children, but great care must be taken to avoid barotrauma. A pressure-regulating device is now available which should be used to decrease the pipeline pressure (4 bar) to a lesser amount and thereafter deliver a more suitable volume to a small child. Pneumothorax, though rare, is a complication. Dissemination of the papilloma virus is a theoretical consideration but as yet is not described.

Apnoeic techniques: the surgeon uses the laser intermittently and the anaesthetist intubates and ventilates the patient for short durations between successive applications of laser.

Deep volatile anaesthesia delivered through a nasopharyngeal airway: for supraglottic and subglottic laryngeal lesions the combination of deep volatile anaesthesia with topical local anaesthetic (as described for laryngoscopy above) allows spontaneous respiration and can provide excellent conditions. ◆

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Anaesthesia for ENT Surgery

Charles Stack

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In the UK, routine ENT surgery accounts for a high proportion of children requiring anaesthesia. Tonsillectomy is undertaken in 2.3/1000 children under 12 years of age. Postoperative haemorrhage occurs in up to 4% and carries a risk of death.

Adenotonsillectomy

Indications for adenotonsillectomy include:

- recurrent tonsillitis
- recurrent otitis media
- obstructive sleep apnoea
- upper airway obstruction leading to pulmonary hypertension, right ventricular hypertrophy and right heart failure
- quinsy
- tuberculous cervical adenitis

The two main surgical techniques are guillotine tonsillectomy (which involves snaring the tonsil and excising it rapidly), and dissection tonsillectomy (which involves dissection and uses diathermy or surgical ties to control bleeding points). For either technique, the airway has to be secured, with a tracheal tube or a laryngeal mask airway (LMA). The surgeon inserts a Boyle–Davis mouth gag to keep the mouth open, the tongue blade of which (the 'Doughty tongue blade') has a groove to keep the tracheal tube or LMA out of the surgical field. It is important to ensure that the airway remains patent when the gag is opened because kinking of the tracheal tube or LMA can easily occur.

Preoperative assessment and premedication – it is important for the anaesthetist to ask specifically about:

- upper respiratory tract infections (adenotonsillectomy should be avoided during active infections because the risk of bleeding increases with adenoidal or tonsillar inflammation)
- features suggesting a bleeding diathesis
- obstructive sleep apnoea.

Children with obstructive sleep apnoea are particularly liable to respiratory depression after sedatives (therefore avoid sedative premedication) and general anaesthesia. Improvement after surgery is not immediate and takes several weeks. Postoperative care on a high dependency unit or ICU is usually required.

Airway protection – the standard method for maintaining the airway during tonsillectomy has been intubation with a south-facing, preformed, disposable tracheal tube followed by a spontaneously breathing anaesthetic technique. However, the results of a study using airway endoscopy showed no soiling of the trachea with blood when using an LMA compared with soiling in over 50% when using a tracheal tube. The LMA and tracheal tube for tonsillectomy are compared in Figure 1. The LMA is preferable because it affords better airway protection from blood until the patient is awake, but the choice depends on the anaesthetist and surgeon.

Use of tracheal tube or laryngeal mask airway (LMA) for tonsillectomy in children

Tracheal tube

Advantages

- Definite placement in trachea
- Smaller size
- Not in surgical field
- Easier to 'take over' respiration

Disadvantages

- Blood in trachea in > 50% of children
- Greater stimulation on insertion
- May need muscle relaxation for intubation
- Removal of airway protection when deeply anaesthetized if extubated 'deep'

LMA

Advantages

- Better airway protection
- No muscle relaxants required
- Protection of the lower airway until awake
- Reduced incidence of postoperative vomiting

Disadvantages

- Large size may impair surgical access
- Placement may encroach on surgical field
- Can be difficult to position correctly

1

Postoperative bleeding – the main complication of tonsil-lectomy is blood loss in the airway. If an anaesthetic technique that involves extubation under deep inhalational anaesthesia is used, it is important to suction the pharynx fully under direct vision (this also allows assessment of whether the surgeon needs to consider further attempts to control bleeding). The patient should be extubated head down on their left side (the 'tonsillar position') and should remain in this position to allow blood to trickle away from the larynx. Mean blood loss is about 4 ml/kg, but it is usually underestimated because most is swallowed.

Primary postoperative haemorrhage usually occurs within 8 hours of surgery. Children should be observed closely post-operatively to detect signs suggesting haemorrhage, such as:

- increased swallowing
- pallor or prolonged capillary refill time
- unexplained tachycardia
- restlessness
- sweating
- signs of airway obstruction
- hypotension (occurs late).

Bleeding tonsil

Death can occur from a bleeding tonsil (usually due to hypotension) following induction of anaesthesia after inadequate resuscitation. Mortality from tonsillectomy is about 1/10,000. The patient loses blood steadily, often quietly swallowing the blood before vomiting. Blood loss is always considerably more than that measured in the vomit; careful preoperative assessment is essential.

Before surgery the child should be given oxygen and resus-citated with intravenous fluids and blood (when available). A full blood count, clotting screen and cross match are required.

- Adequate fluid resuscitation with colloid and blood products is essential before inducing anaesthesia.
- Restlessness is often due to hypovolaemia, therefore sedation preoperatively should be avoided.
- Abnormal clotting may occur, therefore non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided and replacing clotting factors considered.
- Blood in the airway may cause obstruction or hinder the view at laryngoscopy.
- Blood in the stomach increases the risk of gastric aspiration at induction.
- The airway may be narrower due to tracheal edema, if so a tracheal tube half a size smaller should be considered.
- Care should be exercised when using anaesthetic agents that may cause vasodilatation and hypotension.
- The effects of the previous general anaesthetic and peri-operative opiates should be considered.

The recommended anaesthetic techniques are compared in Figure 2. Two suckers should be available at induction because haemorrhage can be brisk. Attempts should be made to empty the stomach before cessation of anaesthesia to reduce the risk of postoperative aspiration.

Uses of rapid sequence induction (RSI) or gaseous induction in the left lateral, head-down position for the child with a bleeding tonsil

RSI

Advantages

- Rapid induction
- Rapid control of the airway
- Less likelihood of regurgitation during induction

Disadvantages

- Blood in airway
- Patient may inhale blood
- May not visualize cords after paralysis
- Cardiovascular depression from induction

Gaseous induction

Advantages

- Maintenance of spontaneous respiration
- Inhalation of blood less likely

Disadvantages

- Blood in airway may precipitate laryngospasm
- Slow
- Less experience with this position therefore intubation difficult
- Restlessness during induction
- Respiratory depression from previous anaesthetic
- Cardiovascular depression from gaseous induction

2

Analgesia

Adenotonsillectomy is painful. Traditionally, opiates have been avoided because of their respiratory depressant and sedative effects (particularly in those with obstructive sleep apnoea) though codeine phosphate, 1 mg/kg i.m., has been used. NSAIDs are as effective as opiates but may increase the risk of primary postoperative haemorrhage (particularly ketorolac). Paracetamol alone is often insufficient.

In one study, the combination of paracetamol and ibuprofen as premedication reduced early requirements for supplementary analgesia compared with paracetamol alone (though pain scores were similar by 4 hours). Primary postoperative haemorrhage occurred but the numbers were too small to be significant. Median blood loss increased during adenotonsillectomy but was not statistically significant in the group receiving ibuprofen.

Most anaesthetists use perioperative opiates with a combination of NSAIDs and paracetamol at operation and then regularly postoperatively. A comparison of fentanyl (intravenous) and morphine (intramuscular) showed reduced frequency of vomiting in the fentanyl group (median: 1 episode versus 2 episodes) but not a reduced incidence (70 versus 78%). 52% of the fentanyl group and 41% of the morphine group required rescue opiate.

Postoperative nausea and vomiting occurs in 5–78% of patients. Vomiting causes distress, delayed discharge, dehydration and possibly bleeding from the tonsillar bed. Swallowed blood is emetogenic. Factors that reduce vomiting following surgery in children are:

- propofol induction and maintenance
- use of LMA
- routine use of anti-emetics
- midazolam, dexamethasone
- adequate analgesia
- avoidance of opioids
- intravenous fluids.

Day case tonsillectomy

The advantages of day case tonsillectomy are mainly socioeconomic; it involves less family disruption and reduces cost. The operation must be in the morning and a significant overnight admission rate may be expected. The disadvantages are the risk of primary postoperative haemorrhage (1–4%), the need for adequate analgesia (over 40% require postoperative opioids) and a significant rate of postoperative nausea and vomiting (5–78%). Distance from hospital, availability of transport and appropriate family circumstances also have to be taken into account. Children with a history of obstructive sleep apnoea should not be admitted as day case patients. Overall, it is probably safer for patients to remain in hospital overnight after tonsillectomy.

Myringotomy

Myringotomy with insertion of grommets is a common day case operation. An anaesthetic technique with spontaneous respiration (usually via a face mask) is used and the head held to the side during examination. Theoretically, nitrous oxide increases the pressure in the middle ear by diffusion of the gas into the air-filled cavity. Mild-to-moderate pain occurs afterwards for which perioperative paracetamol is useful. ◆

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Assessment of Pain in Children

Neil S Morton

Neil S Morton is Consultant in Paediatric Anaesthesia, Intensive Care and Pain Management at the Royal Hospital for Sick Children, Glasgow, UK. He qualified from Aberdeen University and trained in Glasgow, Dundee and Montreal, Canada. His interests are in developing pain management services for children and improvements in the management of children undergoing diagnostic and therapeutic procedures.

Pain is difficult to measure precisely and reliably in children and many pain measurement tools and scores have been developed (Figure 1). The clinician needs a pragmatic system that reliably tracks both the child's pain experience and the efficacy of pain control over time.

Pain assessment is a broader concept than pain measurement and takes into account cognitive, physiological, sensory, behavioural, affective, sociocultural and environmental factors. The assessment must be appropriate for the child's stage of development, the severity and chronicity of the child's illness, the surgical or medical procedure and the medical environment.

- Self-reported assessment – pain assessment is most accurate when children can tell staff about their pain. It is possible for children from age 3 years to self-report the location, severity and nature of pain using words appropriate to their stage of development.
- Observed assessment – to detect the symptoms and signs of pain in the younger child (or in the older child with mental or physical disabilities), behavioural cues and physiological values are used. These are open to misinterpretation; for example the same changes may be caused by things other than pain (e.g. hunger). Experienced paediatric staff are better at interpreting these cues than novices, and parents are often better than nurses.

Pain assessment must be linked to appropriate interventions based on the assessment with the aim of ensuring that the child experiences no pain or only mild pain. Measurement with pain tools or scores should be regarded as an aid to this more complex holistic assessment process. For severe or acute pain that is likely to persist over a number of days it is important to assess anxiety and depression.

Whichever scoring system is used, pain assessments should be repeated regularly, appropriate interventions should be prescribed and their effectiveness should be documented.

Pain scoring

Pain measurement tool	Appropriate age range	Clinical utility	Indicators included	Advantages	Disadvantages
Behavioural and physiological signs of distress					
Objective Pain Scale (OPS)	< 3 years	• Acute postoperative pain	• Blood pressure • Crying • Movement • Agitation • Verbal expression • Body language	• Easy to use • Validated • Reliable • Tracks pain over time • Scores decrease with analgesia	
'CRIES' Score (Cry, Requires oxygen, Increased heart rate and blood pressure, Expression, Sleeplessness)	32–60 weeks' gestational age	• Neonates and infants • For acute procedural and postoperative pain	• Cry • Oxygen saturation and requirements • Heart rate and blood pressure • Expression • Sleeplessness	• Easy to remember and use • Validated • Reliable • Tracks pain over time • Scores decrease with analgesia	• Uses oxygenation as measure which can be affected by many other factors • Blood pressure measurement may upset the baby and falsely increase the score
COMFORT Score	0–17 years	• Distress in paediatric intensive care	• Alertness • Agitation • Calmness • Respiratory response • Physical movement • Blood pressure • Heart rate • Muscle tone • Facial tension	• Validated • Reliable • Tracks pain over time • Scores decrease with analgesia and/or sedation	• Complicated • Unsuitable for intubated or paralysed patients
CHEOPS (Children's Hospital of Eastern Ontario Pain Scale)	1–7 years	• Acute postoperative pain • Venepuncture pain	• Cry • Facial expression • Verbal expression • Torso position or movement • Touching wound • Leg position and movement	• Validated • Scores decrease with analgesia	• Complicated • May not track postoperative pain over time in 3–7 year age group because pain behaviours become inhibited or habituated
TPPPS (Toddler-Preschool Paediatric Pain Scale)	1–5 years	• Acute postoperative pain	• Verbal expression • Facial expression • Body language	• Tracks pain relief	• Seven categories to score
Self reporting tools					
Poker chip tool (Figure 2)	> 4 years	• Procedural pain • Acute postoperative pain	• Four tokens to indicate pieces of hurt corresponding to nil, mild, moderate and severe pain	• Validated • Easy to use	• Unsuitable for the critically ill or sedated child
Four faces scale (Figure 3)	> 4 years	• Procedural pain • Acute postoperative pain	• Four faces from neutral to sad corresponding to nil, mild, moderate and severe pain	• Validated • Easy to use	• Unsuitable for the critically ill or sedated child
Vertical colour analogue slide-rule (Figure 4)	> 4 years	• Procedural pain • Acute postoperative pain	• Vertically oriented coloured wedge • Calibrated 0–100	• Validated • Easy to use	• Unsuitable for the critically ill or sedated child
Horizontal linear analogue	> 7 years	• Procedural pain • Acute postoperative pain	• Horizontal 100 mm line • No markings as anchor	• Validated • Easy to use	• Unsuitable for the critically ill or sedated child
Adjectival self-report	> 4 years	• Procedural pain • Acute postoperative pain	• Key words with four choices	• Validated • Easy to use	• Unsuitable for the critically ill or sedated child

Source: Finley G A, McGrath P J, eds. *Measurement of Pain in Infants and Children. Progress in Pain Research and Management*. Vol. 10. Seattle: IASP, 1998.

1

Children younger than 3 years

In the assessment tools used for children younger than 3 years, observations of behaviour (e.g. facial expression, body position, mobility, crying, sleep pattern), skin colour and vital sign measurements (e.g. arterial pressure, heart rate, arterial haemoglobin saturation) are given numerical scores that are added to give a total. This static assessment is much less useful than a dynamic one, in which the nurse is looking for the total score to improve in response to comforting, analgesia or sedation. This responsive (or interactive) scoring can be used to guide, for example, the titration of analgesic drugs. Good documentation of the score, the intervention used and its effect is important.

Many scores of this type are confounded in the less mature, sick or sedated, paralysed, intubated or ventilated child, so it is reasonable to assume that such children who have had surgery may be in pain and ensure that adequate analgesia is given.

Pain-related behaviour in toddlers may be 'all-or-nothing' in nature. They can often locate pain precisely (e.g. by grabbing at the site of operation). This suggests that a simple scoring system (e.g. pain present/absent) may be enough to guide analgesic therapy in this age group.

Children older than 3 years

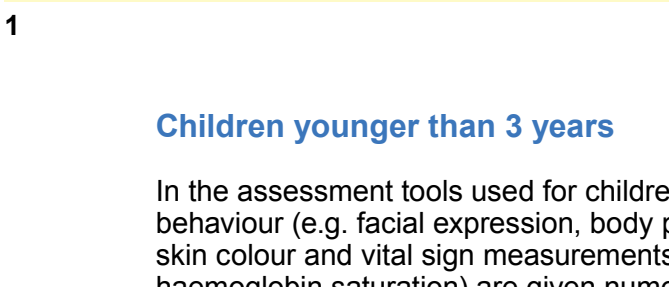
Many children over 3 years can differentiate between the presence or absence of pain, and indicate its nature, intensity and site. They can categorize pain reasonably accurately into one of four choices corresponding to nil, mild, moderate or severe.

Many children can explain whether they are feeling pain and indicate how bad it is providing they understand the language and phrases used. They can comprehend the concept of 'pieces of hurt' as used, for example, with the poker-chip tool (Figure 2).

Indicating severity using a faces scale can work well, but the choice of faces is best limited to four, with the first face appearing 'neutral' rather than 'happy' (Figure 3). Some children are unable to relate the faces to their own pain experiences, while others tend to choose those at the extremes of the scales.

Many children relate to previous pain experiences to indicate whether their current experience is worse or better, for example by comparing it with a previous injury. These earlier experiences may influence their assessments (e.g. the same injury may be scored as 'severe' by a young child with no previous pain experiences, while an older child, who has had a worse pain before, may score the pain as 'mild'). Some children who have undergone repeated, painful procedures may be sensitized and have a lowered pain threshold.

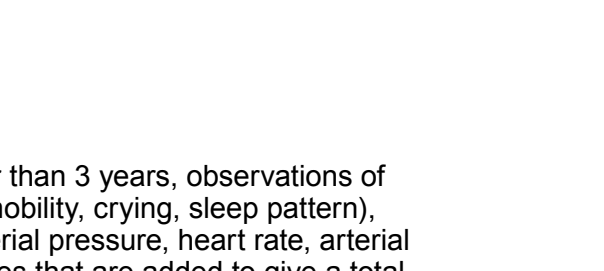
Poker chip tool



Tokens acting as pieces of pain are stacked by the child to indicate how much pain they are experiencing

2

The four faces scale



Note: the first face should be neutral, not happy

3

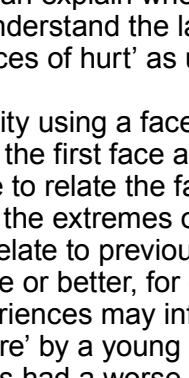
Children older than 5 years

Visual analogue tools and scales can be operated successfully by children from the age of 5 years, however, the classical 100 mm horizontal line is not well understood by younger children.

Adding colour gradations is helpful and making the scale into a vertical colour wedge is best (Figure 4).

Vertical colour analogue slide-rule tool

The child indicates the pain level with the slider. The obverse side is calibrated from 0 to 100



4

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Central Blocks in Children

Edward Doyle

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The use of central neural blocks in children is now a routine part of paediatric anaesthesia. In selected children they reduce the morbidity associated with surgery and anaesthesia and can favourably influence the postoperative course. These techniques often result in dense intraoperative and postoperative analgesia, reduced requirements for volatile agents, minimal postoperative vomiting and a reduction in opioid use. The same standards of preoperative assessment used in adults, regarding contraindications, technical competence, sterility and postoperative monitoring are required in children. In most patients, a central block is combined with general anaesthesia. There is an incidence of predictable side-effects and a low incidence of potentially serious complications. Most of these are easily managed if competent personnel and appropriate facilities are available.

Subarachnoid and epidural blocks in young children seldom result in hypotension unless there is significant hypovolaemia or a high thoracic block. This is probably because children under 8 years of age have a reduced sympathetic tone and reduced blood volume in the splanchnic circulation and lower limbs, compared with older children and adults. Consequently, fluid loading or the administration of vasopressors are seldom necessary and this can make the practical conduct of central blocks easier than in adults. In older children, who have a more adult physiology, there is occasionally a variable decrease in both heart rate and blood pressure.

Subarachnoid (spinal) anaesthesia

Subarachnoid anaesthesia has a rapid onset, produces profound sensory and motor block without systemic effects, and when used alone avoids volatile anaesthetic agents or tracheal intubation. It provides definite benefits compared with general anaesthesia in certain children at high risk (e.g. infants born prematurely) but requires experience and the ability to manage any complications that may occur.

The most common indication is probably inguinal hernia repair in infants who were premature. 30% of premature infants with a birth weight less than 1000 g develop an inguinal hernia. Postoperative apnoea occurs in 30–40% of these babies if they undergo general anaesthesia for repair and is particularly common in those less than 44 weeks postconceptional age.

Three prospective, randomized, controlled studies have demonstrated a significant reduction in the incidence of postoperative apnoea, episodes of bradycardia and hypoxia, or requirement for postoperative ventilation, when subarachnoid anaesthesia rather than general anaesthesia is used in infants who were premature. In one study, in which a subgroup received sedation as well as subarachnoid anaesthesia, over 80% developed prolonged postoperative apnoeas with bradycardia and this technique probably offers no advantages over general anaesthesia in reducing the incidence of respiratory complications.

Other indications for subarachnoid blockade include most operations below the umbilicus (though it has also been used for upper abdominal or thoracic surgery). In combination with general anaesthesia, the technique has been used for spinal and cardiac surgery to reduce the requirements for opioids or postoperative ventilation in high-risk children, and to minimize the perioperative stress response to surgery. In many centres outside the UK, the technique is not restricted to high-risk patients but is also used in ASA I and II patients having lower- body surgery, simply because of the good anaesthetic and surgical conditions it provides.

Short narrow-gauge spinal needles ranging from 22 G to 24 G are available for use in children. Narrower-gauge adult needles may also be used in older children particularly if post-dural puncture headache is a concern. Hollow hypodermic needles or intravenous cannulae should not be used because they may introduce a core of epithelial tissue into the subarachnoid space. Injection should be performed at a low lumbar interspace because the neonatal spinal cord usually reaches the L3 vertebral level. Injection is often performed with the baby in the sitting position restrained by an assistant who also ensures that episodes of airway obstruction do not occur during the procedure.

Drugs

Bupivacaine is the local anaesthetic used most commonly in Europe whereas tetracaine (amethocaine) tends to be used in North America (Figure 1). Larger doses of local anaesthetic on a mg/kg basis are required than in adults. Children, and especially neonates, have a larger volume per kg of CSF than adults, with a higher proportion contained in the lumbar region, resulting in more dilution of the local anaesthetic. The greater cardiac output relative to body weight in infants and neonates results in more rapid systemic uptake of local anaesthetic contributing to a relatively short duration of subarachnoid anaesthesia compared with adults (usually about 50–120 minutes). The addition of adrenaline prolongs the duration of effective subarachnoid blockade by 20–40%.

There is limited pharmacokinetic data concerning subarachnoid bupivacaine in children. The mean plasma bupivacaine concentration in neonates 10 minutes after intrathecal administration of isobaric bupivacaine, 1 mg/kg, was 0.31 μg/ml (range 0.13–0.79 μg/ml) and 0.25 μg/ml (range 0.1–0.38 μg/ml) after intrathecal administration of isobaric bupivacaine, 1 mg/kg, with 1/200,000 adrenaline (epinephrine). Bupivacaine is extensively bound to plasma proteins, mainly albumin and α_1 acid glycoprotein. Neonates have lower levels of these proteins than adults, resulting in a decreased binding capacity for bupivacaine and an increased risk of toxicity from free bupivacaine. The mean free bupivacaine levels in this study were 0.047 μg/ml (range 0.01–0.11 μg/ml) in the group receiving bupivacaine alone and 0.062 μg/ml (range 0.03–0.1 μg/ml) in the group receiving bupivacaine and adrenaline (epinephrine). These values are reassuringly low.

Local anaesthetics and doses for subarachnoid anaesthesia in infants

Drug	Dose range[1] (mg/kg)
• 0.5% tetracaine hyperbaric plain	0.32
• 0.5% tetracaine hyperbaric plus adrenaline (epinephrine)	0.5–0.6
• 0.5% bupivacaine isobaric plain	0.75–1.0
• 0.5% bupivacaine plain with or without adrenaline (epinephrine)	0.6–1.0

[1]Recommendations from different authors

Problems

The technique of subarachnoid blockade in neonates and infants has a significant incidence of problems. The duration of the block is short and is reliable only for procedures lasting less than 1 hour. There is no significant postoperative analgesia and alternative analgesia must be provided. There is a failure rate of about 10% and an incidence of high blockade, which can cause respiratory compromise. These problems are well demonstrated in a series of 164 infants, who were premature, undergoing subarachnoid anaesthesia. In 137 patients (83.5%) there was a block that was adequate for surgery. Successful lumbar puncture could not be performed in 12 patients (7.3%). A further 15 (9.1%) required supplementation with infiltration anaesthesia, systemic analgesia or anaesthesia. Two patients became apnoeic during the lumbar puncture and five developed a high block producing respiratory weakness. Postdural puncture headache is seldom a clinical problem in children aged less than 10 years, but does occur in older children. Efforts to prevent this include the use of a pencil-type or a fine cutting needle. Hypotension during a subarachnoid block is also unusual in babies or children and if it occurs may indicate unanticipated hypovolaemia or a high block.

Epidural analgesia

The introduction of paediatric epidural needles (5 cm long, either 19 G or 20 G) and fine epidural catheters has made epidural analgesia feasible in the smallest of children. Single injection or infusion epidural analgesia at the thoracic or lumbar levels has become popular and often allows the use of light anaesthesia and minimal opioid administration, and may help avoid postoperative ventilation in some high-risk patients. Children in whom these techniques are particularly important include those with gastro-oesophageal reflux undergoing fundoplication, children with respiratory disabilities undergoing abdominal surgery or neonates undergoing repair of oesophageal atresia. In neonates and infants it is possible to thread a catheter from the sacral hiatus to the thoracic region and to provide analgesia for abdominal or thoracic surgery. This technique is popular because it allows the epidural space to be cannulated below the spinal cord. However, attempts to thread catheters to the thoracic region from the caudal hiatus or a low lumbar approach are generally ineffective in children aged over 2 years.

Conservative doses for epidural infusion in children after a loading dose of bupivacaine, 2–2.5 mg/kg, are a maximum of 0.2–0.25 mg/kg/hour in neonates or 0.3–0.4 mg/kg/hour in older children. Data from various sampling studies during continuous infusion of extradural bupivacaine of less than 0.5 mg/kg/hour are generally reassuring. Mean plasma concentrations are usually low and less than 2–4 μg/ml, a level often associated with the risk of toxicity. However, concentrations in individual patients may sometimes be high. There is particular concern about toxicity in children aged less than 6 months in whom drug elimination is variable as a result of diminished clearance and prolonged half-lives and prolonged infusions are associated with rising plasma levels of bupivacaine.

The simultaneous use of other analgesics such as opioids or non-steroidal analgesic drugs, increases the efficacy of epidural analgesia and reduces the dose of local anaesthetic required. After major surgery, an opioid (commonly fentanyl, morphine or diamorphine) is usually required in addition to local anaesthetic. This acts synergistically with the local anaesthetic to improve analgesia and to reduce the requirement for local anaesthetics. It will also treat discomfort from areas of the body that are not covered by the epidermal block and provide a mild degree of sedation. Opioids are conventionally given mixed with the local anaesthetic solution but may also be given systemically. Opioids have also been used alone by intermittent injection or continuous infusion to provide epidural analgesia.

Problems

Common problems associated with epidural anaesthesia in children are listed in Figure 2. The incidence of dural tap is variable and is influenced by various factors including the experience of the anaesthetist, the technique used, the age of the patient and the type of epidural needle used. More dural punctures occur if inappropriately large epidural needles are used or if air, rather than saline, is used to detect loss of resistance. The incidence of dural tap is usually quoted at less than 10%.

Technical problems with epidural catheters may occur and cause premature discontinuation of epidural analgesia. The incidence of problems is considerably higher with the fine catheters (e.g. 23 G) designed for babies or small children, than with the larger catheters (e.g. 21 G). Potential problems include leakage at the site of entry of the catheter through the skin, misplaced or occluded catheter and disconnection between the epidural catheter and the bacterial filter.

Common potential side-effects include urinary retention, leg weakness, nausea and vomiting. Intravenous or subarachnoid injection, epidural haematoma or infection are uncommon, but possible. Lack of sensation may cause problems if not anticipated and heel blisters or pressure sores may occur in analgesic skin unless patients are repositioned regularly.

When epidural opioids are used there is a possibility of respiratory depression. This is a particular risk if the child is aged under 1 year, is given concurrent parenteral opioids or large doses are used. Appropriate doses associated with a low incidence of respiratory depression are fentanyl, 0.1–0.5 μg/kg/hour, or morphine, 5 μg/kg/hour. The best method of detecting respiratory depression at an early stage is the use of continuous pulse oximetry while the patient is breathing air.

Postoperative nausea and vomiting in infants and young children tends to be less common and severe than in adults, though older children behave more like adults. The use of epidural opioids probably makes this problem worse, but it is impossible to quantify this effect in children. The incidence of postoperative nausea and vomiting during epidural infusions containing fentanyl has been reported as 0–80%. This should be compared with the significant incidence when systemic opioids are used to provide analgesia after major surgery.

The incidence of urinary retention is unknown because many patients are catheterized perioperatively. The reported incidence varies with age, opioid use and the criteria used to define urinary retention. The reported incidence is zero in neonates, 18% in infants and 62% in those aged 10–17 years. The relative contributions of opioid and local anaesthetic are difficult to determine because it occurs when both types of analgesic are used alone.

Epidural abscess or haematoma associated with the use of epidural analgesia for acute pain have not been reported in children. Other serious complications that result in permanent neurological deficit or death have a low incidence (5 of 7200 epidurals in a retrospective survey of practice between 1982 and 1991 of members of the Society of French Speaking Paediatric Anaesthetists). Risk factors for serious complications in this study included multiple traumatic attempts at epidural cannulation, age less than 3 months, or the use of the loss of resistance to air technique for identifying the epidural space.

Common problems of epidural analgesia in children

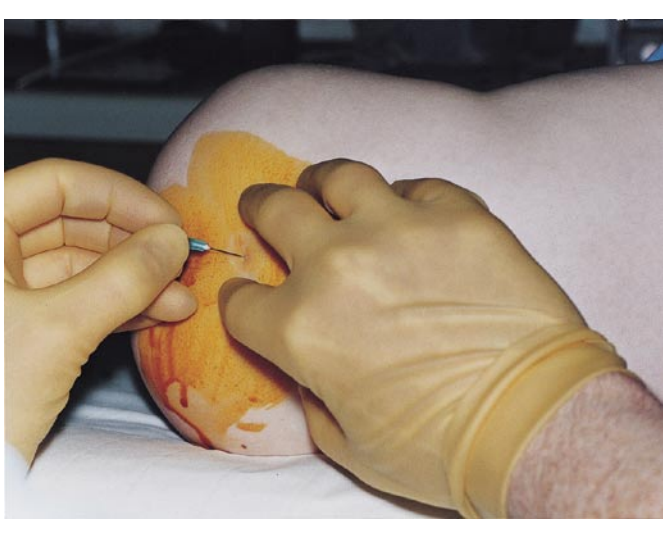
Problem	Incidence[1] (%)
• Dural puncture	< 10
• Catheter disconnection or obstruction	0–17
• Respiratory depression	< 1
• Hypotension	< 10
• Urinary retention	0–60
• Nausea and vomiting	0–80

[1]Composite figures from a number of series

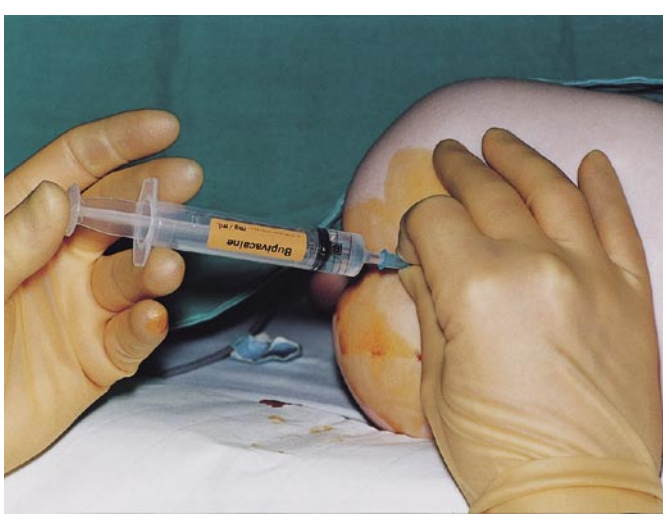
Caudal epidural blockade

Single-injection caudal epidural blockade is a simple technique with a high success rate and a low incidence of serious complications. It can be used to provide intraoperative anaesthesia and postoperative analgesia for many operations below the umbilicus. It reduces the requirement for volatile anaesthetic agents and opioids, which reduces the incidence of postoperative nausea and vomiting. Children may then resume oral intake and take oral analgesics after quite major surgery without the need for parenteral analgesic drugs. In most patients, the caudal block is combined with light general anaesthesia, though it has been used as the sole technique for inguinal hernia repair in infants who were premature. It has also been combined with simultaneous subarachnoid block to provide prolonged anaesthesia after a subarachnoid block has worn off.

Injection is performed through the sacral hiatus, well below the termination of the spinal cord, therefore there is little risk of serious neurological damage during caudal epidural blockade. The main potential for serious complications comes from the possibility of intravenous injection or dural puncture followed by a subarachnoid injection. This is especially the case in small children in whom the termination of the dural sac may lie as low as the second sacral vertebra. Both of these problems can be almost eliminated if the initial puncture of the sacral hiatus is performed with a needle without the syringe of local anaesthetic attached (Figures 3 and 4). If this needle is left open to the atmosphere for a few seconds, blood or CSF will appear if there has been a puncture. This will prevent the injection of local anaesthetic into the CSF or a vein. If the needle is not left open to the atmosphere for a few seconds then it may be impossible to aspirate blood or CSF and an injection of local anaesthetic into the wrong compartment may be given.



3 Initial puncture of sacral hiatus performed with a needle without the syringe attached.



4 Slow injection of local anaesthetic without moving the needle.

Drugs

Local anaesthetics: bupivacaine is the local anaesthetic agent used most commonly for caudal epidural blockade. Pharmacokinetic data show that single epidural doses of bupivacaine, 2–2.5 mg/kg, are associated with low plasma levels of the drug (Figure 5).

Plasma levels of bupivacaine after caudal epidural injection

Drug	Dose (mg/kg)	Number of children	C_{max} mean (range) (μg/ml)	T_{max} mean (range) (minutes)
Bupivacaine	2.5	6	1.25 (0.96–1.64)	29 (19–38)
Bupivacaine	2.5	13	0.97 (0.55–1.93)	28 (10–60)
Bupivacaine	3.0	45	1.4 (maximum 2)	
Bupivacaine	2.0	14	0.9	16
Bupivacaine plus adrenaline (epinephrine)	3.7	10	0.67	45

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Additives to local anaesthetic solutions have been used in an attempt to prolong the duration of caudal analgesia provided by a single injection of local anaesthetic.

Adrenaline (epinephrine) – vasoconstrictors decrease the rate of vascular absorption of local anaesthetic and increase the density and duration of the block. The most common is adrenaline (epinephrine) in a concentration of 5 μg/ml (1/200,000). When used for caudal epidural injection the effects of adrenaline (epinephrine) tend to be less pronounced with longer-acting local anaesthetics (e.g. bupivacaine) than with more hydrophilic drugs (e.g. lidocaine (lignocaine)). The high lipid solubility of bupivacaine causes it to be deposited in epidural fat and released slowly and adrenaline (epinephrine) tends to have little effect in prolonging its duration of action.

Opioids – the administration of caudal epidural opioids usually produces profound long-lasting analgesia. The median duration of analgesia after caudal morphine, 0.1 mg/kg, for lower-body surgery is 12 hours (range 4–24 hours) compared with 5 hours (range 3.5–24 hours) for 0.25% bupivacaine, 1 ml/kg, plus 1/200,000 adrenaline (epinephrine) and 45 minutes (range 0.3–24 hours) for intravenous morphine, 0.1 mg/kg. Side-effects of caudal epidural opioids include nausea, urinary retention, pruritus and respiratory depression. The latter is particularly worrying because its onset may be delayed for several hours after opioid administration, particularly if morphine is used. The largest reported series of children given caudal epidural morphine reported 11 cases of clinically important hypoventilation in 138 cases (8%). Of these, eight patients were younger than 3 months of age and seven received parenteral opioids in addition to caudal morphine. Assays of blood for plasma morphine levels after the administration of caudal epidural morphine show levels much less than those required for analgesia after systemic administration and strongly suggest that the synergistic effect of epidural opioids on analgesia results from a local action at spinal cord level as opposed to an effect after systemic absorption.

Clonidine also prolongs the duration of caudal epidural blockade produced with a local anaesthetic solution. Three groups of 15 patients undergoing lower-body general or urological surgery under combined general anaesthesia and caudal epidural blockade were given caudal injections of 0.25% bupivacaine. Two groups had added to this clonidine, 1 μg/kg, or adrenaline (epinephrine), 5 μg/ml. The quality and duration of postoperative analgesia assessed as the time to first analgesic requirement using an objective pain score was significantly longer with clonidine (mean 16.5 hours) than with bupivacaine (mean 7.6 hours) or bupivacaine plus adrenaline (epinephrine), (mean 6.3 hour). In a comparison of 0.25% bupivacaine, 1 ml/kg, with or without clonidine, 2 μg/kg, for lower-limb orthopaedic surgery, there was a significantly increased duration of postoperative analgesia in the group given clonidine (mean 9.8 hours) compared with the group receiving bupivacaine (mean 5.2 hours).

Ketamine – a comparison of ketamine, clonidine or adrenaline (epinephrine) added to 0.25% bupivacaine showed that ketamine, 0.5 mg/kg, provided a longer duration of postoperative analgesia after orchidopexy (median duration 12.5 hours) than clonidine, 2 μg/kg (5.8 hours) or adrenaline (epinephrine) 5 μg/ml (3.2 hours). There were no differences between groups in the incidence of urinary retention, motor block or postoperative sedation.

Problems

The incidence of failed caudal block has been reported to be as high as 11%. Failure appears to be more common in children weighing less than 10 kg in whom there may be difficulty identifying the sacral hiatus and in children aged over 7 years. Failure may also result from using an inadequate volume to block the required nerve roots.

The incidence of motor block as shown by leg weakness is variable after caudal blockade. Moderate weakness of the legs is common and occurs in about 30% of patients given 0.5% bupivacaine to block lumbar dermatomes. The incidence is less than 10% if more dilute solutions of bupivacaine are used. The optimal concentration of bupivacaine for caudal epidural blockade in children may be 0.125%. This has been shown to produce a block with an equal duration of analgesic effect and the same requirements for supplementary analgesia as 0.25%, but with a much lower incidence of leg weakness.

Venous puncture has an incidence of 1.6–10.6%. This is reduced when experienced anaesthetists, rather than trainees, perform the procedure and if short bevelled, rather than hypodermic, needles are used. There are no reports of extradural haematoma after caudal epidural blockade in children. The incidence of dural tap has been described as 1/500 and 1/1100 in various series. Negative aspiration for CSF is possible despite a dural puncture. A total spinal block is uncommon but has been reported.

FURTHER READING

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The Child with Associated Medical Disease

Ann E Black

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Anaesthetists often have to deal with a child suffering from a common medical condition such as upper respiratory tract infection or asthma. Less commonly, a child may have a medical condition presenting early in life that may have important anaesthetic implications. This article addresses some common medical conditions; a textbook should be consulted for unusual or rare conditions.

Respiratory disease

Wheezing in children may be caused by:
- asthma
- infection (especially respiratory syncytial virus bronchiolitis in those less than 2 years of age)
- foreign body aspiration
- cystic fibrosis
- laryngotracheomalacia
- chronic lung disease (e.g. bronchopulmonary dysplasia, bronchiectasis, recurrent gastro-oesophageal reflux).

Asthma

Asthma affects about 10% of children, leading to reversible obstructive airways disease. Symptoms include wheezing, intermittent cough or dyspnoea. The incidence of asthma may be increasing owing to environmental changes and pollution. Most children with mild asthma become asymptomatic as they grow older. A smaller number continue to require long-term medication, including corticosteroids, and have severe exacerbations of the disease requiring repeated hospital admissions. Asthma attacks may be precipitated by respiratory infections, environmental factors, anxiety or stress.

Management: preoperative management of children with asthma includes optimizing lung function with bronchodilators, disodium cromoglycate and corticosteroids. Regular peak flow charts may be useful to assess the severity of the disease. An anaesthetic is planned to avoid histamine-releasing drugs. The use of diclofenac in asthmatic children has not been shown to be associated with drug-induced asthma or change in measured respiratory function therefore non-steroid anti-inflammatory drugs (NSAIDs) are not contraindicated for short-term use in children with mild asthma.

Upper respiratory tract infection (URTI)

On average, children have two to nine episodes of URTI per year. It may be difficult to decide whether to proceed with anaesthesia for elective surgery if a child has had a recent URTI. The evidence of additional morbidity associated with general anaesthesia is conflicting. Although severe morbidity, and even mortality, have been reported in children with URTI caused by severe lung infection, pulmonary collapse or myocarditis, this is rare. Most large studies have dealt with children undergoing day-case surgery, who are healthy or have mild systemic disease (ASA groups I and II), with minor symptoms of URTI. The adverse outcomes noted during anaesthesia in children with URTI include laryngospasm, apnoea, bronchospasm, cough, arterial desaturation, and postoperative stridor. Some studies suggest that complications with anaesthesia are 11 times more common if a child has an URTI or recent symptoms of URTI. The reasons include an increase in bronchial sensitivity, increased airway secretions and a tendency for closure of the small airways. Infants under 1 year of age are at increased risk of complications, particularly croup, and some studies have shown that children who are intubated may also be at additional risk.

Management: a child who is obviously systemically unwell with a high fever, chest signs or malaise, should have his surgery postponed. However, there is a large group of children in whom the benefit of cancellation is unclear. In general, the decision to postpone elective surgery can be made on history and examination (including WBC count and radiography), particularly taking into account the view of the parent. The length of postponement is also debated. It has been recommended that elective surgery is postponed for 3–6 weeks after an URTI. However, if this were implemented in some children with frequent mild URTI symptoms it would be difficult to find any period in the year when the child is considered free of the potential risk of complications associated with an URTI.

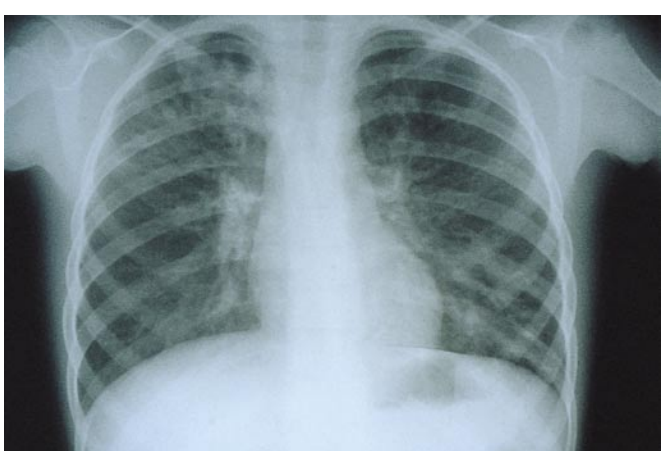
Cystic fibrosis

Cystic fibrosis is an autosomal recessive condition that affects 1/2000 live births. It is a progressive, multisystem disease affecting mainly the lungs and pancreatic exocrine function. Babies may present with meconium ileus, but infants tend to present with recurrent respiratory symptoms or failure to thrive. A diagnostic sweat test reveals a high sodium content of the sweat. The respiratory effects of cystic fibrosis include respiratory failure as a result of increasing ventilation–perfusion mismatch, bronchiectasis and pulmonary haemorrhage. Other sequelae include cor pulmonale, clubbing, cirrhosis, portal hypertension, malabsorption or failure to thrive. Diabetes occurs in about 10% of children with cystic fibrosis.

Management includes physiotherapy, bronchodilator therapy and systemic and inhaled antibiotics. Preoperative preparation involves maximizing these therapies. Pulmonary function tests show a mixed obstructive and restrictive pattern and quantify the degree of impairment. A chest radiograph reveals the extent of chronic lung damage (Figure 1). The ECG may indicate right heart hypertrophy. If liver function is affected, clotting may be abnormal and require preoperative correction.

Premedication is not contraindicated, but some of these children will not tolerate sedation and anticholinergics are often avoided because they make secretions more difficult to clear. Pancreatic supplements, salt supplements and vitamins are continued. Following intubation, physiotherapy and suctioning of the bronchial secretions in the anaesthetic room is useful, particularly if surgery is likely to take a long time. Tracheal tubes and suction catheters must be used with a careful aseptic technique. Intravenous fluids are given routinely and prolonged periods of fasting avoided.

Postoperatively, frequent chest physiotherapy and effective pain management are essential. Supplementary regional analgesia is useful if coagulation is normal.



1 Chronic changes of cystic fibrosis seen on a chest radiograph include hyperinflation of the lung fields, bronchiectasis and peribronchial thickening.

Neurological and muscular disease

Developmental delay and autism

Many conditions result in a child who has difficulties with understanding or behaviour, and the effects vary. Causes of developmental delay include genetic abnormalities, severe cerebral palsy, complicated epilepsy or following head injuries or trauma. Autism is a disease of unknown cause that has a distinctive pattern of behaviour, starting in early childhood, which results in the child being unable to relate to other people. Children with autism tend to be quiet, have a short attention span, be withdrawn and solitary and appear unconnected to their environment. These children may find the process of admission to hospital very stressful.

Management: regardless of their disability, children must be treated sympathetically. The family will be able to indicate the best way to help the child feel comfortable and prepare for anaesthesia. It is important to involve the child whenever possible and a play specialist can be helpful. Assessment of the cause of any apparent distress can be difficult and many systems in routine use (e.g. pain scores) are of little use in these children. Some children benefit from premedication, but in others behavioural difficulties may increase following sedation. Fasting policies may be difficult to implement and these children are often best treated early on a theatre list and allowed home as soon as their family feel ready to continue their care.

Cerebral palsy

Cerebral palsy is a non-progressive neurological disorder that results in abnormalities of motor function. Learning difficulties occur in over 50% of these children. The disorder can be associated with birth asphyxia, preterm delivery and cerebrovascular insults (including intraventricular haemorrhage, congenital infection or metabolic disorders); however, in many cases the cause is unknown. The resultant physical and neurological effect in the child is variable. Limb spasticity is common, as is scoliosis, poor mobility, restrictive lung disease secondary to chest abnormalities, seizure disorder, gastro-oesophageal reflux, feeding problems and failure to thrive. Intelligence may be normal, but speech may be seriously affected and there is often developmental delay. Particular issues to consider include respiratory compromise, restricted lung function, associated infection, frequency of fits, developmental delay, sensory compromise and nutritional status.

Management: preoperative respiratory care with physiotherapy and bronchodilators, if used, is beneficial. There may be an increased risk of respiratory depression and aspiration (owing to oesophageal incoordination), therefore sedative premedication should be used cautiously. Some children are sensitive to the respiratory and sedative effects of opiates. Anti-epileptic medication is continued. Positioning for surgery can be difficult. Postoperative apnoea can occur and oxygen saturation monitoring is useful. Analgesics, such as paracetamol, diclofenac and codeine, are advised. Assessment of postoperative pain can be difficult because routine pain assessment tools are often unusable. An epidural is often successful as an adjunct to general anaesthesia during major abdominal or hip surgery. Painful muscular spasms are common, particularly after orthopaedic surgery, and are best treated with benzodiazapines. Intensive care may be needed postoperatively and weaning from the ventilator following major surgery can be difficult if restrictive lung disease is significant.

Hydrocephalus

Hydrocephalus can be congenital (associated with meningomyelocele as in the Arnold–Chiari malformation), acquired (as in post-haemorrhagic ventricular dilatation) or less commonly the result of tumours, cysts or meningitis. In the neonate and young infant, the skull can increase in size to accommodate additional fluid, but in the child with fused cranial sutures, signs of raised intracranial pressure, such as vomiting, headache or decreased level of consciousness, occur earlier. Treatment requires insertion of a ventriculoperitoneal shunt if the cause cannot be cured.

Management: preoperative assessment of the child's level of consciousness is important. Excessive vomiting may result in electrolyte disturbance. A blood cross-match is usually required. Tapping the CSF in the neonate provides temporary relief and a ventriculoperitoneal shunt is usually inserted later when the neonate's naturally high CSF protein levels have decreased and the risk of obstruction of the shunt is reduced, though there is no consensus in management. If a temporary external ventricular drain is used, the resultant loss of CSF volume must be replaced with intravenous saline.

Neuromuscular disease

Neuromuscular disease includes muscular dystrophies, myotonias, myopathies and myasthenia. In many children the cause of the myopathic disease is unknown. Common operations in this group of children include muscle biopsy, surgery for scoliosis, squint or talipes repair.

General considerations include the presence of associated conditions, particularly respiratory, cardiac or airway abnormalities. Abnormal responses to anaesthetic drugs can occur, including the potential for severe reactions to suxamethonium or other relaxants, sensitivity to sedatives or the risk of precipitating malignant hyperthermia.

Duchenne muscular dystrophy

Duchenne muscular dystrophy is a dominantly inherited, sex-linked disorder. It produces progressive muscle weakness resulting in death in late adolescence, usually as a result of respiratory failure or cardiac disease. It is the most common muscular dystrophy and occurs in about 1/3300 live male births. Presentation is with weakness, slow walking, clumsiness and classically pseudohypertrophy of the calf muscles.The associated features significant to anaesthesia are summarized in Figure 2. It is not associated with malignant hyperpyrexia though there have been some reports of a malignant hyperpyrexia-like syndrome occurring in children with Duchenne muscular dystrophy. Suxamethonium is contraindicated because it can cause acute hyperkalaemia, resulting in cardiac arrest, and is also associated with rhabdomyolysis. Preoperative assessment includes ECG, echocardiography, pulmonary function test, physiotherapy review, full blood count and urea and electrolytes.

Myopathies

Myopathies are a mixed group of conditions and present a wide spectrum of disease, which can be difficult to diagnose. The potential for metabolic instability, drug sensitivity to opiates, sedatives or muscle relaxants, and the associated risk of malignant hyperthermia, must be considered. Specific types should be reviewed in specialist textbooks. Of the congenital myopathies, central core disease is of most relevance to the anaesthetist because it is associated with malignant hyperthermia.

Associated features in Duchenne muscular dystrophy

Features	Effect
• Respiratory muscle weakness	Recurrent chest infection, sputum retention, long-term ventilation
• Scoliosis	
• Cardiac	Arrhythmias, mitral valve prolapse, ventricular dysfunction, sudden death
• Gastric distension	Risk of aspiration
• Sensitivity to sedation	
• Suxamethonium	Produces hyperkalaemia, cardiac contraindicated arrest, muscle rigidity, rhabdomyolysis

2

Myopathies
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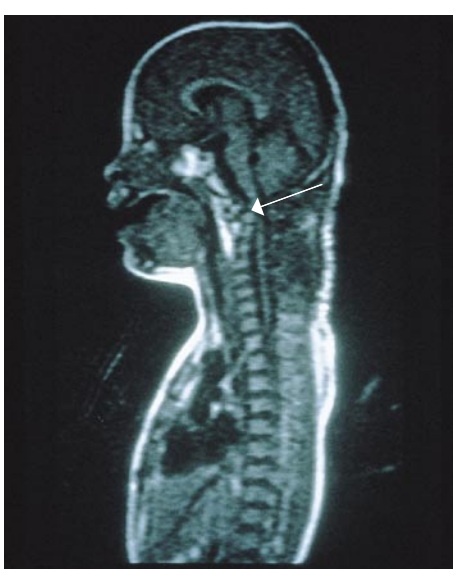
Other conditions

Down's syndrome
Down's syndrome is one of the most common chromosomal disorders. It results in characteristic facial features, developmental delay, and problems with the airway, heart and joints. Specific anaesthetic issues include behavioural problems and difficulty with vascular access.

Snoring or sleep apnoea may be present and preoperative sedation is sometimes contraindicated because of the risk of obstruction. Both post-intubation stridor and subglottic stenosis are more common in children with Down's syndrome. Congenital heart disease (e.g. atrioventricular septal defects, Fallot's tetralogy) is present in 40% of children with Down's syndrome. Assessment by a paediatrician or cardiologist and echocardiography or ECG are useful. Antibiotic prophylaxis for the prevention of bacterial endocarditis is essential for most cardiac lesions.

Laxity of the ligaments of the neck at the atlanto-axial joint occurs in 15–18% of patients with Down's syndrome and the risk increases with age. C1–C2 dislocation and spinal cord damage can occur (Figure 3). Some centres routinely screen the cervical spine at regular intervals, but this practice is not widespread. Any child with Down's syndrome who has neurological symptoms, such as paraesthesia of the hands or motor instability, must be screened with flexion and extension views of the neck. Additional care must be taken with positioning these children during anaesthesia.



3 MRI of a child with Down's syndrome showing C1–C2 instability with spinal canal narrowing (arrow).

Renal disease
The most common cause of renal impairment in infants is pelvic renal dilatation from either posterior urethral valves or pelviureteric obstruction. In children, the causes include congenital abnormalities, glomerulonephritis or nephrotic syndrome. In the child with established renal disease and a degree of chronic renal failure, symptoms are unusual until the glomerular filtration rate is less than 25% of normal. Then chronic anaemia, failure to thrive, renal osteodystrophy, hypertension, metabolic effects of uraemia, acidosis, salt loss or hyperkalaemia become more common.

Management: Preoperative assessment includes haemoglobin level, urea and electrolytes and creatinine. Fluid and electrolyte requirements are variable and should be assessed and discussed with the renal team before surgery. A child on dialysis will require post-dialysis bloods, including clotting studies (if heparin is used as in haemodialysis). Surgery should be avoided soon after dialysis so that time is given for fluid shifts to occur. Arm vessels are preserved because they may be required later for vascular shunts.

Drugs best avoided in children with significant renal impairment include known nephrotoxic drugs (e.g. aminoglycosides, diclofenac) and drugs dependent on renal excretion. Suxamethonium is contraindicated in the presence of hyperkalaemia because of the potential of producing severe hyperkalaemia. Renal patients should not be fasted excessively and fluid replacement should be maintained carefully. Perioperative hypotension should be avoided. Regular antihypertensive medication should be continued. If hypertension is poorly controlled a review of medical management before planned surgery is wise.

Diabetes
Type 1 diabetes occurs in about 1/500 children and most commonly presents at 6–7 years or at puberty. Control of blood sugar levels can be difficult because of the changing nutritional and insulin needs of the growing child and because older children may be non-compliant with their therapy. The long-term complications of diabetes (retinopathy, autonomic neuropathy or nephropathy) do not occur in children before puberty and good metabolic control minimizes their development in adulthood.

Management: routine surgery in diabetic children usually requires that they be admitted the day before surgery. Their diabetes should be under good control and ideally they should be scheduled first on the theatre list. Preoperative measurements of urea and electrolytes and blood sugar are taken. Preoperatively, bedside blood sugar estimates are checked regularly and the urine screened for sugar and ketones. The morning dose of insulin is omitted and an infusion of 10% dextrose with added potassium is started with an infusion of soluble insulin (e.g. 50 ml syringe with 1 unit of insulin per ml), with the rate adjusted according to hourly sugar results. This is continued until the child returns to a normal diet and his insulin regimen is restarted.

If diabetic control is poor, or emergency surgery is required and the child is systemically unwell and has a high blood sugar (with or without ketoacidosis) it is best to treat the metabolic condition first because surgery in the ketoacidotic child is associated with a high morbidity.

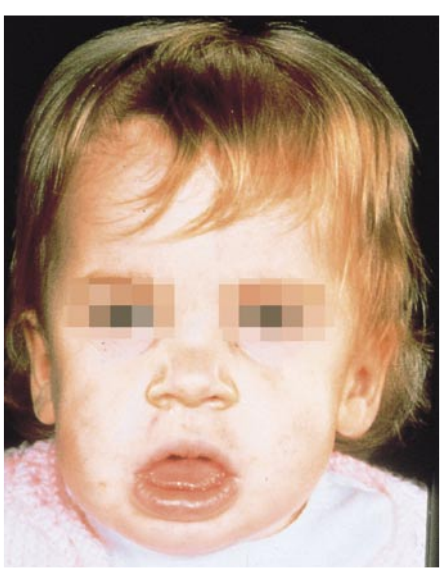
Sickle cell disease
All children from ethnic groups with a high incidence of sickle cell disease should be screened preoperatively, unless their sickle cell status is known. Routine screening is with a *Sickledex* test, which, if positive, must be followed by haemoglobin electrophoresis to identify the relevant haemoglobin types present. *Sickledex* tests are unreliable in babies less than 3 months of age because they have a high percentage of fetal haemoglobin, therefore electrophoresis should be carried out instead. Sickle haemoglobin may occur in association with other haemoglobinopathies, such as thalassaemia. Sickle cell trait is associated with a normal haemoglobin level and HbS and HbA on electrophoresis. These children are managed routinely and do not have additional risks during carefully conducted general anaesthesia.

Management: the preoperative management of children with sickle cell disease is under review. All cases should be discussed with the haematologist so that the risks and benefits of blood transfusion before surgery are considered. Blood transfusions are avoided if possible, so that the development of antibodies and other complications related to blood transfusion do not occur. These would make later management of the disease more difficult, particularly if a bone marrow transplant were required. Many children with sickle cell disease have a mild course and few symptoms.

For minor surgery, exchange or top-up transfusion is not routine, though some centres will give blood to increase the haemoglobin levels to 10 g/dl.

For more extensive surgery, or in children with a history of severe disease (e.g. painful crises of the bones, joints, spleen, lung or brain) a regimen of exchange transfusion is undertaken in the weeks before surgery to raise the haemoglobin level above 10 g/dl and the percentage of HbS to less than 30%. In all these patients, careful anaesthesia is essential, ensuring that the child is kept warm, well hydrated and that additional oxygen is administered perioperatively and even transient episodes of hypoxia avoided. Use of tourniquets is contraindicated owing to the risks of acidosis and tissue hypoxia in the exsanguinated limb. In these children, most surgery requires antibiotic cover. Effective pain management is important so that mobility is encouraged and early chest physiotherapy can be used to minimize the likelihood of a sickle crisis occurring.

Mucopolysaccharidosis
There are many different forms of mucopolysaccharidosis, which are genetic abnormalities resulting from an inborn error of metabolism. The most common are Hurler's syndrome and Hunter's disease. Children with Hurler's syndrome have characteristic facies and often have obstructive airway symptoms. Depending on the abnormality present they develop learning difficulties, cardiac disease, kyphoscoliosis, respiratory failure and neck instability. The airway can be difficult to manage during anaesthesia (Figure 4).



4 Child with Hurler's syndrome illustrating the typical coarsened facial features that are associated with difficulties in managing the airway.

Oncological disease and chemotherapy
Many children's cancers are now treated successfully. Common childhood oncological diseases include leukaemia (most commonly acute lymphocytic leukaemia), cerebral tumours, neuroblastoma and Wilms' tumour. In most patients, care is shared between the tertiary referral centre and the local hospital. Anaesthetic implications are related to the disease or to the effect of treatment such as corticosteroids or cytotoxic drugs, some of which have specific renal, haemopoietic or cardiac toxic side-effects.

Management: most children require chemotherapy, multiple blood tests, blood component therapy and repeat anaesthesia. To assist this management, indwelling catheters (e.g. Hickman catheters, Portacath) are placed early after diagnosis. Children can become quite fond of their catheters. An aseptic technique is essential when accessing these catheters and if carefully looked after they may be kept for many months. These children are frequent attenders at hospital and they often have particular requests about the conduct of their anaesthesia and need sensitive management.

A full blood count should be available preoperatively. Additional investigations may include urea and electrolytes and clotting studies. Blood component therapy is often required before or during surgery. Blood products may need to be leucodepleted and irradiated in these children, and this should always be discussed with the oncology team. The requirements depend partly on the intended surgery and on local clinical guidelines. A platelet count of at least 100,000 is required for the insertion of indwelling intravascular catheters or general surgery. For a lumbar puncture, a platelet count above 50,000 is acceptable, providing the clotting results are normal. Epidural and caudal anaesthesia are often contraindicated because of coagulation abnormalities. These children are often immunocompromised and great care is needed to avoid potential infection. Suppositories are contraindicated if the child is neutropenic owing to the risk of infection.

Latex allergy
Sensitivity to latex products is the most common cause of anaphylaxis during anaesthesia. It is a type 1, IgE-mediated hypersensitivity reaction and can be severe. Children most at risk include those with:

- a history of sensitivity to latex (e.g. balloons, toys)
- atopy
- specific food allergies (e.g. kiwi fruit, chestnuts, avocado, banana) owing to cross-sensitivity to specific food proteins
- a history of repeated surgery (particularly urological surgery)
- spina bifida.

Children at risk should be screened with a radioallergosorbent test (RAST) and enzyme linked immunosorbent assay (ELISA). These tests are non-specific and up to 45% of patients with negative RAST tests have a positive skin test to latex, so this should be considered if the history is strong. The management of children at risk from latex allergy is debated. In many centres, children at risk from latex allergy are admitted for preoperative treatment with methylprednisolone, ranitidine and chlorpheniramine, each given 6-hourly intravenously, started 12 hours preoperatively and continued for 24 hours postoperatively. This management precludes the use of day-care surgery and therefore the use of such regimens has been questioned and in some centres abandoned in favour of providing a latex-free environment for all children in the group at risk. It would seem wise to try to prevent sensitization of any patients by avoiding exposure of a child in an at-risk group to latex.

Long-term corticosteroid use

The long-term use of corticosteroids may occur in severe asthma, juvenile arthritis, nephrotic syndrome, in many chemotheraputic regimens and in replacement therapy for adrenal or pituitary failure or congenital adrenal hyperplasia. Long-term corticosteroid therapy can result in steroid facies, hypertension and diabetes. Children at risk of having inadequate endogenous corticosteroid production require additional cover during surgery. The dose of replacement corticosteroids is debated and more is probably given than is required.

- Give children taking regular corticosteroid therapy, hydrocortisone, 1 mg/kg i.v. on induction and 6-hourly until their routine corticosteroid treatment restarts.
- In children who have used corticosteroids in the last 2 months give hydrocortisone, 1 mg/kg i.v. until 24–48 hours postoperatively.
- Children who have had inhaled corticosteroids, for example in asthma medication, do not require additional corticosteroid perioperatively.

FURTHER READING

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Cleft Lip and Palate

John Currie

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Cleft lip and palate occur in 1.5/1000 live births. Cleft palate alone has an incidence of 0.5/1000 live births. Accompanying congenital abnormalities may be present (e.g. Pierre Robin syndrome). Often there are supernumerary teeth or absence of the incisor in line with the cleft. There may also be widening of the middle portion of the face (telecanthus) or even true hypertelorism. Several operations may be required to correct these abnormalities.

Cleft lip

Cleft lip is best repaired in the neonatal period. This produces a better scar and reduces the mother's emotional stress. Babies with congenital abnormalities are often premature and surgery should be delayed until feeding is well established and any other congenital abnormalities, respiratory problems or jaundice have been identified and treated. A detailed history of the baby's post-natal progress is essential.

Anaesthesia – babies with cleft palate tend to have enlarged tongues and micrognathia. Therefore, an inhalation induction may be preferred. Once the anaesthetist has confirmed that he can ventilate the lungs, a muscle relaxant may be given to facilitate intubation (a south-facing RAE tube is preferred to give good surgical access). A mouth pack is then inserted in case of intraoperative bleeding. Perioperative analgesia can be provided with an infra-orbital block, though the surgeon may prefer to inject local anaesthetic and adrenaline (epinephrine) to optimize the field. At the end of surgery, it is essential to remove the tracheal tube when the baby is awake to prevent laryngeal spasm.

Surgery also involves improving the appearance of the ipsilateral nostril (which is always flattened) by moving tissue medially from the lateral side of the cleft and repositioning the displaced cartilage. To maintain this position, the surgeon often sews a piece of sponge into the nostril. This may impair breathing postoperatively, so a small length of feeding tube should be included in the sponge, to provide an airway.

Postoperative care – babies may have difficulty feeding postoperatively and be unsettled (perhaps due to numbness of the lip from local anaesthetic). This can be helped by giving codeine phosphate, 1 mg/kg i.m., before extubation. Once feeding is re-established, paracetamol (regularly for 24 hours) maintains analgesia.

Cleft palate

Cleft palate should be repaired ideally at about 6 months of age. This is when the baby is learning to imitate speech, and is using the levator palatini and the aponeurotic tensor palatini muscles to close the velo-pharangeal aperture to make oral (as distinct from nasal) sounds. Modern techniques involve repositioning these muscles to obtain normal palatal function.

Anaesthesia – no premedication is required and (in the absence of other serious airway anomalies) intubation seldom presents a problem. A south-facing RAE tube is preferred. Before repair, the surgeon inserts a Boyle–Davies gag to open the mouth and provide access. It is essential to check the tracheal tube position carefully because it is often kinked or pushed into a main stem bronchus by the gag. Bilateral air entry should be checked by listening with a stethoscope after the gag has been positioned. Local anaesthetic and adrenaline (epinephrine) help to produce a dry field and analgesia. However, it is also wise to give an opiate (e.g. fentanyl, 1 μg/kg) to avoid tachycardia if the surgeon strays beyond the 'blocked' area (particularly likely when making lateral 'relieving' incisions to facilitate a difficult repair). Codeine, 1 mg/kg i.m., before extubation is useful, especially if combined with rectal diclofenac at induction. Diclofenac and paracetamol should then be given regularly for 24 hours, with paracetamol 'as required' thereafter.

Postoperative care – the repair tends to lift the palate towards the roof of the nasopharynx, narrowing the airway (which may be worsened by spasm of the levator palatini) and causing upper airway obstruction after extubation. The obstruction may be overcome by inserting a nasopharyngeal airway (usually a tracheal tube one size less than that used for intubation). Ideally the surgeon should insert this before removing the gag if the repair is 'tight'. The nasopharyngeal airway must be kept patent postoperatively (e.g. by suction). These babies should be nursed on a high dependency unit.

Fistula repair

The child may require further operations if it is impossible to close the cleft completely or the repair breaks down. Occasionally, a tongue flap is needed to provide enough tissue to close an anterior fistula. Initially, the surgeon fashions the flap and attaches it to the defect in the roof of the mouth. These children should be nursed on a high dependency unit for 24 hours. The child returns 2 weeks later for division of the flap. Intubating a child with its tongue attached to the roof of the mouth is challenging and best achieved fibre-optically by the nasal route. This can be practised during anaesthesia for the first stage to determine the most suitable nostril and the optimum position for the best view.

Alveolar bone graft

The final stage of repair is to close the defect in the alveolar arch (usually at about 8–9 years of age) using bone from the iliac crest. Postoperatively, infusion of local anaesthetic subcutaneously at the donor site provides excellent analgesia. ◆

Common Local Anaesthetic Techniques in Children

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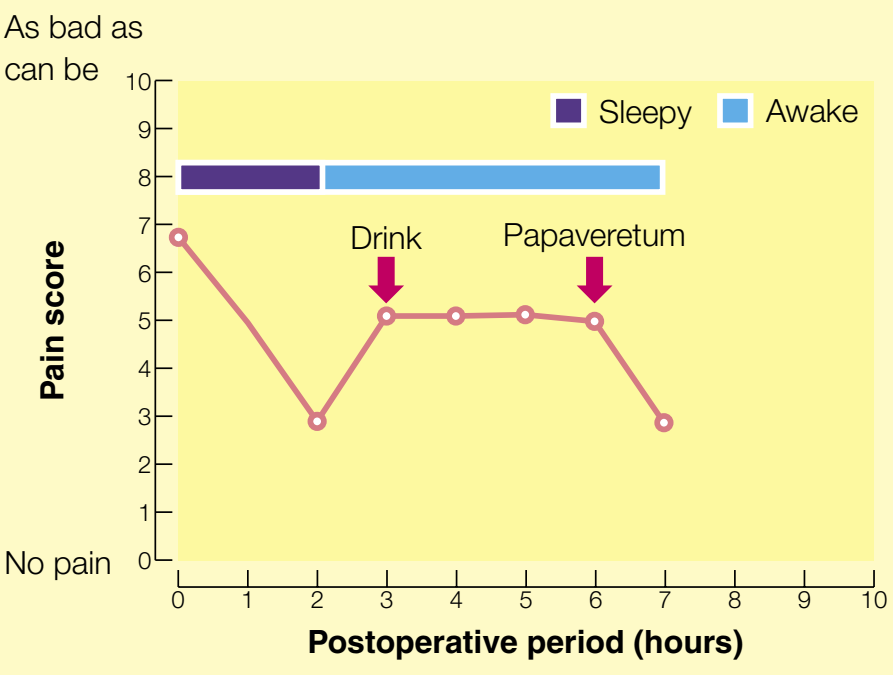
Paediatric regional anaesthesia is not a scaled-down version of adult practice. It is important to be aware of the anatomical and pharmacological differences between children and adults and to apply that knowledge appropriately so that regional anaesthesia becomes an integral part of day-to-day practice.

In children, regional analgesia is usually combined with a general anaesthetic to provide balanced anaesthesia. The depth of anaesthesia can be reduced because regional blocks provide excellent intraoperative analgesia and a predictable period of postoperative pain relief. Local anaesthetic techniques combined with mild-to-moderate oral analgesics, such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), decrease the requirements for opioids and reduce the incidence of unwanted side-effects (e.g. nausea and vomiting, respiratory depression, excess sedation).

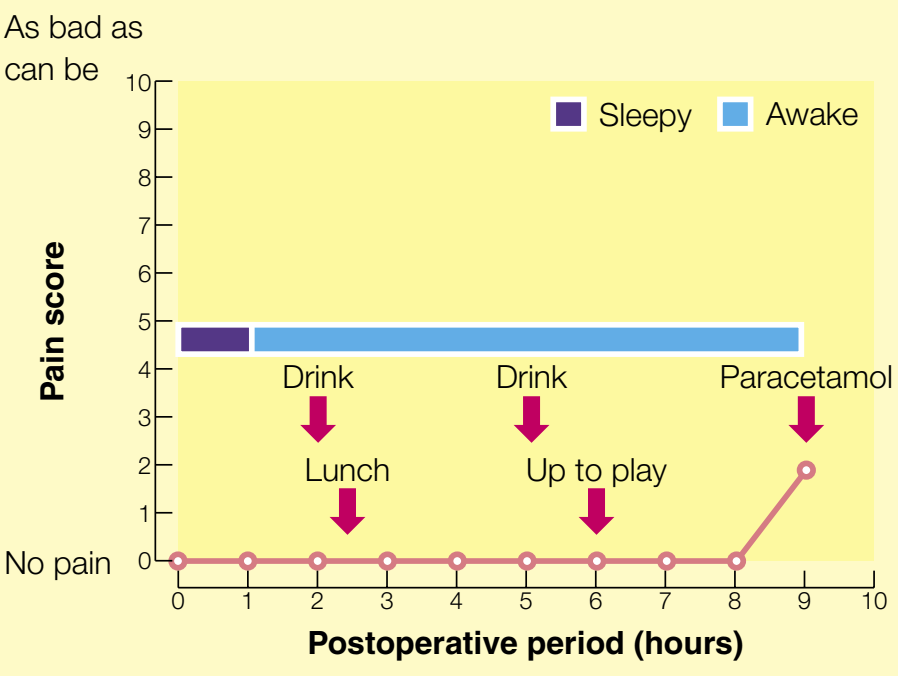
The advantages of regional anaesthesia in the postoperative period are shown in Figure 1. Both children received similar anaesthetics, but different analgesics. The boy given the penile block had excellent pain relief for almost 8 hours before he became uncomfortable and required simple analgesics. The girl given papaveretum had poorer pain control complicated by side-effects (e.g. vomiting).

Contribution of regional anaesthesia during and after surgery

12-year-old girl given papaveretum during and after surgery



5-year-old boy given a penile block



1

Applying local anaesthesia

Topical anaesthesia

The ability of local anaesthetics to penetrate intact skin and produce anaesthesia and analgesia proved to be a difficult pharmacological challenge until the development of a eutectic mixture of local anaesthetic (*Emla* cream) in the 1980s. *Emla* is an oily emulsion containing 25 mg/ml each of lidocaine (lignocaine) and prilocaine. 'Eutectic' refers to the lowering of the melting points, the physical transformation that occurs when lidocaine (lignocaine) and prilocaine crystals are mixed together in equal quantities. When applied to the skin under an occlusive dressing for 60–90 minutes, the emulsion produces analgesia of the skin which is useful for:

- venepuncture
- division of prepucial adhesions
- myringotomy and ventilation tube insertion when applied to the tympanic membrane
- minor surgical procedures when given before superficial infiltration of local anaesthetic.

Emla occasionally causes transient blanching of the skin owing to vasoconstriction of blood vessels, and erythema and oedema, which can make cannulation difficult. Ingestion of the occlusive dressing and *Emla* cream have both been described, and methaemoglobinaemia has occurred in a child following application of *Emla* cream over a large area, leading to systemic absorption and toxicity.

A new alternative to *Emla* is tetracaine (amethocaine) 4% gel (*Ametop*), which provides more rapid and longer-lasting analgesia before venous cannulation.

Mucosal analgesia

Topical analgesia of mucosal surfaces is simple and effective, and can be used for the following indications:

- strabismus surgery, using 0.4% oxybuprocaine hydrochloride eye drops into the conjunctival sac before the conclusion of surgery
- circumcision, using 2% lidocaine (lignocaine) gel applied at the end of surgery or during the postoperative period
- anal stretch for the treatment of anal fissures, using lidocaine (lignocaine) gel.

Instillation of local anaesthetics

Local anaesthetics can be instilled directly into wounds (e.g. inguinal hernia). The analgesia is of shorter duration, but can equal that produced by an iliohypogastric/ilioinguinal nerve block.

Local anaesthetic can also be instilled before cleaning or suturing small superficial wounds in the Accident and Emergency Department. The local anaesthetic can be applied either by dropping it on to the wound or applying a swab soaked in the local anaesthetic. Solutions of either lidocaine (lignocaine) or bupivacaine combined with a vasoconstrictor, such as adrenaline (epinephrine), are most commonly used.

The technique of instillation can be useful in children requiring regular dressing changes (e.g. split skin graft donor sites); the wound dressing can be soaked with a combination of local anaesthetic and adrenaline (epinephrine). Alternatively, an epidural catheter can be incorporated into the wound dressing and local anaesthetic (e.g. 0.125% or 0.25% bupivacaine with 1:400,000 adrenaline (epinephrine)) can be continuously infused on to the wound at a rate of 1–3 ml/hour. Care must be taken not to exceed the maximum recommended dose of 0.5 mg/kg/hour or 2 mg/kg/4 hours.

Infiltration

The infiltration of local anaesthetics, alone or combined with vasoconstrictors, is used regularly to provide anaesthesia and analgesia for many operations (e.g. suturing superficial wounds, or excision of cysts, accessory auricles, naevi). It is particularly useful in the neonate undergoing pyloromyotomy; infiltrating the wound edge before completion of surgery can produce excellent postoperative analgesia. Combined with paracetamol, this avoids the use of opioids and reduces the incidence of side-effects, particularly respiratory depression or apnoea.

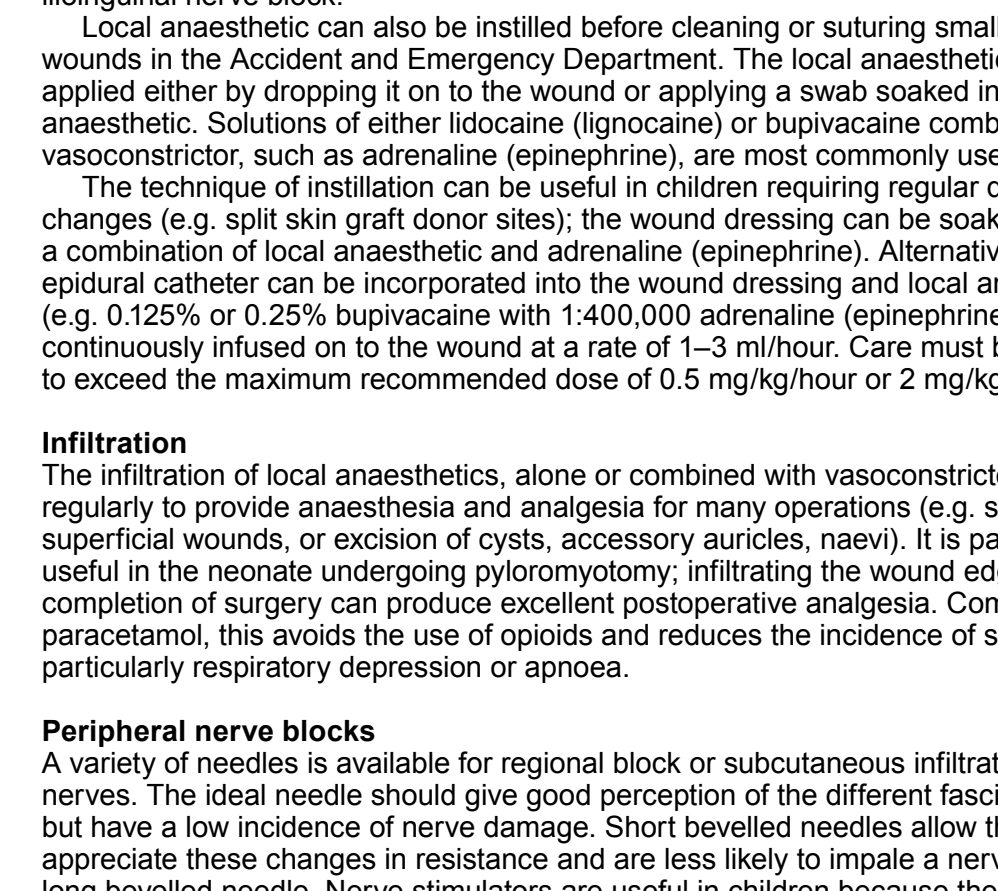
Peripheral nerve blocks

A variety of needles is available for regional block or subcutaneous infiltration of nerves. The ideal needle should give good perception of the different fascial planes, but have a low incidence of nerve damage. Short bevelled needles allow the user to appreciate these changes in resistance and are less likely to impale a nerve than a long bevelled needle. Nerve stimulators are useful in children because their anatomy is variable and most children are anaesthetized before the block therefore the technique of paraesthesia cannot be used.

Great auricular nerve block is used for pinnaplasty; a common operation in children. The sensory supply of the ear is largely from the great auricular nerve derived from the superficial cervical plexus (Figure 2).

The great auricular nerve divides into pre- and post-auricular branches, which can be blocked by infiltrating the tip of the mastoid process anteriorly and posteriorly with 2–3 ml of local anaesthetic (Figure 3). A branch of the mandibular division of the trigeminal nerve, the auriculotemporal nerve, supplies the external auditory meatus and the temple region. This can be blocked by infiltrating a further 2–3 ml of local anaesthetic anterior to the external auditory meatus.

Great auricular nerve block



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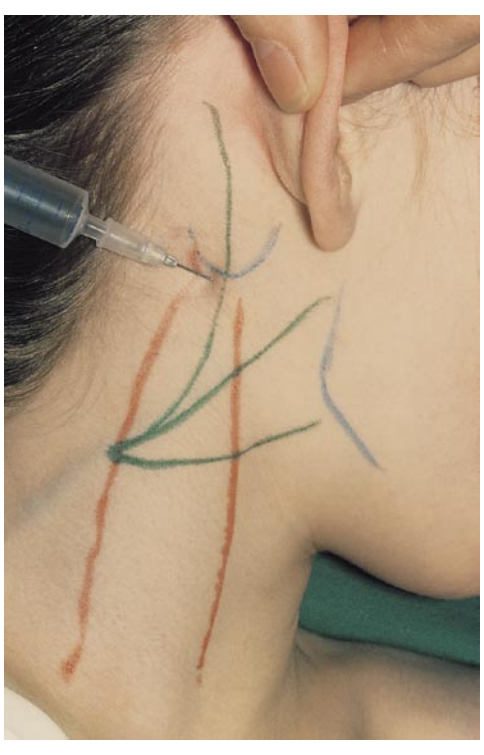
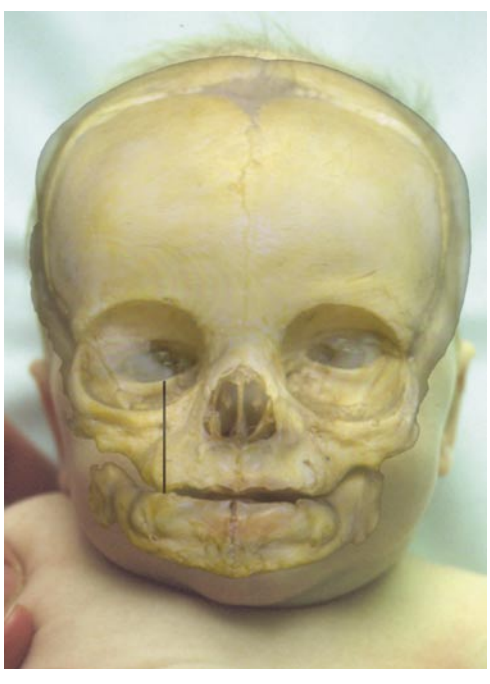
Infraorbital nerve block is excellent for providing analgesia for neonates undergoing cleft lip repair. It removes the need for opioids and reduces the risk of respiratory depression or apnoea. This is particularly important because these neonates are often either preterm or have associated congenital anomalies.

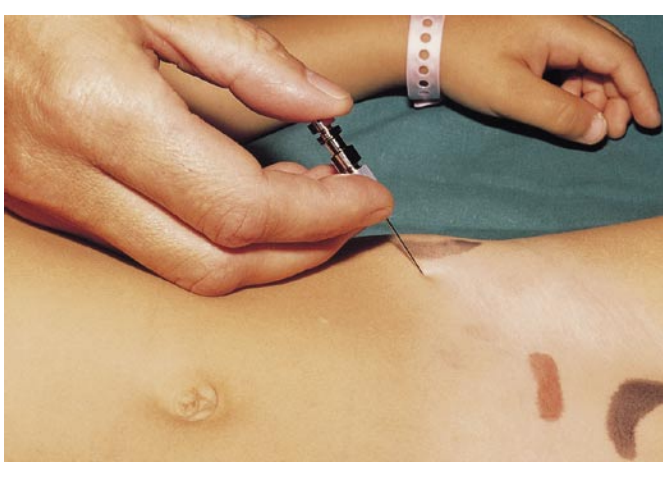
The infraorbital nerve is a branch of the maxillary division of the trigeminal nerve and provides the sensory innervation to the skin and mucus membranes from upper lip to the lower eyelid and medially to the side of the nose. The landmark for locating the infraorbital nerve is found by drawing a line from the angle of the mouth to the midpoint of the palpebral fissure; the nerve is situated about halfway along this line and can be approached either percutaneously or buccally (Figure 4). For the percutaneous technique a 25 G needle is used and is introduced perpendicular to the skin and advanced until bony resistance is felt. The needle is then withdrawn slightly and, following a negative aspiration test, the local anaesthetic (usually 0.5% bupivacaine, 0.5–0.75 ml with 1:200,000 adrenaline (epinephrine)) is injected.



3 Site of great auricular nerve block.



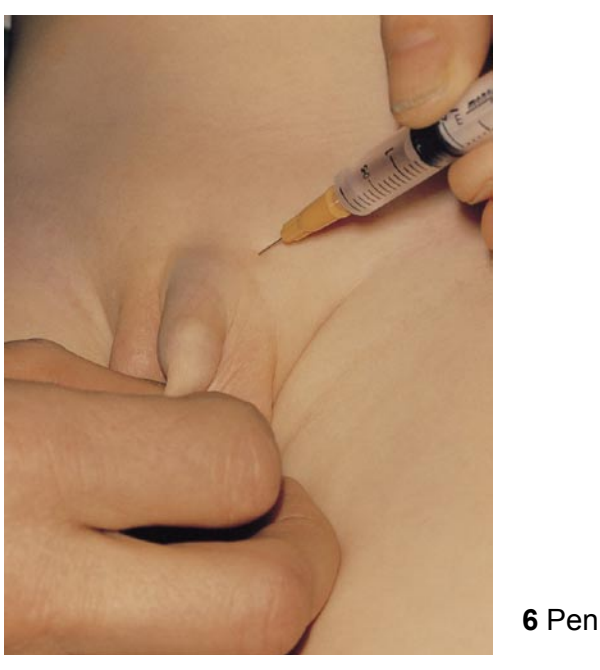
4 Landmarks for infraorbital nerve block. A line is drawn from the angle of the mouth to th emidpoint of the palpebral fissure. The nerve is situated about half way along this line.



5 Ilioinguinal and iliohypogastric nerve block. X marks the position of the anterior superior iliac spine.

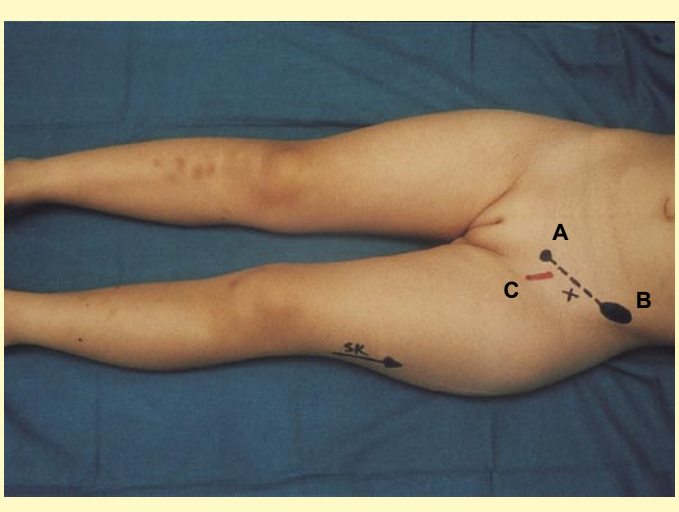
Combined ilioinguinal and iliohypogastric nerve block provides anaesthesia and postoperative analgesia for operations in the groin. These nerves are derived from T12, L1 and L2. A 22 G short bevelled needle is inserted at a point one patient's fingerbreadth medial to the anterior superior iliac spin (Figure 5). The needle is inserted perpendicular to the skin. A 'pop' is felt as the needle passes through the aponeurosis of the external oblique. After a negative aspiration test, about one-third of the local anaesthetic is injected at this point. The needle is then withdrawn and redirected caudally and laterally until it strikes the ilium, and a further third of the solution is injected. The remaining local anaesthetic is injected as the needle is withdrawn.

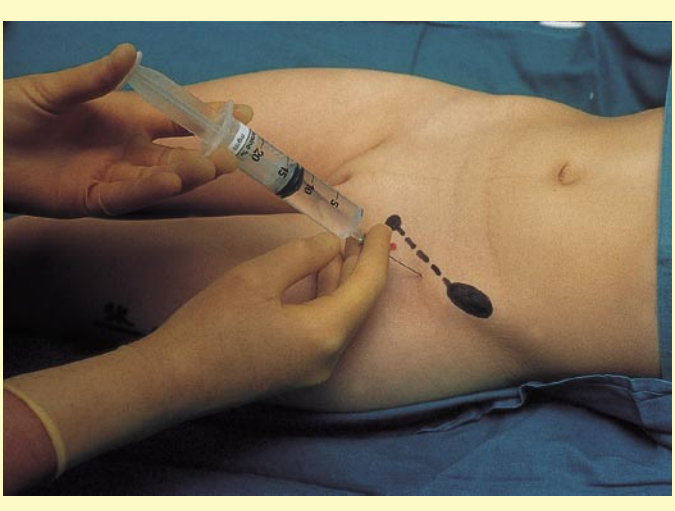
Genitofemoral nerve block: if the child is undergoing an orchidopexy, the genital branch of the genitofemoral nerve has to be blocked. Depositing one-third of the solution adjacent to the pubic tubercle and infiltrating subcutaneously across the midline blocks the genital branch and any innervation from the contralateral nerve. 0.25% bupivacaine, 2 mg/kg, is the recommended safe dose. In the older child, 0.5% bupivacaine may be used.



6 Penile block.

Penile block: the dorsal nerve of the penis is the terminal branch of the pudendal nerve (S2, 3 and 4) and is commonly blocked to provide postoperative analgesia following circumcision. The patient lies supine and a short bevelled needle is inserted 0.5–1.0 cm lateral to the pubic symphysis (Figure 6), depending on the age of the child. The needle is advanced posteriorly, caudally and medially; a 'pop' is felt twice as the needle penetrates the superficial fascia then Scarpa's fascia. Plain 0.5% bupivacaine, 0.1 ml/kg, is then injected. Vasoconstrictors should never be added to the local anaesthetic solution because of the risk of ischaemia.
Fascia iliaca block: the femoral, lateral cutaneous and obturator nerves can be blocked with a single injection using the fascia iliaca compartment block devised by Dalens. It has superseded the femoral '3 in 1' block because it is a simple technique with a high success rate (particularly in children) and lower complication rate. The fascia iliaca block can be used for a number of operations on the hip and thigh, for example femoral osteotomy, reduction of femoral fracture, surface operations on the thigh, femoral biopsies and the removal of metal screws and plates from the femur. The child lies supine and an imaginary line is drawn between the anterior superior iliac spine and the pubic tubercle (Figure 7).





7

This line is divided into thirds and the junction of the lateral with the medial two-thirds is located. A short bevelled needle is inserted at an angle of 60° about 0.5 cm below this point. As the needle is advanced, two 'pops' are felt as the needle penetrates the fascia lata then the fascia iliaca. The needle is aspirated to ensure that it is not lying intravascularly and the local anaesthetic is then injected. 0.25% bupivacaine can be used alone or in combination with 1:200,000 adrenaline (epinephrine) and the recommended doses are given in Figure 8.

Dosing guidelines for fascia iliaca nerve block

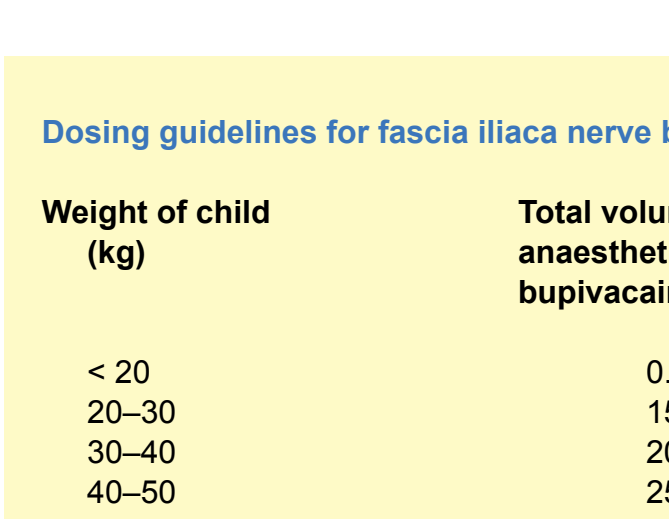
Weight of child (kg)	Total volume of local anaesthetic (0.25% bupivacaine ml/kg)
< 20	0.7
20–30	15
30–40	20
40–50	25
> 50	27.5

8

Metacarpal and metatarsal blocks are used for operations on the fingers and toes, respectively. These techniques are simple and provide good intraoperative and postoperative analgesia. They are preferred to blocks within the digits because the digits are small and injecting large volumes into a confined space can damage the end artery, producing ischaemia or distorting anatomy and impairing surgical access. The common digital nerves are derived from the ulnar and median nerves, and divide into dorsal and ventral branches in the distal palm. They run on the dorsolateral and ventrolateral aspects of the digit, respectively, and are accompanied by the digital vessels.

To perform a metacarpal block, a short bevelled needle is inserted through the skin on the dorsal aspect of the hand adjacent to the proximal end of the metacarpal bone and advanced until it can be felt by the operator's hand on the palmar surface (Figure 9). Following a negative aspiration test, 0.25% bupivacaine , 0.5–1.0 ml, is injected until a small swelling is felt. The technique can be repeated at several interspaces, depending on the number of digits involved.

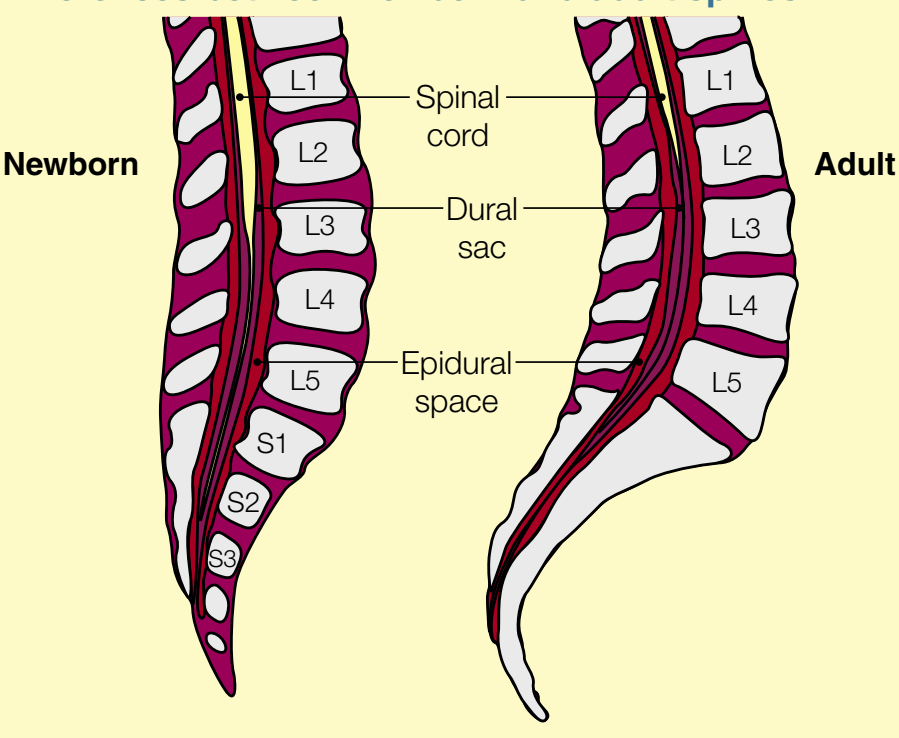
Analgesia of the toes can be obtained similarly with a metatarsal block. A needle is inserted through the skin on the dorsum of the foot at the proximal end of the metatarsal bone. 0.25% or 0.5% bupivacaine, 0.5–1.0 ml, is injected. Vasoconstrictors should not be added because of the risk of ischaemia.



9 Metacarpal block.

Central neuroaxial blocks
There are important anatomical differences between babies, children and adults (Figure 10). Following neuroaxial blockade in children, there is less haemodynamic instability because of the immaturity of the sympathetic nervous system and less pooling of blood in the legs.

Differences between newborn and adult spines



The tip of the spinal cord lies at L3 at birth and the dura extends to S2–3. Only at the age of 1 year does the cord assume the adult position of the L1–2 interspace and the dural level of S2. The intercristal line in the neonate lies at the level of L5–S1 and in the slightly older child at L5

10

Spinal anaesthesia
Spinal anaesthesia is most commonly used in neonates or ex-premature babies for operations of short duration on the lower abdomen (e.g. hernia repair, orchidopexy). There is a 10% absolute failure rate for this technique as well as a 10% rate of inadequate blockade.

In the neonate, the CSF pressure is low and many therefore recommend the use of a 22 G Quincke point needle, which allows better flow of CSF once in the spinal canal. A short bevelled needle allows better perception of the 'pops' as the needle traverses the posterior spinal ligaments and dura. Atraumatic tipped spinal needles (Whitacre needles) are not recommended for neonates because of the tendency of the orifice of the needle to straddle the dura. The incidence of post-dural puncture headaches is low in neonates, but increases as the child ages. It is therefore prudent to use a smaller-gauge needle (e.g. 26 G) in older children and adolescents.

Either hyperbaric or isobaric 0.5% bupivacaine can be used. If hyperbaric bupivacaine is used, the appropriate dose can be calculated using the formula: 0.06 ml/kg + 0.1 ml. If isobaric bupivacaine is used, the dose is 1 mg/kg. As a guide, the distance from the skin to the subarachnoid space is 10 mm in a full-term baby and 7 mm in a premature baby. Spinal anaesthesia lasts for 20–110 minutes, but the block is unreliable for operations longer than 40 minutes.

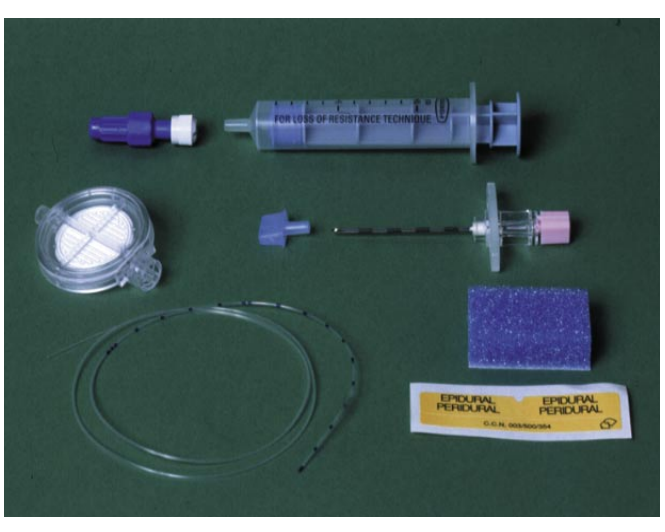
One of the main indications for performing spinal anaesthesia is to reduce the incidence of postoperative apnoea, which can be a problem following general anaesthesia. If spinal anaesthesia is used, it is of paramount importance to monitor the baby postoperatively for oxygen saturation and apnoea.

Epidural anaesthesia
Epidural analgesia (usually combined with general anaesthesia) is useful for orthopaedic surgery on the legs, orchidopexy and operations involving the perineum. Commercially available paediatric epidural kits are available (i.e. 18, 19, 20 G Tuohy needles with 21 G, 23 G and 24 G catheters, respectively; Figure 11). The 18 G Tuohy needle with its 21 G catheter can be used in babies weighing more than 3 kg; the larger gauge of catheter allows better flow of blood, if the catheter has breached an epidural vessel, or CSF, if the catheter has traversed the dura inadvertently. There are fewer technical problems, such as kinking and blocking, with the larger gauge of catheter.

A guide to the depth of the lumbar epidural space in children can be calculated according to either their age or weight (e.g. (body weight in kg + 10) x 0.8 mm). Alternatively, for children 6 months to 10 years of age, the distance to the epidural space is about 1 mm/kg body weight.

In children, the epidural space can also be accessed through the sacral intervertebral spaces, because the sacrum does not ossify until the age of 25–30 years.

The complications following epidurals in children are similar to those seen in adults and include:
- dural puncture with total spinal block
- post-dural puncture headache – age increases incidence
- hypotension – uncommon in children less than 6 years old
- nerve damage – occasionally the catheter may press against nerve roots
- infection
- urinary retention
- unilateral or patchy blocks.



11 Paediatric epidural kit containing 19 G, 5 cm Tuohy needle with 23 G catheter.

Epidurals are most commonly inserted in the lumbar region and then threaded to the appropriate dermatomal level. The epidural space in children contains gelatinous fat globules instead of the densely packed fat divided by fibrous bands found in adults. This allows more longitudinal spread of local anaesthetic within the space and makes it possible to thread a catheter the entire length of the vertebral column. The volume of local anaesthetic required can be calculated using the formula devised by Takasaki for caudal anaesthesia (Figure 12), which may also be applied to lumbar epidural anaesthesia. Alternatively, 0.25% bupivacaine, 0.5–1 ml/kg can be used for lumbar epidurals and half this dose for a thoracic block.

Formulae for calculating the volume of local anaesthetic for caudal block

Armitage
- Lumbosacral blocks = 0.5 ml/kg of 0.25% bupivacaine
- Thoracolumbar = 1 ml/kg of 0.25% bupivacaine
- Mid-thoracic = 1.25 ml/kg of 0.25% bupivacaine

Takasaki
- Volume = 0.05 ml x body weight x no. of spinal segments to be blocked

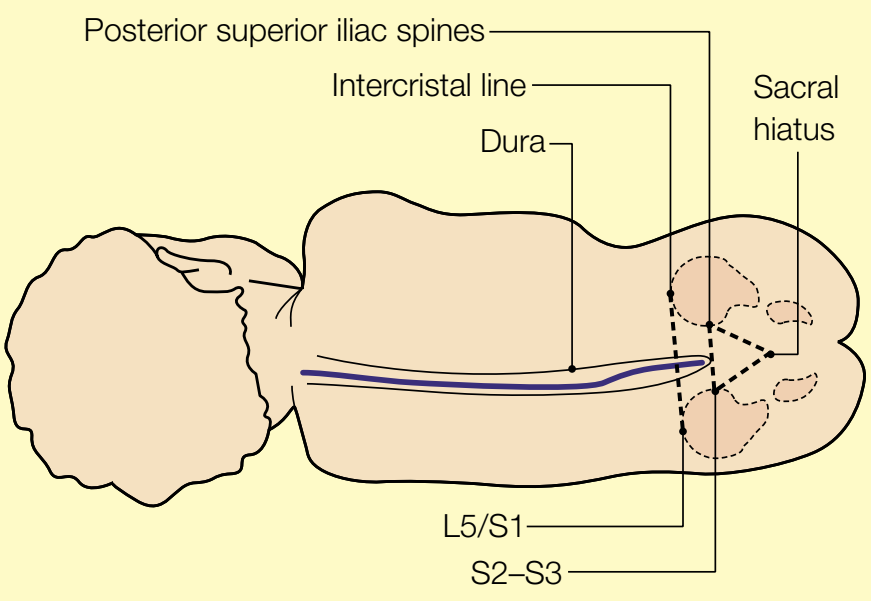
12

Caudal anaesthesia
Caudal anaesthesia is a simple and safe technique. It is performed by injecting local anaesthetic through the sacral hiatus, which is easily palpated as a dimple flanked by the sacral cornua (Figure 13).

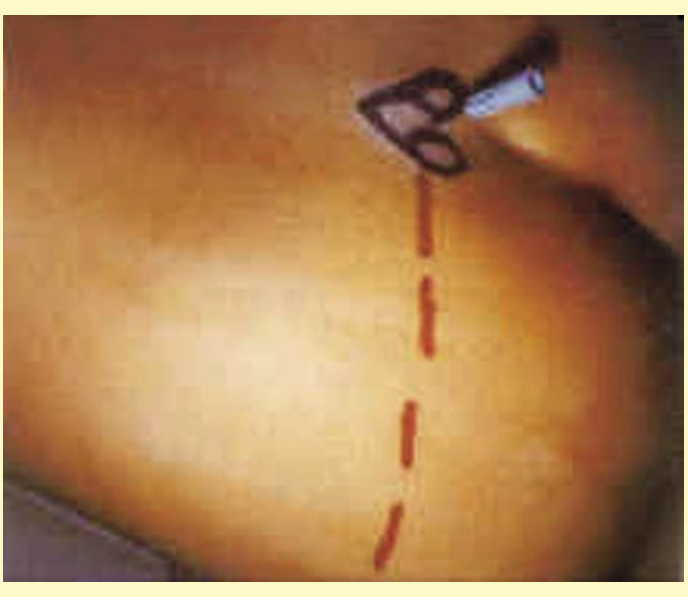
Single-shot caudal blocks can be performed using either a short (2.5 cm) 23 G intramuscular needle, a short bevelled needle with a solid obturator, or a 22 G cannula. However, the risks of vascular penetration or the production of a dermoid cyst due to implantation of skin are recognized problems that favour the use of the cannula technique. The technique of insertion is different depending on the age of the child. In babies, the needle should be inserted in the centre of the hiatus at an angle of 15° to the skin because of the flatness of the sacrum. In older children, the needle is placed at the apex of the hiatus at an angle of 45° to the skin. For continuous caudal anaesthesia, a 20 G intravenous cannula can be used ensuring the cannula is not advanced too far up the caudal space for fear of damaging the dura. A catheter (23 G) from a 19 G epidural set can then be passed easily through the cannula to the desired dermatomal level.

Caudal block

Landmarks for caudal block in babies



Site of caudal block



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ACKNOWLEDGEMENTS
Figures 3, 5, 6, 9 and 13 are reproduced from Morton N S, Raine P A M, eds. Paediatric Day Case Surgery. Oxford: Oxford Medical Publications, 1994, by kind permission of the publisher.

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Congenital Heart Disease

Monica Stokes

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The incidence of congenital heart disease (CHD) is about 6–8/1000 births, and is more common in premature infants. There is a broad range of lesions and severity, with differing implications for morbidity and life expectancy. The multifact-orial causes include known teratogens such as maternal alcohol, rubella, and diabetes. In some instances there is an association with a chromosomal abnormality (e.g. trisomy 21, Down's syndrome), or other recognized pattern of malformation or syndrome. Significant musculoskeletal defects such as diaphragmatic hernia, exomphalos, tracheo-oesophageal fistula, and imperforate anus may co-exist.

The pathophysiological effects of CHD vary with the nature of the lesion and change as time passes. Some septal defects, for instance, close spontaneously without medical intervention. Other lesions tend to worsen as the child grows, and some are lethal without intervention. Therefore, regular evaluation of anatomical and functional status is essential. There is often an optimal time for surgical intervention to achieve the best outcome, and many defects are palliated or treated at an early age.

Pathophysiology

Classifications of CHD based on detailed anatomical descriptions are unhelpful for practical purposes because it is the pathophysiology that determines the presentation, natural history and management of a particular condition. A simple distinction between cyanotic and acyanotic is too broad, however, because it gives no sense of the potential for systemic and pulmonary circulatory patterns to change. It is more useful to consider whether the dominant lesion is a shunt between systemic and pulmonary circulations, with increased or decreased pulmonary blood flow, or obstruction to systemic or pulmonary blood flow (Figure 1).

Simple classification of congenital heart disease

Lesions causing primary left-to right shunts
- Patent ductus arteriosus
- Atrial septal defect
- Ventricular septal defect

Lesions causing primary right-to-left shunts
- Transposition of the great vessels
- Tetralogy of Fallot
- Tricuspid atresia

Lesions obstructing ventricular function
- Left heart
  - Coarctation of the aorta
  - Aortic stenosis
  - Mitral stenosis
- Right heart
  - Pulmonary stenosis

1

Shunts

A shunt is a communication between systemic and pulmonary circulations. It may occur outside the heart (e.g. collateral vessels, patent ductus arteriosus) or within it (at atrial, ventricular, or great artery level). It may be a component of the congenital heart lesion or be created to palliate it. (A conduit, by contrast, is a channel fashioned between vessels or chambers normally in continuity.)

The magnitude and direction of blood flow across a shunt are determined primarily by the size of the communication and by the relative resistances of the pulmonary and systemic circulations.

• A dependent shunt is one where the flow varies according to the relative resistances of the vascular beds. It may be left-to right or right-to-left.

• A small communication may be restrictive in that systemic and pulmonary vascular resistances are less important in determining the amount of shunting. This is usually the case in children with mild heart disease that is asymptomatic or minimally symptomatic (e.g. small artial septal defect, ventricular septal defect, patent ductus arteriosus).

• A non-restrictive defect is defined as one across which no pressure gradient exists, the direction and degree of shunting being determined by the relative compliances of the two atria and ventricles.

• An obligatory shunt occurs when resistances are fixed and flow occurs because of pressure differences of an order of magnitude.

Shunting may be essential for survival: a patent ductus arteriosus for instance, may supply the pulmonary blood in pulmonary atresia or the systemic flow in aortic atresia. In other words, where there is partial or complete obstruction to a circulatory path, a communication at another level is necessary.

Left-to-right shunts

Children with left-to-right shunts are typically pink with pulmonary plethora on chest radiography. The physical signs reflect the shunt volume. The cardiac chambers enlarge and hypertrophy to cope with the excessive volume and increased flow across a valve causes a murmur.

Unchecked, volume overload can lead to ventricular failure, and sustained high pulmonary blood flow damages small peripheral pulmonary arteries. This damage consists of medial hypertrophy of the arterial wall, followed by intimal damage and ultimately elevated pulmonary vascular resistance, which may be irreversible. At this point, flow through the shunt diminishes and eventually reverses, the patient becoming cyanosed (Eisenmenger reaction).

Atrial septal defect

The secundum atrial septal defect is the most common type of interatrial communication. It is a true defect of the atrial septum, unlike the more complex ostium primum septal defect. The direction of blood flow is determined by the relative compliances of the two atria and ventricles, which in the newborn are equally thick walled. Shunting between the atria does not occur until the pulmonary vascular resistance has fallen after birth, and the right ventricle has become more compliant.

Of the excessive blood returning to the left atrium, enough enters the left ventricle to sustain a normal systemic output
but a greater volume is recirculated through the atrial defect, right heart and lungs. Flow through the pulmonary circulation can be three times that through the systemic circulation, producing the characteristic mid-diastolic tricuspid flow murmur, pulmonary ejection murmur, and prolonged right ventricular ejection.

Some infants with isolated interatrial communications develop symptoms of intractable congestive heart failure and failure to thrive. Many children are initially asymptomatic but with time, particularly if a large shunt (2:1 or greater) persists through childhood, pulmonary vascular disease and arrhythmias can develop.

Large defects may be closed surgically but it is possible to occlude smaller defects with devices placed percutaneously under radiological imaging, avoiding the need for cardiopulmonary bypass.

Ventricular septal defect

In ventricular septal defect, blood flows from the left to the right ventricle in systole and recirculates through the lungs. Both ventricles and the left atrium dilate and the liver enlarges secondary to right ventricular volume overload.

A large defect may present in early infancy with tachypnoea and failure to thrive, because the lungs are stiff and non-compliant. The high left ventricular pressure is transmitted to the pulmonary circulation and the hypertensive pulmonary arteries may compress small airways. Therefore, respiratory tract infections are common. Both ventricles enlarge making the chest wall bulge and the apical beat is typically forceful.

The characteristic murmur is pansystolic, and when the pulmonary flow is more than about twice systemic, a mitral diastolic murmur appears. As pulmonary vascular resistance increases, the pulmonary artery diastolic pressure rises; pulmonary flow decreases, and the mitral diastolic murmur disappears. Eventually, when the pulmonary vascular resistance approaches systemic levels, the pansystolic murmur shortens and disappears. On chest radiography the enlarged heart becomes small and the plethoric lung field become oligaemic with pruning of the peripheral vessels.

Medical management depends on the size of the defect. Most defects are small and close spontaneously. About 10% of the larger defects will also close. In some patients, obstruction to the right ventricular outflow tract develops. These patients become cyanosed, the physiology coming to resemble that of tetralogy of Fallot. Pulmonary vascular disease develops if the defect remains large so surgery is often performed in infancy.

Patent ductus arteriosus

Patent ductus arteriosus is a shunt at arterial level and flow occurs during both systole and diastole. The magnitude of shunting is dependent on the size of the duct and the relative resistance of the pulmonary and systemic vascular beds. There is a continuous flow of blood from the aorta to the pulmonary artery, producing a continuous murmur. If the ductus is large, pulmonary venous return is high, the left heart is overloaded and so the apical impulse is prominent and a mitral mid-diastolic flow murmur is heard. During diastole the blood 'steals' from the aorta to the pulmonary artery, and therefore the aortic diastolic pressure is low and the upstroke of the pulse is abrupt as blood is ejected into an empty aorta. This produces the characteristic bounding pulse.

Most children with patent ductus arteriosus are asymptomatic. Premature babies, however, are often symptomatic. The work of breathing is increased and attempts to wean from mechanical respiratory support are unsuccessful.

Treatment with indomethacin is often successful in promoting closure of the ductus but when it fails, surgical ligation is indicated via a left thoracotomy. It is extremely unlikely that a patent ductus arteriosus will close spontaneously after 1 year.

A large duct can lead to progressive pulmonary vascular disease, while those with smaller shunts are at risk for endocarditis, aneurysm, calcification and paradoxical emboli. Nowadays, it is common for ducts in older children to be occluded by devices placed percutaneously at cardiac catheterization.

Pulmonary venous obstruction

Patients with pulmonary venous obstruction may be cyanosed or acyanotic but have signs of pulmonary oedema clinically and on chest radiography.

Obstruction to pulmonary venous return can occur at several places; in the pulmonary venous pathway (obstructed total anomalous pulmonary venous drainage), within the atrium (cor triatriatum) or by obstruction to left ventricular inflow at supravalvar, valvar, or submitral level. Children with pulmonary venous obstruction usually present in early infancy with cyanosis and dyspnoea caused by pulmonary oedema. In less severe cases, presentation is with failure to thrive and respiratory symptoms.

The major effect of total anomalous pulmonary venous drainage is that all systemic and pulmonary venous return is to the right atrium. The pulmonary veins drain into a confluence behind the heart and from there to the right atrium, usually indirectly via the innominate vein, coronary sinus or portal system. Saturated and desaturated blood mixes in the right atrium; sufficient oxygenated blood crosses an atrial sepal defect to support the systemic circulation while the remainder re-enters the right ventricle. The long pulmonary venous pathway is usually obstructive, causing pulmonary venous hypertension and pulmonary oedema and contributing to a high pulmonary vascular resistance. This is a life-threatening situation requiring emergency corrective surgery.

Obstruction to systemic perfusion

The dominant features of an obstruction to systemic perfusion are poor peripheral pulses and metabolic acidosis. This can be a result of aortic obstruction (interrupted aortic arch and coarctation) left ventricular outflow tract obstruction (aortic valve stenosis) or low left ventricular stroke volume (hypoplastic left heart syndrome). Even when the anatomical obstruction is severe, the fetus survives because the right ventricle can provide systemic perfusion through the ductus arteriosus. Once the duct starts to close in early neonatal life, systemic hypoperfusion, or lower body hypoperfusion in coarctation, develops. The pulses become impalpable, urine output diminishes, metabolic acidosis develops and a vicious cycle of generalized organ dysfunction develops.

Resuscitation includes maintaining the patency of the ductus with prostaglandin infusion. Mechanical ventilation and inotropic support of the failing left ventricle is often required.

Coarctation of the aorta

Narrowing of the aortic lumen usually occurs at the level of the insertion of the ductus arteriosus. In neonates, the pressure load on the left ventricle may produce congestive failure, metabolic acidosis and respiratory insufficiency.

Older children are usually asymptomatic but have diminished femoral pulses and upper limb hypertension. Collateral vessels tend to be well developed: enlarged intercostal arteries produce the characteristic rib notching seen on chest radiography in older children and adults with coarctation.

Tetralogy of Fallot

The tetralogy of Fallot is the combination of a ventricular septal defect and obstruction to pulmonary blood flow (usually at the outlet of the right ventricle, the infundibulum). There is secondary right ventricular hypertrophy and an abnormally positioned aortic outflow, which 'overrides' the ventricular septal defect.

Blood flow to the lungs is reduced but by variable amounts – some children have very few symptoms unless stressed, whereas others present early in infancy with cyanosis, particularly if the pulmonary arteries are also small. Cyanotic 'spells' are a result of spasm of the infundibular muscle and cause an increased shunt across the ventricular septal defect to the systemic circulation (right to left). It is this dynamic aspect of the obstruction to pulmonary blood flow that accounts for both the intermittent nature of 'spells', and therapeutic interventions that may curtail them. Intraoperative spells are detected by desaturation, a reduction in end-tidal carbon dioxide and systemic hypotension.

Management is directed towards improving forward pulmonary blood flow including:

- hyperventilating with 100% oxygen to reduce pulmonary vascular resistance
- optimizing intravascular volume with a bolus of colloid
- increasing venous return by elevation of the legs
- increasing systemic vascular resistance by administering phenylephrine or noradrenaline (norepinephrine).

Analgesia and β-blockade are also helpful (Figure 2).

Transposition of the great arteries

In transposition of the great arteries, the aorta arises from the right ventricle and the pulmonary artery comes off the left ventricle. To be compatible with life, mixing must occur through a septal defect or patent ductus. If the neonate has an intact septum, an atrial communication is made by percutaneous balloon septostomy.

Transposition of the great arteries is usually lethal without cardiac surgery. There are two surgical approaches.

Anaesthetic considerations in tetralogy of Fallot

- Give preoperative hydration (see right-to-left shunts)
- Prescribe sedative premedication (helps reduce 'spells')
- Hypoxia and hypotension on induction should be avoided because they tend to increase shunting
- Intraoperative desaturation and reduced end tidal carbon dioxide tension values occur in other acute situations such as hypovolaemia and air embolus
- Treatment of infundibular spasm
  - Oxygen
  - Pain relief
  - β−blockade (propranolol, 0.1 mg/kg i.v.)
  - Intravascular volume replacement
  - α−agonist (e.g. phenylephrine, noradrenaline (norepinephrine)) to increase systemic vascular resistance
- Risk of embolization

2

Physiological correction: a physiological correction involves making channels in the atria such that venous blood returning from the body is diverted into the left ventricle, and then into the pulmonary artery (the Mustard or Senning procedures). Longer term, the right ventricle is unable to power the systemic circulation indefinitely and right ventricular failure eventually occurs.

Anatomical correction: an anatomical correction can be made, in which the aorta and pulmonary arteries are 'switched' and the coronary arteries are reimplanted. Although technically complicated, cardiovascular function is usually good afterwards.

Perioperative management

Anatomy and function of the heart are variable, therefore each patient must be assessed individually (Figure 3). A thoughtful approach to anaesthetic management will avoid unnecessary upset of the child's cardiorespiratory balance. Sedative, anxiolytic premedication is very useful, for instance, but large doses of opioid premedication should be avoided because of the potential for respiratory depression. The aim is for a smooth induction of anaesthesia, with impeccable airway control and balanced pulmonary and systemic vascular resistances.

Children with mild-to-moderate functional impairment tolerate inhalation induction and intravenous induction well. Intravenous ketamine is a useful alternative for more severely impaired patients because it has little effect on either systemic or pulmonary vascular resistance.

Preoperative assessment

History and examination

- Level of activity (cardiac reserve) and symptoms
- Murmurs, peripheral pulses and skin temperature

Investigations

- Chest radiography (heart position, size and shape; increased or decreased pulmonary vascular markings)
- ECG (R axis deviation is normal in infancy; evidence of ventricular hypertrophy)
- Echocardiography (anatomy, function, cardiac output)
- Cardiac catheterization (site and size of shunts, pressures, saturations)
- Haematocrit (increased in cyanotic lesions; significant risk of thrombosis if > 60%).

Medications

- Diuretics, digoxin, captopril
- Warfarin, aspirin
- Antibiotics (endocarditis prophylaxis)

Previous surgery

- Review records
- Note airway problems
- Review dental hygiene

3

Left-to-right shunts

- An increase in systemic vascular resistance increases left-to-right shunting. An increase in pulmonary vascular resistance reduces left-to-right shunting.
- Intravenous induction may be prolonged because of recirculation in the lung.
- Uptake of inhalational agents is not really influenced by left-to-right shunt unless there is poor cardiac output. An agent with low blood gas solubility coefficient will then show increased speed of uptake. Pulmonary congestion increases the risk of atelectasis.

Right-to-left shunts:

- Prolonged starvation times should be avoided. Dehydration produces haemoconcentration, worsening the effects of the high haematocrit associated with cyanotic heart disease (e.g. increased risk of thrombosis and stroke). Consider starting intravenous fluids if the time of surgery is uncertain.
- Accidental air embolization should be avoided.
- The aim is not to make the shunt any worse (e.g. by hypoxia or hypotension).
- Raised intrathoracic pressure decreases pulmonary blood flow.
- Cyanotic patients have an abnormal response to hypoxia because they do not increase breathing rate in the same way as healthy individuals.
- Intravenous induction is rapid, however, the dose should be reduced to avoid a large drop in systemic vascular resistance.
- Uptake of volatile anaesthetic gases is slow

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Equipment for Paediatric Anaesthesia

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There are physiological and anatomical differences between babies, children and adults, therefore the anaesthetic equipment required for each needs to be different. Differences are greatest for neonates (under 4 weeks old) and infants (under a year). The laws of physics also determine that the behaviour of some equipment depends on size. However, cultural differences between centres, which sometimes seem to have little scientific basis, may dictate which anaesthetic equipment is used.

Environment

A child-friendly environment is important. However, when designing paediatric anaesthetic or recovery areas, it should be remembered that 13-year-olds may be insulted if they are put in an area better suited to 3-year-olds. Fashions change and durable cartoon characters are more suitable than current fads that may soon be outdated.

Temperature maintenance

Infants have a high surface area/body mass ratio and therefore lose heat rapidly, mainly by radiation, though convection, conduction and evaporation also have a role. Strategies to maintain temperature should take account of all these. In general, the following factors should be considered:

- warming the patient's environment
- warming and humidifying inhaled gases
- limiting evaporative heat loss
- warming topical and intravenous fluids.

Even within the hospital, neonates should travel in a heated incubator. Paediatric theatres should be warm, but temperatures above 25°C are uncomfortable for staff; therefore, the microenvironment of the patient needs attention. For infants, a radiant overhead heater should be used during induction and reversal of anaesthesia and during application of skin preparation, when heat loss (through the latent heat of vaporization) is high. Manufacturer's guidelines concerning patients' proximity to the heater should be followed to avoid overheating or burns. Forced-air warming systems blow filtered, warm air from a cover or mattress and can be used throughout the operation. When draped, the patient lies in a microenvironment of warm air. Simple techniques are also available; for example, partial wrapping in aluminium foil reduces radiant heat loss, and wrapping in cotton wool padding reduces conductive and convective losses.

Humidification of gases

Some active water-bath humidifiers incorporate a heating wire in the patient tubing. This reduces 'rain-out' – condensation that occurs when gases cool below the dew point. A temperature sensor at the patient end of the tubing prevents the gases overheating beyond 35°C. Use of sterile water and disposable components reduces bacterial colonization.

The heat and moisture exchanger (HME), or condenser humidifier, is a passive humidifier using a membrane that is hygroscopic (water absorbing) or hydrophobic (water collects as surface droplets). The membrane warms during expiration, both from the expired gases and the release of latent heat of evaporation. HMEs are efficient with small tidal flows (with larger tidal volumes the membrane may saturate before expiration ends). Efficiency over short periods is limited but improves with time – after 1 hour the humidity of the inspired gases may be 30 g/m^3 (equivalent to 95% relative humidity in the trachea at 32°C). Modern HMEs are small, adding less dead space and less flow resistance (even when saturated), and are suitable for paediatric use.

Viruses can be transmitted via the breathing system, mainly in liquid secretions. Heat and moisture-exchanging filters act as barriers to all microorganisms and may allow 'single-use' systems to be re-used. However, their volume adds dead space and they are not suitable for neonates.

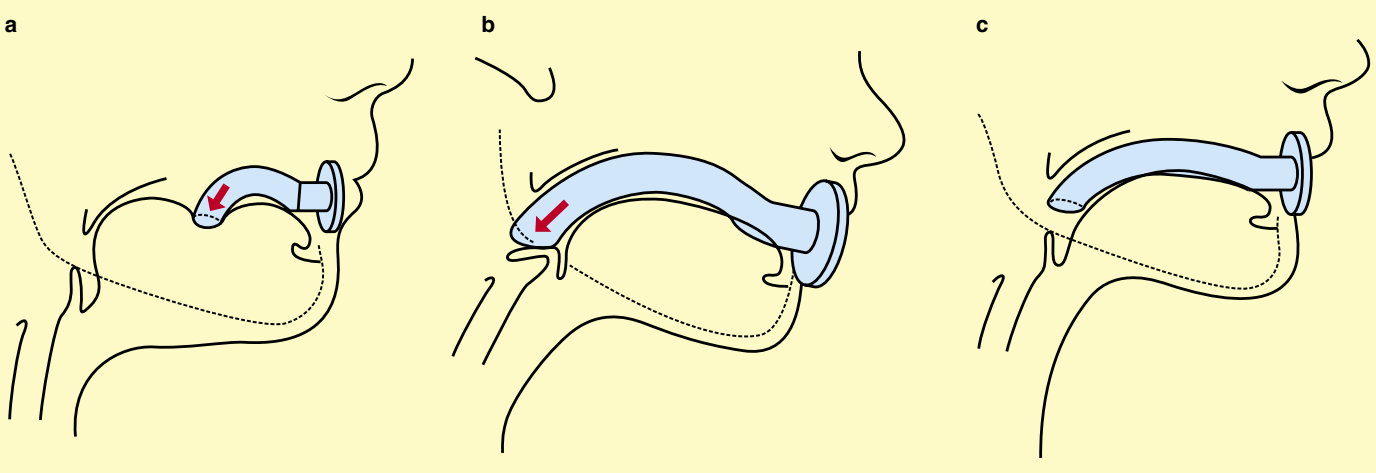
Intravenous infusions

Cannulae
Cannulae are available in sizes as small as 26 G. Nicking the skin before insertion reduces the chance of a fine cannula buckling. An extension set can be attached via a three-way tap to facilitate drug administration. Using a narrow-bore extension (100 cm long, 0.8 ml volume) avoids having to give large volumes of flush each time a drug is given. Giving fluids to babies by syringe (either manually or using a syringe driver) allows small volumes to be given accurately and reduces the possible danger of the fluid from a full burette inadvertently running into the patient.

Intravenous filters
Care should be taken to exclude bubbles from the system. In the case of a patient with a known atrioventricular malformation or atrial septal defect, an air filter is recommended because there is a risk of air emboli entering the left side of the circulation. However, blood cannot be given through air filters.

Fluid warmers
Various types are available. Some use a special concentric double-tubing system. The infusion in the central tube is kept warm by heated water circulating in the outer tube, which also prevents gases coming out of solution and forming bubbles. However, the tubing sets are expensive.

Guedel airway



A Guedel airway is unnecessary if the airway can be managed without it. Sizing guide: with the flange at the centre of the lips, the end should be nearly at the angle of the jaw (**c**). An incorrectly sized airway will make matters worse (**a** and **b**). Sizing and colour-coding is not consistent between manufacturers.

Adapted from: Advanced Life Support Group. *Advanced Paediatric Life Support.* 2nd ed. London: BMJ Publishing Group, 1997. © BMJ Publishing Group, 1997.

Anaesthetic machines

An air flowmeter allows mixtures containing less than 100% oxygen to be given when nitrous oxide is contraindicated. Availability of carbon dioxide is controversial, but is some-times useful in preventing hypocarbia. Some flowmeters are limited to 0.5 litre/minute to prevent excessive carbon dioxide administration.

It is a good idea to have a pressure blow-off valve at the fresh gas port of the anaesthetic machine, functioning at 5–6 kPa, to avoid inadvertently exposing the patient to high pressures.

Equipment for managing the airway

Face masks
The Rendell-Baker–Soucek mask, designed specifically for babies, is shaped to give a low dead space, but can be difficult to use. Because most anaesthetists intubate babies, a face mask is used principally during ventilation before intubation, so a good seal is more important than low dead space. Round masks with moulded face seals, often made of clear silicone rubber, are increasingly popular for this reason.

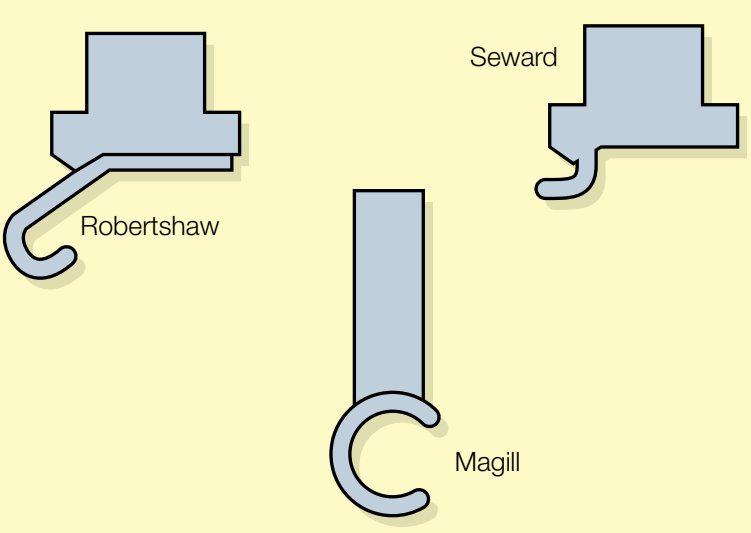
Laryngeal mask airways (LMAs)
The wide LMA tube has a low resistance to gas flow during spontaneous breathing compared with a small tracheal tube, thus reducing the work of breathing. This is indicated by a lower incidence of paradoxical respiratory movements. (The Hagen–Poiseuille equation states that the laminar flow is proportional to the fourth power of the radius.)

A range of sizes is available, down to size 1, recommended by the manufacturers for babies less than 6.5 kg (see Figure 1, *Anaesthesia and Intensive Care Medicine* **1:1:** 33). However, LMAs are not used routinely in neonates because dead space is excessive, obtaining a laryngeal seal is difficult, and most anaesthetists use intermittent positive-pressure ventilation (IPPV) delivered through a tracheal tube. However, LMAs have been used for neonatal emergencies and difficult airways such as the Pierre Robin syndrome.

In small children, it has been suggested that the LMA is easier to insert with the cuff partially inflated, or inserted sideways and then rotated 90°. Positioning is not always satisfactory, and gas leaks are common. Reinforced LMAs have made their use practicable for adenotonsillectomy.

In view of the potential for distending the stomach with gas, LMAs are not recommended for IPPV in small children.

Laryngoscope blades



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Intubation equipment
Straight-bladed laryngoscopes are usually preferred in younger patients. There are several designs (Figure 1), which may be broadly divided into open designs (e.g. the Robertshaw and Seward), and those with a semi-circular blade (e.g. the Magill). Open blades are often easier to use, especially when using forceps to place nasal tubes. Laryngoscopes are better balanced if a lightweight paediatric handle is used. Fibre-optics give superior illumination. Green bands indicate International Standards Organization compatibility with interchangeable blades and handles from different manufacturers. The age of the child at which the straight blade is replaced with a curved adult blade is a matter of personal preference, but is often around 5 years.

Infants have relatively large heads, therefore the traditional adult 'sniffing the morning air' position with the head on a pillow is inappropriate. An infant's head should be flat on the trolley or table. A rolled-up pillowcase under the nape of the neck helps stabilize the head.

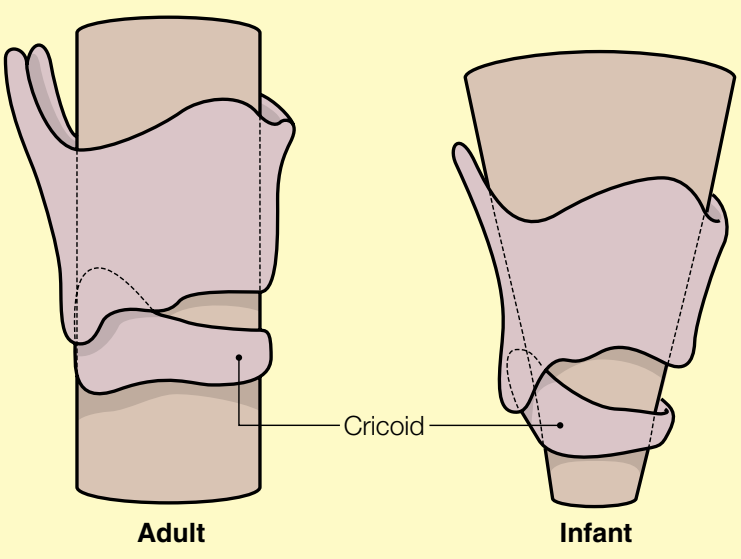
With straight open blades, intubation technique is a matter of choice. There are three possible techniques:

- the tip of the blade placed in the vallecula
- the epiglottis lifted with the blade
- the tip of the blade initially placed in the oesophagus, then withdrawn until the cords appear.

Tracheal tubes
In infants and children the airway narrows beyond the cords, at the cricoid ring (Figure 2), and the tracheal mucosa may be damaged by excessive tube or cuff pressure, resulting in temporary swelling or even permanent subglottic stenosis. With modern materials and soft cuffs it is debatable whether cuffed tubes do much harm for short-term use. However, absence of a cuff may allow a slightly larger tube size, improving gas flow. It is still normal practice to use uncuffed tubes and there are no rigid rules about the age at which to switch to cuffed tubes, though 8–10 years is reasonable.

Disposable tubes are often made of polyvinyl chloride (PVC), which is implantation tested in rabbit paravertebral muscle or tested in cell culture. Tubes are marked IT or Z-79 to indicate this. PVC softens at body temperature, conforming to the patient's airway. (Tubes soften when repeatedly handled. If practising intubations on manikin heads, they are best kept in iced water). Thin-walled paediatric tubes kink easily.
Tube sizing: a correctly sized tube passes easily through the cords, giving a slight leak at maximum, or just over maximum, inflationary pressure. The necessity for significant leaks at normal ventilator pressures is less emphasized than previously. Suggested tube sizes for infants are shown in Figure 3.

Infant airway anatomy showing narrowing at cricoid



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Tube sizes for infants

Age	Weight (kg)	Tube size (internal diameter, mm)
Small premature	< 0.7	2.0
Premature	0.7–1.5	2.5
Small term	1.5–3.0	3.0
Term	3.0–4.0	3.5
6 months	7	4.0
1 year	10	4.5

3

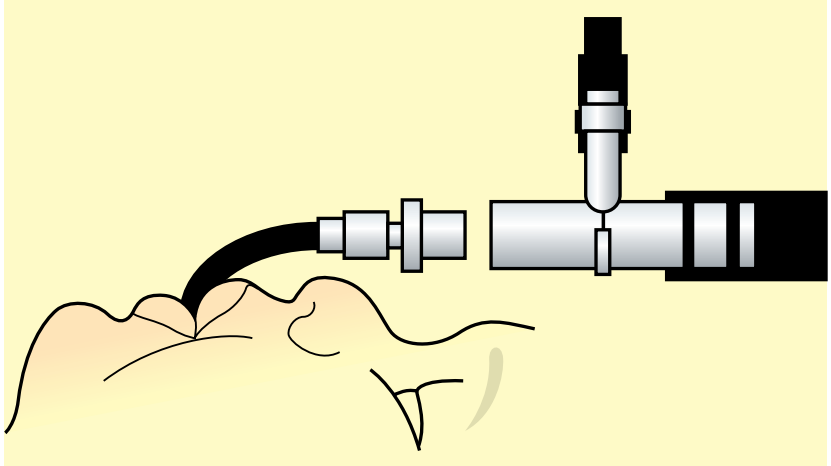
For older children: tube size (mm) = age (years)/4 + 4.5. For emergencies, a tube size of age/4 + 4 should be used (a small tube is usable, whereas one that is too big is useless). It is also sensible to have ready a smaller and a larger tube than the one planned.

A formula for the length of an oral tube in a child older than 12 months is: [½ (age in years) + 12] cm. In some countries it is usual to leave a length protruding from the mouth and different formulas are used. In emergencies it may better to leave a tube uncut, because one cut too short is useless.

The ideal position for the tip of the tube is the mid-trachea. This can be obtained by passing a 3.0 or 3.5 mm tracheal tube 3 cm, a 4.0 or 4.5 mm tube 4 cm, or a 5.0 or 5.5 mm tube 5 cm through the cords. However, the tube position should always be checked by auscultation (and radiography for long-term ventilation).

Reinforced tubes can simply be folded over the lip and stuck down, making adjustment of the intratracheal length simple (Figure 4). Some anaesthetists use them routinely. An intubation stylet is needed for insertion. Overall tube diameter depends on wall thickness, therefore reinforced tubes (with thick walls) may need to be half a size smaller than predicted.

Reinforced tracheal tube



The use of a reinforced tube allows easy adjustment of length, and the tube can be securely stuck down to the upper lip

4

Other tubes: double-lumen tubes do not exist in infant sizes and single lung anaesthesia is achieved by endobronchial intubation. Cole pattern tubes have wider bores, narrowing at a shoulder to a section that passes the cords. They may be easier to use for neonatal emergency intubation but have associated problems. Airflow is turbulent at the shoulder, increasing flow resistance. If the tube slips and the shoulder presses on the glottis, there is a risk of damage.

Connectors: standard 15 mm connectors are bulky when used with small tracheal tubes. For this reason, neater 8.5 mm systems were developed. However, the small demand has led to limited commercial success and their future is uncertain. Nevertheless, awareness of different connectors is important, particularly for transportation between centres.

Breathing systems

Paediatric breathing systems should be lightweight with low dead space. For spontaneously breathing patients, resistance to flow should be low (though the greatest resistance will be at the narrow endotracheal tube). It is desirable to have a low compressible volume of gas, particularly for ventilation at small tidal volumes, and stiff, non-compliant tubing.

Breathing systems may be divided into absorber and non-absorber systems. Non-absorbing systems have had greater use in paediatrics.

Mapleson classification: this is the usual classification of semi-closed systems . There are no unidirectional valves to direct gas flow, and no absorbant, so the fresh gas flow (FGF) must wash away the carbon dioxide.

The Mapleson A system is efficient for spontaneously breathing patients, and low gas flows, equivalent to the alveolar ventilation, may be used (alveolar ventilation in litre/minute 0.6 √bodyweight in kg). However, the system is inefficient for ventilated patients.

The Mapleson D and F systems are the most efficient for use with IPPV. The Humphrey ADE system is a combination of three systems – Lack (Mapleson A), Mapleson D and Mapleson E, and has been used successfully in paediatric anaesthesia.

The T-piece

Ayre's original form was a Mapleson E system. It was later modified by Jackson Rees, by including an open-ended reservoir bag and using a longer reservoir tube. In this form it is a Mapleson F. The Jackson Rees modification is commonly used for patients under about 20 kg, though with a high enough FGF and an expiratory limb greater than tidal volume there is no upper weight limit. It has several advantages:

- lightweight
- low flow resistance
- suitable for spontaneous or controlled ventilation
- simple design with no valves.

It also has some disadvantages:

- exhaust gases difficult to scavenge
- obstruction of expiratory limb exposes patients to high pressures
- high FGF required in larger patients.

Carbon dioxide elimination is affected by several factors:

- FGF
- tidal volume
- rate of ventilation.

Classically it was taught that an FGF of two-and-a-half to three times the patient's minute ventilation should be used. The patient's minute ventilation is not known, thus the FGF is estimated from bodyweight (BW); for example: FGF = 3 x (1000 + 100 ml/kg) for an intubated patient who is breathing spontaneously. Alternative formulas are: FGF = 2√BW for spontaneous respiration; FGF = √BW for controlled ventilation. It is now usual to monitor end-tidal carbon dioxide and make adjustments accordingly.

Increasing FGF pushes expired alveolar gas further down the reservoir tube, reducing rebreathing of exhaled gases during inspiration. Above a certain FGF there is no rebreathing of alveolar gas. Increasing FGF beyond this point is wasteful. The use of high gas flows in a T-piece results in a degree of positive end-expiratory pressure, as a result of the pressure needed to expel gas through the expiratory limb.

At low FGFs it is largely the FGF that determines the degree of rebreathing and hence the elimination of the patient's carbon dioxide. If the patient is ventilated, increasing the tidal volume may have little effect on carbon dioxide. This characteristic allows generous tidal volumes to be given to the patient, reducing basal atelectasis, without blowing off excessive carbon dioxide.

Increasing the rate of ventilation may not increase carbon dioxide exhaled gases to be driven out of the reservoir tube.

A simple increase in rate may even lead to paradoxical carbon dioxide retention unless the FGF is also increased.

Circle systems

Paediatric circle systems are not widely used in the UK because of concerns about flow resistance, dead space and leaks around the uncuffed endotracheal tube. Disposable circle systems are also expensive. However, many of these concerns are spurious. Recognition of physiological differences has led most anaesthetists to use controlled ventilation during anaesthetia in infants. The use of filters reduces infection risk and small paediatric soda lime canisters and narrow-bore tubing reduce compressible volume.

It is important to monitor gases within the circle, because there may be significant differences between the composition of fresh gas compared with gas in the circle.

Ventilators

Paediatric ventilators can be classified under familiar headings (e.g. power source, cycling mechanism, pressure or flow generator). Most mechanical ventilation in small children is defined by the fraction of oxygen in inspired air (Fi_{O_2}), inspiratory and expiratory times (or inspiratory/expiratory ratio and rate), and the pressures (maximum, mean and end-expiratory). Ventilation is not usually defined by setting tidal volume. Tidal volume is unknown with pressure-controlled ventilation, but will be reasonably constant with unchanging compliance. In practice, ventilation is set up according to sensible predicted values and then modified according to the monitoring figures.

T-piece occluding ventilators

Ventilation requirements in the operating theatre are different from those in the ICU. In the ICU, compliance changes are usually gradual, and the chest wall can be observed. The lowest acceptable mean airway pressure is used to prevent barotrauma. ICU ventilators are often time cycled, pressure limited, pressure pre-set and of the T-piece occluder type (e.g. Sechrist). There is no separate driving gas. Gas flows continually in the T-piece and the ventilators function by occluding the T-piece outflow, when gas flows into the patient. The patient can always make spontaneous breaths, with low resistance to flow. In effect, the patient is always given intermittent mandatory ventilation. High fresh gas flows are often used in the ICU to maintain a rapid upsweep in inspiratory pressure, allowing optimal recruitment of alveoli.

In the operating theatre, ventilators with a separate driving gas are favoured, because simple T-piece occluders are not ideal. Compliance and tidal volume can fall if one of the surgical team leans on the chest or splints the diaphragm. The endotracheal tube may block or kink and this may cause tidal volume to fall without much change in the ventilator pressure display.

Bag squeezer

Gas-driven, 'bag-squeezing', ventilators are easily connected to a T-piece or Bain system, replacing the anaesthetist's hand squeezing the bag. Some are pure flow generators and produce a constant tidal volume (provided the safety blow-off pressure is not exceeded).

The Penlon–Nuffield anaesthesia ventilator is used in many centres in the UK and Australasia, and in some centres in the USA. It is a gas-driven flow generator. It is fitted with a Newton valve for use in infants, which introduces a fixed leak and has a pressure relief valve set at 40 cm H_2O. With the Newton valve the Nuffield ventilator works predominantly as a flow generator at low pressures and as a pressure generator at higher pressures. A drawback is the slow inspiratory pressure rise, because with short inspiratory times this gives sub-optimal alveolar recruitment.

A bag squeezer can provide stable ventilation that is unaffected by small changes in compliance. As discussed earlier (see page 58), at low fresh gas flows it is the FGF that governs the elimination of carbon dioxide in the T-piece or Bain system, not small changes in patient tidal volume. In contrast, using high gas flows with no rebreathing, where carbon dioxide elimination is determined by adjusting minute ventilation, may produce unstable ventilation that needs frequent fine-tuning in theatre.

Other ventilators

Complex intensive care ventilators with a variety of volume or pressure modes may be used for theatre ventilation. However, these ventilators, though flexible, are not always ideal because the alarms are easily triggered.

Adult circles, with bag-in-bottle ventilators using volume control, are not recommended for infants because accurate control of tidal volume is impossible as a result of the large compressible volume of gas in the system. Smaller bellows and tubing are used to reduce compressible volume in paediatric circles.

Disconnection alarms
Some T-piece occluders require a separate alarm that detects pressure cycling. The alarm limits are adjusted by the user; if set incorrectly, system leaks may not be sensed. It is also possible that a high flow rate through a small tracheal tube will generate sufficient pressure for an accidental extubation to go undetected.

Hand ventilation
Once practised, hand ventilation is easy and reliable with the T-piece.

Advantages
- Pressure on the chest or diaphragm is felt immediately.
- The 'educated thumb' can detect disconnection, or occlusion of the tube (assuming the system is non-compliant).
- The anaesthetist stays near the patient.
- There is useful back-up in case of ventilator problems.

Disadvantages
- The anaesthetist will need assistance for some manoeuvres (e.g. giving drugs or changing fluid bags).
- The technique is suitable for the T-piece only. Hand ventilation is possible with other circuits, but the higher compressible volumes mean that problems are detected less reliably.

Resuscitation equipment

Pocket resuscitation masks
Pocket resuscitation masks are of one 'adult' size only, but may be used upside down in infants by forcibly folding the nose end over the chin.

Self-inflating bags
Three sizes are available: neonatal (240 ml), child (500 ml) and adult (1600 ml). With care, the child size may be used on neonates. It is essential to have one available during transportation, when exhaustion of the oxygen cylinder would render a T-piece unusable. A reservoir limb or bag should be attached to deliver a high inspired oxygen concentration.

Defibrillators
Defibrillators are seldom needed in paediatrics. If the patient is less than 10 kg, paediatric (4.5 cm) paddles are used, often revealed by sliding off the adult paddles. Separate paediatric paddles clipped over adult ones are easily lost.

FURTHER READING

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Fluid and Electrolyte Balance for Children

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Applied physiology

Renal function matures rapidly from 34 weeks' gestation. At birth, term babies have a glomerular filtration rate one-third that of the adult, rising to mature values by 12–18 months of age. Infant tubular function is poorly developed at birth and matures over the first months of life. Function can be regulated only under physiological conditions. Neonates in the first week of life are unable to tolerate large acute water or salt loads. Equally, faced with fluid restriction, neonates are able to concentrate to only half of the adult capacity. Preterm neonates have a much slower increase in glomerular and tubular function after birth. Greatly reduced renal function persists until at least 18 months postconceptional age, reaching mature values only by 8 years of age.

Glucose homeostasis: neonates have reduced hepatic glycogen stores and are at risk of developing hypoglycaemia. They usually require fluids containing 10% glucose. Critically ill neonates may require greater concentrations of glucose. However, the stress response to surgery or illness may cause hyperglycaemia. With reduced glomerular filtration, the ensuing glycosuria may cause an osmotic diuresis. Neonates should be closely monitored for both hypo- and hyperglycaemia.

Body water: total body water of a term neonate is 80% of body weight or 800 ml/kg. This value falls to 60% (600 ml/kg) by 1 year of age. The intracellular fluid (ICF) volume is constant, at about 40% of body weight. The extracellular fluid (ECF) comprises the plasma volume within the circulation and the interstitial fluid volume. In relative terms, the ECF volume falls to 20% by 1 or 2 years of age (Figure 1). Most of the decrease in ECF results from a decrease in interstitial fluid. Plasma volume within the circulation is one-third to one-quarter of the total ECF volume, the remainder consisting of the interstitial fluid volume. Blood volume is 90–100 ml/kg at birth, falling to 80 ml/kg at 1 year of age and to 70 ml/kg by adulthood.

Fluid compartments as percentage of body weight

	Total body water (%)	Extracellular fluid (%)	Intracellular fluid (%)
Neonate	80	40	40
Child (2 years)	60	20	40

1

Acute loss of circulating fluid as in blood loss (trauma, surgery) or plasma loss (burns) can be replaced with rapid infusion of relatively small volumes of fluid (i.e. 20 ml/kg boluses). Dehydration is usually of slower onset with loss of fluid from all fluid compartments. The vascular compartment is maintained unless fluid loss is rapid (overwhelming diarrhoea in small children) or has exceeded compensatory mechanisms. Evidence of dehydration is not clinically apparent until the overall loss is greater than 5% of body weight (50 ml/kg).

Normal fluid and electrolyte requirements

Normal daily fluid intake is variable. Urine output is adjusted to account for diminished or excessive fluid intake. Maintenance fluids are required to compensate for water losses from skin, respiratory tract and stools, water for essential urine output and growth, and to maintain a reasonable diuresis. Water requirements can be calculated by one of three methods.

Body surface area (BSA) – this requires measurement of weight and height and the use of nomograms. Measuring height in neonates and infants is difficult and in children under 3 kg BSA errors of 20% occur.

Calorie requirements – metabolism of 1 calorie requires 1 ml of water, therefore knowledge of a child's calorie requirement can be used to determine fluid requirement.

Body weight is the simplest method of calculating fluid and electrolyte requirements (Figure 2). Continuing measurement of body weight also gives a reliable indication of changing volume status.

The examples in Figure 3 show that maintenance fluid volumes are easily calculated. However, calculated requirements are an initial estimate and, when based on body weight, do not take account of variations in lean body mass, metabolic rate and variable growth rates.

Normal fluid and electrolyte requirements

Body weight	Daily requirement (ml/kg)	Hourly requirement (ml/kg)	Sodium[1] (mmol/kg/day)	Potassium[1] (mmol/kg/day)
First 10 kg	100	4	2–4	1.5–2.5
Second 10 kg	50	2	1–2	0.5–1.5
Subsequent 10 kg	25	1	0.5–1	0.2–0.7

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Calculating daily maintenance fluid and electrolyte requirements

5 kg infant

- Water100 ml/kg for the first 10 kg of body weight = 500 ml
- Sodium 2–4 mmol/kg for the first 10 kg of body weight = 10–20 mmol
- Potassium1.5–2.5 mmol/kg for the first 10 kg of body weight = 7.5–12.5 mmol

The fluid that best meets this requirement is 500 ml of 0.18% saline in glucose, which would supply 15 mmol sodium (0.18% saline contains 30 mmol/litre of sodium). Potassium requirement could be met by addition of 10 mmol KCl to each 500 ml bag of fluid, assuming adequate urine output and need for continuing parenteral fluid

16 kg child

- Water100 ml/kg for the first 10 kg of body weight
  + 50 ml/kg for the second 10 kg of body weight
  = 1000 ml + 300 ml = 1300 ml
- Sodium2–4 mmol/kg for the first 10 kg body weight
  + 1–2 mmol/kg for the second 10 kg body weight
  = (20–40) + (6–12) mmol = 26–52 mmol
- Potassium1.5–2.5 mmol/kg for the first 10 kg of body weight
  + 0.5–1.5 mmol/kg for the second 10 kg body weight
  = (15–25) + (3–9) = 18–34 mmol

1300 ml of 0.18% saline would supply 39 mmol of sodium/day
Adding 20 mmol/litre of KCl would supply 26 mmol of potassium

3

Dehydration

Dehydration reflects whole body fluid loss in excess of fluid intake and compensatory mechanisms. Severity of dehydration is classified as mild (5% of body weight or less), moderate (5–10%), or severe (10% or greater) (Figure 4).

Clinical signs of dehydration

Signs/symptoms	Mild < 5%	Moderate 5–10%	Severe > 10%
Decreased urine output (beware watery diarrhoea)	+	+	+
Dry mouth (mouth breathers are dry)	+/–	+	+
Decreased skin turgor (use several sites)	–	+/–	+
Sunken anterior fontanelle (crying increases pressure)	–	+	+
Sunken eyes	–	+	+
Decreased eyeball turgor (difficult in young)	–	+/–	+
Tachypnoea (acidosis and pyrexia worsen this)	–	+/–	+
Tachycardia (hypovolaemia plus pyrexia and irritability cause this)	–	+/–	+
Drowsiness, irritability	–	+/–	+

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Mild dehydration is associated with up to 50 ml/kg fluid deficit and can usually be managed with oral rehydration.

Moderate to severe dehydration always requires intravenous fluid replacement. It is important that an initial assessment of circulatory status is performed. Most of the child's body weight consists of water, therefore 10% dehydration equates to a 10% reduction in body weight caused by fluid loss. This value in grams is equivalent to millilitres of fluid deficit (Figure 5). Large volume and/or particularly rapid fluid loss may precipitate shock. When dehydration exceeds 10%, shock is invariably present. The child with sunken eyes, dry mouth, tachypnoea, tachycardia, cool peripheries, prolonged capillary refill and drowsiness or irritability requires rapid intravascular volume replacement. Treatment of shock involves administration of high flow oxygen, attention to airway and breathing, and administ-ration of a fluid bolus (20 ml/kg). Crystalloids, either 0.9% saline or Ringer's lactate are given initially. These fluids are isotonic and restore the ECF volume. Once the circulatory status has improved (based on continuing assessment and repeat fluid bolus if necessary) further fluid therapy is initiated to correct the associated dehydration. This requires calculation of fluid deficit and maintenance fluid requirements (Figure 6). Blood samples are taken to calculate electrolyte values to guide fluid therapy, particularly speed of rehydration.

Estimating fluid deficit in a dehydrated child

A 10 kg child with diarrhoea is estimated from clinical assessment to have 10% dehydration

The fluid deficit is therefore 10% of 10 kg = 1 kg = 1000 g
1000 g = 1000 ml of fluid deficit (100 ml/kg)

This can be more easily calculated as % dehydration × body weight (kg) × 10 ml

5

Types of dehydration

The three types of dehydration are isotonic, hyponatraemic and hypernatraemic. All are associated with water and sodium loss but the speed of replacement depends on serum sodium values.

Calculating fluid requirements in dehydration

Fluid requirements for a 4 kg baby with pyloric stenosis and an estimated 10% dehydration

Maintenance fluid requirement (see Figures 2 and 3)
100 ml/kg/day = 400 ml/day
Ideally given as 0.18% saline in glucose

Deficit fluid requirement (see Figure 5)
4 (wt in kg) × 10 (% dehydration) × 10 = 400 ml/day

This should be given as 0.9% saline, reflecting the predominant loss of extracellular fluid volume in dehydration (gastric fluid is isotonic and has large quantities of sodium, chloride and hydrogen ions)

Combined fluid requirement = 800 ml

The deficit can be replaced over 24 hours, assuming the child is not hypernatraemic. Continuing fluid type and volume needs adjustment based on clinical assessment of hydration status and electrolyte values

Isotonic or hyponatraemic dehydration: the baby with pyloric stenosis (Figure 6) could be given maintenance fluid using 400 ml of 0.18% saline (which gives 12 mmol sodium ions/30 mmol/litre) while replacing the fluid deficit caused by de-hydration with 400 ml 0.9% saline (150 mmol/litre), to give an additional 60 mmol of sodium ions. A total of 72 mmol sodium ions would then be infused over 24 hours. However, it is more practical to infuse a single type of fluid to provide both maintenance and deficit volumes and sodium requirements. By calculating the sodium ion concentrations, it can be seen that a solution of 0.45% saline (75 mmol/litre) matches best. For example, giving 800 ml of 0.45% saline in 5% glucose would deliver 60 mmol sodium ions and provide adequate sodium requirement for fluid maintenance and deficit requirements. This solution is isotonic and prevents hypoglycaemia.

For more complex situations (e.g. children with severe cardiac or renal dysfunction, particularly the critically ill) it may be appropriate to provide separate infusions for maintenance requirement, fluid deficit and continuing losses. In these situations, frequent measurements of serum and urinary electrolytes and clinical assessments of hydration are required.

Hypernatraemic dehydration: if the serum sodium concentration is above 145 mmol/litre, rapid infusion of fluid causes the serum sodium concentration to fall. Water then moves into cells to maintain osmotic equilibrium and there is a risk of cerebral oedema and death. The serum sodium concentration should be lowered by no more that 5 mmol/day to avoid this and the values measured every 4 hours. The aim is to correct dehydration over 48 hours.

Colloids or crystalloids?

The relative merits of colloids and crystalloids for volume replacement during surgery and intensive care are still debated.

Isotonic crystalloids (e.g. normal saline, Ringer's lactate) are used to restore the intravascular volume but are distributed evenly within the ECF volume. As plasma makes up only one-third to one-quarter of the ECF volume, only one-third of the infused fluid remains in the intravascular space, the remainder lying in the interstitial fluid space. Therefore, if crystalloid is used to replace blood loss, then three times the volume of blood lost is required as crystalloid therapy. There is concern that excessive crystalloid fluid administration may result in overhydration of the interstitial space with resultant oedema formation. On the other hand, faced with plasma volume depletion, fluid shifts from the interstitial space into the circulating volume so that in hypovolaemic states there is generalized depletion of ECF volume. The whole of the ECF volume requires resuscitation and therefore crystalloids are most appropriate.

Crystalloids are readily available, cheap and generally free of adverse reactions. They are widely used as first choice therapy in the USA. In other countries, colloids are preferred to treat hypovolaemia, particularly in neonates who have large body water volumes, susceptibility to oedema and inability to deal with water and solute loads. Human albumin solution is most widely used because there is concern about the effects of synthetic colloids such as gelatin and hydroxyethyl starch (accumulation in the reticuloendothelial system) on the newborn and young children. A recent review of 30 published studies suggested a higher mortality in patients receiving albumin. However, there is criticism of some of the studies included and no published comparisons of crystalloids with colloids in children. Albumin is still preferred for intravascular volume replacement in critically ill children, especially neonates. For older children, the choice of initial fluid is less important than recognizing circulatory compromise and treating it promptly.

Perioperative fluid requirements

The volume and type of fluid required perioperatively depends on:

- the duration of preoperative fasting
- additional preoperative deficits from abnormal loss of fluid and electrolytes (e.g. diarrhoea, vomiting, ileus, burns, blood loss)
- intraoperative losses include evaporation from the wound (e.g. during laparotomy) or airway (if anaesthetic gases are not humidified), blood loss, and third-space loss associated with surgical manipulation and tissue trauma
- retention of water and sodium postoperatively, due to the stress response to surgery.

The stress response to major surgery includes release of aldosterone and antidiuretic hormone with retention of salt and water. It is important to limit the use of non-crystalloid solutions (e.g. 5% glucose) because of a tendency to cause haemodilution and hyponatraemia. This is particularly relevant because third-space fluid losses, blood loss and the circulatory effects of anaesthesia (including reduced cardiac output and vasodilatation) mandate crystalloid fluid therapy.

Intraoperative fluids are given based on maintenance fluid requirements and replacement of pre-existing deficits (e.g. because of fasting) and additional losses during surgery (e.g. bleeding or extravasation of fluids in major surgery). For simple surgical procedures, the fluid deficit can be replaced by resuming oral fluid intake postoperatively. For more major surgery, starvation fluid deficit can be calculated by multiplying hourly maintenance fluid requirement by the duration of fast in hours. Half the deficit is replaced in the first hour and a further quarter in the subsequent 2 hours given in addition to the hourly maintenance fluid.

Perioperative administration of glucose: neonates have inadequate glycogen stores and a tendency to hypoglycaemia. They require infusion of 10% glucose at maintenance rates. Additional crystalloid and colloid may be needed depending on the type of surgery. Sick neonates may require higher concentrations of glucose. If fluid restriction is required, glucose may have to be given centrally in 20% or 50% concentrations. Sometimes, the stress response causes hyperglycaemia. It is important to monitor blood sugar concentrations closely to avoid hypo- or hyperglycaemia.

Older children, unless fasted for prolonged periods, or critically ill, are able to maintain adequate blood sugar levels by metabolism of glycogen stores. Crystalloids are indicated for perioperative fluid infusion. Infusion of crystalloid with low concentrations of glucose (2%) avoids hypo- and hyperglycaemia in children receiving variable fluid infusion rates. Such fluids are not available commercially and must be prepared, as required, by adding 20 ml of 50% glucose to 500 ml of 0.9% saline.

Practical fluid administration in the operating room
Neonates should receive 10% glucose at maintenance rates and additional crystalloid, colloid or blood, as necessary. The blood glucose should be monitored carefully.

Children having day case or body surface surgery do not require intravenous fluids because of liberal fluid fasting policies (2 hours preoperatively for clear fluids), minimal fluid loss and the ability to take oral fluids rapidly after surgery.

Children having prolonged surgery (over 1 hour duration) or those having major surgery (especially within a body cavity or associated with blood loss exceeding 10% of the circulating volume) require intravenous fluids perioperatively. Other factors to consider include the age of the child and the likelihood of rapid return to oral intake. If large intraoperative fluid losses are not anticipated, then 0.18%/0.45% saline in glucose can be infused at maintenance rates. If larger losses or fluid shifts are predicted, Ringer's lactate (with or without additional glucose) may be administered. Hourly fluids infused at up to 2–3 times maintenance rates may be required. It is important that the cardiovascular variables (e.g. peripheral perfusion and capillary refill time, heart rate and blood pressure) are continually reviewed in the light of fluid administration. Invasive monitoring of arterial and central venous pressures may be indicated if large fluid shifts are predicted.

Hypervolaemia
Hypervolaemia is usually secondary to cardiac or renal failure. Occasionally, it results from deliberate excessive ingestion of water. The signs of hypervolaemia are those of heart failure, which is treated by fluid restriction and diuretics. Patients with water intoxication present with confusion, convulsions and coma from cerebral oedema and hyponatraemia. The treatment is to restrict fluids and manage the symptoms.
Specific electrolyte abnormalities

Sodium abnormalities are linked with dehydration or over-hydration, and are considered above.

Potassium – the usual daily requirements are listed in Figure 2. The upper limit of normal is 5.8 mmol/litre for neonates and 5.0 mmol/litre for infants and children. High values are found at birth and are tolerated without ECG changes. The clinical features (especially the ECG abnormalities) and causes of hypo- and hyperkalaemia are given in Figure 7. Treatment for hyperkalaemia is described in Figure 8.

Features and management of hypo- and hyperkalaemia in children

Hypokalaemia	**Hyperkalaemia**
Clinical features	
Muscle weakness	Tingling
Hypotonicity	Paraesthesia
Ileus	Muscle weakness
Ventricular and atrial tachycardias	Flaccid paralysis
ECG changes	
Prolonged PR interval	Peaked T waves
T wave inversion	Prolonged PR interval
Prominent U waves	Widened QRS complex
	Deep S wave and eventually asystole (arrhythmias rare < 7.5 mmol/litre)
Causes	
Inadequate intake	***Excessive intake***
Abnormal losses	***Endogenous release***
Gastrointestinal (e.g. diarrhoea)	Burns
Renal (e.g. hyperaldosteronism, diuretic therapy, volume depletion)	Rhabdomyolysis
	Haemolysis
Compartmental shift	***Decreased renal excretion***
Alkalosis	Renal failure
Insulin therapy	Drugs (e.g. potassium-sparing diuretics, ACE inhibitors)
β_2-agonists	***Compartmental shift***
	Acidosis
	Insulin deficiency
	Succinylcholine administration
Treatment	
KCl, oral or i.v. slowly (centrally if concentration > 40 mmol/litre)	See Figure 8

Guidelines for potassium administration
Total daily maintenance dose = 2 mmol/kg (0.08 mmol/kg/hour)

K to be replaced = weight x (C_D–C_M) x 0.3 = mmol required
where C_D = serum concentration desired; C_M = serum concentration measured

Max concentration for i.v. administration = 20 mmol/500 ml fluid

KCl, 2 mmol/ml, is diluted in 5% dextrose or 0.9% saline

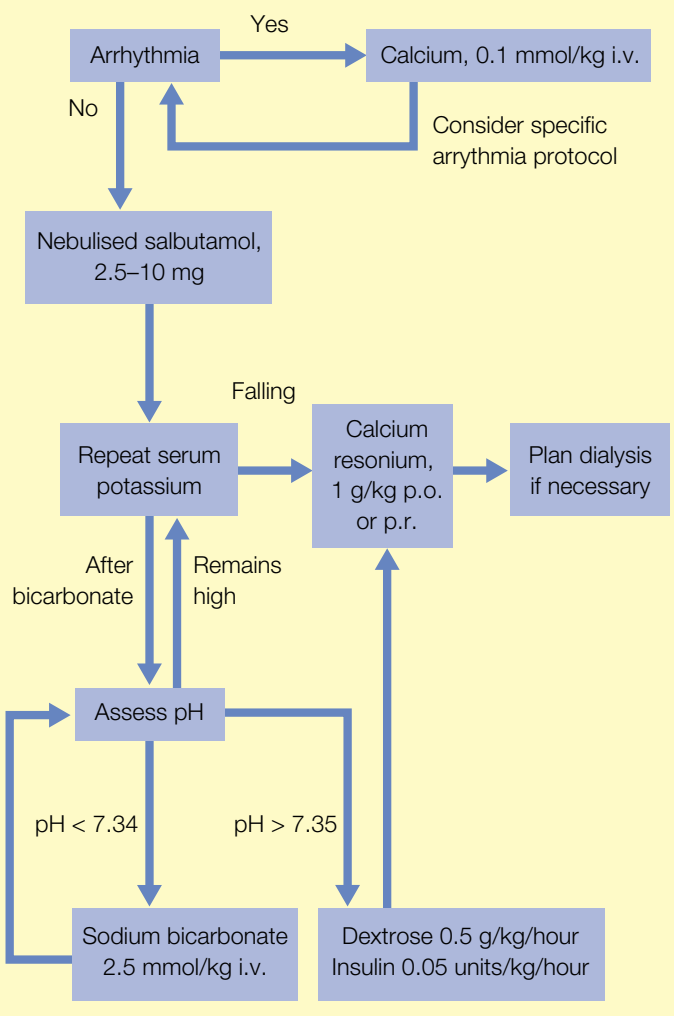
Maximum infusion rate = 0.5 mmol/kg/hour

Higher infusion rates (up to 2 mmol/kg/hour) used in cardiac ICU

Electrolyte status and ECG should be monitored

Oral K supplements can be given as effervescent or slow release tablets 1–2 mmol/kg/day in up to 3 divided doses given with or after food

Algorithm for the management of hyperkalaemia



Salbutamol dose by age

< 2.5 years 2.5 mg
2.5–7.5 years 5 mg
> 7.5 years 10 mg

Calcium abnormalities, particularly hypocalcaemia, are associated with acute illness including septicaemia or renal failure. Hypocalcaemia can produce muscle weakness, tetany, hypotension and arrhythmias, or convulsions. Treatment is of the underlying condition but intravenous calcium may be required. It is best administered as a continuous infusion via a central line using calcium gluconate 10% (0.225 mmol calcium/litre). The total daily dose is 1 mmol/kg given as 0.2 ml/kg/hour of 10% solution. However, calcium gluconate should be diluted in 5% dextrose or 0.9% saline to at least a 2% (20 mg/ml) solution. Doses for neonates are halved. Hazards include precipitation, if given with sodium bicarbonate, tissue necrosis, if the drug extravasates, and the possibility of cardiac arrhythmias, if given with cardiac glycoside drugs. Hypercalcaemia is treated with volume expansion using 0.9% saline. ◆

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Cardiorespiratory Arrest

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Cardiorespiratory arrests in children are uncommon and their aetiology differs from those in adults. Progressive respiratory insufficiency accounts for 60% of all paediatric arrests. This may result from upper or lower airway disease (e.g. croup, bronchiolitis, pneumonia, asthma, foreign body aspiration) or respiratory depression caused, for example, by prolonged convulsions, raised intracranial pressure, neuromuscular disease or drug overdose. Other important causes include sepsis, dehydration and hypovolaemia.

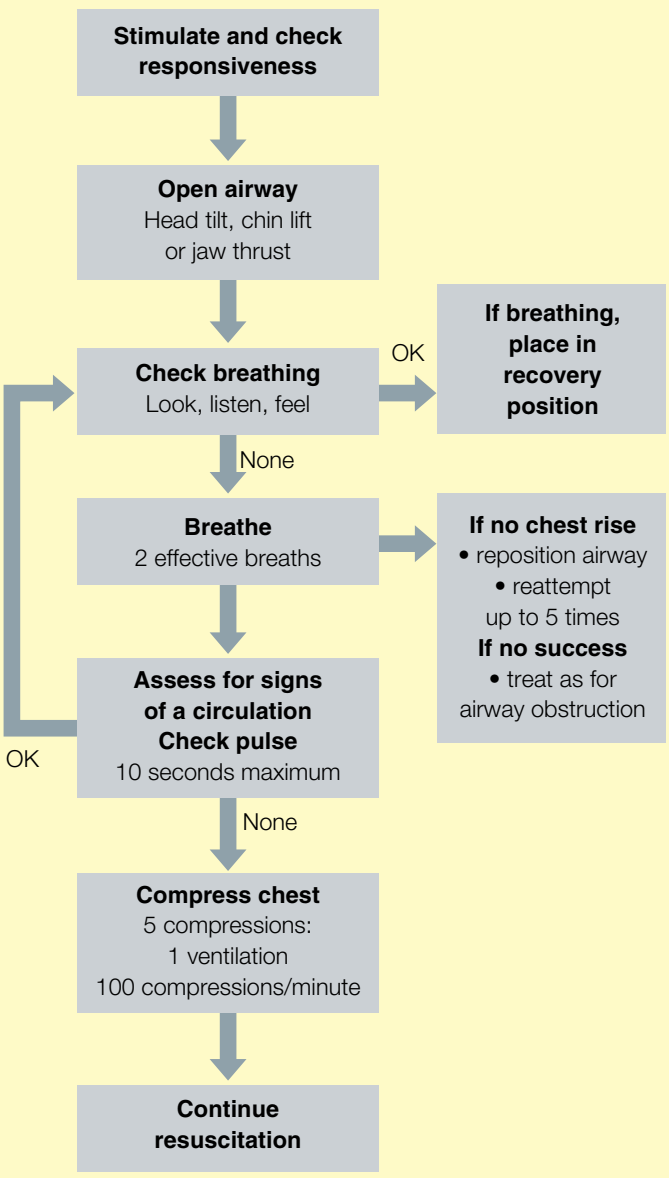
Primary cardiac arrest in children is rare and ventricular fibrillation has been reported in less than 10% of cases. Many children have a relatively long 'pre-arrest' phase (i.e. cardiac arrest following prolonged physiological deterioration). Impending cardiopulmonary arrest may be averted by early recognition of the child's distress and prompt intervention. Once cardiac arrest occurs, the outcome is dismal with survival rates of 3–17%. Often the child is resuscitated only to die of multi-organ failure in the ICU or to survive with significant neurological impairment.

Guidelines for paediatric life support are published by several national organizations. The most recent recommendations are those of the International Liaison Committee on Resuscitation (ILCOR) in 1997 and the European Resuscitation Council in 1998. The cardiopulmonary resuscitation (CPR) algorithms described in this article are based on these guidelines. The CPR sequence and general resuscitative principles are similar for infants and children. An artificial line is generally drawn between infants (< 1 year) and children (1–8 years). Older children and teenagers should be resuscitated using adult algorithms and techniques.

Basic life support

Basic life support (Figure 1) refers to maintenance of the airway and support of respiration and circulation without the use of equipment.

Paediatric basic life support



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Initial approach and assessment of responsiveness

Before starting resuscitation it is important to evaluate the site for any danger or physical hazards. Only in extreme situations should the child be moved. The first step in any resuscitation is to assess the level of responsiveness. If the child does not respond to voice or gentle shaking, a rapid cardiopulmonary assessment should be performed (Figure 2). Assessment should take no longer than 10 seconds. Infants should not be shaken vigorously. If trauma is suspected, the cervical spine should be immobilized. Resuscitation should start immediately and help should be summoned.

Rapid cardiopulmonary assessment

A Airway
- Patency

B Breathing
- Respiratory rate
- Work of breathing
- Stridor
- Wheeze
- Air entry
- Skin colour

C Circulation
- Heart rate
- Pulse volume
- Capillary refill
- Skin temperature
- Mental status

D Disability
- Conscious level
- Posture
- Pupils

2

Airway

The tongue is the most common cause of airway obstruction in children. Simple head tilt, chin lift or jaw thrust manoeuvres may relieve the obstruction. Infants are primarily nose breathers; this is an inbuilt mechanism to overcome obstruction caused by a relatively large tongue. Only the jaw thrust procedure is recommended in suspected spinal injury. If a foreign body is obstructing the airway it should be removed carefully under direct vision. The blind finger sweep technique used in adults is not recommended because it may cause trauma and bleeding or displace the foreign body further into the trachea.

Breathing

The adequacy of breathing should be assessed by looking for chest movement, listening over the airway for breath sounds and feeling for exhaled air over the mouth and nose. If the child is not breathing despite an adequate airway, expired air ventilation should be started. The mouth of the rescuer should cover the nose and mouth of the infant. In the child, mouth-to-mouth expired air ventilation is recommended. A minimum of two, but up to five breaths, may be required for effective ventilation in the hypoxic child. The breaths should be delivered slowly, over 1–1.5 seconds, with a force sufficient to make the chest rise. By giving the breaths slowly, an adequate volume is delivered at the lowest possible pressure thereby avoiding gastric distension and possible regurgitation of gastric contents. If chest movement does not occur or is inadequate, the airway position should be readjusted and the possibility of a foreign body considered.

Circulation

Check the presence, rate and volume of the pulse. In infants, the brachial or femoral pulse is easiest to feel. In older children, the carotid should be palpated. It may be difficult to locate a pulse in a collapsed child owing to the intense vasoconstriction. If no detectable pulse is felt within 10 seconds or the rate is less than 60 beats/minute in an infant, chest compressions should be started.

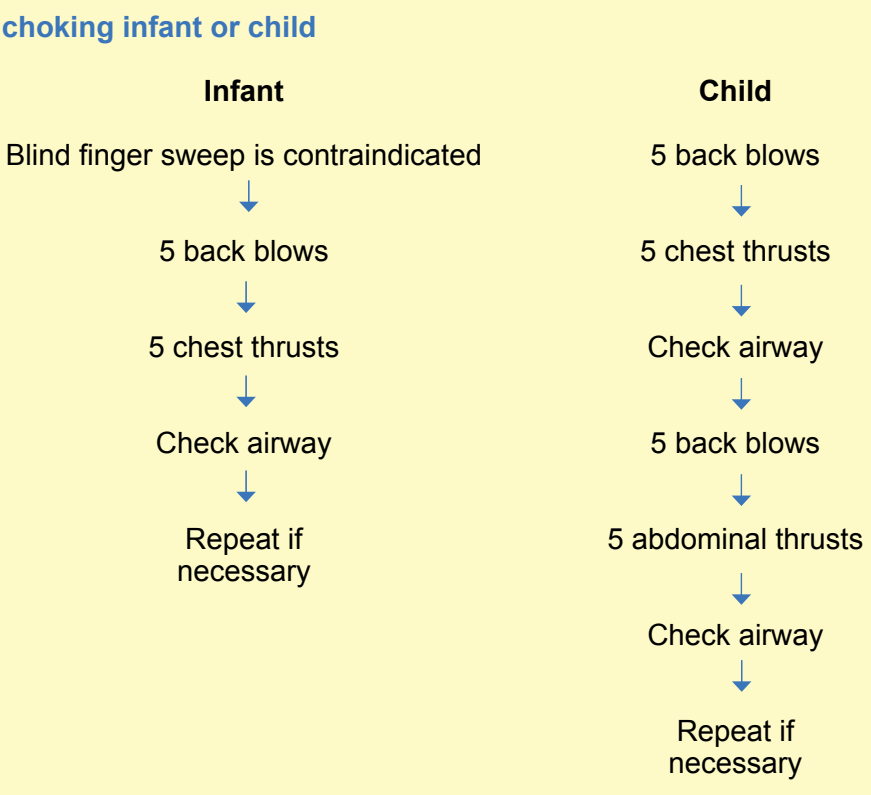
The chest is compressed over the lower half of the sternum and the technique differs slightly between age groups.
- In infants, the chest is compressed using two fingers placed one finger's breath below an imaginary line joining the nipples.
- In the child, the heel of the hand is used and positioned one finger's breath up from the xiphisternum.
- In the child over 8 years, the two-handed compression technique is recommended.

The chest should be compressed to one-third its resting diameter at a rate of 100/minute. One breath should be given after each five compressions.

Airway obstruction from a foreign body

If upper airway obstruction due to foreign body aspiration is witnessed or strongly suspected, special measures to clear the airway must be undertaken (Figure 3). If the child is breathing spontaneously, their own efforts to clear the obstruction should be encouraged. Intervention is necessary only if these attempts are ineffective and respiration is inadequate. The manoeuvres suggested for removing impacted foreign bodies are:
- back blows
- chest thrusts
- abdominal thrusts.

The choking infant or child



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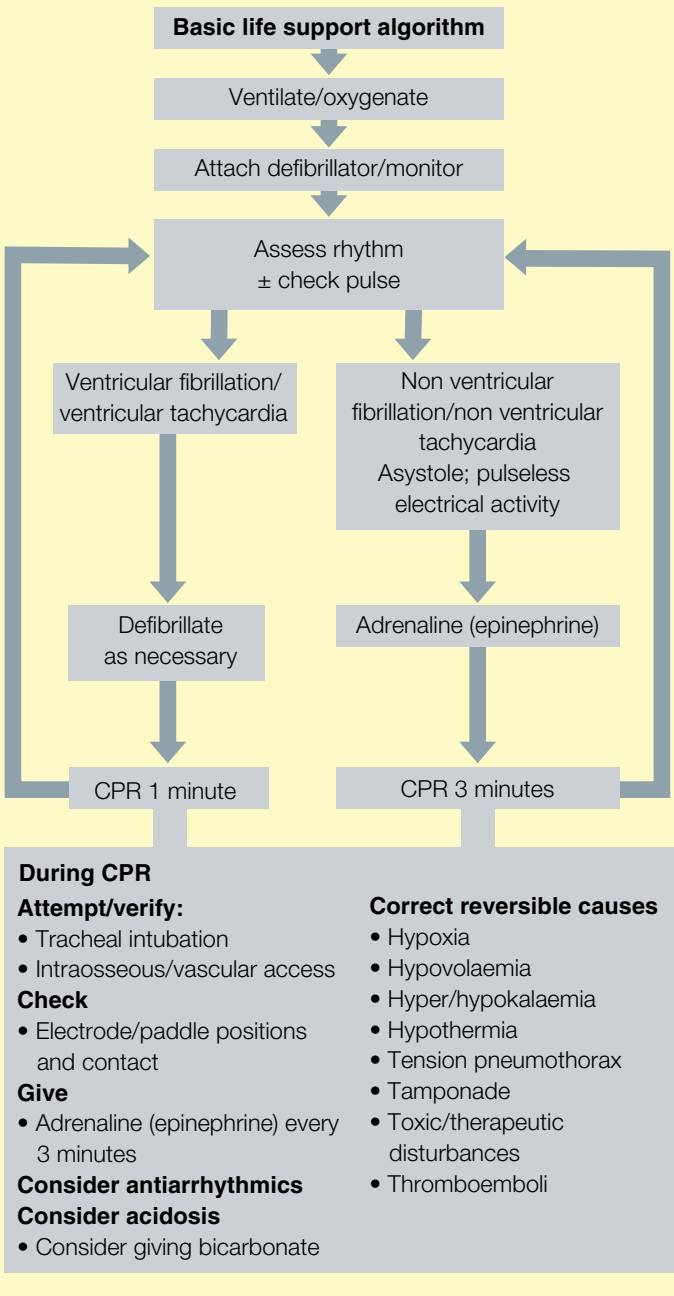
A combination of back blows and chest thrusts are recommended for infants. Abdominal thrusts are not recommended because damage to the abdominal contents may occur. In children, back blows with alternate cycles of chest thrusts and abdominal thrusts are preferred. After each cycle, the mouth should be checked for the presence of a foreign body and ventilation attempted.

Advanced life support

As soon as skilled help and equipment arrive, advanced life support should be started (Figures 4 and 5). The aim of advanced life support is to restore spontaneous cardiac activity. Asystole is presumed to be the primary arrhythmia because ventricular fibrillation has been documented in less than 10% of paediatric cardiac arrests. Monitoring equipment (including a pulse oximeter, ECG and end-tidal carbon dioxide analyser) should be attached as soon as possible. The priorities are to secure the airway and provide adequate oxygenation and ventilation followed by vascular access and drug administration.

Paediatric advanced life support



4

Advanced life support

- Perform basic life support algorithm
- Ventilate the lungs with 100% oxygen
- Establish a secure airway by intubating the trachea
- Establish reliable vascular access
- Administer adrenaline (epinephrine) every 3–5 minutes
- If resuscitation attempts exceed 15 minutes, consider giving sodium bicarbonate
- Correct reversible causes

5

Airway and ventilation
A secure airway and effective ventilation are vital in advanced life support. Respiratory failure is the primary cause of paediatric cardiac arrest, therefore the highest available oxygen concentration should be given immediately by bag, valve mask ventilation. An oropharyngeal airway may be used to aid airway management in the short term.

Tracheal intubation is the most effective method of securing the paediatric airway during CPR. It allows optimum ventilation, protects the airways from aspiration of gastric contents, and provides a route for drug administration. Intubation should be achieved rapidly. Any attempt lasting longer than 30 seconds should be abandoned and the child's lungs reoxygenated before further attempts are made. The position of the tracheal tube should be checked and the tube secured to prevent dislodgement or displacement. The place of the laryngeal mask airway in paediatric resuscitation has yet to be established.

Circulation
Rapid vascular access is critical in paediatric resuscitation for drug and fluid administration. In small children this may be difficult owing to the extreme vasoconstriction. The intravenous or intraosseous routes are preferred for drug delivery.

Intravenous access: the choice of venous access is determined by the skill of the resuscitator and the relative risks of the procedure. In practice, the largest, most accessible vein that does not require the interruption of CPR is used. Attempts at peripheral venous cannulation should be limited to 90 seconds. Useful central venous routes during resuscitation include the femoral and external jugular veins. The internal jugular and subclavian routes require interruption of external cardiac compressions and are prone to serious complications in young children. Drugs administered centrally act more rapidly than those administered peripherally.

Alternative routes of drug and fluid administration: when rapid venous access is impossible an intraosseous cannula should be inserted. This is relatively easy to perform, safe and usually rapidly achieved. Drugs and fluids can be administered by this route and gain rapid access to the central circulation.

The trachea is often intubated early in the resuscitation and is a useful alternative route for drug administration. It is best used when there has been, or is likely to be, a significant delay in establishing venous access. Lipid-soluble drugs, adrenaline (epinephrine), atropine, lidocaine (lignocaine), naloxone and diazepam are suitable for this route. Animal studies suggest that peak plasma concentrations of drugs are significantly lower than those achieved by intravenous administration, hence a tenfold increase in the adrenaline (epinephrine) dose is recommended for the tracheal route. Depot storage of adrenaline (epinephrine) in the lungs may cause prolonged post-arrest hypertension.

Drug and fluid therapy
Adrenaline (epinephrine) is the most useful drug during paediatric CPR. The α-adrenergic action increases systemic vascular resistance, elevates aortic diastolic pressure and thereby improves coronary perfusion. The recommended initial dose is 0.01 mg/kg, intravenously or intraosseously, or 0.1 mg/kg by the tracheal route. Because the outcome of asystolic arrest in children is poor and a beneficial effect of higher dose adrenaline (epinephrine) has been demonstrated in some studies, second and all subsequent doses should be 0.1 mg/kg regardless of route of administration. As the action of adrenaline (epinephrine) is short lived, it should be repeated every 3–5 minutes during resuscitation. If there is no return of spontaneous cardiac activity after two doses, despite adequate CPR, the outlook is likely to be dismal.

Sodium bicarbonate: after the initial treatment of cardiac arrest (ventilation, chest compression, adrenaline (epinephrine)), severe acidosis is treated with sodium bicarbonate. Its use remains controversial because it has not been shown to improve survival. Nevertheless, during prolonged resuscitation (i.e. over 15 minutes), sodium bicarbonate, 1 meq/kg, may be administered intravenously or intraosseously.

Other drugs: neither calcium chloride nor atropine is recommended in the treatment of asystole or pulseless electrical activity.

Fluids: expansion of the circulating blood volume is vital in children who are hypovolaemic secondary to fluid loss or fluid maldistribution. The intravascular fluid of choice is isotonic crystalloid. An initial bolus of 20 ml/kg is given and repeated until there is an improvement in circulatory status.

Treatment algorithms
Non-ventricular fibrillation/non-ventricular tachycardia: asystole and pulseless electrical activity are the most common rhythms in childhood cardiac arrest. Profound bradycardia should be treated in the same way as asystole. The drug of choice is adrenaline (epinephrine), 0.01 mg/kg, intravenous or intraosseous or 0.1 mg/kg via the tracheal route. This should be followed by 3 minutes of CPR. If the child does not respond to the initial dose of adrenaline (epinephrine), another dose of 0.1 mg/kg should be given. All subsequent doses should be the higher dose of 0.1 mg/kg intravenous or intraosseous.

Any underlying reversible cause of the arrest should be treated and resuscitation should not be abandoned until reasonable attempts have been made to do so. Reversible causes of pulseless electrical activity include:
- hypovolaemia
- tension pneumothorax
- cardiac tamponade
- drug overdose
- electrolyte imbalance.

Ventricular fibrillation and ventricular tachycardia are relatively uncommon in infants and children; they are treated by defibrillation. The recommended sequence is to give two rapid defibrillatory shocks of 2 joules/kg, followed by a single shock of 4 joules/kg. If the initial third shock fails, CPR should be continued for 1 minute and adrenaline (epinephrine), 0.01 mg/kg, given. The heart is then defibrillated with three further shocks at 4 joules/kg. The cycle of defibrillation and 1 minute of CPR is repeated until defibrillation is achieved. In children there is often an underlying cause and correction of hypothermia, drug overdose and electrolyte imbalance should be considered.

Post-arrest stabilization
Following a cardiac arrest, children are often poorly perfused, hypotensive and very acidotic. Most require continuing pharmacological support to maintain blood pressure and improve tissue perfusion. Management is similar to the general management of critically ill infants and children in cardiogenic shock. The goals are rapid restoration of blood pressure, effective organ perfusion, and correction of hypoxia and acidosis. Normocapnic ventilation should be continued until cardiorespiratory stability is achieved.

Cerebral resuscitation aims to provide a sufficient supply of oxygenated blood to the brain to meet its demands. Hypo-glycaemia and hyperglycaemia should be avoided, and factors that increase cerebral oxygen requirements (e.g. hyperthermia, inadequate analgesia, seizures) should be treated. Mild hypothermia (34°C) is beneficial after global brain ischaemia. In animal studies, lowering brain temperature from 36° to 33°C with local cranial cooling during the first hour of post-ischaemic recirculation improves neuronal survival. The protective effect of mild hypothermia is presumably multifactorial as it cannot be explained by the modest reduction in oxygen consumption. The clinical impact of mild hypothermia on long-term outcome remains to be tested. It is probably wise to avoid aggressive rewarming of patients in the early post-arrest period. Cerebral resuscitative strategies such as thiopental (thiopentone), calcium channel blockers and steroids do not improve outcome.

Outcome
The combined mortality and morbidity rate of children who are pulseless on arrival in the accident and emergency department approaches 100%. Children who have a delayed response to resuscitation have little chance of surviving without neurological damage. The length of resuscitation is another predictor of outcome. Prolonged resuscitation requiring more than two doses of adrenaline (epinephrine) leads to a dismal outcome and attempts beyond 25 minutes are unsuccessful. Respiratory arrest alone is associated with a better outcome. The most effective treatment of cardiorespiratory arrest is prevention. The early recognition and aggressive treatment of impending cardiac or respiratory failure in children is essential. ◆

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Intraosseous Cannulation

Jane M Peutrell

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The technique of obtaining vascular access through intraosseous cannulae became popular during the 1940s but was forgotten as equipment and methods for venous cannulation improved. The technique was rediscovered in the 1980s for use during paediatric resuscitation and quickly became accepted practice because:

- access is rapid
- landmarks are easily identified
- success rates are high (85% of babies, 50% of adults) and complications infrequent
- a variety of drugs and fluids (including all those given during resuscitation) can be injected.

Intraosseous cannulation is now indicated in babies or children during resuscitation or in an emergency when intravenous access cannot be obtained quickly or after two failed attempts. However, it is essentially a resuscitation technique and conventional intravenous access should be obtained as soon as possible (certainly within 24 hours) to reduce the risk of complications, particularly osteomyelitis.

Applied anatomy

The marrow cavity in long bones contains a spongy mesh of non-collapsible venous sinusoids, which drain into a wide central venous canal. The central canal leaves the bone through nutrient veins (running with the arteries) or sometimes through independent emissary veins that pierce the shaft elsewhere.

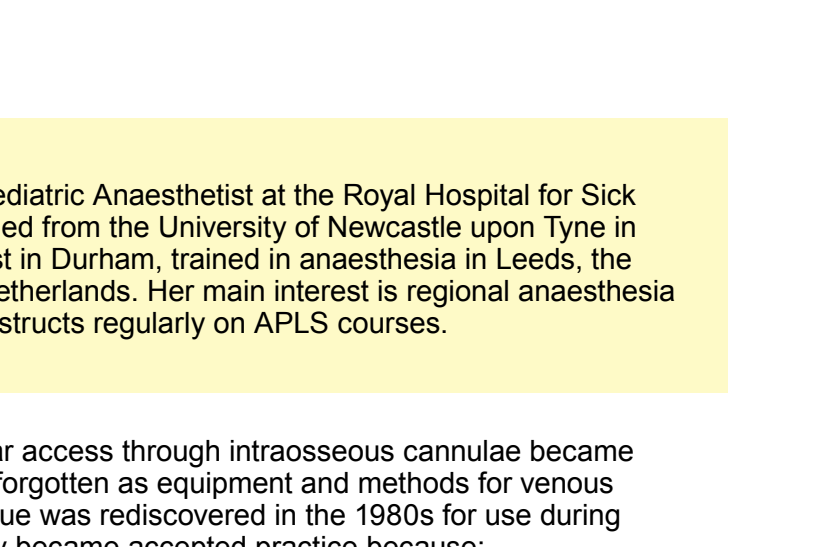
The skeleton of a baby contains very vascular red marrow, which is gradually replaced by less vascular yellow marrow from about 5 years of age. Although intraosseous cannulation is recommended for children less than 6 years of age, it is useful throughout childhood. Even adults have numerous venous sinusoids, allowing infusion rates of 20–25 ml/minute (sufficient for drug administration).

Technique

Equipment: intraosseous cannulation using hypodermic, spinal, or standard bone marrow needles has been described, though specifically designed equipment is also available. Cook® have developed two types (Figure 1).

Intraosseous needles developed by Cook®

a A smooth external, non-threaded needle with inner stylet showing the standard tip (left) and one with two lateral side ports (right). This needle is available in different gauges (18/16/14), lengths (2.5/3/4 cm) and tips (35° lancet/pencil-point/45° trochar). Having two laterally opposed side ports allows flow if the end-hole obstructs. **b** Threaded, self-tapping needles with large or small handles are available in either 15G, 1.8 cm (for babies < 9 months) or 12G, 2.3 cm (for children > 9 months). They have trifaceted cutting tips, relatively short lengths (therefore low centre of gravity making them easier to handle) and two lateral side ports. The screw thread allows controlled and atraumatic access to the marrow and better stabilization (reducing the risks of dislodgement, leakage, or penetration of both cortices)



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Site: the proximal tibia is the most common site for insertion (Figure 2). The sternum is no longer used because of the risk of mediastinal damage.

Cannulation: as far as practicable, use an aseptic technique. The landmarks and technique of insertion in the proximal tibia are shown in Figure 3.

Recommended sites for intraosseous cannulation

Common

- Proximal tibia – most common site in children, but difficult to access in adults
- Distal tibia – just above the centre of the medial malleolus, better access to red marrow in adults
- Distal femur – approached from the anterior aspect

Others

- Clavicle
- Humerus
- Ilium

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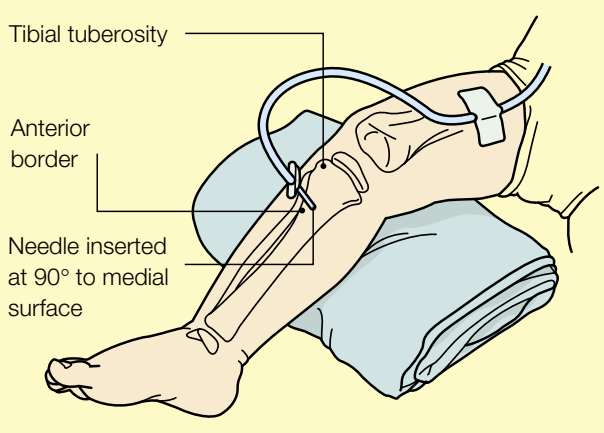
Intraosseous cannulation at the proximal tibia



The site of needle insertion is 1–3 cm (children) or 0.5–1 cm (babies) below and just medial to the tibial tuberosity on the flat, medial aspect of the tibia where the bone lies subcutaneously. Support the leg on a firm surface, grasping the thigh and knee above and lateral to the site of insertion. Insert the needle at right angles to the coronal plane, directing the needle tip slightly caudally and away from the tibial growth plate. To prevent dislodgement, carefully immobilize the cannula and splint the limb

3

To insert the needle, use a boring, twisting, or screwing action (depending on design), applying axial pressure through the needle shaft. Avoid rocking movements (which produce a larger diameter hole than the needle) or repeated attempts, which can cause leakage of drugs or fluid during infusion. Stop once there is a loss of resistance and then unscrew the cap or handle. Try aspirating to confirm correct placement and to obtain marrow for laboratory investigations. Test the position by injecting 10 ml of 0.9% saline. Signs suggesting correct placement include:

- a sudden loss of resistance as the needle tip passes through the cortex into the marrow (does not occur with screw-threaded needles)
- aspiration of marrow (reassuring, but not always possible despite correct placement)
- the needle remains upright without support
- fluid can be injected easily, without evidence of extravasation (e.g. increased limb circumference or tissue firmness).

Intraosseous cannulation should take about 2 minutes. If unsuccessful on one side, make the second attempt on another limb or bone to prevent leakage through the original hole.

Contraindications include fracture of the ipsilateral, proximal limb; repeated attempts in the same bone; local infection; osteogenesis imperfecta; osteoporosis; osteopetrosis and osteomyelitis.

Complications are uncommon, but include:

- dislodgement of the cannula (10%)
- extravasation around the needle or through a secondary site (e.g. previous attempts in the same bone, penetration through the posterior cortex) or failure to penetrate the cortex, producing:
  - haematoma
  - severe tissue necrosis, particularly with hypertonic solutions (e.g. bicarbonate, glucose), catecholamines or cytotoxic drugs
  - compartment syndrome
- subcutaneous abscess or skin infection (0.7%)
- osteomyelitis with prolonged infusion (0.6%)
- tibial fracture (in babies).
  Growth plate injury or fat emboli are not problems unless osteomyelitis occurs.

Intraosseous infusions or injections: all drugs and fluids used in a sick child can be given (Figure 4). Circulation times are similar to standard intravenous delivery and drugs should be given in the same doses.

Drugs reported given by the intraosseous route

- Adenosine
- Analgesics
- Antibiotics
- Anticonvulsants
- Atropine
- Blood products
- Calcium gluconate
- Digitalis
- Fluids
- Glucose
- Heparin
- Inotropes, including adrenaline (epinephrine)
- Lidocaine (lignocaine)
- Muscle relaxants
- Sedatives
- Sodium bicarbonate

4

Flow rates for gravity-driven infusions are low (1–25 ml/minute), but can be doubled by infusing under pressure (40 ml/minute through a 13G needle at 40 kPa/300 mm Hg). Bone and marrow vessels have vasomotor responses to humeral and neurological stimuli and flow is significantly and unpredictably reduced in shock (because of the physiological stress response or locally injected catecholamines). To prevent local sequestration and ensure systemic uptake, drugs should be infused under pressure or 'flushed in' with saline.

To prevent dislodgement, carefully secure the needle, immobilize the limb in a splint and avoid transferring the child until conventional intravenous access has been obtained.

Assess the distal pulses, limb diameter and tissue turgor every 10–15 minutes to identify extravasation or vascular compromise.

Using marrow for laboratory investigations

The acid–base status of marrow can be used as an estimate for mixed venous blood during haemorrhagic shock and the early stages of cardiac resuscitation (< 15 minutes). During longer periods, the correlation deteriorates because of local stasis and intraosseous delivery of drugs (especially bicarbonate or catecholamines).

Other biochemical variables (Na^+, Cl^-, Ca^{2+}, K^+, Mg^{2+}, urea, creatinine and glucose) are similar to central venous values in stable patients or during less than 30 minutes of cardiopulmonary resuscitation if no intraosseous drugs are given. Once drugs have been delivered, differences develop as resuscitation progresses, but are unlikely to lead to erroneous treatment, except for glucose and K^+.

Haemoglobin values are consistently lower than for mixed venous samples (especially after 30 minutes of resuscitation), perhaps because of 'wash-out' of red cells. Marrow samples also poorly predict mixed venous platelet and leucocyte concen-trations, but can be used to group and cross-match blood. ◆

The Law and Ethics of Consent and Research in Children

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Consent

Most of the ethical and legal issues in caring for children arise from uncertainties about consent. In common with adults, if no legally effective consent has been given, the doctor is liable for criminal or civil charges of assault if he makes contact with the patient. The five preconditions of consent are given in Figure 1.

The five preconditions of consent

- The person has to be of competent mind
- There must be full disclosure of information regarding the nature of the procedure, including the associated risks
- The person must understand the information they have been given
- The decision must be made voluntarily
- The person must give authorization

The law gives a child's parents authority to make decisions on behalf of the child (a form of proxy consent). In addition, a child may make decisions about their own treatment. In 1997, The United Nations Convention on the Rights of the Child stated that the child's views should 'be given weight in accordance with the age and maturity of the child'. The age at which a child is considered a 'mature minor' or 'emancipated minor' in legal terms differs between various legal systems.

In England and Wales the age of majority is 18 years. However, the Family Reform Act of 1969, section 8, clearly states that once a person reaches the age of 16 years, he or she can consent to any surgical, medical or dental treatment. The principle of the 'mature minor' in English law was defined in the Gillick case (Gillick v. West Norfolk AHA (1984)). This case concerned the validity of a minor's consent to contraceptive treatment without parental knowledge. It was held that consent would be legally valid when the child, in the opinion of the doctor, had sufficient maturity and intelligence to understand the implications of the treatment proposed. Furthermore, since it would be the doctor who would decide whether the minor was mature enough, legal authority regarding treatment would appear to have passed from the parents to the doctor. In his judgement in the Gillick case, Lord Templeman gave as examples the removal of tonsils or an appendix as occasions when parental consent might not be required. On the other hand, it has been suggested that when the minor's own future welfare is at stake and the consequences of a procedure might be serious, traumatic or irreversible, parents should probably be involved. There is little doubt that the law would distinguish between the requirements for consent for an adenoidectomy and consent for cancer chemotherapy. A child may be deemed mature enough to appreciate fully the nature and consequences of an adenoidectomy but not mature enough to give effective consent for cancer chemotherapy. In delicate cases concerning a minor consenting to treatment, it may be prudent to seek the opinion of a colleague, and document this clearly in the patient's notes.

Scottish law explicitly gives those over the age of 16 years the right of consent, through the Age of Legal Capacity (Scotland) Act 1991 and Children (Scotland) Act 1995. Similarly, a child under the age of 16 who meets the requirements of the 'mature minor' test has the legal capacity to consent to medical treatment.

The immature minor: consent by one parent is sufficient because parents may act independently, unless a Court order has been made restricting his or her right to consent (Figure 2). Thus, if the parents disagree, the doctor may proceed with treatment provided the consent of one parent has been given.

The following people may give consent on behalf of an incapable child

- The child's natural mother whether married to the father or not
- The child's natural father whether married or divorced
- An unmarried father who has entered and registered a formal parental responsibilities and rights agreement with the mother
- A legal guardian nominated in writing by a parent before the parent's death
- A person holding a Court order giving them the right to consent on the child's behalf
- A person who has had delegated to them by a parent or legal guardian the right to consent to medical procedures or treatment of the child
- A person aged 16 years or more who has care and control of the child (e.g. foster carers) except those involved in the school setting and procedures such as organ donation, non-therapeutic research or treatment (e.g. cosmetic surgery)

Refusal of elective or emergency treatment

Refusal by parents: parents have the authority to make decisions on behalf of their legally incompetent children, but this authority is a form of 'proxy consent' and must be used reasonably. It may be taken away if the Courts believe that the parents are abusing the power given by the law.

From the anaesthetist's point of view, the two most common situations when this arises are:

- when parents refuse to consent to the surgical treatment proposed for their children
- when parents who are Jehovah's Witnesses refuse to allow a blood transfusion to be administered to their child.

In a free society it is a major step to override religious convictions. It significantly interferes with the principle that parents should have the freedom to choose the religious and social upbringing of their children. However, parental refusal to agree to life-saving treatment for their child on religious grounds has been regularly overridden in the courts. Courts, however, have not endorsed every medical judgement, and there have been occasions when the Courts have upheld parental refusal of treatment. Medical staff cannot assume that the Courts will always endorse their view.

If urgent life-saving treatment is required doctors should proceed with treatment. Justification stems from the defence of 'necessity'. The reasons for proceeding and confirmation of the urgency by another doctor should be entered in the case notes. The prevailing ethical principle is the child's right to live, and it has been asserted that in the case of Jehovah's Witnesses the civil law will protect doctors who administer a blood transfusion despite parental opposition. If treatment is not urgent, then doctors cannot proceed without parental consent.

If treatment is not required immediately the medical team can proceed in one of two ways. The clinical staff may elect to try to resolve the matter through discussions with the parents. Particularly in cases concerning religious beliefs, this may require the parents to act in a way that is not in keeping with their principles. The implications for them within their religious communities may include a belief that they have sinned, and for this reason, these discussions should be undertaken with tact and diplomacy. The second approach is to make the child a ward of Court. If the Court agrees with the medical evidence, treatment can then be given with official authorization.

Refusal by the child: the situation is more complex when a mature, under-age child refuses treatment that has been accepted as necessary by the parents and the medical staff.

In England and Wales it would appear that, following the House of Lords decision in Gillick (1985), the child has every right to refuse treatment, provided he has sufficient maturity and intelligence to understand the implications of refusing the treatment proposed. If one is legally entitled to consent, one must be legally entitled to dissent. The problem, however, is not so clear cut because the Courts have the responsibility to act in the child's best interests. They may therefore hold that a child who refuses treatment (especially if life saving) cannot be mature enough to fully understand the implications of such a refusal. Thus, it would appear that a child is mature enough to decide on treatment only if his decision agrees with the view of the Courts. Some believe that section 8(3) of the Family Law Reform Act 1969 gives parents the right to consent to treatment against the expressed wishes of the minor. This has been tested in case law. The Courts are prepared to ignore the statutory rights of legally competent 16-year-olds following the case of a 16-year-old girl suffering from anorexia nervosa who was ordered to be treated against her will.

In Scotland the Age of Legal Capacity (Scotland) Act 1991, and, later, the Children (Scotland) Act 1995 gave young people aged 16 years or over the same right to consent or refuse as adults. Furthermore, in contrast to English law, it would appear that a legally competent minor has the same right to refuse medical treatment as an adult. Thus, in the elective situation, the wishes of a child under 16 years of age who satisfies the 'mature minor' test should prevail, even when their refusal of treatment is counter to the wishes of both their parents and doctors. This has never been tested in a court of law. However, one can foresee a child under the age of 16 who refuses treatment and appears competent bringing a case against medical staff who fail to honour his wishes. In an urgent life-saving situation, a legally competent minor, it could be argued, cannot be overruled if they refuse treatment. However, one could doubt the competency of a child refusing treatment that is clearly in his best interests. That child would then fail the 'mature minor' test and the refusal of treatment overruled due to incompetency. It must be pointed out, once again, that these issues have not been tested in a court of law. As always in such situations, if possible, legal advice should be sought.

Research

Undertaking research in children creates many legal and ethical dilemmas. The importance of advancing medical knowledge must be balanced against the potential risks to a vulnerable group. It must be remembered that for a child a simple procedure, such as taking blood, may be distressing and therefore cause harm. Research should be done on children only if comparable research on adults could not answer the same question. Older children should be involved in preference to younger ones. All proposals involving medical research on children should be submitted to a research ethics committee, and legally valid consent should be obtained. Consent should be given voluntarily, with a full explanation of all risks. Consent may be withdrawn at any time.

Simplistically, research can be considered as therapeutic or non-therapeutic. In therapeutic research it is hoped that the research will directly benefit the patient. Non-therapeutic research will not directly treat the patient, though the results may benefit other patients. The ethical approach to these two types of research differs in children.

In therapeutic research the general rule applies that it is the duty of the doctor to act in the best interests of the patient and not to do harm. It would be wrong for the doctor to withhold information about experimental therapy for fear that the patient might refuse that treatment, even though the doctor believes it is in the patient's best interests to receive it. If the child fulfils the criteria for maturity and understands the risks and implications of a particular experimental treatment, then his consent would appear to be legally valid. This has never been debated in a court of law. However, the consent of an immature child is insufficient. In this situation, the parents appear to have the legal right to consent because it could be argued that the therapeutic research is in the child's best interests. For therapeutic research to be undertaken on their child, the parents (or guardian) must give voluntary consent. They must fully understand the principles of research and believe the risk:benefit ratio of that research favours their child. Good medical practice dictates that the child should also assent to being involved in the research. If he dissents, depending on the degree of discomfort to the child, he should be withdrawn from the study.

In non-therapeutic research in babies and children, consent is more complex. The child would appear not to gain from this research, and indeed may be harmed. Although parents have been given legal authority to consent on behalf of their children, they cannot use this power to harm their child. Therefore, it can be argued that parents cannot consent to their children being involved in non-therapeutic research.

The Medical Research Council in 1964 stated that parents could not give legal consent on behalf of their children to any procedure that would be of no benefit to them. However, this is not based on any solid legal foundation. There are no statutes or Court decisions on this matter in the UK, and so general ethical principles have to be invoked. The extreme arguments advocate either no research at all, as legally valid consent can never be given, or justifying non-therapeutic research on an altruistic basis.

The Royal College of Paediatrics and Child Health has issued guidelines for the ethical conduct of medical research involving children (*Ethics Advisory Committee Archives of Diseases in Childhood* 2000; **82:** 177–82). These include guidelines for the conduct of non-therapeutic research. Risks are estimated to be minimal, low or high. It is claimed that it would be unethical to submit children to more than minimal risk when the procedure offers no benefit to them, or only a slight or very uncertain one. Minimal risk describes procedures such as questioning, observing and measuring children, provided that procedures are carried out in a sensitive way, and that consent has been given. Procedures with minimal risk include collecting a single urine sample, or using blood from a sample that has already been taken as part of treatment. The College states that for many children injections and venepuncture are classified as low rather than minimal risk. This recognizes the fear with which many children regard needles. It may be possible for a child to allow blood to be taken following careful explanation and the use of local anaesthetic cream. The College is clear that it is completely inappropriate to insist on taking blood for non-therapeutic reasons if a child indicates significant unwillingness before the start or significant stress during the procedure. Despite the ethical framework and Royal College guidelines, it is still unclear whether proxy consent for non-therapeutic research is legally valid. Local research ethics committees have an important part to play in ensuring that research in children continues, but that due to their vulnerability, they are not exploited.

Non-therapeutic surgery

Male circumcision: one of the few occasions when one is asked to anaesthetize healthy children who appear not to benefit from the procedure is when young boys undergo circumcision for religious reasons. The child obtains no immediate benefit and yet is exposed to all the risks of surgery and anaesthesia. The legality of parental consent in these cases has never been challenged in a court of law but in the UK it would probably be upheld on grounds of religious toleration. However, the ethical debate is more complex, with two opposing views being taken. Brazier has commented that male circumcision is a matter of medical debate and that for Jewish and Muslim parents it is an article of faith. The child suffers momentary pain and though medical opinion may not regard it as beneficial, it is not medically harmful if properly performed. The community as a whole regards it as a decision for the infants' parents. The counter-argument claims that there is an extensive literature on the harm of circumcision and that everyone has a right to bodily integrity and proxy consent must be used reasonably and in the interests of the child. Giving consent to medical treatment of a child is a clear example of parental responsibility arising from a duty to protect the child. How can a parent be said to be protecting the child while exposing him to such risk? How can the procedure be ethically justified? Why cannot the procedure wait until the child is old enough to make his own decision?

In the UK, female circumcision is prohibited by the UK Prohibition of Female Circumcision Act of 1985.

Transplantation: the first kidney transplants were undertaken between identical minors. Couples are now having children for the express purpose of providing genetically compatible sibling donors of, at present, regenerative tissues. Whether these practices are ethically and legally acceptable is debatable, but they appear likely to increase. While different legal jurisdictions have come to different conclusions about their acceptability, the UK situation is unclear. A strong argument can be made to distinguish between various types of donation. The risk assessment depends in part on the regenerative capacity of the tissue or organ being donated.

It would appear, from the arguments discussed earlier, that the 'Gillick' competent minor would be able to consent, subject to the restrictions of the minor understanding the risks and benefits involved. Clearly, donation of non-regenerative organs involves greater risks than removal of those that can be replaced. Similarly, the risks inherent in the surgery to obtain the organs are relevant. It is far riskier to obtain a part of a liver than to obtain bone marrow, even though both are capable of regeneration. Thus, blood donation is ethically acceptable whereas kidney or skin is probably not. In common with non-therapeutic research, it would be foolish to proceed without parental consent, even when the minor has consented to the procedure. If this situation were to arise, it would be wise to seek the guidance of other doctors, and to apply to the Courts for guidance.

The situation regarding incompetent minors is even less clear. The debate hinges on whether parents have the right to consent on behalf of their child to something that will not benefit, and may harm, the child. Once again, the separation into regenerative and non-regenerative tissue helps to assess the risk. Assessment of what benefit would accrue to the child, such as the survival of a sibling or parent, also has to be undertaken. In the UK, application to the Courts would be needed in most cases. ◆

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Managing the Difficult Airway

Robert Walker

Robert Walker is Consultant Paediatric Anaesthetist at the Manchester Children's Hospital, UK. He qualified from Glasgow University Medical School and trained in paediatrics and anaesthesia in Manchester. His main area of interest is the development of fibre-optic intubation techniques in infants and children.

In normal infants, anatomical differences, compared with those of older children or adults, can make airway management and intubation slightly more difficult. These differences give rise to the 'high anterior larynx' and include:

- a more cephalad larynx (lying at the level of C3/4, compared with C5/6 in adults)
- a relatively large tongue, which is displaced posteriorly into the oropharynx, thus obscuring laryngeal structures
- a large, floppy, inverted, Ω-shaped epiglottis that is firm and lies at 45° to the long axis of the pharynx.

In addition, the mandible (and the space defined by it) is relatively deficient, so there is little space anteriorly in which to push the tongue and other tissues during laryngoscopy, making laryngeal structures more difficult to see.

Preoperative assessment

There are no tests that accurately predict difficult tracheal intubation in babies or children, though some features of history and examination alert the anaesthetist to potential problems (e.g. congenital or acquired abnormalities, previous anaesthetic difficulties). Features suggesting obstructive sleep apnoea (e.g. snoring, apnoea during sleep, day-time somnolence) may suggest a difficult airway, and examining mouth opening and mobility of the cervical spine can be helpful. Obstructive sleep apnoea indicates a high likelihood of airway obstruction during induction of anaesthesia but does not indicate any likelihood of difficulty to intubate the trachea. The presence of cervical spine disease makes positioning the head into the desired 'sniffing the morning air' position difficult.

For any child with a difficult airway, the anaesthetist must discuss the anaesthetic risks fully with the parents (and child, if appropriate), including the possibilities of tracheostomy or failure to secure the airway. The benefit of the procedure should always outweigh the risk of the anaesthetic.

Patient characteristics

Congenital and acquired problems associated with difficulty in airway management and tracheal intubation are listed in Figure 1.

Causes of difficulty in airway management and tracheal intubation in babies and children

Congenital

Craniofacial disorders
- Pierre Robin syndrome
- Treacher-Collins syndrome
- Goldenhar's syndrome
- Cleft palate

Lysosomal enzyme defects
- Mucopolysaccharidoses
- Mucolipidoses

Congenital swellings
- Cystic hygroma
- Haemangioma

Cervical spine abnormalities
- Klippel–Feil syndrome (congenital synostosis of cervical vertebrae)

Acquired

Inflammatory
- Acute epiglottitis
- Croup
- Diphtheria
- Retropharyngeal abscess

Others
- Trauma
- Burns
- Still's disease
- Radiotherapy
- Malignancy of the head and neck

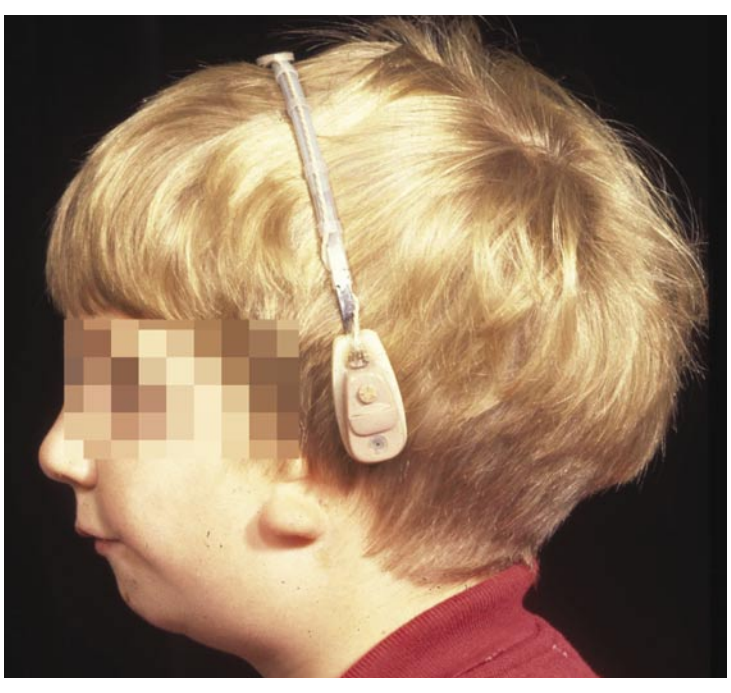
1

Craniofacial abnormalities: the most common are the Pierre Robin syndrome, Treacher-Collins and Goldenhar's syndromes. Both Treacher-Collins and Goldenhar's syndromes present major airway challenges to the anaesthetist, similar to those found in the Pierre Robin sequence.

The Pierre Robin syndrome consists of micrognathia and relative macroglossia, with or without cleft palate. In severely affected babies, airway obstruction develops in the first 4 weeks of life. When supine, the nasopharynx fills with the tongue, causing varying degrees of obstruction. When the baby then struggles, an even greater negative intrathoracic pressure is generated, sucking the tongue into the nasopharynx (via the cleft palate, if present). The obstruction is often ameliorated by nursing these babies prone, though a tracheostomy may be necessary. Children with this problem often have feeding difficulties and failure to thrive and may require nasogastric or gastrostomy feeding.

The combination of severe micrognathia with relative macroglossia and the cephalad displacement of the larynx can make visualization of the larynx with conventional laryngoscopes almost impossible.

The Treacher-Collins syndrome (mandibulofacial dysostosis) (Figure 2) consists of abnormalities of the external, middle and inner ear with hearing loss, mandibular deformities and minor eye abnormalities. The facial bones may be hypoplastic (typically the zygoma and mandible). These children may also have macrostomia (with or without a cleft palate), high arched palates and abnormal dentition.



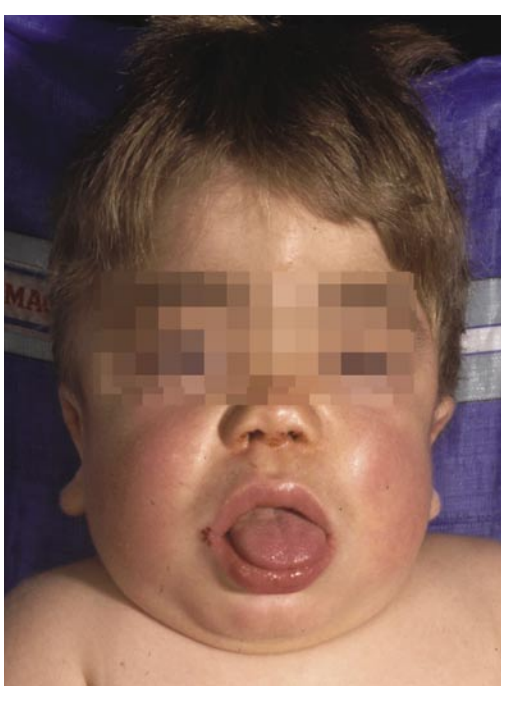
2 Lateral view of a child with Treacher-Collins syndrome.

Goldenhar's syndrome (oculoauriculovertebral dysplasia) consists of mandibular hypoplasia, eye and ear abnormalities sometimes with hearing loss. In addition, 40% have a Klippel–Feil anomaly (congenital fusion of the bodies of two or more cervical vertebrae), which makes appropriate positioning of the head and neck difficult.

Mucopolysaccharidoses (e.g. Hurler's, Hunter's, Marateaux–Lamy syndromes) (Figure 3) are hereditary progressive disorders caused by a deficient lysosomal enzyme, resulting in excessive intralysosomal accumulation of glycosaminoglycans (mucopolysaccharides). There is progressive, generalized infiltration and thickening of soft tissues making anaesthesia and airway management hazardous. Particularly important clinical features include:

- a large tongue (and sometimes hypertrophied tonsils) that obstructs the oropharynx
- progressive narrowing of the nasal airway ed by thickened mucous membranes, adenoidal hypertrophy and redundant 'granulomatous' tissue
- a typically short and immobile neck that may be unstable
- temporomandibular joint involvement with fibrosis, stiffness and limited mouth opening
- progressive thickening of the supra- and infra-glottic regions.

Difficulties with anaesthesia and intubation worsen with age.



3 A child with Hurler's syndrome.

Anaesthesia

Premedication decreases the child's anxiety and improves cooperation at induction and dries airway secretions. It can be achieved safely with oral midazolam, 0.5 mg/kg, and oral atropine, 20 μg/kg. Sedative premedication is best avoided in patients with pre-existing severe airway obstruction.

Induction

Induction using a spontaneous breathing technique with oxygen and either halothane or sevoflurane is the technique of choice. The anaesthetist should aim to attain a sufficiently deep level of anaesthesia to attempt to visualize the larynx using conventional laryngoscopes and then intubate the trachea. If this proves impossible, the anaesthetist must have a clear plan of how to proceed, either to abandon the procedure or to use alternative means to aid tracheal intubation (see below).

Following inhalational induction of anaesthesia and loss of consciousness, airway obstruction may occur rapidly. This can be treated by laying the patient in the lateral or semi-prone position to clear the airway. Other helpful manoeuvres to clear the airway further and allow deepening of anaesthesia before laryngoscopy include:

- inserting an oral airway (may precipitate coughing, and even laryngospasm, if inserted too early) or nasal airway (may cause bleeding, but better tolerated at an earlier stage than an oral airway)
- anterior traction of the tongue to clear the pharynx (e.g. with a tongue suture or forceps)
- inserting a laryngeal mask airway (LMA) when the child is sufficiently deeply anaesthetized.

Muscle relaxants should never be given until the airway is secure because this may result in the anaesthetist being unable to inflate the patient's lungs manually or to intubate the trachea and having to attempt a surgical airway rapidly. Maintaining spontaneous breathing allows the anaesthetist a way out should securing the airway prove impossible.

Equipment

Conventional laryngoscopes: a full range of curved and straight-bladed laryngoscopes should be available. Experienced practitioners often prefer straight-bladed instruments. The normal technique of intubation involves placing a laryngoscope into the mouth over the right side of the tongue, compressing the structures into the mandibular space and lifting to reveal the glottis. If the mandible is small or the tongue is large, a straight-bladed laryngoscope can be used lateral to the tongue in the paraglossal sulcus. Popular blades include the Miller and Wisconsin. The Storz laryngoscope (favoured by ENT surgeons) is also an excellent instrument and anaesthetists working with children with difficult airways should obtain experience using it. The smaller straight-bladed laryngoscopes, preferred by many paediatric anaesthetists, take up less space in the mouth and can be used to lift up the epiglottis and provide clear views of the glottis.

Fibre-optic bronchoscopes: although certain manoeuvres using conventional equipment can succeed, fibre-optic intubation techniques are often necessary.

Adult bronchoscopes – many flexible fibre-optic bronchoscopes are available. It is relatively easy to attain competency using one with an outer diameter of 3.5–3.8 mm, and these have good suction channels. However, they are only suitable for railroading tracheal tubes of internal diameter 4.0 mm or more, which limits their use to children less than 1 year of age.

Ultrathin flexible bronchoscopes have outer diameters of 2.2 mm, allowing a 2.5 mm internal diameter tracheal tube to be railroaded over them. Their optical quality is superb, but they have no suction channel (secretions must be aspirated with normal suction catheters), are 'whippy' to handle (requiring practice to become competent) and easily damaged.

Fibre-optic intubation techniques

Before attempting fibre-optic intubation, the baby or child must be deeply anaesthetized, well oxygenated, and have a clear airway to give the operator time to visualize the structures. Fibre-optic intubation is (almost) never done in babies or children who are awake. Topical anaesthesia is useful. A second anaesthetist is desirable to monitor the patient and check the airway during the fibre-optic intubation. Successful intubation is confirmed by capnography.

General strategies

Preloading the tube onto the bronchoscope, then railroading it into the trachea necessitates careful selection of the tube. If the tube is too large for the larynx, then the bronchoscope must be removed and the procedure repeated with a smaller tube.

A guide-wire technique has the advantage of being able to use an adult-sized bronchoscope for all sizes of tubes. A guide-wire is passed through the suction channel of the bronchoscope and guided into the trachea under direct vision. The bronchoscope is then removed and the tube passed over the wire. Pre-selection of the tube is not an issue because it is easily changed for a smaller one without having to re-insert the bronchoscope. A stiffening device is generally required using this technique prior to railroading of the tube.

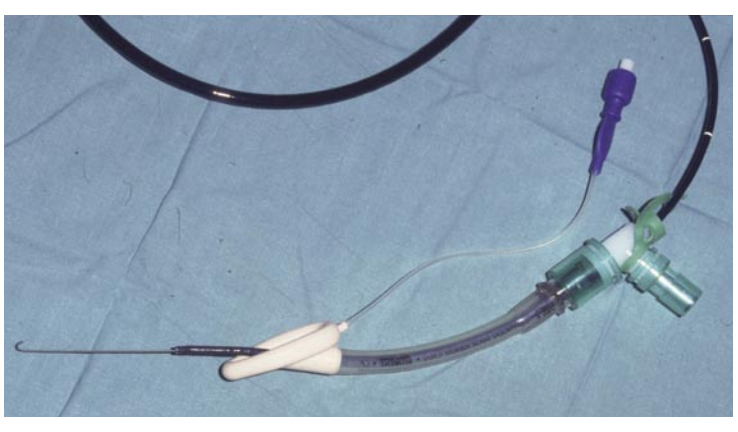
Route of intubation

The nasal route is often favoured in adults and can be used in children. Despite the belief that the angles to the larynx are easier when the fibre-optic bronchoscope is introduced through the nose, the risk of bleeding (caused either by the bronchoscope or railroading of the tube) can make this hazardous. Therefore, if the nasal route is chosen, careful preparation with vaso-constrictor solutions is essential. Adrenaline (epinephrine) 1:10,000, 1–2 ml, can be used before fibre-optic examination. Cocaine is best avoided.

The oral route is often preferred in children. The airway is commonly maintained during intubation through a nasal airway, a specially adapted face mask or an LMA.

The use of the LMA

The LMA is an extremely effective method of maintaining a difficult airway in a baby or child, allowing good oxygenation and a deep level of anaesthesia while affording the anaesthetist time to bronchoscope through the lumen of the device (Figure 4). However, it is difficult to railroad a tracheal tube through an LMA because it may stick in the lumen or at the distal bars of the LMA, or at the level of the glottis. A good alternative is to use a guide-wire inserted into the trachea through the suction channel of the bronchoscope, which is then removed. The guide-wire should be very long (in excess of 120 cm). These wires are often found in cardiac catheter laboratories. A 'stiffening' device (e.g. *Cook* airway exchange catheter) is passed over the wire and the wire, followed by the LMA, are then removed allowing the tracheal tube to be railroaded over the stiffening device and into the trachea. ◆



4 A laryngeal mask airway with a flexible bronchoscope inserted through it and a long guide-wire emerging from the suction channel of the bronchoscope.

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Monitoring during Paediatric Anaesthesia

Franco Moscuzza

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Monitoring during paediatric anaesthesia should comply with the recommendations of the Association of Anaesthetists. The most important 'monitor' is the presence of an appropriately trained and vigilant anaesthetist whose role is to interpret the information obtained from a range of sources. There are also many subtle physical and clinical signs that are either not detectable by electronic or electrical methods or may precede equipment warnings. Examples include observation of the eyes (pupillary dilation and divergence of gaze), capillary refill time, changes in the character of peripheral pulses, and early signs of airway obstruction (which may occur before changes in capnography or oxygen saturation). Because of the physiological differences between children and adults, changes in cardiovascular and respiratory variables occur more rapidly in children (particularly in babies), and monitoring assumes a greater role in safe management.

Cardiovascular monitoring

Precordial and oesophageal stethoscope

Auscultation with a precordial or oesophageal stethoscope is a cheap and simple method of obtaining direct and continuous information about the respiratory and cardiovascular systems. Both types of stethoscope can be connected to a conventional or a moulded monaural earpiece.

The precordial stethoscope can give continuous information about heart rate and some indication of blood pressure (the heart sounds can become 'muffled' with a major fall in cardiac output). The best position is usually at the left sternal border at the second or third intercostal space where both breath sounds and heart sounds can be heard. However, this does not exclude endo-bronchial intubation of the ipsilateral lung or provide information about the adequacy of gas exchange. Wheeze or secretions are generally easily detected. Background noise in the operating theatre may interfere with auscultatory monitoring.

The oesophageal stethoscope is a soft catheter with holes in the distal 2–3 cm covered by a balloon cuff. To position the catheter appropriately, connect it to the distal tubing of a stethoscope and then advance it into the oesophagus (through a nostril or the mouth) until the heart and breath sounds are loudest. The tip then lies in the mid-oesophagus. It should be used only in intubated patients and it can also incorporate a thermistor or ECG electrode. Contraindications include laser surgery of the airway and oesophageal atresia.

ECG

Myocardial ischaemia is uncommon in children except those with congenital heart disease having cardiac surgery. Therefore, the principal function of the ECG is to monitor heart rate and detect arrhythmias, particularly bradycardia. Primary cardiac arrhythmias are rare but secondary arrhythmias (caused by hypoxia, hypercarbia, surgical stimulation or anaesthetic agents) occur more commonly. Ensuring an adequate heart rate is essential in babies because cardiac output is largely rate dependent.

Lead II is the most useful for detecting arrhythmias because it provides the most information about the P wave. In neonates and young infants the right ventricle is dominant (precordial leads V1 ± V2 according to age) and there is right axis deviation. The T wave is large because of the proximity of the electrodes to the heart and the monitor can mistake this for another QRS complex resulting in an erroneous double counting of the heart rate. Electrolyte disturbances can occur rapidly in babies and the first clue may be a change in the morphology of the ECG (e.g. peaked T waves with hyperkalaemia, increased QT interval with hypocalcaemia). Monitoring the ECG during regional analgesia may also help to detect inadvertent intravenous injection of local anaesthetics.

Blood pressure

Non-invasive: systolic and diastolic blood pressure can be measured by auscultation of the Korotkoff sounds using a sphygmomanometer. However, this is impractical during surgery in babies or small children and has long been replaced by automated devices using Doppler or (more commonly) oscillometry.

Oscillometry (e.g. the Dinamap – device for indirect non-invasive mean arterial pressure) is the most common technique for automated blood pressure measurement in paediatrics and is generally accurate for systolic, diastolic and mean pressures if an appropriately sized cuff is chosen. If the cuff is too narrow, the blood pressure reads falsely high and if too wide, falsely low. Care should be taken to ensure that the cuff does not cause nerve injury (for example, by over-frequent measurement) and that the tubing does not cause pressure damage. An appropriate blood pressure cuff should cover two-thirds of the length of the upper arm or thigh or have a width equivalent to 40% of the circumference of the limb (4 cm width is recommended for a term neonate).

Invasive: direct, intra-arterial monitoring is the most accurate measure of blood pressure and provides a 'beat to beat' assessment. However, it is usually restricted to critically ill children or those undergoing major surgery with significant blood loss or fluid shifts because of the associated risks (e.g. thrombosis, embolism). Possible sites for arterial cannulation include all the proximal and distal arteries of the arms and legs (e.g. radial, brachial, femoral, dorsalis pedis) and the umbilical artery in a newborn baby up to 3 days old, though this cannot be used in cases of intra-abdominal surgery. Care should be taken to try to ensure that a collateral blood supply is present although Allen's test is difficult in young children and the efficacy debatable. The size of catheter varies according to the site but as an approximation a 24G is used in neonates, 22G in infants and young children up to about 20 kg and 20G in older children. A solution of heparinized saline (heparin, 0.5 or 1 iu/ml) is flushed through the transducer mechanism at a constant rate (usually 3 ml/hour) to maintain patency. However, 0.5 ml/hour delivered through a syringe driver, rather than a pressurized bag, is more appropriate in infants, especially premature babies whose maintenance fluids need to be carefully regulated.

Inaccuracies are minimized by ensuring that the tubing between the cannula and the transducer is rigid and as short as possible to prevent high-frequency harmonic interference. Other causes of a 'damped' trace include air bubbles, arterial spasm and kinking of the tubing or cannula. Care needs to be taken in babies or small children to avoid retrograde flow into the cardiac or cerebral circulations (which can occur with as little as 0.5–1 ml of injectate) or the inadvertent administration of large volumes of fluid during flushing. It is preferable to inject a small amount of fluid through a syringe at relatively low pressure rather than 'flush' directly through the transducer (which will deliver an unmeasured volume at relatively high pressure). Other complications of arterial cannulation include local haematoma, haemorrhage from inadvertent disconnection, infection (local or generalized sepsis), thrombosis and distal embolization.

Central venous pressure monitoring

Indications for direct central venous pressure monitoring include:

- major surgery with anticipated large fluid shifts
- massive blood loss
- cardiac surgery
- critically ill children.

As in adults, the trend of readings is more important than absolute values. If right ventricular function is normal, then values are a reasonable indication of intravascular volume. Measurements are accurate when made from either the superior (SVC) or inferior vena cava (IVC) provided there is no obstruction to drainage. The SVC is usually accessed via the internal jugular or subclavian vein and the IVC is approached through the femoral (or in the newborn, umbilical) vein. Care must be taken in neonates to ensure that the tip of a central line does not extend into the right atrium because there have been reports of lines eroding though the atrial wall. As with arterial pressure monitoring, the tubing between the transducer and line should be short and rigid. The zero baseline is crucial and should be taken at the mid-axillary level. Measurement is influenced by respiration and should be made at the end of expiration, which corresponds to the lowest level on the wave form.

Pulmonary artery pressure and cardiac output monitoring

Although pulmonary artery catheters are available for children, in the author's experience they are seldom used. Accurate positioning is harder to achieve in the small child than in adults and data interpretation is more difficult. Complications (e.g. catheter knotting, infection, bleeding) though uncommon, are a significant source of morbidity. In surgery for congenital heart disease, the catheter often lies directly in the surgical field and left-sided filling and pulmonary artery pressures are better measured (if required) from lines placed by the surgeon at the end of the procedure.

Alternatives for measuring cardiac output accurately in children are becoming increasingly available though most are confined to the paediatric ICU. The systems most likely to develop more widespread use are transoesophageal Doppler, transpulmonary thermodilution (COLD Z-021) and pulse contour analysis. Measurement of mixed venous oxygen saturation is also used to determine changes in cardiac output indirectly.

Respiratory monitoring

Pulse oximetry

Hypoxia, usually associated with airway problems, is the most common critical incident in paediatric anaesthesia. Hypoxia develops quickly, particularly in babies in whom the functional residual capacity is low and oxygen consumption high. Clinical evaluation by detecting cyanosis is difficult even for the most experienced anaesthetist. Oximetry provides an invaluable early warning of hypoxia.

The pulse oximeter provides no information on the adequacy of ventilation. For example, a baby with severe respiratory failure and hypercarbia may have normal saturations if breathing oxygen-enriched air. Nor does it measure the partial pressure of oxygen, which may vary for the same saturation according to shifts in the oxyhaemoglobin dissociation curve. Because of the plateau of the oxyhaemoglobin dissociation curve, saturation monitoring is an inappropriate monitor for avoiding hyperoxia in preterm neonates at risk of retinopathy. Although calibrated for adult haemoglobin, the absorption spectrum is virtually identical for fetal haemoglobin and pulse oximeters can be used reliably in neonates. Other forms of haemoglobin may introduce errors in the saturation obtained. For example, carboxyhaemoglobin is detected by the oximeter as normal oxyhaemoglobin therefore the oxygen saturation is overestimated. Figure 1 indicates factors that may affect the accuracy of pulse oximeters. Thermal injury and pressure necrosis due to too tight application of the sensor probe have been described (Figure 2).

Limitations of pulse oximetery

Physiological

- Abnormal haemoglobin (oxyhaemoglobin dissociation curve shift)
  – methaemoglobin decreases oxygen saturation (SpO_2 – to 85% with high concentrations)
  – anaemia causes no problem if haemoglobin > 5 g/dl
  – carboxyhaemoglobin produces a falsely high SpO_2
- Poor perfusion (from hypovolaemia, low cardiac output or hypothermia)
- Dyes (e.g. methylene blue causing transient low SpO_2)
- Venous pulsation (e.g. tricuspid regurgitation causing a falsely low SpO_2)

Technical

- Accuracy decreases with SpO_2 < 80% (e.g. cyanotic congenital heart disease)
- Response delay/motion artefacts
- Light interference (especially fluctuating light sources)
- Electrical or magnetic interference

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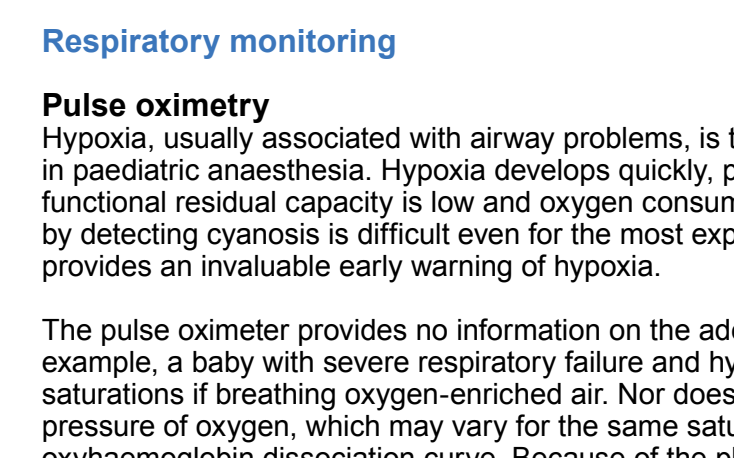

2 Injury sustained from saturation probe.

Capnography

Capnography is the measurement of PCO_2 in inspired or expired gases during breathing. In fit babies and children, the end-tidal carbon dioxide ($EtCO_2$ or alveolar PCO_2) provides a good measure of arterial PCO_2 ($EtCO_2$ is usually 2–5 mm Hg lower), but the difference may be increased if there is a large V/Q mismatch, particularly with a large dead space (e.g. bronchopulmonary dysplasia). Children with congenital heart disease, particularly those with large shunts, also show larger variations. Capnographs use infrared absorption for measurement.

Main-stream analysers have a sensor placed in the breathing system, preferably as close to the patient as possible, and give an instantaneous reading. However, they are heavy and can significantly increase the dead space of small paediatric circuits. Sensors with smaller dead spaces are available.

Side-stream analysers have a line leading to the analyser from a sampling port and consequently, there is a lag time for measurement. Gas can be monitored more proximally than with a main stream, the tubing is narrow and lightweight, and has no effect on dead space. However, there is a greater potential for obstruction either from kinking, external compression or blockage of the tube due to water condensation from the expired gases. When using a side-stream analyser to monitor a low-flow circle system, allowance must be made for the volume of gases removed for sampling or the exhaust gases from the analyser must be returned to the circuit. Side-stream analysers can also measure other gases such as nitrous oxide and volatile agents.

Capnography is not only a monitor of the adequacy of ventilation but also gives warning of disruption in gas supply (e.g. disconnection of the circuit), inadequate fresh gas flow, and oesophageal intubation. A falling $EtCO_2$ may indicate a sudden decrease in cardiac output or a pulmonary embolus (both reduce pulmonary blood flow) and a rapid rise may be the earliest warning sign of malignant hyperpyrexia. Changes in the capnographic trace may indicate recovery from muscle relaxation. Some characteristic changes are described in Figure 3.

Some causes of abnormal end-tidal CO_2 readings

Decrease

Complete disappearance

- Disconnection
- Complete obstruction (either airway or sampling line)
- Cardiac arrest

Slow decrease

- Hyperventilation
- Pulmonary hypoperfusion
- Leak around tracheal tube (may be variable)

Increase

Slow

- Hypoventilation
- Rebreathing (may become rapid)
- Faulty unidirectional valve in circle (causing rebreathing)
- Muscle relaxation reversal

Rapid

- Malignant hyperpyrexia (progressive despite adequate ventilation)

Temperature

Measuring temperature is important in babies and children because of the increased risks of hyperthermia and hypothermia. In infants, thermoregulatory mechanisms are poorly developed and the relatively large surface area to weight ratio means that hypothermia may develop rapidly. It is also easy to overheat children with the enthusiastic use of modern warming devices. Temperature monitoring is also indicated because of the potential risk of malignant hyperpyrexia. Temperature probes may be thermistors, thermocouples or liquid crystals.

Thermistors are metal semiconductors and the resistance varies with temperature. They can be covered by plastic tubing and placed in the nasopharynx, oesophagus or rectum or incorporated into catheters (e.g. urinary or pulmonary artery catheters).

Thermocouples work on the principle that the potential difference generated at the junction of two different metals varies according to the temperature – the tympanic thermometer is a good example of this type.

Liquid crystal thermometers are often incorporated into adhesive strips, which are applied to skin. The crystals change colour with changes in temperature.

Neuromuscular blockade

In young children, particularly infants and neonates, there is a much greater individual response to muscle relaxants. Variability may be increased by underlying medical conditions and interactions with other agents. Monitoring neuromuscular blockade with a peripheral nerve stimulator is, therefore, essential in paediatric anaesthesia and highly recommended in intensive care, particularly if infusions of relaxants are given. ◆

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Preoperative Assessment and Preparation

Peter Stoddart

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Admission to hospital for surgery is stressful for a child and his or her family. The preoperative assessment allows the anaesthetist to establish a rapport with the child and parents, allaying many fears and concerns. In addition, the anaesthetist must assess the child, then plan and discuss the anaesthetic and analgesic management with the family, surgeon and nurses. This time is crucial to the subsequent success of the anaesthesia and is a rewarding component of paediatric practice.

Assessment

Most children requiring anaesthesia are healthy, have large physiological reserves, and are having relatively uncomplicated surgery. However, they all require a full history and examination to exclude any potential hazards or difficulties for the anaesthetist. The importance and relevance of these may change with the age of the child; for example, the airway in a child with Pierre Robin syndrome often becomes easier to manage as the mandible grows.

With the increasing numbers of day-case and same-day admissions, many hospitals have established successful pre-admission clinics. These are usually run by nurses and play therapists who obtain a standardized anaesthetic history. They also help families to become familiar with the sights and sounds of the hospital environment. The routines are explained, especially the fasting requirements, and the child is able to play, ask questions and learn what to expect on admission.

The child must also be seen by an anaesthetist, preferably the one giving the anaesthetic on the day of the surgery. It is important to review the notes and speak to the nurses and surgeon before seeing the child. The anaesthetist should gain the family's confidence before obtaining a more detailed history. Making eye contact with children by, for example, sitting at their level, involving them in the discussion, or asking them about other non-medical, and therefore less-threatening topics (e.g. their favourite toy/doll, television programme, football team), helps to reduce their anxiety, makes them feel important and increases their trust. Children will often listen to an anaesthetist who is speaking to their parents while appearing to play close by. These children should be drawn into the discussion and certainly should not be ignored.

History – the following factors must be noted in the history:

- age
- weight
- diagnosis
- starvation time
- important factors in the medical history that are of relevance to the anaesthetist (see Figure 1)
- past anaesthetic history – airway problems, endotracheal tube size, behavioural problems in anaesthetic/recovery room, previous premedication and its effect, nausea/vomiting
- family history – malignant hyperthermia, muscle disease, pseudocholinesterase deficiency, porphyria, sickle cell disease
- drug history – current medication, recent corticosteroid therapy, previous chemotherapy
- allergies (including latex).

Examination – much of the examination and assessment, especially of small children, can be done by watching and observing the child while taking the history. School-age children are usually happy to be examined once the anaesthetist has gained their trust, though some can be easily embarrassed and require more time and privacy. Toddlers and preschool children may be more of a challenge and are best examined while sitting on their parent's knee rather than laid flat on a bed or in a cot. Examining the child's hands first allows the anaesthetist to look for potential venous access and makes an initial contact in an open, non-threatening way. The features that should be assessed in the examination are listed in Figure 2.

Investigations – few children about to undergo routine minor surgery require further investigations. However, if they have a significant underlying history (e.g. recent chemotherapy) or are having major surgery (e.g. a fundoplication, multilevel osteotomies), then blood should be taken for a full blood count, urea, blood sugar and electrolytes, and a blood group and save or cross-match (if appropriate). Further tests such as an ECG, echocardiography, haemoglobin electrophoresis, clotting studies, chest radiograph and lung function tests may be required if indicated by the history or examination.

The child with a runny nose is a common problem in paediatric anaesthetic practice. The indications for cancelling elective surgery are signs of active viraemia (i.e. the child is unwell and miserable or has a fever) or signs of lower respiratory tract infection. A child who is obviously recovering from an upper respiratory tract infection or who has an allergic rhinitis has an increased risk of laryngospasm and bronchospasm but should not present difficulties for an experienced anaesthetist.

Factors in the medical history of relevance to the anaesthetist

Perinatal
- Maternal health and delivery
- Prematurity and management on neonatal ICU
- Congenital anomalies or syndromes

Respiratory
- Respiratory distress syndrome, apnoeas, bradycardias
- Recent upper respiratory tract infection
- Asthma
- Croup
- Snoring, sleep apnoea
- Cystic fibrosis

Cardiovascular
- Hypertension (e.g. secondary to renal or endocrine disease, or associated coarctation of the aorta)
- Murmurs, pulmonary hypertension
- Cyanotic episodes
- Dyspnoea/exercise tolerance

Gastrointestinal
- Vomiting
- Gastro-oesophageal reflux
- Diarrhoea
- Liver disease
- Nutritional requirements – total parenteral nutrition, enteral supplements

Renal
- Thirst, urine output, wet nappies
- Renal failure

Neurological
- Cerebral palsy
- Developmental delay
- Seizures – frequency, type, treatment
- Hydrocephalus – shunts
- Meningomyelocele

Metabolic/endocrine
- Inborn errors of metabolism
- Diabetes, thyroid, pituitary, adrenal disease

Haematological
- Sickle cell disease
- Bruising/bleeding tendency
- HIV

Oncological
- Leukaemias
- Solid tumours (e.g. nephroblastoma, neuroblastoma)
- Recent chemotherapy or marrow suppression

Dental
- Loose teeth – these may need to be extracted, if so the child should be informed

1

Examination of the preoperative child

Vital signs (especially before emergency surgery)
- Colour/cyanosis
- SpO_2 with a pulse oximeter
- Hydration (assessed by examining fontanelle, mucous membranes, skin)
- Pulse rate and volume
- Capillary refill time
- Conscious level/activity
- Temperature

Head and neck
- Dysmorphic features, especially craniofacial
- Dentition – loose teeth
- Size of tongue
- Cervical lymphadenopathy
- Tracheal deviation

Respiratory
- Respiratory pattern
- Work of breathing – look for nasal flaring, tracheal tug, sternal recession
- Use of accessory muscles
- Wheeze/stridor/grunting
- Breath sounds

Cardiovascular
- Murmurs
- Peripheral pulses
- Venous access

Abdominal
- Distension
- Hepatic/splenic enlargement

Neurological
- Neurodevelopment
- Spasticity
- Scoliosis
- Myelomeningocele

2

Psychological preparation

The psychological needs of both the child and the parent must be considered. Time invested in preparing the family will improve cooperation and behaviour before surgery and cause fewer upsets and long-term behavioural changes afterwards.

The nature of the child's fears will be related to their age, stage of neurodevelopment, emotional maturity, previous anaesthetic experience and parental support. Toddlers and pre-school children are unhappy if they are separated from their parents and may benefit from bringing a favourite toy or comforter into the anaesthetic room. Schoolchildren are less concerned about leaving their parents but may be needle-phobic, fear a loss of control, be embarrassed by the loss of privacy, or be concerned that they will wake up during the surgery or not at all. Adolescents have similar fears that they may suppress, appearing calm and controlled on the ward only to revert to an immature state in the anaesthetic room. They can be very concerned about their body image, loss of autonomy, the long-term consequences of the surgery and the potential complications of the anaesthesia.

Most parents are extremely anxious and stressed during the perioperative period, which can add to the child's apprehension. Parents may experience a sense of guilt because their child needs surgery and worry that the child may have pain postoperatively. They can become very upset when separated from the child and embarrassed by their loss of control. Parents are concerned for their child's safety while they are anaesthetized and worry about the outcome of the surgery.

The fears and reservations of each child and their parents must be addressed and individualized for that particular family. A careful explanation of what is planned, with their involvement, must be given using appropriate language. Care should be taken not to use condescending phrases that can be taken out of context (e.g. the innocent reference to 'being put to sleep'). Postoperative pain control should be discussed, including epidural analgesia and patient-controlled analgesia if these techniques are required, as should the need for catheters or drains. Children and parents expect and accept a truthful description of any discomfort or pain they may experience. If the need for postoperative intensive care is anticipated, the family should be allowed to visit the unit before surgery.

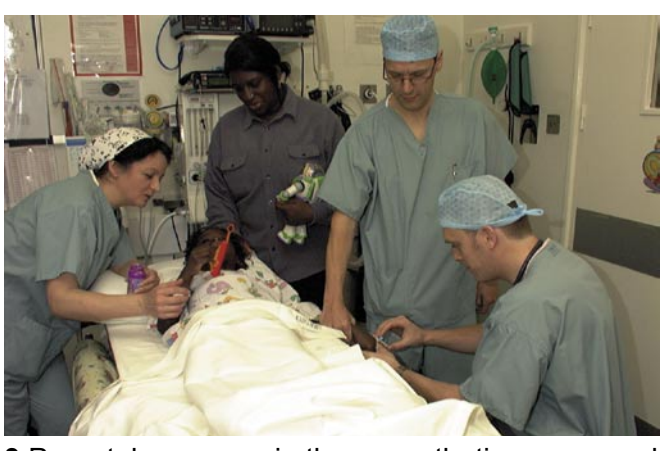
Having established a rapport and gained the trust of the child, subsequent induction of anaesthesia is achieved in a much more simple and peaceful fashion. Additional anxiolysis may be induced by judicious premedication, but simple distraction using musical books, bubbles or enlisting a play therapist is often as effective for the nervous child. The induction room should have a relaxed, 'child-friendly' atmosphere with one person (i.e. the anaesthetist) obviously in control.

Parents are usually encouraged, and have an expectation that they should come to the anaesthetic room (Figure 3). This may be helpful if the parent is calm and reassures an anxious child, especially if a small child prefers to sit on the parent's knee. However, parental presence is not beneficial to all children. Indeed, parents may hinder the smooth induction of anaesthesia by upsetting the child, distracting the anaesthetist and requiring nurses to look after them. Many parents dislike the feeling of their child being induced in their arms and worry that the child looks lifeless. Some parents panic or faint.

After explaining what to anticipate during induction, the relative merits, or otherwise, of a parent being in the anaesthetic room should be discussed. If parents do not wish to come to the anaesthetic room they should be encouraged to stay on the ward and reassured so that they do not feel guilty or inadequate. Additionally, if the child is a small baby or has potential anaesthetic difficulties, the anaesthetist should not be forced to have the parents present; the child's safety is paramount.

Emergency surgery is acutely stressful for most children and their families. There may be little time to counsel them fully preoperatively. Often they are tired and may have travelled a long distance to a specialist centre. However, many families are also relieved that something positive is being done for their child.

Some children require repeated anaesthesia (e.g. radiotherapy, repeated oesophageal dilatations). They need careful consideration and may develop obsessional behaviour in the anaesthetic room. These children are best treated by the same anaesthetic team members or, if this is impossible, by discussing their needs, preferences and routines well in advance of anaesthesia.



3 Parental presence in the anaesthetic room may help in achieving a smooth induction of anaesthesia.

Premedication

Premedication may be used to assist the induction of anaesthesia by providing:

- anxiolysis, amnesia and sedation
- topical analgesia before venepuncture
- reduced airway secretions and vagolytic action
- analgesia
- anti-emesis.

Sedative premedication – many sedatives have been used over the years as premedicants for anxious children. Their use has reduced as the rate of day-case surgery has increased and the emphasis is now on gaining the child's confidence before induction of anaesthesia, allowing parents to accompany the child, using distraction techniques, and applying topical analgesia before venous cannulation. However, some children benefit from sedation. Commonly used drugs are shown in Figure 4.

Oral premedication is the most acceptable, and many children's nurses are now unwilling to administer intramuscular injections. However, some children refuse an oral premedicant and exhibit such combative behaviour in the anaesthetic room that intramuscular sedation is the only option.

Topical local anaesthesia with *Emla* (a eutectic mixture of lignocaine and prilocaine) or *Ametop* (amethocaine gel) has simplified and increased the acceptance of awake, venous cannulation, enabling a smooth intravenous induction. However, both need to be applied 30–60 minutes before venepuncture. *Emla* has a slower onset time, may cause marked venoconstriction, and has been reported to cause methaemaglobinaemia. *Ametop* can occasionally cause local allergic skin reactions.

Anticholinergics – atropine, 20 µg/kg i.m. or 40 µg/kg p.o., reduces the incidence of hypoxic episodes or bradycardias secondary to laryngospasm or excessive airway secretions during induction and emergence from a halothane anaesthetic. However, its routine use has decreased since the introduction of sevoflurane for gaseous induction and the more widespread use of intravenous induction.

Analgesics – paracetamol, 20–30 mg/kg, and/or non-steroidal anti-inflammatory drugs such as ibuprofen, 5 mg/kg, or diclofenac, 1 mg/kg, are often given orally before elective surgery. This reduces the requirement for postoperative opioids and supplements intraoperative local anaesthetic blocks by ensuring adequate absorption before the end of surgery.

Anti-emetics – children with a history of postoperative nausea and vomiting or having high-risk surgery (e.g. strabismus or middle ear surgery) should be given preoperative anti-emetics such as ondansetron, 0.1–0.2 mg/kg, or metoclopramide, 0.15 mg/kg.

Fasting guidelines

All patients are fasted before elective surgery to reduce the risk of pulmonary aspiration of acidic gastric contents, which may lead to a pneumonitis or occlusion of the airway with solid material. Balanced against these risks is the danger of occult hypoglycaemia or dehydration, especially in small babies following a prolonged fluid fast. Residual gastric acid content and volume are not increased by allowing children to drink clear fluid (apple juice, squash or oral dehydration fluid) until 2 hours before anaesthesia and these more liberal guidelines have improved compliance and comfort. The Bristol Children's Hospital fasting guidelines for elective surgery in otherwise normal children are shown in Figure 5.

These guidelines are not appropriate for children needing emergency surgery or if the child is known to have delayed gastric emptying as a result of, for example, pyloric stenosis, ileus or peritonitis. A nasogastric tube must be inserted on the ward before children with bowel obstruction come to theatre and this should be aspirated before inducing anaesthesia. Following trauma, the time between the last meal and the subsequent injury gives a more useful guide to the probability of an empty stomach, rather than the duration of fasting, because of the frequent development of gastric paresis exacerbated by opioid administration. Many children, especially those with cerebral palsy, have marked gastro-oseophageal reflux. They are usually taking medicines such as H_2-antagonists or a proton pump inhibitor (e.g. omeprazole) and these should be continued preoperatively. In children with a high risk of aspiration, anaesthesia should be induced using a rapid sequence technique.

Sedative premedicants

Drug	Route and dose	Comments
Benzodiazepines		
• Midazolam	Oral, 0.5–0.75 mg/kg, max. 20 mg	Intravenous preparation actually used. Has an unpleasant taste, therefore disguise in blackcurrant juice or paracetamol elixir. NB Syrups are available (e.g. the Alder Hey recipe). Onset 20–30 minutes
	Intranasal, 0.2–0.3 mg/kg	Irritant. Onset about 10 minutes
• Temazepam	Oral, 0.5–1.0 mg/kg, max. 20 mg	
• Diazepam	Oral, 0.2–0.4 mg/kg, max. 15 mg	
Opioids		
• Morphine	Intramuscular, 0.2 mg/kg	Especially before cardiac surgery. Intramuscular injection painful
• Oral transmucosal fentanyl citrate	Oral, 10–15 µg/kg	*Oralet* in North America. Associated with vomiting and pruritus
Others		
• Triclofos	Oral, 50–75 mg/kg, max. 1000 mg	Pleasant taste compared with parent compound chloral hydrate
• Trimeprazine	Oral, 2 mg/kg	This dose often ineffective but has potentially useful anti-emetic properties
• Methohexitone	Rectal, 30 mg/kg	Popular in North America. Induces anaesthesia in a child while in parent's arms before transfer to theatre
• Ketamine	Oral, 5–6 mg/kg; intramuscular, 2–5 mg/kg	Associated with increased salivation, hallucinations and emergence delirium

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Fasting guidelines – Bristol Children's Hospital

Age (months)	Food (hours)		Clear fluid (hours)
< 12	Solids	6	2
	Formula milk	4	
	Breast milk	3	
> 12	6	3	

5

FURTHER READING

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Coté C J, Todres I D, Ryan J F. Preoperative Evaluation of Pediatric Patients. In: Coté C J, Ryan J F, Todres I D, Goudsouzian N G, eds. *A Practice of Anesthesia for Infants and Children.* 2nd ed. Philadelphia: Saunders, 1993.

Principles of Anaesthesia for Common Elective and Emergency Operations in Children

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This article describes the principles of anaesthesia for children and discusses the important considerations and anaesthetic techniques for specific elective and emergency surgical procedures. Principles of anaesthesia for babies and techniques for ENT surgery are discussed in other issues of *Anaesthesia and intensive care medicine*.

General considerations

Standards for the delivery of a surgical service for children in the UK are summarized in Figure 1.

Standards for the delivery of a surgical service for children in the UK

Clinicians
Anaesthetists and surgeons should have adequate training and continuing experience in the management of children. Occasional paediatric practice has been widely condemned

Specialist paediatric centres
Children are managed by specialist paediatric surgeons and anaesthetists

District general hospital
Surgeons treating children must:
- have a minimum of 6 months' training in paediatric surgery
- care for a sufficient number of children annually to maintain a high level of competence
- operate on children on at least one operating list every fortnight

Anaesthetists treating children must:
- have a minimum of 6 months' training in paediatric anaesthesia
- anaesthetize children on at least one operating list per week

It has been recommended that adequate continuing paediatric experience requires the anaesthetist to anaesthetize per year:
- 12 children < 6 months
- 50 children < 3 years
- 300 children < 10 years

Paediatricians should be involved in the care of children when appropriate

There must be close liaison with a specialist paediatric surgical centre

Other staff and facilities
- In all areas, staff should include nurses with special paediatric training
- An accident and emergency department must have appropriate children's facilities
- Protocols must be in place for prompt access to paediatric ICU beds

Environment
- Children should be nursed on children's wards and should not be cared for alongside adults
- Separate safe and appropriate facilities should be available for children perioperatively including a preoperative play area, designated theatres and a paediatric recovery bay
- Surgery for day-case patients should take place on designated paediatric lists in the day-case unit

Equipment
- Suitable, appropriately organized paediatric equipment must be available, arranged on trolleys or in designated anaesthetic rooms

Induction of anaesthesia
The choice of induction method depends on several factors, including the wishes of the child, parent or anaesthetist and the general condition of the child. A rapid-sequence induction is indicated if there is bowel obstruction, an acute abdomen or significant gastro-oesophageal reflux. Gaseous induction is essential if there is airway obstruction. Total intravenous anaesthesia may be used in children susceptible to malignant hyperthermia or to reduce vomiting after specific operations.

Perioperative intravenous fluid therapy is summarized in Figure 2.

Temperature regulation: body temperature preservation is important particularly

Perioperative intravenous fluid therapy

Replacement of starvation deficit
- Depends on length of starvation
- Equals hourly maintenance intravenous fluids (ml/hour) x duration of starvation (hours)

Maintenance intravenous fluids
- 4 ml/kg/hour for first 10 kg body weight
- 2 ml/kg/hour for next 10 kg body weight
- 1 ml/kg/hour for every additional kg body weight
- Use 5% dextrose,1/2 strength Hartmann's solution or lactated Ringer's solution, depending on age

Replacement of third-space losses
- Depends on site of operation and extent of surgical exposure
- Use lactated Ringer's solution

Suggestions:
- Laparotomy, 6 ml/kg/hour
- Thoracotomy, 4 ml/kg/hour
- Femoral osteotomy, 2 ml/kg/hour

Replacement of blood loss
- Type of intravenous fluid used depends on haemoglobin (Hb)

Calculate allowable blood loss

$$\frac{(\text{preoperative Hb} - \text{acceptable Hb}) \times \text{circulating blood volume}}{\text{mean Hb}}$$

Acceptable Hb
- Depends on clinical condition of child
- Suggest Hb = 8 g/dl in a healthy child

Circulating blood volume
- 72 ml/kg for children > 2 years old

Replacement intravenous fluids
- Give 1 ml colloid/blood or 3 ml crystalloid for every ml blood loss
- Use colloid or crystalloid if Hb > 8 g/dl
- Use blood if Hb ≤ 8 g/dl

during major surgery. Children are at greater risk of heat loss than adults because of their higher surface area to mass ratio. Core temperature should be monitored during anaesthesia in small children or those undergoing major surgery. It should also be monitored continuously in children at risk of malignant hyperthermia.

The main method of cutaneous heat loss is thermal radiation. Conduction and convection from exposed tissues are less important. Evaporation may be substantial from large incisions. Methods of preserving body temperature perioperatively are summarized in Figure 3.

Analgesia: perioperative analgesia for different procedures is summarized in Figure 4. **Preventing postoperative vomiting** is described in Figure 5. Side-effects of some of the frequently used anti-emetics are more common in children. Metoclopramide and cyclizine are associated with extrapyramidal effects. Cyclizine may cause anticholinergic effects. Droperidol, particularly in large doses, may cause drowsiness, sedation, dysphoria or restlessness. Ondansetron is comparatively free of side-effects and is the first-line treatment for postoperative vomiting at Derriford Hospital, Plymouth.

Methods of preserving body temperature perioperatively

Prevent heat loss from the body to adjacent structures
- Keep child covered during procedures (e.g. wrap body and head in an insulating cover, gamgee or polythene)
- Lay the child on a warming mattress or a mattress of low thermal conductance
- Use a forced-air patient-warming system

Reduce evaporative losses
- Keep large surgical incisions covered up
- Use 'bowel bags' during laparotomy
- Use water-repellent surgical drapes

Warm intravenous fluids
- Use a blood and intravenous fluid warmer

Prevent heat loss from the respiratory tract
- Humidify and (if necessary) warm inspired gases using a heated humidifier or a heat and moisture exchange filter

Perioperative analgesia in children

	At induction	Intraoperatively	In recovery	Postoperatively
Minor surgery (no opioids required)	Diclofenac, 1–1.5 mg/kg p.r. Local block or infiltration if applicable		Paracetamol, 40 mg/kg p.r. or 20 mg/kg p.o., if required	**a** Paracetamol, 15–20 mg/kg p.o. or p.r. 6 hourly (max. 90 mg/kg/day) **b** Diclofenac, 3 mg/kg/day in divided doses
Intermediate surgery (opioids required for ≤ 24 hours)	Paracetamol, 40 mg/kg p.r. and diclofenac,1–1.5 mg/kg p.r. Regional or local block if indicated Opioid boluses[1]	Opioid boluses[1] as required	Morphine, 50 µg/kg i.v. boluses every 10 minutes (max. 200 µg/kg i.v.)	*Oramorph*, 0.5 mg/kg 4 hourly p.o., as required or morphine, 50 µg/kg i.v., as required and regular prescriptions of **a** and **b** as above
Major surgery (opioids required for > 24 hours)	Paracetamol, 40 mg/kg p.r. and diclofenac, 1–1.5 mg/kg p.r. Epidural if indicated Opioid boluses[1]	Opioid boluses[1] as required	As for intermediate surgery	Epidural infusion ± *Oramorph* or patient-controlled morphine or morphine i.v. infusion and regular prescriptions of **a** and **b** as above

[1]Opioid boluses are fentanyl, 1–2 µg/kg i.v. or morphine, 50–100 µg/kg i.v., at induction, and fentanyl, 1 µg/kg i.v., or morphine, 50 µg/kg i.v., boluses as required intraoperatively.

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Reducing postoperative vomiting

Give prophylactic intravenous anti-emetics at induction to children:
- scheduled for surgery associated with a high incidence of postoperative vomiting (e.g. squint correction, major ear surgery, adenotonsillectomy, emergency abdominal surgery)
- with a history of motion sickness or previous postoperative vomiting

Give prophylactic anti-emetics to children receiving perioperative opioids
- For example, a single dose intravenously before commencing patient-controlled analgesia or an intravenous morphine infusion

Suggested anti-emetic regimen

First-line therapy	*Receptor antagonism site*
• Ondansetron, 0.15 mg/kg i.v. 8-hourly	• Serotonin (5-HT)
Second-line therapy	
• Metoclopramide, 0.15 mg/kg i.v. 8-hourly	• Dopamine
• Droperidol, 25–50 µg/kg i.v.	• Dopamine
• Cyclizine, 1 mg/kg i.v.	• Histamine

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Major elective surgery

Childhood tumours
Nephroblastoma and neuroblastoma are the most common extracranial solid childhood tumours, each occurring in about 1/30,000 children.

Nephroblastoma (Wilms' tumour) arises from embryonic cells in the kidney. It usually presents as an asymptomatic renal mass in children under 5 years, and is more common in boys. Bilateral disease occurs in 10% of those affected. Nephroblastoma is associated with aniridia, other genitourinary abnormalities and hemihypertrophy of the body. The tumour may spread to lymph nodes or, via the blood stream, to the lungs. Treatment is nephrectomy either before or after chemotherapy. Children may also require urgent anaesthesia for investigations (e.g. bone marrow or scans). The anaesthetic considerations for excision of a nephroblastoma are summarized in Figure 6.

Anaesthesia should be induced with a rapid-sequence induction. Large-bore intravenous cannulae and central lines should be inserted into the upper body because venous drainage from the lower body may be impaired. Considerable haemorrhage and third-space losses may occur and adequate intravenous fluids must be given to maintain normovolaemia and to ensure adequate urine output. Urinary output should be measured hourly via an indwelling catheter. Blood pressure may vary considerably because of major blood loss, inferior vena cava compression and catecholamine release. Blood pressure should be monitored from an arterial line. Central temperature should be measured because there are large intraoperative heat losses. Intravenous fluids should be warmed. Perioperative analgesia may be provided by an epidural if the platelet count and coagulation studies are normal. Alternatively, morphine may be given either as an intravenous infusion or by a non-continuous method.

Anaesthetic considerations for excision of nephroblastoma

The child may:
- be anaemic
- have a coagulopathy
- vomit frequently
- have lung and liver metastases
- be hypertensive
- have impaired cardiac function, haematology and immunology secondary to chemo-therapy

The presence of a large abdominal mass may:
- predispose the child to regurgitate on induction
- compress the inferior vena cava (IVC) pre- or intra-operatively
- compromise ventilation by diaphragmatic splinting

Blood pressure changes may be marked owing to:
- intermittent IVC compression
- large blood loss
- catecholamine release

Ventilation may be compromised by lung metastases

The tumour may embolize in the IVC

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Neuroblastomas arise in sympathetic nervous tissue. The primary tumour is retroperitoneal in 50% of patients and arises from either the adrenal medulla or the sympathetic ganglion. It generally presents as an abdominal mass in children under5 years and has usually metastasized at presentation. Prognosis worsens with increasing age. Treatment is surgical excision with chemotherapy and radiotherapy as required.

Preoperative assessment identifies the symptoms and signs detailed in Figure 7. The anaesthetic management of excision of neuroblastoma is similar to that for nephroblastoma. Children with catecholamine-secreting tumours may become tachycardic and hypertensive when the tumour is handled. Treatment with α and β-blockers may be required perioperatively.

Anaesthetic considerations for excision of neuroblastoma

The child may:
- be anaemic and thrombocytopenic owing to bone marrow infiltration
- have metastases in bone, lymph nodes, bone marrow, the brain and spinal cord, and less commonly, in the liver or skin
- have impaired cardiac function, haematology and immunology secondary to chemotherapy

The tumour may secrete vasoactive peptides and catecholamines (adrenaline and noradrenaline) resulting in:
- sweating, pallor and diarrhoea
- hypertension
- cardiac arrhythmias
- an increased level of vanillyl mandelic acid in the urine

Local invasion and compression by the retroperitoneal mass may:
- predispose the child to regurgitate on induction
- compress the inferior vena cava pre- or intra-operatively
- compromise ventilation by diaphragmatic splinting

Blood pressure changes may be marked owing to:
- intermittent inferior vena caval compression
- large blood loss
- catecholamine release

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Fundoplication
Fundoplication is used for severe, persistent gastro-oesophageal reflux. A hiatus hernia may be associated and cerebral palsy is common. Nissen's fundoplication, in which the lower oesophagus is encircled by the fundus of the stomach, is the usual technique. The effects of severe reflux and indications for fundoplication are given in Figure 8. Usually an open operation through a limited incision is used, though a laparoscopic technique is increasingly used.

An antacid and ranitidine, 2 mg/kg orally, should be prescribed as premedication. Anaesthesia should be induced with a rapid-sequence technique. Suxamethonium is safe for children with cerebral palsy. Anaesthesia is usually maintained with an inhalation agent. A non-depolarizing muscle relaxant is given as indicated. There is evidence that epidural analgesia is associated with less morbidity than an opioid technique. A nasogastric tube is inserted after induction to act as a stent to guide the surgeon. It should be secured carefully so that it can be used postoperatively.

Effects of severe oesophageal reflux and indications for fundoplication

Severe oesophageal reflux may cause:
- malnutrition, producing failure to thrive, particularly in young children
- oesophagitis
- bleeding
- heartburn or chest pain in older children
- pulmonary aspiration particularly in children with total body cerebral palsy who have impaired bulbar control

Reflux commonly occurs in children with chronic disease
- Cerebral palsy

Indications for surgery
- Failure to thrive
- Failure to respond to medical treatment
- Oesophagitis or oesophageal stricture formation
- Anaemia

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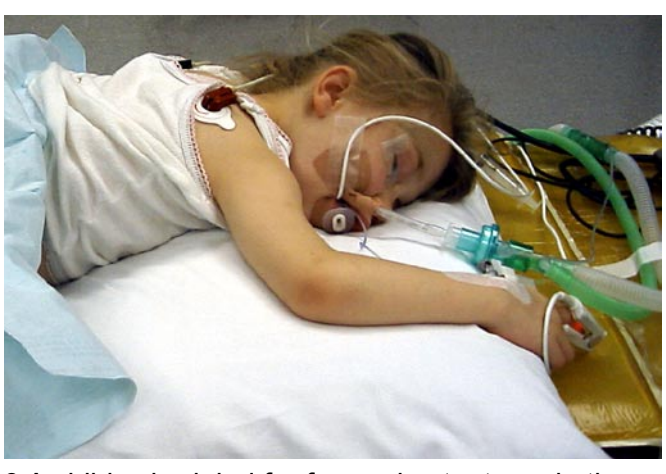
Urinary tract surgery
Children undergo major elective surgery to correct congenital malformations of the urinary tract. Examples are nephrectomy, pyeloplasty, reimplantation of the ureters into the bladder or hypospadias surgery. Most children are generally well and have normal renal function. In addition, many children with spina bifida undergo urological surgery. Compared with other children, they have 500–1000 times the risk of latex allergy and should be treated as being allergic to latex.

Inhalational or intravenous induction may be used. A general anaesthetic combined with a regional analgesic technique, usually an epidural, is common. Anaesthesia is usually uncomplicated but blood loss may be large during nephrectomy. The anaesthetic considerations are those of major surgery: adequate replacement of fluid, body temperature preservation and adequate perioperative analgesia. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided if renal function is impaired.

Orthopaedic surgery

Open reduction of a congenital hip dislocation or femoral osteotomy: children having osteotomies are otherwise healthy with congenital deformity (e.g. a congenital dislocation of the hip or Perthes' disease) or have cerebral palsy or muscular disease and may be scheduled for single or multiple procedures. Open reduction for congenital dislocation of the hip is becoming less common owing to improved neonatal screening and ultrasound, but is indicated if the hip is unstable in a spica or if diagnosis is late. Femoral osteotomy may occur from early childhood to adolescence.

The anaesthetic management for open reduction of a hip or femoral osteotomy is similar. Induction may be intravenous or by inhalation. A large-bore intravenous cannula should be inserted. Although not always required, blood should be cross-matched. Tracheal intubation (facilitated by muscle relaxants) and positive-pressure ventilation is common because the procedure may take several hours. Anaesthesia is usually maintained with a volatile agent in nitrous oxide/oxygen or air/oxygen. During surgery the child is usually supine but sometimes may lie prone (Figure 9).



9 A child scheduled for femoral osteotomy in the prone position.

Care must be taken to replace blood loss, preserve body temperature and provide adequate analgesia. A regional technique such as a continuous lumbar epidural or a fascia iliaca block is preferable. Clonidine, 1–2 μg/kg, may improve the quality of block obtained from local anaesthetics during the first 12 hours and can be used safely in children older than 12 months of age. Analgesia is also improved by giving NSAIDs (e.g. diclofenac, paracetamol). After an open reduction, the surgeon applies a hip spica, for which the child is raised on a box or special frame to allow access around the trunk and buttocks.

Cerebral palsy is a non-progressive brain disorder in young children causing impaired motor function. It has a spectrum of severity from spastic diplegia (where the child, commonly born prematurely, is often intellectually normal and seldom epileptic) to total body cerebral palsy (where the child may be blind, deaf, epileptic, have severe learning and communication difficulties, quadraparesis, pseudobulbar palsy and feeding difficulties). Children with cerebral palsy may have complex multilevel surgery at one operation, such as bilateral femoral and tibial osteotomies, and multiple tendon and soft tissue releases. Children with cerebral palsy benefit from regional analgesic techniques. They often experience postoperative muscle spasm, which is inadequately controlled with epidural infusions alone. A low-dose intravenous midazolam infusion, 25–50 μg/kg/hour, or diazepam, 0.1–0.3 mg/kg 3-hourly p.o. or p.r., effectively reduces tone and relieves spasm.

Correction of talipes equinovarus (club foot): babies with congenital talipes equinovarus usually have surgery before they are weight bearing, often at 5–7 months of age. They are usually otherwise healthy. Operations to revise a correction of talipes equinovarus may be required later.

Induction of anaesthesia may be intravenous or by inhalation. Intravenous access is obtained and tracheal intubation is usual. The child lies supine or prone, depending on surgical preference. Maintenance of anaesthesia is usually by inhalational agents (e.g. isoflurane, 0.75–1% in nitrous oxide/oxygen or air/oxygen) using positive-pressure ventilation facilitated by muscle relaxation. During surgery, the lower leg is exsanguinated with a tourniquet. Blood loss, when the tourniquet is released, is usually easily replaced with appropriate crystalloid or colloid and blood transfusion is seldom required for unilateral surgery. At the end, an above-knee plaster of Paris is usually applied.

Regional analgesia techniques are ideal for operations on the foot. Options include a continuous lumbar epidural, a caudal or blocks of the sciatic nerve (and femoral nerve at the groin or saphenous nerve at the knee, if necessary). In addition, paracetamol and NSAIDs should be given at induction and regularly postoperatively. Care should be taken to observe the foot in plaster carefully after a regional block because the leg may be totally anaesthetized initially.

Minor elective surgery

Eyes

Examination of the eyes may be performed to assess parts of the eye or to measure intraocular pressure. It is usually carried out under general anaesthetic. A light general anaesthetic is required to maintain the intraocular pressure at as normal a level as possible (e.g. gaseous induction and maintenance with sevoflurane in nitrous oxide/oxygen or intravenous induction with propofol, 3–4 mg/kg). The airway can be maintained with a laryngeal mask airway or a face mask. Postoperative analgesia is not required.

Strabismus surgery is usually a day-case procedure. A suitable and effective anaesthetic technique for strabismus surgery is intravenous induction with propofol, 3–4 mg/kg, and glycopyrrolate, 3–5 μg/kg, insertion of a laryngeal mask and maintenance by spontaneous respiration of a volatile agent in nitrous oxide and oxygen. Analgesia is provided by topical anaesthesia and by NSAIDs and paracetamol given at induction. There are several special considerations for anaesthesia for strabismus surgery.

Postoperative vomiting occurs in up to 88% of children. It is the most common complication and the most frequent cause of hospital admission overnight. Anaesthetic techniques used to try to reduce this problem include: a propofol infusion for induction and maintenance of anaesthesia; giving a prophylactic intravenous anti-emetic at induction (e.g. ondansetron, 0.1–0.15 mg/kg, granisetron, 40 μg/kg, metoclopramide, 0.1–0.25 mg/kg, droperidol, 25 μg/kg); or avoiding opioids if possible.

Pain is mainly conjunctival in origin. Topical analgesia using amethocaine, oxybuprocaine or a NSAID (e.g. diclofenac) can be used instead of parenteral opioids. Non-opioid systemic analgesia, provided by a NSAID (e.g. diclofenac, ketorolac) and paracetamol is usually adequate and associated with a lower incidence of postoperative vomiting.

Oculocardiac reflex or 'trigeminal vagal reflex' is caused by traction on the extraocular muscles. It usually produces bradycardia, but occasionally chaotic arrhythmia or sinoatrial arrest with serious complications may result. It is managed by stopping traction and injecting intravenous anticholinergics. This reflex is common and a prophylactic intravenous anticholinergic drug is often injected at induction (e.g. atropine, 10 μg/kg, or glycopyrrolate, 3–5 μg/kg).

Associated diseases – squint surgery may be required in children with generalized muscle disorders associated with malignant hyperthermia. However, the risk of malignant hyperthermia in other children undergoing strabismus surgery is no greater than in the general population.

Otoplasty

The anaesthetic technique aims to reduce postoperative vomiting and provide adequate perioperative analgesia. Anaesthesia for otoplasty is summarized in Figure 10.

Anaesthesia for otoplasty

Otoplasty is associated with:

Postoperative vomiting

- Incidence 50–85%
- May require hospital admission
- Multifactorial
- Increased by:
  - Perioperative opioids
  - Packing the ears after surgery (a similar mechanism to that used by Romans to induce vomiting after large meals: stimulation of the vagal branch to the external auditory meatus and conchal hollow of the ear)

Severe postoperative pain

Suggested anaesthetic techniques

- Local infiltration or regional block only (suitable for the older child)
- Light general anaesthetic with preoperative local infiltration/ regional block
  - Give a prophylactic intravenous anti-emetic at induction
  - Airway maintenance with a laryngeal mask or an endotracheal tube
  - Avoid opioids
  - NSAID and paracetamol suppositories at induction and regular NSAIDs postoperatively

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Scrotum and groin surgery

Elective scrotal and groin surgery includes inguinal herniotomy, orchiopexy, removal of hydrocele, circumcision, or hypospadias repair. Many of these are day-case procedures.

Anaesthesia is induced by intravenous or inhalational agents and maintained by inhalation via a face mask or a laryngeal mask airway. Muscle relaxation is not required. Analgesia is best provided by a regional technique (e.g. a caudal epidural) combined with diclofenac and paracetamol suppositories. Bupivacaine, 0.125%, 0.5 ml/kg, for operations on the penis or scrotum or 1 ml/kg for groin surgery or orchiopexy, provides good analgesia but avoids prolonged motor block and delayed hospital discharge. Adding preservative-free clonidine, 1 μg/kg, or ketamine, 0.5 mg/kg, increases the median duration of caudal analgesia from 4–6 hours to over 8 hours. Caudal ketamine, 0.5 mg/kg, does not produce behavioural side-effects or sedation and is more suitable for day surgery than clonidine, which causes marked sedation postoperatively. Local anaesthetic infiltration or ilio-inguinal nerve block is also satisfactory for analgesia for groin surgery. A penile block may be used for circumcision.

Community dentistry

Every year, deaths and critical incidents occur in dental anaesthesia. They usually occur in young, apparently healthy patients, often children, and are associated with shortfalls in clinical practice. The General Dental Council and the Royal College of Anaesthetists (RCA) have recently issued guidelines to change practice. The RCA expects anaesthesia for dentistry to be of the same standard as for all other procedures. The prerequisites for general anaesthesia for dentistry are summarized in Figure 11.

Standards required for general anaesthesia for dentistry

The anaesthetist

- Is on the Specialist Register (Anaesthetics)
  OR is a trainee working under his/her supervision
  OR is a non-consultant career grade doctor with a NHS appointment working under the responsibility of a named consultant anaesthetist
- Must have had appropriate experience of and training in dental anaesthesia
- Paediatric anaesthetists should anaesthetize very young children
- Dentists can no longer provide general anaesthesia for dental surgery

Anaesthetic assistance

- Skilled assistance is mandatory

Anaesthetic equipment

- All anaesthetic equipment, monitoring and resuscitation equipment must be available as in theatre

Resuscitation training

- All personnel working where general anaesthesia is used for dental surgery must be capable of basic life support
- The anaesthetic team must have expertise in advanced life support and regular updates in resuscitation

The community dental facility

- Centralization is recommended to a dental anaesthetic facility in the district general hospital (with emergency services immediately available and direct access to intensive care beds)

Where this is impossible

- Clear written protocols must be agreed in advance by both parties, on the provision of additional support if resuscitation or transfer become necessary
- The site of the dental department must allow easy access for emergency services

11

The risks of general anaesthesia must be explained to the parents. General anaesthesia should be used only if there are no alternatives (e.g. very young children, those with infected teeth in whom local anaesthetics may not be effective, older children requiring orthodontic extractions, or children with special needs). The responsibility for recommending dental treatment under general anaesthesia rests with the referring dentist, the dentists performing the procedure and the anaesthetist administering the anaesthetic. Routine dental surgery for children is usually an outpatient service. Inpatient general anaesthetics are required for children with specific medical problems or severe learning difficulties.

Paediatric dental anaesthesia is often challenging. The children arrive 'off the street', about 15–20 minutes before anaesthesia, having been starved at home. There is seldom time to apply topical local anaesthetic for venepuncture and premedication is seldom used. These children have often experienced failed attempts to extract teeth under local anaesthetic and may be uncooperative. They are often discharged within 30 minutes of completing the dental procedure.

A health questionnaire, accurately completed at home, speeds up preoperative assessment. It must be confirmed that fasting guidelines have been followed. The anaesthetist should specifically examine for a heart murmur and give prophylactic antibiotics if indicated; see guidelines in Figure 12.

Antibiotic prophylaxis for prevention of bacterial endocarditis during dental surgery

Standard regimen

Indications

All children with structural abnormalities of the heart undergoing procedures causing gingival bleeding

Exceptions not requiring prophylaxis

Uncomplicated secundum atrial septal defects (ASD2)

Repaired ASD2, repaired patent ductus arteriosus, and repaired ventricular septal defect do not require prophylaxis

Children not allergic to penicillin

1 hour preoperatively give amoxicillin, 50 mg/kg orally, and 6 hours later give amoxicillin, 25 mg/kg orally

Children allergic to penicillin

1 hour preoperatively give clindamycin 10 mg/kg orally, and 6 hours later give clindamycin 5 mg/kg orally

Regimen for high-risk patients

Indications

Children with prosthetic valves, systemic–pulmonary shunts or previous endocarditis

Children not allergic to penicillin

At induction give ampicillin, 50 mg/kg i.v. and gentamicin, 3 mg/kg i.v., 6 hours later give amoxicillin, 25 mg/kg orally

Children allergic to penicillin

1 hour before procedure give vancomycin, 20 mg/kg as an intravenous infusion over 1 hour, and gentamicin, 3 mg/kg i.v.

Consent for suppositories, if required, should be obtained from the parent (and the child, if appropriate). The anaesthetic technique usually involves short-acting agents, for example, induction with sevoflurane 1–8% in nitrous oxide and oxygen, or propofol, 3–4 mg/kg, and maintenance with sevoflurane or isoflurane. Halothane may no longer be used in remote sites because of the increased incidence of cardiac arrhythmias. An intravenous cannula should always be inserted for safety. The child usually lies supine on a trolley. Paracetamol, 20 mg/kg orally 1 hour preoperatively, or rectal diclofenac, 1–1.5 mg/kg, and/or paracetamol, 40 mg/kg, at induction provides adequate postoperative analgesia. Local anaesthetic infiltration is beneficial after extracting permanent molars. Monitoring is usually by ECG, pulse oximetry and a capnograph, but a blood pressure monitor should be available.

In dental anaesthesia, the airway is shared between the anaesthetist and the dentist and outcome depends on the skill of both. Anaesthesia is usually maintained with an inhalational agent delivered through a nasal mask, but a laryngeal mask may be preferred during extraction of permanent molars or multiple teeth. The airway is protected from blood and tooth fragments with a dental pack. At the end of the procedure, the dentist places gauze swabs over the tooth sockets for haemostasis and the child recovers in the left lateral position with the head down. The child may be discharged when he or she is awake, able to stand, and bleeding has ceased.

Imaging

Anaesthetizing children in remote locations is challenging. Skilled assistance and familiarity with the anaesthetic equipment and monitoring are vital. Children often require heavy sedation or a general anaesthetic for imaging. Spiral CT scans usually take several minutes. MRI lasts 20–60 minutes and the child must remain still for several 10-minute episodes to avoid image distortion.

Specific considerations for MRI scanning: the magnetic field strength poses hazards to everyone near the scanner. All equipment containing ferromagnetic components is strongly attracted to the magnet and is a potential projectile. Patients with metal implants (e.g. a pacemaker, an aneurysm clip, a ferromagnetic artificial heart valve, a metal prosthesis or plates) cannot undergo MRI scanning. A strong electrical current may be induced in any wire coil placed within the magnetic field and may cause burns. Routine monitors and motorized equipment (i.e. syringe infusion devices) do not function reliably. A non-ferromagnetic anaesthetic machine is required in the scanner room and monitoring equipment must be carefully selected. All monitors applied to the child must be MRI-compatible to avoid burns. Usually the monitors are located outside the scanner room and connected to the patient via extension tubing. Standard hospital trolleys are unsuitable and a special trolley made of non-ferromagnetic materials (e.g. aluminium, stainless steel, brass or other alloys) must be used in the scanner room.

Anaesthetic techniques: several anaesthetic or sedative techniques have been described for MRI or other painless radiological procedures in children. Inhalational anaesthesia via a laryngeal mask is common, though propofol sedation is sometimes used for MRI or CT scanning, with oxygen administered via nasal cannulae or a clear plastic mask. Recovery is rapid, with little postoperative vomiting. Intravenous sedation is particularly useful for MRI because it permits careful titration of sedatives to achieve clinical effect, does not require a non-ferromagnetic anaesthetic machine or scavenging of waste gases and can be given to a child requiring several scans in different sites on the same occasion. The infusion pump is housed outside the scanner room and long lengths of tubing are threaded through a hole in the scanner room wall to be attached to an indwelling intravenous cannula.

Other sedative techniques include oral or rectal midazolam, intramuscular ketamine or barbiturates (e.g. rectal methohexitone). Disadvantages are an unpredictable onset, a variable depth of sedation or anaesthesia and prolonged recovery.

Oncology procedures

Children with malignancy may require sedation or general anaesthesia for haematological investigations (lumbar puncture and bone marrow aspiration and trephine biopsy) or for insertion of a central line. The anaesthetic considerations and suitable techniques are summarized in Figure 13.

Oncology procedures

The child may have:

- anaemia, neutropenia or thrombocytopenia
- lung and liver metastases
- impaired cardiac function, haematology and immunology secondary to chemotherapy

Suitable sedation and anaesthetic techniques:

- ketamine, 0.5–1 mg/kg boluses and oxygen via plastic mask
- intravenous propofol or inhalational induction and inhalational maintenance

Perioperative analgesia may be provided by:

- local anaesthetic infiltration
- paracetamol, 20 mg/kg orally 1 hour preoperatively

Emergency surgery

There are several important considerations when anaesthetizing a child for emergency surgery.

- The child may be unwell, vomiting and dehydrated, and in pain.
- Vital signs, urine output and electrolytes must be assessed carefully to determine fluid and electrolyte requirements. It is essential to correct electrolyte abnormalities and fluid deficits before anaesthesia and to provide adequate analgesia.
- The theatre and anaesthetic equipment should be prepared thoroughly before the child's arrival.
- Before induction, intravenous access with a good working drip must be confirmed and full monitoring applied. The child is considered to have a full stomach and induction with a rapid-sequence technique using suxamethonium must be performed.
- A parent may be present if the anaesthetist agrees and the parent understands the importance of leaving quickly as soon as the child has lost consciousness.
- Anaesthesia is maintained using air/oxygen or nitrous oxide/oxygen with a volatile agent and muscle relaxation is obtained with a short-acting muscl relaxant (e.g. atracurium, vecuronium).•Intraoperative analgesia is usually provided by opioids.• The child must emerge from anaesthesia in the left lateral head-down position with tracheal extubation when awake.

Appendicectomy

Acute appendicitis usually presents in older children. Severity of the illness ranges from mild abdominal symptoms to peritonitis, secondary to perforation. Although these children usually present to the emergency surgical team, avoiding operating during the night does not increase morbidity or mortality. This is consistent with the recommendations of the authors of NCEPOD 1990.

Intravenous opioid analgesia should be provided at diagnosis (either by boluses, continuous infusion or with patient-controlled analgesia). Additional intravenous opioids are given perioperatively as necessary. NSAIDs and local anaesthetic injected into the peritoneum and skin may reduce postoperative opioid requirements. With regular NSAIDs, patient-controlled morphine is often discontinued after 24 hours. Urine output must be adequate postoperatively (i.e. greater than 0.5 ml/kg/hour), particularly if NSAIDs are given.

Some surgeons remove the appendix laparoscopically. To date, this prolongs surgery and intraoperative opioid requirements without significantly improving postoperative analgesia or allowing earlier discharge.

Perforated Meckel's diverticulum

A Meckel's diverticulum is the persistent proximal portion of the vitelline duct. It is usually situated on the anti-mesenteric surface of the ileum about 25 cm from the ileocaecal junction. It contains all layers of intestinal wall and often ectopic gastric mucosa. Ileal peptic ulceration may occur adjacent to the diverticulum producing perforation or haemorrhage. A perforated Meckel's diverticulum is a differential diagnosis of acute appendicitis and the anaesthetic management is similar.

Torsion of the testis

Torsion of a testis is a surgical emergency, usually occurring in older boys. Anaesthesia is induced without waiting for the usual 6-hour starvation period because of the risks of testicular damage and necrosis if surgery is delayed. A rapid-sequence induction is used to protect the airway because gastric emptying may be delayed because of pain. Muscle paralysis is unnecessary for surgery.

A one-shot caudal epidural provides good analgesia in combination with rectal NSAIDs and paracetamol at induction. Alternatives are opioids or local anaesthetic infiltration.

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Principles of Day Surgery for Children

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Day surgery was first used extensively for children by Nicholl in Glasgow as early as 1909. Since the 1970s, there has been a resurgence of interest. Although the main drive for expansion during recent years has been economic, day surgery remains in the best clinical interests of many children. They are particularly suited to day surgery because they are usually healthy with no serious concomitant disease and generally require only minor or intermediate surgical procedures. The advantages of paediatric day surgery are:

- minimal disruption of the family
- reduction in behavioural disturbance
- cost effectiveness
- reduction in hospital-acquired infection.

Almost without exception, children are accompanied by a parent or adult who provides support.

Organizational aspects

In 1991, a report *Just for the Day; Children Admitted to Hospital for Day Treatment*, was published by Thornes on behalf of Caring for Children in the Health Services (CCHS). The authors of the report made recommendations for the improvement and expansion of day services for children, emphasizing the importance of a child-friendly environment and covering all aspects of day care.

Design of the day surgery unit: a day ward should provide separate facilities for the admission and recovery of children; they should not be admitted or treated alongside adults. The design should separate day case patients from in-patients and provide a safe but pleasant environment in which healthy children can play while awaiting treatment. The anaesthetic and recovery rooms should also be child friendly. Facilities for unexpected overnight stay must be available.

Pre-admission education pays dividends. Patients and their parents are invited to attend the ward a few weeks before admission to familiarize themselves with the environment, 'play' with simple equipment (e.g. stethoscopes, face masks), and visit the theatre suite (particularly the recovery room). Short videos can also be shown and comprehensive written and oral information given to parents and children, preparing them for admission and discharge.

All nursing staff working in the paediatric day unit should be trained in the care of children and be specifically and regularly designated to the day ward, theatres and recovery area. The service should be consultant based (though there are excellent teaching opportunities) and both the anaesthetist and surgeon should have appropriate training and a regular commitment to the care of children.

Preoperative assessment and selection

Careful preoperative assessment by questionnaire or telephone some weeks before admission helps to reduce cancellation rates. However, it does not obviate the need for preoperative assessment by both the surgeon and anaesthetist on the day of surgery. Routine preoperative investigations are generally unnecessary.

Selection criteria can be categorized into surgical, patient and social factors. Procedures suitable for day surgery are listed in Figure 1. The list is not comprehensive. Any procedure that is associated with a risk of postoperative bleeding, swelling, pain or vomiting or which requires specialized postoperative care is unsuitable as a day case. Prolonged surgery of more than 1 hour is probably unsuitable though tracheal intubation is not a contraindication. Some units perform adenotonsillectomy on a day case basis.

Procedures suitable for day surgery

General surgery
Inguinal or femoral herniotomy, ligation of patent processus vaginalis (excision of hydrocele), circumcision, orchidopexy, epigastric or umbilical hernia, division of tongue tie, excision of skin lesions, examination under anaesthesia (EUA), anal dilatation, endoscopy, muscle biopsies

Urology
Cystourethroscopy, meatotomy, urethral dilatation, change of urinary catheter, minor hypospadias repair

ENT/dental
Myringotomy and grommets, foreign body removal (aural or nasal), EUA, nasal cautery, antral lavage, pack removal, (possibly) adenotonsillectomy, conservation or extraction of teeth

Orthopaedics
Removal of metal work, change of plaster cast, arthroscopy

Plastic surgery
Removal of minor skin lesions, suture removal, dressing changes, removal of scars, otoplasty

Oncology
Bone marrow biopsy, lumbar puncture, intrathecal injections, radiotherapy

Ophthalmology
EUA, strabismus correction, lacrimal duct probing

Radiology/investigations
CT, MRI

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Patient factors

Most children are healthy (ASA I or II) and well suited for day surgery. Occasionally, ASA III patients are also admitted to the day ward, for example those with cystic fibrosis or immunodeficiency following chemotherapy, who may benefit from avoiding contact with in-patients. Frequent attenders with stable concomitant diseases who have behavioural problems or learning difficulties may also benefit from treatment in a day unit.

Age – the lower age limit depends on postconceptional age, the experience of the anaesthetist, the facilities of the day unit and certain social factors. Outside specialized centres, the lower age limit may be as high as 6 or even 12 months. In larger units with the appropriate facilities, healthy full-term neonates may be treated as day cases. All preterm or ex-preterm babies of up to 60 weeks' postconceptional age are generally considered unsuitable because they are vulnerable to postoperative apnoeic spells. They require overnight admission and close respiratory monitoring.

Family history of sudden infant death syndrome (SIDS) or near-SIDS – although there is no association with postoperative apnoea, siblings of babies who have been the victim of SIDS or near-SIDS should probably not be treated as day cases.

Upper respiratory tract infections (URTI) – many small children have a 'runny nose' for much of the time and cancellation of a minor procedure is unnecessary if the child is otherwise well. If there are more florid symptoms (e.g. fever, general malaise or irritability, or an unpleasant nasal discharge) the procedure should be cancelled. Such patients are at greater risk of perioperative respiratory complications, particularly if less than 1 year of age or if the trachea is intubated. Surgery should also be delayed for patients with lower respiratory signs on auscultation (e.g. bronchospasm, persistent 'crackles'). Postponement for 4–6 weeks is usually recommended.

A previously undetected heart murmur is a common dilemma. A flow murmur must be distinguished from a pathological murmur, which may require specialized assessment. However, children with stable uncomplicated congenital heart disease can often be managed as day patients, provided they are given endocarditis prophylaxis (if indicated).

Miscellaneous conditions – children with mild well-controlled asthma or epilepsy can be admitted for day surgery. Those with diabetes or metabolic disorders are unsuitable because of the problems associated with pre-operative fasting.

Social factors

Parents should be capable of coping with the pre-procedure instructions and with the post-discharge care of their child and be willing to do so. Home facilities should be adequate. In some units, a travelling time of less than 1 hour is a requirement for day case surgery and should be by private car or hospital transport. Community paediatric nurses can provide invaluable support.

Preoperative preparation

Fasting guidelines: clear written instructions about the period of preoperative fasting should be issued and the importance of compliance stressed. Solids, cows' milk or formula feeds are usually permitted until 6 hours before surgery, breast milk until 4 hours and clear fluids until 2 hours beforehand. It is often more practical to issue simple instructions to parents in relation to the time of admission rather than the time of operation.

Psychological preparation: pre-admission educational programmes reduce the stress of admission for parents and children. On the day ward, plenty of space and toys and a relaxed atmosphere are essential. Avoiding separating the child from the parent is also important.

Premedication*:* it is unusual for sedative premedication to be necessary in children undergoing day surgery, particularly if a parent is present at the induction of anaesthesia, as is now widely accepted. Separation anxiety is not usually a problem until about 8–9 months of age, therefore parental presence at induction is usually not necessary or desirable before this age. Oral midazolam, 0.5 mg/kg (maximum 10–15 mg), is occasionally indicated for the particularly anxious child and has the advantage of rapid onset with minimal delay in recovery. It is bitter and should be flavoured with undiluted blackcurrant juice or paracetamol elixir. Midazolam may also be given by the intranasal route, though this can be unpleasant. Anticholinergic premedication is seldom used. Topical local anaesthetic creams such as *Emla* or *Ametop* are routinely used to enable virtually painless cannulation. Concerns that they make cannulation more difficult are largely unfounded.

Anaesthesia

Induction

Induction is via the intravenous or inhalational route. Having a parent present is often helpful, though anxious parents may transmit their anxiety to the child. It is often preferable to allow the child to sit on the parent's lap during induction.

Intravenous induction: the use of *Emla* or *Ametop* cream has made intravenous induction the most common mode of induction and there are advantages to having intravenous access from the start of anaesthesia, provided this is not at the expense of distressing the child. Anaesthesia can be induced intravenously with thiopental (thiopentone) or propofol. In unpremedicated children, thiopental (thiopentone), 5–6 mg/kg, is required and, compared with propofol, may be associated with delayed recovery (though probably not in children less than 5 years of age). An advantage of thiopental (thiopentone) is that the onset of sleep is clear, which is reassuring to the accompanying parent about to leave the anaesthetic room. Propofol induction may be associated with involuntary movements that may be alarming to the parent. Such movements are usually overcome by additional doses of propofol. The dose requirement for propofol is higher in unpremedicated children (3–4 mg/kg) than in adults. Propofol obtunds airway reflexes facilitating the insertion of an oropharyngeal airway or laryngeal mask airway (LMA), though it is also associated with respiratory depression, breath holding, and hiccups. Pain on injection is the main drawback but can be minimized by adding lidocaine (lignocaine), 0.2 mg/kg. In the UK, the rectal route for induction is uncommon.

Inhalational induction is useful for the child with a needle phobia or in whom intravenous access is difficult. Using a transparent face mask impregnated with food flavouring or the 'cupped hand' is more acceptable than the old-style opaque masks. Halothane has been used for many years, though its use may have been superseded by sevoflurane which, although expensive, has a pleasant smell, is non-irritant and has a rapid onset. The inspired concentration can be increased rapidly, though marked respiratory depression and breath holding occur unless the concentration is reduced immediately after induction. Isoflurane is pungent, more irritant to the airway and requires considerable skill to effect a smooth induction.

Maintenance of anaesthesia

Most day case procedures do not require intubation of the trachea or muscle relaxation. Spontaneous ventilation with oxygen, nitrous oxide and a volatile agent via a face mask or LMA is common. An LMA provides a patent airway, freeing the anaesthetist to carry out local anaesthetic blocks, but does not prevent soiling of the airway. When surgery is completed there seem to be fewer transient airway complications if the LMA is removed while the patient is deeply anaesthetized. Any accumulated secretions are removed if the LMA is removed gently with the cuff inflated.

Tracheal intubation is occasionally required and is not a contraindication to day case surgery. Although suxamethonium pains are less common in young children than in adults its use should be kept to a minimum in ambulant children (it may be necessary if laryngospasm occurs). Alternatively, tracheal intubation can be facilitated by deep halothane or sevoflurane anaesthesia.

Modern guidelines for preoperative starvation and the early resumption of oral intake postoperatively make the routine use of intravenous fluids unnecessary. Significant fluid loss is not a feature of day case surgery. An intravenous infusion of a balanced salt solution may sometimes be indicated if starvation has been prolonged, if there is a history of postoperative nausea or vomiting or if the procedure is associated with a higher incidence of postoperative vomiting (e.g. orchidopexy, strabismus surgery).

Analgesic techniques

Analgesia is best provided by an appropriate regional or nerve block combined with simple analgesics. Opioids should be avoided, if possible, because they delay recovery and markedly increase postoperative vomiting.

Simple analgesics

Early administration of simple analgesics is preferable, either in the form of oral premedication or per rectum after induction. It is good practice to obtain consent from a parent (and/or, if appropriate, the child) for the rectal administration of any drug.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used because of their lack of serious adverse effects. The lower limits for NSAIDs are 1 year of age for diclofenac, 1–3 mg/kg/day in divided doses, either orally or rectally, and 7 kg in weight for ibuprofen, 20–30 mg/kg/day in divided doses orally. NSAIDs may be given to patients with mild well-controlled asthma but should be avoided in those with severe asthma or renal impairment.

Paracetamol is a valuable adjunct and can be given to children initially as an oral loading dose of 30 mg/kg then 15 mg/kg 4 or 6 hourly (maximum total daily dose of 90 mg/kg) for a limited period. Alternatively, a rectal loading dose of 30 mg/kg followed by 20 mg/kg 4–6 hourly per rectum (again, not exceeding a daily dose of 90 mg/kg) may be given, though absorption is more erratic. Doses for neonates are reduced with a maximum daily dose of 60 mg/kg.

Local anaesthetic techniques

Many procedures performed on a day surgical unit are suitable for supplementary local anaesthetic blocks, which are virtually always undertaken after induction of anaesthesia. Contra-indications include:

- refusal of consent
- infection at the injection site
- allergy to local anaesthetic agent
- coagulopathy.

Anatomical abnormalities or pre-existing neurological abnormalities are relative contraindications. Blocks commonly used are listed in Figure 2.

Commonly performed local anaesthetic techniques

- Local infiltration
- Caudal extradural block
- Ilioinguinal-iliohypogastric block
- Penile block
- Periumbilical or rectus sheath block
- Fascia iliaca block
- Greater auricular block

2

Caudal blockade is commonly used for surgery below the umbilicus. The procedure is safe and simple. Full aseptic precautions should be taken. The type of needle used depends on operator preference. The use of a 22G intravenous plastic cannula allows removal of the needle immediately after puncture of the sacrococcygeal membrane. Advancing the plastic cannula only may reduce the chances of intravascular or intrathecal puncture. It may also permit a more cephalad delivery of local anaesthetic, which is useful if higher levels of blockade are needed. 0.25% bupivacaine is commonly used up to a maximum of 2–2.5 mg/kg and the duration of action is about 4–6 hours. Levobupivacaine and ropivacaine have a reduced potential for systemic toxicity but experience with these agents in children is limited. The duration of effect of local anaesthetic solutions following single-shot caudal blockade is not significantly increased by the addition of adrenaline (epinephrine) and the use of other additives (opioids, ketamine or clonidine) is best confined to in-patients.

Practical guidelines relating the spread of analgesia to the dose of local anaesthetic injected, originally described by Armitage, are still in widespread use. He recommended 0.25% bupivacaine, 0.5 ml/kg, for a lumbosacral block (e.g. circumcision or hypospadias operations), 1.0 ml/kg for thoracolumbar blockade (e.g. inguinal herniotomy), and 1.25 ml/kg for a mid-thoracic block (e.g. orchidopexy). If the calculated volume exceeds 20 ml, Armitage recommended diluting the bupivacaine to 0.19% (3:1). However, spread to the inguinal and thoracic dermatomes becomes inconsistent in patients who weigh more than 20 kg and, for an orchidopexy, the combination of ilioinguinal/iliohypogastric block and NSAIDs may be more effective. Dalens found the caudal injection of 0.75–1.0 ml/kg to be appropriate for a variety of operations and more recently 0.25% bupivacaine, 0.75 ml/kg, for herniotomy or orchidopexy was found to produce 4 hours of postoperative analgesia in almost 70% of patients. Venous and dural puncture are rare complications of caudal blockade. Motor blockade, as manifested by leg weakness, may occur and can be distressing to the patient. Urinary retention is almost unknown in children who are well hydrated.

Complications of day surgery

The incidence of postoperative complications is low and hospital admission rates are generally quoted as 1–2%. The more common complications include:

- nausea and vomiting
- pain
- unsteadiness of gait
- delayed micturition
- unexpected bleeding necessitating a return to theatre.

Nausea and vomiting

The incidence of postoperative nausea and vomiting (PONV) varies according to age, previous history of PONV or motion sickness, the type of surgical procedure and the anaesthetic technique. Children have a higher incidence than adults, but it is lowest during childhood in infants or pre-school children. Adenotonsillectomy, strabismus surgery, otoplasty and orchidopexy are associated with a high incidence. Opioids significantly increase the probability of vomiting, and nitrous oxide may be a contributory factor. The use of total intravenous anaesthesia in certain circumstances, such as strabismus surgery, may be beneficial. Avoiding prolonged preoperative fasting and maintaining good perioperative hydration may help to reduce the incidence of PONV. Encouraging oral fluids early postoperatively may be counterproductive. Early mobilization should also be avoided. The routine use of anti-emetics in children is uncommon because of sedation or extrapyramidal effects. The introduction of 5-HT_3 antagonists (e.g. ondansetron, granisetron) has reduced the incidence of PONV. They have few adverse effects and offer significant advantages over other anti-emetic agents. They should be used prophylactically in situations associated with a high risk of PONV. Dexamethasone reduces postoperative vomiting following tonsillectomy either alone or in combination with other anti-emetic agents. The mechanism of action is unknown.

Discharge and follow-up

Guidelines for the discharge of patients to home should be in place (Figure 3). It is desirable but not essential for patients to drink before discharge. Some units require children to have passed urine, though retention of urine is uncommon. After certain types of surgery (e.g. hypospadias repair) there may be surgical reasons for insisting that the patient has voided before discharge. Community paediatric nurses or health visitors should carry out home visits. Some units telephone the parent the day after surgery to check satisfactory progress and answer questions. This also provides a good opportunity for audit. ◆

Criteria for discharge from hospital

- Vital signs and conscious level normal
- No respiratory distress/croup/stridor[1]
- No bleeding or other surgical complications
- Minimal or no pain
- Minimal or no nausea or vomiting
- Minimal or no unsteadiness of gait
- Written/verbal instructions issued
- Lines of contact established
- Appropriate transport arranged

[1] If tracheal intubation is performed it is generally recommended that patients should be kept a minimum of 2 hours following extubation before discharge from hospital.

3

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Managing Trauma

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The priorities for the initial assessment and intervention in trauma are the same for adults and children.

The primary phase involves a rapid physiological assessment to identify immediate threats to life in a structured order: airway, breathing, circulation and disability. Plain radiographs of the chest and pelvis and an ultrasound scan of the abdomen should be instantly available as adjuncts to the clinical examination. At this stage the focus is on physiological control.

The secondary phase – the focus shifts to the control of damaged anatomical structures. A more detailed clinical examination (head to toe, front and back, including the orifices, cavities and skeleton), complemented by imaging and other investigations, should be carried out. Pain relief should be given as soon as possible after completing the primary assessment.

Primary assessment and intervention

Airway (with cervical spine control)

In serious blunt trauma, the spine should be maintained in a neutral position from the outset. Applying a hard collar, blocks and straps safely in a bewildered young child requires gentle coaxing, reassurance and subtle distraction. Force should not be used to immobilize an agitated child, because the neck may inadvertently act as a fulcrum in the struggle, increasing the risk of further damage. In small children lying on a flat surface, the relatively large head tends to leave the neck in flexion. Neutral neck positioning may be achieved by placing a folded towel beneath the shoulders.

The child's airway is smaller and floppier than an adult's. Care should be taken not to cause obstruction by compressing the floor of the mouth with inaccurate hand positioning under the chin. It is conventional to insert an oropharyngeal airway without rotation. The size of the airway may be estimated by placing its concavity over the child's face and measuring from the centre of the teeth to the angle of the mandible (or, equivalently, from the angle of the mouth to the external auditory meatus). The diameter of a nasopharyngeal airway is the same as a tracheal tube (internal diameter age/4 + 4 in mm), and is about the same size as the child's little finger. The nasal route is contraindicated in basal skull fracture.

The subglottic segment is the narrowest part of the upper airway and is vulnerable to critical narrowing from mucosal oedema or scarring. A cuffed tracheal tube and surgical cricothyroidotomy are contraindicated before puberty.

If a child whose spine has not been cleared starts to vomit, it is tempting to turn them on to their side. This is feasible in an infant but impossible in a larger child unless he is still on the spinal board with the body straps done up tightly. Even then, several attendants are needed instantly. It is far easier (and safer) to tip the trolley head-down temporarily, while the airway is sucked out.

Orotracheal intubation with manual in-line mobilization following rapid sequence induction should be used to secure the airway in blunt trauma with an uncleared spine. The collar and blocks should be removed before intubation and replaced afterwards. Intubation is indicated immediately in head-injured children with a GCS less than 9. If the GCS is 9–12 it may still be necessary, to protect against deterioration or to facilitate investigations, particularly if the child is restless. In extreme situations (e.g. a very low GCS or severe shock) it may be necessary to intubate with minimal analgesia or sedation (e.g. fentanyl, 0.25–0.5 μg/kg, and/or midazolam, 20–40 μg/kg) or even without drugs. The circulatory state and the conscious level must be taken into account when choosing the induction agents and their dose.

Thiopental (thiopentone) in a reduced dose (e.g. 1–2 mg/kg) is suitable for induction in those with a low GCS or circulatory shock. Etomidate is not licensed for use in those less than 10 years. Ketamine, 1–2 mg/kg, is safe for all ages. Its use in head injury has often been dismissed unfairly, but it is popular in circulatory compromise without head injury.

Suxamethonium is widely used in children. It is not contra-indicated at initial presentation in burns or spinal cord injury, but can produce severe hyperkalaemia and cardiac arrest after the first day. It is contraindicated at the outset in major crush injury because of the risk of massive potassium release from damaged muscle. Rocuronium, 1–1.2 mg/kg, is an alternative but the consequences of prolonged paralysis in the event of failure to intubate must be considered.

If the airway is damaged or distorted (e.g. in airway burns), there is a risk of losing the airway and alternatives (e.g. gas induction) should be considered.

Cricothyroidotomy is indicated for failed tracheal intubation. The surgical method is contraindicated in children below 12 years. Following needle cricothyroidotomy a Y-piece breathing system may be used to supply oxygen for 1 second followed by expiration for 4 seconds (or less in a small child). To reduce the risk of barotrauma, the initial inspiratory flow should be set at the child's age in litres/minute and increased according to chest movement. Expiration occurs through the upper airway, not through the cannula: the peak inspiratory pressure in the chest is insufficient to push gas back through the cannula.

Breathing

Children have greater oxygen consumption and a smaller residual volume, predisposing to earlier hypoxia. They have less developed musculature so that accessory muscle use is less obvious, but sternal and intercostal recession is more noticeable. They are also prone to apnoea after head injury. Tables of normal ranges for resting respiratory rate with age (Figure 1) are useful in assessing respiratory distress.

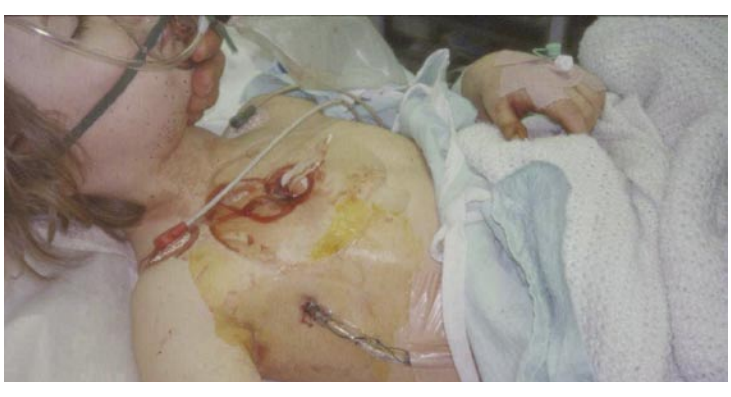
Tension pneumothorax must be identified clinically and treated by needle decompression using a 14–18G cannula in the second intercostal space in the mid-clavicular line. The size of the subsequent drain may be found in tables (Figure 1); estimated by the diameter of the child's little finger; or the largest size that will just fit between the ribs can be used. If the child is obese the 'mating forceps' technique is useful to guide the drain into the pleural cavity; an artery clip is inserted through the incision and held open while the other, grasping the tip of the tube, is rotated into position between the open jaws.

Variation of respiratory rate, chest drain size, pulse rate and blood pressure with age

Age	Respiratory rate (breaths/minute)	Chest drain size (French gauge)	Pulse rate (beats/minute)	Systolic blood pressure (mm Hg)
< 1 year	30–40	12–16	110–160	70–90
1–4 years	25–35	16–20	95–150	80–100
5–11 years	20–25	20–24	80–120	90–110
≥ 12 years	15–20	24–32	60–100	100–120

1

An open pneumothorax (or 'sucking chest wound') allows air to be sucked in through the chest wall defect at the expense of inspiratory flow through the trachea. Temporary treatment with an Ashermann chest seal (Figure 2) is generally more effective than an occlusive dressing, taped on three sides. The base encloses the defect, while the pipe acts as a one-way valve. Massive haemothorax is distinguished from tension pneumothorax by the dull percussion note. Venous access should be secured before inserting a chest drain.



2 Ashermann chest seal.

Circulation

Children compensate well after major haemorrhage, but can deteriorate suddenly. Tachycardia is a valuable sign, though it may also reflect pain and fear. In small children, intravenous access is often easier in the hands and feet than in the antecubital fossae. If not achieved within 1 minute in a severely injured child less than 7 years of age, intraosseous access is appropriate.

It is vital to warm infusion fluids. Boluses are given according to conventional guidelines: 2 x 20 ml/kg of saline-based crystalloid or colloid, then blood 20 ml/kg. Weight is obtained from the parents or estimated from the body length (e.g. Broselow tape) or age (weight in kg = 2 x (age + 4) up to age 11 years). Fluid loading may be harmful in the face of uncontrolled haemorrhage particularly after penetrating trauma. It can exacerbate bleeding and contribute to coagulopathy and hypothermia. Fluid restriction (or permissive hypotension) may then be appropriate, providing it is combined with immediate surgical intervention to control the bleeding. Fluid loading with normal saline can also cause hyperchloraemic acidosis with an abnormal base excess. This can lead to the erroneous diagnosis of inadequate tissue perfusion requiring more fluid, leading to fluid overload. Lactate is a more appropriate end-point than base excess in this situation.

Sources of haemorrhage should be sought externally and internally. In an infant, scalp bleeding or an intracranial haematoma may cause shock. Major bleeding from an unstable open-book pelvic fracture may be significantly reduced by a pelvic sling. A sling can be made from sheets twisted round at the level of the greater trochanters with the legs internally rotated. If no bleeding source can be identified or if the shock does not respond as expected look for alternative causes (e.g. cardiac tamponade, spinal cord injury, overwhelming head injury). Distended neck veins, warm peripheries, bradycardia, priapism or fixed dilated pupils may provide clues.

Disability

The primary assessment comprises the GCS, which is modified in children under 4 years (Figure 3), and examination of the pupils. To minimize the risk of secondary insult in a decompensating, head-injured child, the PaO_2 should be above 12 kPa, the $PaCO_2$ at 4–4.5 kPa and the mean blood pressure normal. Provided that uncontrolled bleeding has been excluded or treated, fluids may be used liberally and inotropes introduced early to maintain the blood pressure. Mannitol, 0.3–0.5 g/kg, should be considered if the conscious level deteriorates, especially if there are focal signs. Hypoglycaemia is a cause of obtundation or fitting, particularly in adolescents after alcohol binging and in infants.

Modified Glasgow Coma Scale in children

Best eye opening

4 Spontaneously
3 To voice
2 To pain
1 None

Best motor response

6 Obeys commands (spontaneous movements aged < 4)
5 Localizes
4 Withdraws
3 Flexes abnormally (decorticate)
2 Extends (decerebrate)
1 None

Best verbal response

	Age ≥ 4	*Age < 4*
5	Orientated	Alert, babbles, coos, words to usual ability
4	Confused	Less than usual words, spontaneous irritable cry
3	Inappropriate	Cries only to pain
2	Incomprehensible	Moans to pain
1	None	No response to pain

3

It is important to minimize the time to surgical decompression of an intracranial haematoma. This requires prompt assessment by CT scan and timely referral to a neurosurgeon.

Secondary assessment and intervention

Exposure

During the secondary assessment, it is vital to examine the whole body surface. Children cool rapidly when exposed. Any benefit from hypothermia in preserving brain function is offset by platelet dysfunction, cardiac arrhythmias, myocardial depression and impaired resistance to infection. An overhead radiant heater should be available for infants and a convective air heater for older children.

Analgesia

For the child in pain, intravenous increments of an opioid are appropriate as soon as possible after the primary assessment. It is now accepted that carefully titrated opioids enhance the clinical evaluation of injuries. Morphine, 25–50 μg/kg, in increments of up to 0.15–0.2 mg/kg is the standard. Fentanyl, 0.5 μg/kg, repeated as necessary, has a faster onset, causes little histamine release or haemodynamic instability, is easy to titrate and, in larger children, can be given without diluting the 50 μg/ml neat solution. In the presence of hypovolaemia or drowsiness, it is wise to halve the incremental dose of these drugs.

Head and neck

Children have large heads and almost adult-sized brains by the age of 3 years. They shed their primary teeth between 7 and 12 years and have a disproportionately small face until after puberty. Up to the age of 9–18 months, the fontanelle is present, allowing a crude evaluation of intracranial hypertension. The elasticity of the skull and the ability of the sutures to widen offer little protection against acute rises in intracranial pressure. Children with diffuse brain injury are more prone to cerebral oedema, punctate haemorrhage and intracranial hypertension than adults.

The scalp, face and neck must be carefully inspected and palpated with the collar removed. The orifices should be examined for signs of basal skull fracture. Evidence of retinal and conjunctival haemorrhage is important if there is any suspicion of non-accidental injury. The GCS should be re-checked and a more detailed neurological examination carried out. If the GCS is less than 9, a CT scan should be obtained immediately the child has been intubated, ventilated and stabilized. If the GCS is 9–13, or there are focal signs, fitting or persistent vomiting, an emergency CT scan is indicated. If the GCS is 14, a CT scan may be deferred overnight and the child carefully observed.

Chest

The elasticity of children's ribs reduces the risk of rib fracture, but allows the transfer of energy to internal structures and pulmonary contusion without rib fracture is common. If there are multiple rib fractures with a flail segment, such is the force involved that mechanical ventilation is usually needed. Simple pulmonary contusions tend to resolve within 72 hours and can usually be managed without intubation though continuous positive airway pressure may be needed.

The chest is re-examined in more detail and the chest radiograph studied. In young children, the thymus may be confused with the mediastinal widening of aortic disruption. A pneumo-thorax identified after trauma should be treated with a chest drain. A drain that bubbles persistently suggests tracheobronchial or oesophageal disruption. If the nature and extent of the thoracic injuries are uncertain, a contrast CT scan should be considered, especially if the mediastinal contour is abnormal.

Abdomen

The child's under-developed thoracic cage and anterior abdominal wall musculature offer less protection to upper abdominal organs. Distressed children are prone to air swallowing and acute gastric dilatation is common in multiple injuries or severe burns. Inserting a gastric tube makes examination more reliable, reduces the risk of aspiration and improves comfort. The urine must be inspected for macroscopic haematuria. Urine collection bags are appropriate in babies. Catheterization of small boys should not be undertaken lightly because of the significant risk of urethral stenosis.

Clinical examination of the abdomen is unreliable. Ultrasonography allows rapid identification of free intraperitoneal fluid and may be repeated without the accumulated radiation risk of CT scanning. A contrast CT scan is more discerning but is contraindicated if the child is haemodynamically unstable.

In blunt injuries to the liver, spleen, kidney or the mesentery, bleeding is often self-limited; free intraperitoneal fluid is no longer an automatic indication for laparotomy. However, conservative management is only appropriate if haemodynamic stability can be achieved and the child observed in an HDU with a capable paediatric surgeon and anaesthetist immediately available. Careful haemodynamic monitoring, frequent clinical examination, repeated blood sampling and further ultrasound scans are essential if the child is treated conservatively. Perforation of the hollow organs (bladder or bowel) indicates laparotomy.

Spine

The cartilaginous vertebral bodies, elastic ligaments and horizontal facet joints contribute to the increased spinal mobility in children compared with adults. This tends to protect the spinal cord from injury by dispersing energy over several segments, but when cord injury does occur, it is more likely to be complete. Spinal cord injury without radiological abnormality is well recognized in children, implying severe ligamentous disruption without demonstrable fracture. The value of steroids in cord injury in children remains uncertain. Cervical spinal injuries tend to occur at a higher level than in adults and often affect adjacent vertebrae. Subluxations and dislocations are more common.

In major blunt trauma, spinal precautions must be taken from the outset (i.e. immobilization on a firm surface and the use of collar, blocks and straps). A spinal board is intended for transfer to hospital and should be removed soon after arrival to avoid pressure injuries.

Clinical examination is similar to adults. If the child is alert and orientated with no spinal symptoms or signs and no distracting pain, the spine may be cleared clinically without imaging. Otherwise, three plain views are required for radiological assessment: the lateral, AP and odontoid peg views (the latter can be omitted in a severe head injury and CT of the occiput to C3 obtained instead). Even if the plain films and/or CT are normal, the spine still cannot be cleared in the persistently obtunded child.

Limbs

Children's bones are more flexible than adults', producing different fracture patterns (e.g. greenstick fractures). Most fractures can be managed without surgery and some deformities accepted without manipulation. Fractures involving the growth plate are of particular concern and accurate repositioning is essential for future growth. Supracondylar humeral fractures and fractures around the knee may damage the brachial and popliteal arteries, respectively, requiring meticulous monitoring of distal pulses and perfusion.

Particular patterns of injury, such as fractured shaft of femur in a child aged less than 3 years, bruising in a finger mark pattern, bite marks or cigarette burns, suggest non-accidental injury. Other supporting evidence includes delay in seeking help, discrepancy between different versions of the history or between the professed mechanism of injury and the resulting injuries, injuries of different ages, abnormal demeanour in the child ('frozen watchfulness'), retinal haemorrhage and injury to the frenulum of the lip or genitalia. Paediatric referral is essential in suspicious circumstances.

In older children, femoral shaft fractures can be immobilized with a Thomas splint. Femoral nerve block provides excellent analgesia, facilitating splint application but a nerve stimulator is inappropriate because of pain caused by muscle twitches.

Initial analgesia for limb injuries can be achieved with intravenous opioids. Long-acting nerve blocks are occasionally useful (as above), but some fractures (e.g. closed tibial fractures) are associated with a higher risk of compartment syndrome, which may be masked by neural blockade. A nitrous oxide/oxygen mixture may be used for immediate pain relief (contraindicated in pneumothorax or significant head, eye or abdominal injuries). Ketamine in subanaesthetic doses (0.2 mg/kg repeated if necessary) given with low-dose midazolam to reduce dysphoria allows simple manipulation, suturing and dressing changes. Ketamine can be given with fentanyl (although synergism should be anticipated), which is useful at the accident scene when extricating from entrapment.

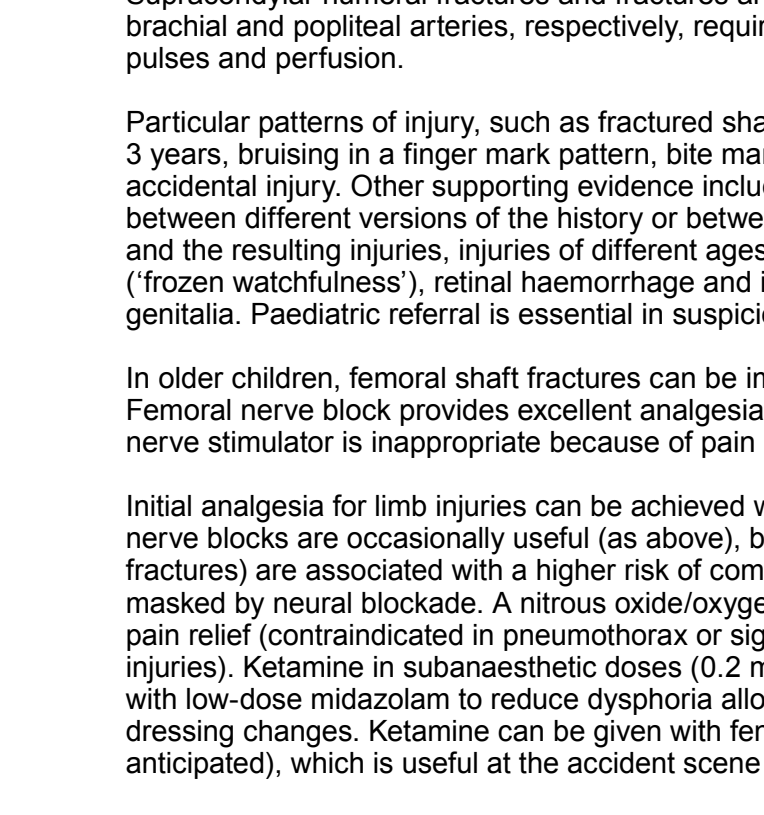
Burns

Children's skin is thinner than adult skin, making them prone to deeper burns. Their higher surface area to body weight ratio makes them susceptible to heat and fluid loss. Particular patterns, compatible with cigarette burns or immersion in very hot water, should raise the possibility of non-accidental injury.

In burns to the head and face, an associated airway burn may be suggested by the history or by peri-oral burns, carbonaceous sputum and hoarseness. Airway oedema is typically maximal at 36 hours, but can cause airway obstruction with little warning. Laryngospasm can occur immediately. If an airway burn is suspected, early intubation by an experienced paediatric anaesthetist should be planned.

Assessing burns – the depth of a burn should be assessed visually. Pin-prick testing of sensation is inappropriate in children. In general, the blistering, weeping appearance and obvious pain of a partial thickness burn distinguishes it from a leathery, charred, non-blanching full-thickness burn. However, some deep dermal burns can be difficult to identify initially. Electrical burns often involve neurovascular bundles and may cause myoglobinuria and cardiac arrhythmias. The 'rule of nines' does not apply to children. Lund and Browder charts (Figure 4) allow more accurate mapping at different ages. The palm of the child's hand also approximates to 1% of the body surface area.

Lund and Browder Charts



Ignore simple erythema

Superficial Deep

Region	%
Head	
Neck	
Anterior trunk	
Posterior trunk	
Right arm	
Left arm	
Buttocks	
Genitalia	
Right leg	
Left leg	
Total burn	

Relative percentage of body surface area affected by growth

Area	Age 0	1	5	10	15	Adult
A = ½ of head	9½	8½	6½	5½	4½	3½
B = ½ of one thigh	2¾	3¼	4	4½	4½	4¾
C = ½ of one leg	2½	2½	2¾	3	3¼	3½

4

Fluid management – fluid loss is crudely predictable after major burns. A widely accepted guideline for the first day's crystalloid requirements is 4 ml/kg/% burn, giving half of this in the first 8 hours and the remainder in the next 16 hours. Alternative colloid-based guidelines recommend 2–4 ml/kg/% burn in the first day. Maintenance fluids are also given. These formulae are only rough estimates and the fluids should be adjusted depending on haemodynamic state and urine output. In the presence of myoglobinuria, after an electrical burn, the fluids should be further increased to promote a diuresis. It is also important to remember that physical injuries (e.g. from an associated explosion or fall), with extra blood and third-space losses, may accompany burns.

Further stabilization

In small children who are mechanically ventilated, a positive end-expiratory pressure of 3–5 cm H_2O is acceptable, even with a severe head injury. Invasive arterial blood pressure monitoring should be established in severe head injury before transfer to the CT scanner, allowing beat-to-beat blood pressure measurements and repeated PaO_2 and $PaCO_2$ estimations. Initially, the blood pressure should be kept (or left) at or above normal. Once intra-cranial pressure monitoring is established, it should be adjusted to maintain a cerebral perfusion pressure of 65–70 mm Hg.

In severe multi-system trauma, the haemoglobin or haematocrit should be monitored hourly initially and clotting checked every few hours. As haemodynamic stability is achieved maintenance fluids should be added according to standard recommendations. If extra third-space losses are predicted, additional fluids are required. A urine output of 2 ml/kg/hour is adequate in infants, 1 ml/kg/hour in older children and 0.5 ml/kg/hour in adolescents.

Two-thirds fluid restriction was conventional after serious head injury. With the current emphasis on maintaining an adequate blood pressure, this is no longer recommended. Inadequate tissue perfusion, indicated by a lactate concentration over 2 mmol/litre, must be avoided which may require extra fluid with careful monitoring. It is also important to avoid inadvertent fluid overload with severe head or chest injuries by accounting for the volumes of all infusions and drugs in fluid balance measurements.

Diabetes insipidus is a particular problem after severe head injury (though seldom evident in the first few hours) which must be distinguished from the diuresis following liberal fluid resuscitation. In diabetes insipidus, urine output may exceed 30 ml/kg/hour, causing severe hypernatraemia and dehydration. The diagnosis should be confirmed by plasma and urine osmolality measurements and treated promptly with desmopressin (DDAVP). Replacing losses with hypotonic or glucose-based fluids (to correct the sodium) may cause cerebral oedema.

Sedation after intubation and ventilation is best achieved with the combination of benzodiazepine and opioid infusions. Muscle relaxants may be added but can mask seizures.

Anaesthesia
In children with a severe head injury, propofol by infusion is contraindicated. Nitrous oxide is no longer favoured because it causes cerebral vasodilatation and increases the cerebral metabolic rate of oxygen consumption slightly and expands any air in the skull. Remifentanil infusion can be used in children and its rate may be rapidly adjusted to match the changes in the surgical stimulus. If it is not planned to wake the child up immediately, it offers few other advantages over opioids (e.g. fentanyl, alfentanil) and has a greater tendency to cause hypotension and bradycardia.

Volatile agents (e.g. isoflurane), though little favoured in head-injured adults because of cerebral vasodilatation, are commonly used in low concentrations in paediatric neuroanaesthesia. If there is evidence of severe intracranial hypertension, it may be best to avoid them or severely limit the inspired concentration. If the surgical stimulus is modest (as it is for a burr hole, especially when local anaesthetic infiltration has been used), an opioid-benzodiazepine combination may suffice until initial decompression has been achieved. If the stimulus is greater, thiopental (thiopentone) by infusion, 2–4 mg/kg/hour, with an opioid infusion, is useful if it is not planned to wake the child up immediately.

If a child with a severe head injury needs urgent surgery for other injuries, similar considerations apply. In these circumstances, ICP monitoring is essential. In comparison, maintaining anaesthesia in injured children without a head injury is relatively straightforward. Opioid infusions should be continued and increased according to the stimulus. Nitrous oxide is permitted if the risk of unrecognized pneumothorax or perforated bowel is small. A volatile agent may be used (reducing the concentration in the face of unavoidable hypovolaemia). When using paralysing agents, it may be difficult to achieve the balance between not exacerbating hypovolaemia and preventing awareness. Once surgical haemo-stasis has been achieved, vigorous warm blood/fluid therapy allows the inspired concentration of the volatile agent to be increased. ◆

FURTHER READING

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Special Considerations in Paediatric Intensive Care

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In the UK, about 15,000 children under 16 years of age are admitted to paediatric intensive care units (PICUs) each year. Half of them are under 2 years of age. Mortality is 5–17% depending on the case mix of the individual unit. Admissions include children who were previously well but develop an acute life-threatening illness, those requiring support after complex surgical procedures and others with chronic conditions (congenital or acquired) who develop a superimposed acute illness. More admissions occur in winter, mainly because of an increase in respiratory infections. Compared with adults, children decompensate quickly when severely ill, but if appropriately treated they recover quickly.

Intensive care delivered to children differs from adult care because of the different social and patient factors. The role of the child's parents or guardians has to be considered as do the legal and ethical considerations relevant to children (see *Anaesthesia and Intensive Care Medicine* **4:1**). Compared with adults, children have different patterns of illness and specific physiological and pharmacological developmental differences.

Organization of care
The specialist, low volume nature of paediatric intensive care medicine has led to the centralization of services in lead centres. These centres must meet defined standards of throughput, staffing, training and facilities and operate a retrieval service for the safe transfer of critically ill children from referring hospitals.

Some intensive care for children continues to be delivered in major acute hospitals, often hospitals with specialist services (e.g. neurosurgery). These must also meet the appropriate standards and care for children within protocols developed in partnership with the local lead centre. Occasional intensive care of children in district general hospitals should no longer occur, except in unusual circumstances and after discussion with the local lead centre.

Care of parents and family
Parents rightly expect to be involved in their child's care. When appropriate, they should be encouraged to participate in routine nursing care. This is often reassuring for child and parents. They also expect to be informed about, and usually participate in, any decisions concerning their child. Since PICU services are usually centralized, it is essential to provide accommodation for parents needing to stay.

Siblings may have considerable difficulty coming to terms with the patient's illness. Their needs have to be considered and it may be appropriate for them to visit regularly.

The death of a child is relatively rare. Many deaths on PICU are because of the elective withdrawal of care. Deaths need to be handled with sensitivity to the families' cultural and religious values. To help with the grieving process, many PICUs offer a bereavement counselling service. The Royal College of Paediatrics and Child Health has produced useful guidance on issues relating to end-of-life decisions.

Audit
In order to compare performance between PICUs, a number of case-mix adjustment tools have been developed. Adult tools (e.g. APACHE) are unsuitable for children because they do not take account of age-related normal ranges for physiological variables or the different patterns of disease. The two most commonly used case-mix adjustment tools are Paediatric Risk of Mortality (PRISM) and Paediatric Index of Mortality (PIM). These were developed in the USA and Australia, respectively, and need to be adjusted for the UK population. The MRC-funded Paediatric Intensive Care Outcome Study (UK PICOS) is being completed to determine and calibrate the most appropriate case-mix adjustment tool for PICU in the UK. The Department of Health has recently funded a national audit database, the Paediatric Intensive Care Audit Network (PICANET).

Airway management
Most children undergoing intensive care require tracheal intubation. Aspiration of gastric contents can increase morbidity and mortality and in the non-arrest, emergency situation, a rapid sequence intubation should be considered. After intubation, a gastric tube should be placed to decompress the stomach. Uncuffed tubes are traditionally used to minimize the risk of subglottic damage. Cuffed tracheal tubes are available in small sizes and their use on PICU is being re-evaluated, especially in situations where lung compliance is poor and the presence of a leak impairs lung recruitment and ventilation.

Nasotracheal intubation: nasotracheal tubes are easier to secure, allow better mouth toilet and are tolerated at lower levels of sedation. They are used unless contraindicated (e.g. possible basal skull fracture, coagulopathy). Tube length is crucial and should be checked with an AP chest radiograph (the tip should be opposite T2). Too long a tube is associated with endobronchial intubation and one too short increases the risk of accidental extubation.

Some children with airway obstruction can be woken once intubated. Nasotracheal tubes are often well tolerated in these situations and avoiding sedation and ventilation reduces complications. These children still require care in an ICU because of the hazards of accidental extubation. Nasotracheal tubes can be used for prolonged periods without apparent sequelae.

Tracheostomy is not usually discussed until after 3–4 weeks of intubation, though it may be indicated earlier in specific circumstances (e.g. in children after head injury who have poor or absent upper airway reflexes). When making the final decision about tracheostomy in a long-term ventilated child, non-invasive modes of ventilation must be carefully considered first, because tracheostomy precludes their use. Surgical tracheostomy remains the method of choice (we have used a percutaneous approach in teenagers, but abandoned the technique because of complications). A percutaneous gastrostomy may be considered at the same time.

Management of respiratory failure
Respiratory failure is the most common cause of emergency admission to PICU (Figure 1). Many children with respiratory failure have predisposing factors that complicate the course of their illness:
- bronchopulmonary dysplasia
- trisomy 21
- congenital anomalies (especially cardiac and respiratory)
- congenital or acquired immunodeficiencies (especially after cancer chemotherapy or organ transplantation).

Successful treatment of severe respiratory failure requires a package of measures that includes physiotherapy and meticulous attention to nutrition, infection control, cardiovascular status and fluid balance.

Causes of respiratory failure in children

Anatomical site	Diseases
Upper airway obstruction	Croup, epiglottitis, foreign body, laryngomalacia, subglottic stenosis
Lower airway obstruction	Asthma, bronchiolitis
Interstitial lung disease	Infective pneumonia/pneumonitis, aspiration pneumonia, acute respiratory distress syndrome from any cause
Pleura and chest wall	Trauma, empyema, kyphoscoliosis,
Neuromuscular diseases	Muscular dystrophy, spinal muscular atrophy, Guillain–Barré syndrome, spinal injury
Central hypoventilation syndromes	'Ondine's curse' (reduced ventilatory drive following neurosurgery)

1

Positive-pressure ventilation
Continuous positive airway pressure (CPAP) and non-invasive positive-pressure ventilation (NIPPV) can be delivered in a number of ways. Nasal prongs are suitable for neonates, while infants and young children may tolerate a short nasal tube (an uncuffed tracheal tube with the tip in the oropharynx). Tight-fitting face or nasal masks in sizes suitable for children are also available and surprisingly well tolerated by some. Positive pressure can be applied either by a CPAP circuit, flow driver, or by attachment to an appropriate ventilator.

Non-invasive pressure support (either NIPPV or CPAP) is becoming increasingly popular. CPAP may be indicated in babies with bronchiolitis and may avoid the need for intubation, but its role in other forms of acute respiratory failure requires further evaluation. Non-invasive support is also used for long-term ventilatory support in children with neuromuscular diseases or central hypoventilation syndromes.

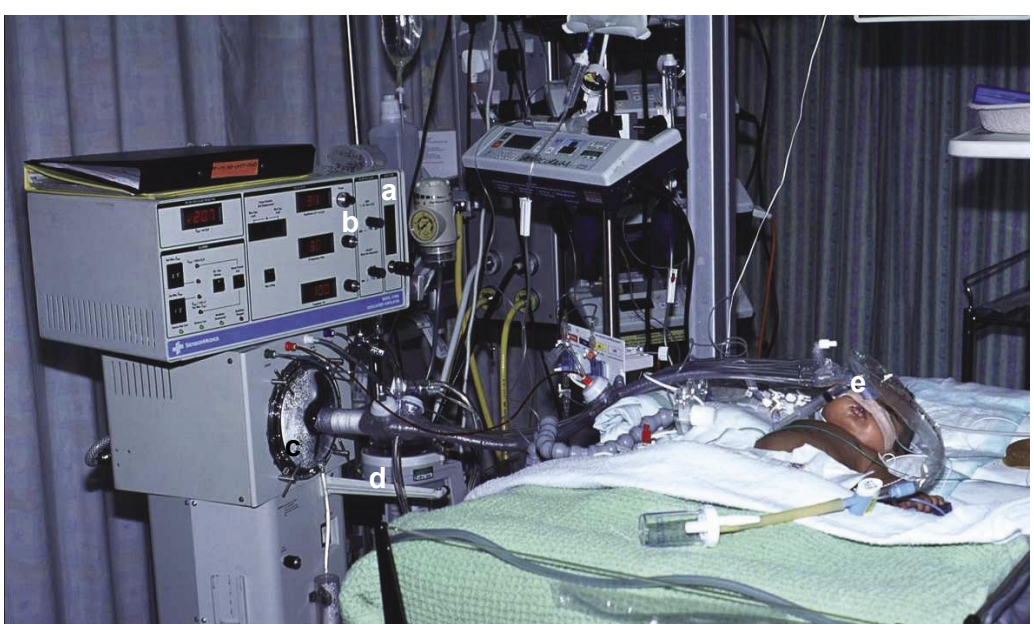
Negative-pressure ventilation: adult intensive care started with the use of cuirass ventilators during the polio epidemics of the middle of the last century. In the last 15 years, similar devices have been developed for use in infants, which can deliver continuous (CNEP) or intermittent (INEP) negative expiratory pressure. A more recent development is the Hayek oscillator, which encloses the trunk only and can be used in all age groups. Theoretically, these devices provide more physiologically normal respiratory support. Although they have enthusiastic proponents, they are not established in mainstream paediatric intensive care.

Pressure-controlled ventilation: most children admitted to PICU receive conventional respiratory support with time-cycled, pressure-controlled ventilation. The objectives of ventilatory support for children with acute respiratory failure are the same as those in adults:
- alveolar recruitment without over-distension
- limitation of tidal volume and pressure to avoid volutrauma and barotrauma
- the acceptance of permissive hypercarbia and possibly hypoxaemia to meet the requirements of the above.

Several ventilators deal successfully with children of all ages. The authors prefer those with near-patient flow sensors, which have allowed improved triggering and tidal volume monitoring. These are particularly useful in the ventilation of infants.

Adequate humidification is essential to prevent heat and moisture loss from the patient and drying of secretions, which crust the lumen of the tracheal tube and encourage blockage. Heated water humidifiers are generally used.

High frequency oscillatory ventilation (HFOV) was popularized by neonatologists. Its main advantage is to allow alveolar recruitment at relatively constant, but often lower, peak pressures than IPPV. Outcome is better in acute respiratory distress syndrome (ARDS) compared with IPPV, presumably because of reduced ventilator-associated lung injury. Ventilation is delivered through a conventional endotracheal tube and adequate humidification is possible in contrast to earlier technologies such as high frequency jet ventilation. Oxygenation and carbon dioxide excretion are independent. Oxygenation depends on FiO_2 and mean airway pressure. Carbon dioxide is removed by imparting energy into the system via an oscillating diaphragm. The threshold for progressing to HFOV has decreased as paediatric intensivists have become increasingly familiar with the technology. The Sensormedics oscillator (Figure 2) is the only machine commercially available in the UK with sufficient power to ventilate children older than neonates. There are two models: one for neonates and smaller children, the other for older children and adults. Some units now use HFOV as the ventilatory mode of first choice for children presenting with moderately severe respiratory failure.



2 The Sensormedics high frequency oscillatory ventilator in use. **a** Flowmeter, **b** amplitude, percentage inspiratory time and frequency controls, **c** oscillating diaphragm, **d** heated humidifier, **e** airway connector with closed suction device.

Nitric oxide
Some years ago nitric oxide became popular as a therapy in severe respiratory failure but with experience its use has declined. In respiratory failure, its main indication appears to be to improve oxygenation before and during transportation of children requiring extracorporeal membrane oxygenation. However, nitric oxide improves outcome in neonates with idiopathic pulmonary hypertension of the newborn and is used to treat pulmonary hypertension in children with congenital heart disease after corrective surgery.

Surfactant
Exogenous surfactants have revolutionized the management of neonatal respiratory distress syndrome. In older patients, many pulmonary disease processes are associated with surfactant deficiency. Clinical trials suggest that there may be some benefit from surfactant administration to babies with bronchiolitis but the authors are not aware of any other evidence to support its use in respiratory failure beyond the neonatal period.

Liquid ventilation
Liquid perfluorocarbon is used to transport oxygen and carbon dioxide through the respiratory tract. In full liquid ventilation, the lung is completely full of fluid and an external pump and gas exchanger are required. Partial liquid ventilation is simpler to use. The lung is filled to the end of the tracheal tube at expiration and the patient attached to a conventional ventilator. The FRC is thus filled with liquid and the gas/liquid interface is intrapulmonary. Although the technique was described over 10 years ago, clinical trials are not completed. The role of liquid ventilation in treating children with respiratory failure is unknown.

Extracorporeal membrane oxygenation (ECMO)
It is unlikely that a randomized controlled trial of the use of ECMO for the treatment of respiratory failure in children will ever take place. However, it has been accepted as an effective rescue therapy for severe acute respiratory failure in children.

Sedation and analgesia
All children in pain, from whatever cause, must receive adequate analgesia. Many routine ICU procedures are painful and the use of local anaesthetics should be considered when indicated.

Sedation of children on PICU remains a problem. It is often needed, but complications are relatively frequent (Figure 3). Sedation scoring is difficult in young children. There are numerous sedative regimens, and the choice of drug may be less important than the philosophy behind its administration. Before sedating a child, other causes of agitation should be sought and, if possible, eliminated. Paramount among these is pain. Others include bladder distension, hypoxaemia, hypercarbia, cold, hunger and separation from parents. Once these issues are addressed, it is appropriate to administer sedation that is titrated to a defined endpoint. The judicious use of restraints may also reduce the need for sedation, but they are considered unacceptable by many nurses.

Advantages and disadvantages of sedation

Advantages
- Comfort
- Safety (retention of lines and tubes, prevention of injury to patient and carers)
- Therapeutic (attenuate rises in intracranial pressure, blood pressure)
- Psychological (reduces distress, may reduce long-term psychological disturbance)

Disadvantages
- Hypotension
- Immobility (pressure area problems, fluid retention)
- Reduced secretion clearance (ventilator-associated pneumonia)
- Immunosuppression (hospital-acquired infection)
- Withdrawal phenomena
- Pharmacodynamic (side-effects, toxicity)

3

Intravenous opiates and benzodiazepines by continuous in-fusion remain popular. Following a directive from the Committee for Safety of Medicines, propofol should no longer be used for the sedation of children because there have been a number of cases of progressive myocardial failure following long-term, high dose propofol infusions in children with respiratory failure. Some units are returning to intermittent boluses of longer acting agents because of the risks of overdose and accumulation with infusions. Once gastric absorption is established many prescribe enteral sedation with chloral hydrate, trimeprazine or clonidine. Muscle relaxants are often used in the acute stages of critical illness. Their use is associated with complications and needs to be carefully considered in each case.

Fluids, electrolytes and nutrition
Resuscitation fluids
Resuscitation fluids are usually given in increments of 20 ml/kg. The type of fluid has been the subject of considerable debate. Human albumin solution remains the most popular agent for large volume resuscitation in babies and small children. Artificial colloids can be used, but with appropriate limits on the volume administered. Normal saline is increasingly used for the first 20–40 ml/kg.

Maintenance fluids
Maintenance fluids need to supply water, electrolytes and energy. The standard formula of 4 ml/kg/hour for the first 10 kg body weight, 2 ml/kg/hour for the second 10 kg, and 1 ml/kg/hour thereafter (see page 459) works reasonably well in children weighing 5–50 kg. However, in smaller babies it considerably underestimates fluid and energy requirements and overestimates them in older children. Fluid requirements per kg increase with decreasing weight and gestational age. The smallest infants admitted to a PICU may require more than 180 ml/kg/day.

0.18% NaCl in 4% dextrose remains a popular first-line maintenance fluid. However, it will just supply basal sodium requirements, and in the face of deficits or losses its use will lead to hyponatraemia (deaths from hyponatraemia and cerebral oedema have resulted). There are strong arguments for replacing it with a fluid with a higher sodium content (e.g. 0.3%) for routine use.

Renal replacement therapy
Haemofiltration is commonly used in paediatric intensive care to manipulate fluid and electrolyte balance. The technique is possible in all but the smallest of babies, but the technical challenges are substantial. Peritoneal dialysis is technically simpler and may give more gradual control of metabolic disturbances.

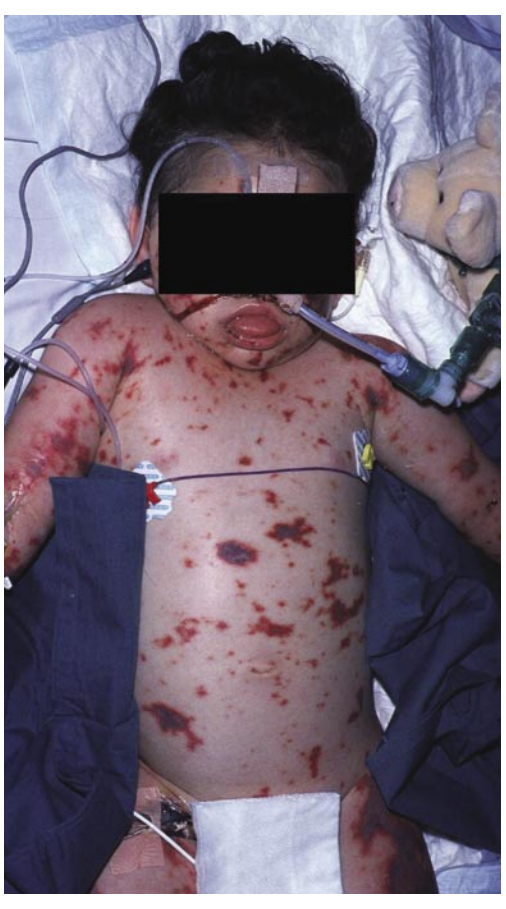
Nutrition
Children have a high metabolic rate because of the energy costs of temperature homeostasis, growth and (often) the work of breathing. They may have very limited energy reserves, particularly because up to 40% are malnourished on admission to PICU.

Adequate nutrition is vital, but can be difficult to achieve because of concerns about fluid retention and volumes of drugs and other fluids. The authors are more liberal with fluids, and therefore nutrition, and control fluid balance with diuretics if necessary. Enteral feeding is preferable, if possible. If full enteral feeds cannot be established within 48 hours, the authors start parenteral nutrition, but, unless contraindicated, continue to deliver small volumes (3–5 ml/hour) of enteral feed.

Monitoring
Monitoring modalities in PICU are broadly the same as those used in adult intensive care. The main difficulties in children arise because of the diameters of the various intravascular catheters available. Most, including intravascular blood gas sensors, are now available in miniature forms. Cardiac output can be measured satisfactorily with proprietary tools that use a variety of indicator dilution methods. Conventional pulmonary artery catheters can be used but, as in adult ICU, their use is declining. The authors have found the cerebral function analysing monitor useful.

Some specific clinical conditions
Sepsis
The systemic inflammatory response syndrome is similar in adults and children but mortality is lower in children. Neonates, premature babies, the immunosuppressed and those children with congenital cardiac or renal anomalies are particularly at risk. Children under 2 years of age are particularly susceptible to polysaccharide-encapsulated bacteria such as *Meningococcus*, *Pneumococcus* and *Haemophilus influenzae*. Surgical sepsis is relatively uncommon.

Meningococcal disease (Figure 4) is the leading infectious cause of death in children. It is hoped that the vaccination programme against Group C disease will reduce the mortality. The disease is often difficult to diagnose in the early stages but can have a fulminant course resulting in death within a few hours of the appearance of the characteristic rash. Most cases occur in children less than 5 years of age, with a peak incidence between 3 months and 2 years of age.



4 A child with meningococcal septicaemia. The characteristic rash is non-blanching and may have necrotic areas surrounded by erythema. This child had fasciotomies to all four limbs and went on to have bilateral below knee amputations.

Initial treatment consists of antibiotics, aggressive fluid resuscitation, inotropic support, intubation and ventilation, treatment of hypoglycaemia, electrolyte imbalances (especially hypocalcaemia) and coagulopathy. A detailed protocol can be found at ***www.meningitis.org***. Several experimental agents have undergone clinical trials with mixed results. PICU mortality is below 20% and it is unlikely that any trial with mortality as a primary endpoint will recruit sufficient numbers to prove efficacy. Fluid requirements can exceed 200 ml/kg in the first 24 hours. Human albumin solution remains the most commonly used colloid, and there is some experimental evidence to support its use. The children remain very oedematous until the systemic inflammatory process and capillary leak have resolved, at which point most will diurese spontaneously. During this period, there may be florid pulmonary oedema, which requires treatment with high positive end-expiratory pressure, HFOV or occasionally extracorporeal membrane oxygenation. Despite the pulmonary oedema, fluid resuscitation may need to continue if the patient shows signs of intravascular volume depletion. The role of treatments such as early haemofiltration, prostacyclin infusion, steroids, plasmapheresis or plasma exchange remains unclear. Death occurs either in the first 24 hours as a failure to stabilize or later as a withdrawal of treatment when catastrophic sequelae (e.g. cerebral infarction) manifest themselves. In survivors, further treatment may include dialysis/haemofiltration for electrolyte imbalance or renal failure and debridement, amputation or skin grafting of necrotic limbs or areas of skin.

Acute brain insults
The response of children to acute brain injury differs from that in adults in a number of ways. Babies with unfused cranial sutures are able to tolerate rises in intracranial volume without the degree of intracranial hypertension seen in older patients. In traumatic brain injury, the response is often predominantly hyperaemic (so a degree of cerebral vasoconstriction may be indicated) and extradural haematoma is less common than in adults. For any severity of injury, the outcome for children appears to be better than for adults, presumably because of the greater adaptability of the developing CNS.

In only a small number of children is a reduced conscious level associated with a structural intracranial injury. In most there has been a diffuse insult, such as hypoxaemia, ischaemia or metabolic insult (commonly hypoglycaemia) (Figure 5).

Traumatic brain injury (TBI) in babies is often non-accidental. Babies with non-accidental injury may have a diffuse injury, with multiple petechial haemorrhages throughout the brain, and/or intracranial haemorrhage. Petechial retinal haemorrhages are pathognomonic of a shaking injury. Care of children with non-accidental injury requires close liaison with the child protection team and careful clinical examination (including photography) to document other injuries. Clotting studies (to exclude a bleeding diathesis), a skeletal survey and fundoscopy (to document retinal haemorrhages) should be obtained. Subdural haematoma may require evacuation, usually by needle puncture.

In older children a more adult pattern is seen. Extradural haematoma is less common, but requires urgent attention if present.

Causes of non-traumatic coma in children

Nature of insult	Disease process
Hypoxic-ischaemic injury	Cardiac arrest Immersion incidents Near miss sudden infant death syndrome Suffocation
Infection	Meningitis, encephalitis Cerebral effects of generalized sepsis
Metabolic injury	Hypoglycaemia Hyper- or hyponatraemia Hepatic encephalopathy Reye's syndrome Haemolytic uraemic syndrome Poisoning Inborn errors of metabolism

Intensive care management is similar to that of adults with head injury with general resuscitative measures and acute reduction in intracranial pressure (ICP). The authors measure ICP and manipulate therapy to maintain cerebral perfusion pressure (CPP), despite the fact that there is little evidence that ICP measurement and the management strategies deriving from it are of any benefit. The targets for CPP need to be age related, but there is a paucity of data to support any particular set of values. Trials are continuing to evaluate moderate hypothermia in the early post-injury period and the role of newer monitoring modalities (e.g. tissue pO_2) needs evaluation. Data obtained from adults may not be directly applicable to children.

Blocked ventriculo-peritoneal shunt: there are increasing numbers of children with shunt devices and blockage can be a neurosurgical emergency (there have been several deaths in our region recently because clinicians did not appreciate the urgency of the situation). If a child with a shunt starts to lose consciousness, urgent referral to a paediatric neurosurgical centre is required. While transfer is being arranged, emergency management must be instituted (i.e. removing CSF through the reservoir, osmotic diuretics to reduce ICP and controlled ventilation to maintain $PaCO_2$ at 3.5–4.5 kPa).

Cardiovascular disease
Acquired cardiac disease is relatively uncommon in childhood, but children with congenital heart disease account for a large proportion of the workload of a PICU. Most are admitted for postoperative care after corrective surgery. They also present with heart failure or arrhythmias at other times. There is also an increasing population of older patients who had surgery for congenital lesions as children. These patients can present with intercurrent illness or for revision of their original surgery.

Children with cyanotic congenital heart disease are prone to respiratory tract infections and can pose management problems. It is important to determine their normal oxygenation status and to set appropriate targets for ventilatory management. Some of these children normally have oxygen saturations below 70%.

Diabetic ketoacidosis
Diabetic ketoacidosis is often the first presentation of diabetes in children. These children can be profoundly acidotic and severely dehydrated. Their conscious level may be impaired and their airway may require protection. Deaths occur from cerebral oedema. The precise cause of this is unclear, but it is thought to be a result of the maintenance of a high intracranial osmotic pressure as glucose and ketones are cleared from the blood. The imperative, therefore, is a gradual normalization of blood sugar, achieved by replacing fluid deficits over 24–48 hours with normal saline. Potassium replacement is also necessary once a urine output is established. A low dose intravenous insulin infusion of 0.1 unit/kg/hour is started. The blood sugar is monitored closely and if the rate of fall is greater than 5 mmol/litre/hour, then either the rate of insulin infusion should be reduced to 0.05 IU/kg/hour or dextrose should be added to the maintenance fluid or both. Once the blood glucose is below 12 mmol/litre, the normal saline is replaced with a solution containing 4% or 5% dextrose. The choice of solution depends on the serum sodium concentration. A detailed management protocol can be found at http://www.diabetes.org.uk/dka_paed/dkapaed.pdf ◆

FURTHER READING

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Stabilization and Transport of Critically Ill Children

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Development of Paediatric Intensive Care Unit (PICU) transport services
In the UK, during the last decade, there has been a drive to centralize paediatric intensive care in a small number of large tertiary centres to try to improve the outcome of critically ill children. Centralization has resulted in increasing numbers of critically ill children requiring inter-hospital transportation. The report, *Standards of Practice for the Transportation of the Critically Ill Child,* published in 1996 by the Paediatric Intensive Care Society (PICS), recommended that transportation should be undertaken by specialized PICU transport teams functioning as an 'intensive care bed on the move'. Alternatives include transportation by the local ambulance paramedic team or by the referring physician and/or nurse. However, critically ill children transported by non-specialized teams suffer significantly more critical incidents during transportation than those transported by specialized teams. The main advantages of specialized teams are that they:

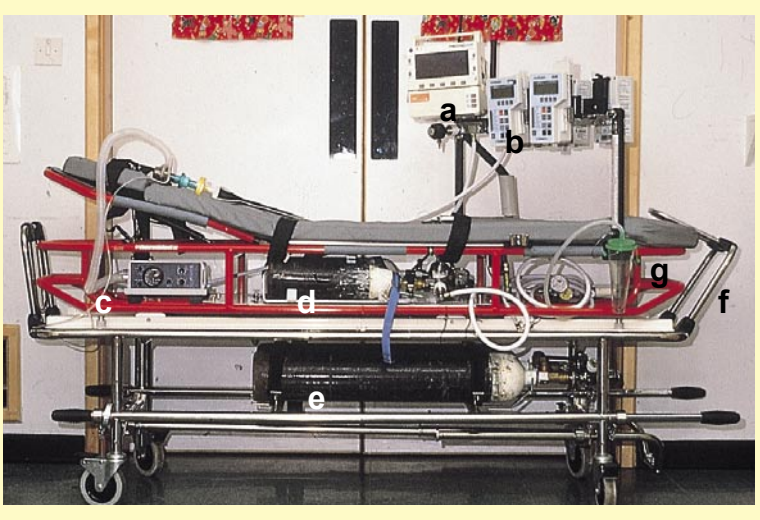
- have training and experience in paediatric intensive care and transportation
- use dedicated transportation equipment
- can operate without rendering the PICU base or referring hospital short staffed.

The transport team
A specialized PICU transport team usually comprises an experienced PICU doctor and nurse. Ideally, the doctor should be a senior trainee with 2 years' experience in anaesthesia, adult or paediatric intensive care medicine, neonatal intensive care or equivalent discipline (including a minimum of 3 months' PICU experience). Nurses have independent professional responsibility towards the child and should have undergone PICU training (ENB 415 or equivalent) and have 2 years' PICU experience. Ideally, these transport personnel should have specialist transport training. Consultants often travel with difficult patients or when new personnel are being trained. The transport service is usually managed by a PICU consultant (the 'Transport Director') and a senior PICU nurse (the 'Transport Coordinator'). They approve equipment and medical supplies, develop transport protocols, establish outreach education programmes, implement audit and a risk management pro-gramme, manage the transport budget and organize staff training.

Equipment (Figures 1–4)
The team should be self-sufficient and carry all the necessary equipment and drugs for stabilization and transportation (smaller hospitals may not be equipped with the full range of consumables for babies and children). These can be pre-packed in special bags with multiple, labelled compartments to allow rapid access to the contents (Figure 1). Important additional equipment includes a mobile telephone, warm protective high-visibility clothing for staff and a sharps disposal box.

Transport equipment and drugs bags (the Paediatric Intensive Care Society has guidelines about equipment and drugs for transport). a Circulation and monitoring; b airway and breathing; c emergency equipment; d suction apparatus; e drugs for resuscitation, anaesthesia, sedation and cardiovascular support; f multiple compartments.

1

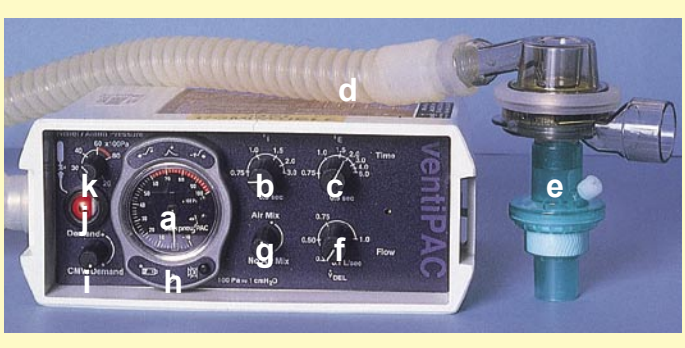


Custom-built transport trolley. **a** Monitor, essential features:
- operates from battery, 12 V DC and 240 V AC power
- visual and audible alarms
- illuminated display with wide viewing angle screen
- suitable for neonates and children
- includes ECG, oxygen saturation, end-tidal CO_2, non-invasive blood pressure, temperature, respiratory rate, central venous pressure, invasive blood pressure and facilities for data storage, download or printing; **b** syringe pumps with visual and audible alarms; **c** ventilator; **d** size D oxygen cylinders (340 litre); **e** size F oxygen cylinder (1360 litre) – take twice the estimated oxygen requirement (O_2 consumption = minute volume + driving gas (specified by the manufacturer) ml/minute). Note: hand ventilating requires more oxygen; **f** modified standard ambulance trolley; **g** Aerosled (red frame) separates from the trolley for air transport.

2

The baby PAC™ ventilator (SIMS pneuPAC Ltd), which is suitable for babies ≤ 10 kg. It is a gas-driven, time-cycled, pressure-controlled ventilator. **a** Pressure gauge; **b** inspiratory time; **c** expiratory time; **d** on/off switch; **e** inspiratory and expiratory circuit; **f** heat and moisture exchanger; **g** pressure control; **h** positive end-expiratory pressure; **i** fraction of oxygen in inspired air; **j** alarm module with visual and audible alarms for high pressure and low pressure (disconnection); **k** air failure visual alarm; **l** oxygen failure visual alarm; **m** pressure relief and audible alarm.

3



The ventiPAC™ ventilator (SIMS pneuPAC Ltd), which is suitable for babies and children > 5 kg. It is a gas-driven, time-cycled, flow generator. **a** Pressure gauge; **b** inspiratory time; **c** expiratory time; **d** inspiratory circuit only; **e** one-way valve heat and moisture exchanger; **f** flow control adjusted to achieve the desired peak airway pressure (NB set pressure relief just above this pressure to protect lungs if leak around the tube decreases); **g** fraction of oxygen in inspired air; **h** alarm module with visual and audible alarms for high pressure and low pressure (disconnection); **i** on/off switch; **j** oxygen failure visual alarm; **k** pressure relief and audible alarm.

4

Modes of transportation
Transportation is either by road (emergency ambulance, dedicated mobile PICU) or air (helicopter or fixed wing (aeroplane) aircraft). The choice depends on the severity of illness, urgency of transportation, availability of vehicles, distance involved, proximity of the hospitals to airfields, time of day, weather conditions and the amount and type of equipment to be carried.

Road transportation is rapidly organized and door-to-door. It is usually more time efficient for distances of less than 75 miles. Some teams use a dedicated mobile PICU, which is designed for easy patient loading, and has adequate lighting and heating, sufficient space for the transport team at the head and both sides of the child, adequate oxygen supplies, 240 V AC electricity and storage space. They also have adequate restraints for the transport team, child, trolley and equipment and an effective communications system.

Air transportation takes longer to organize and requires secondary road transportation to and from the aircraft. It is a realistic option for distances over 75 miles or when road transport will take more than 2 hours. A variety of helicopter (Figure 5) and fixed wing (Figure 6) aircraft are available from the Ambulance Service, the Royal Navy and RAF Search and Rescue Services and charter companies. In transit, the transport team is in charge of patient management decisions but the pilot is in command of the aircraft and all passengers. The pilot decides when to fly, the route, how many passengers to carry and whether to divert in poor weather conditions. Effective communication and discussion between the team and the pilot is essential.

5 The Scottish Ambulance Service EC 135 helicopter ambulance is unpressurized, which limits its altitude, affecting routing and fuel consumption and increasing the importance of weather conditions.

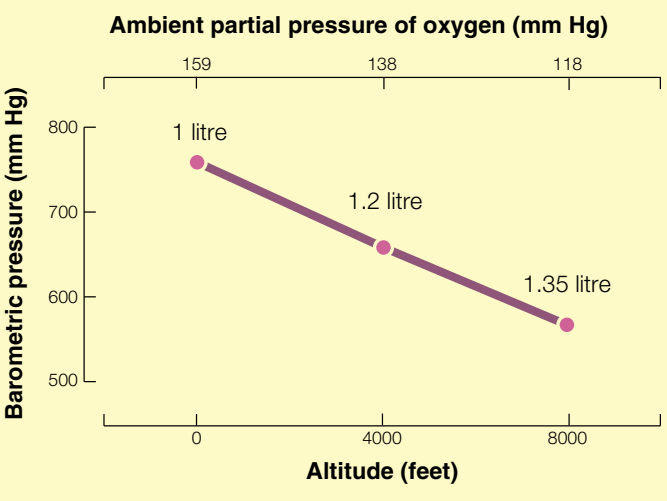
6 The Scottish Ambulance Service Air King fixed wing air ambulance, which is pressurized and can therefore fly higher, above bad weather, faster and further than unpressurized air ambulances (e.g. the Islander).

Special transport considerations
Isolation and the unfamiliar environment: the transport team is isolated from assistance and working in a relatively unfamiliar environment. These effects can be minimized by training, experience and using expertise at referring hospitals. The use of mobile telephones in aircraft is often prohibited.

Movement (including acceleration, deceleration, head up/down tilt and vibration) has significant physiological effects. If the child's head is towards the front of the vehicle, acceleration causes venous pulling in the legs and reduces cardiac output. Baroreceptor-induced vasoconstriction increases systemic vascular resistance maintaining arterial pressure. This normal response is obtunded in children with septicaemia, hypovolaemia or CNS injury. Deceleration (e.g. sharp braking) increases venous return and intracranial pressure, which is exaggerated by head-down tilt when travelling down hill. The effects of these forces can be minimized by good communication with the driver and using a police escort to negotiate traffic congestion at a steady speed. Procedures such as intubation or cannulation are easier in a stationary ambulance (ideally before commencing the journey). Aircraft transmit vibration to passengers, exacerbating motion sickness, impairing co-ordination and interfering with the vestibulo-ocular and pursuit reflexes, which are important when trying to visualize a monitor display. Children with fractures may require additional analgesia. Movement and vibration can also cause displacement of tracheal tubes, chest drains and venous and arterial cannulae.

Altitude: pressurized aircraft usually fly with a cabin altitude of 6000–8000 feet (1800–2500 m). Barometric pressure falls with altitude from 760 mm Hg (100 kPa) at sea level to 565 mm Hg (74 kPa) at 8000 feet, which affects enclosed gas spaces and patient oxygenation (Figure 7). Boyle's law states that volume is proportional to 1/pressure. Therefore, enclosed air spaces could expand by up to 35% at 8000 feet with the risks of ear, sinus and dental pain, expansion of pneumothoraces and tracheal tube cuffs and abdominal distension. Altitude affects equipment containing gas spaces (including non-invasive blood pressure cuffs, glass intravenous giving bottles, pressure bags and vacuum mattresses). The percentage of oxygen in atmospheric air remains unchanged with altitude, but as barometric pressure falls the partial pressure of oxygen in dry air falls from 159 mm Hg (21 kPa) at sea level to 118 mm Hg (16 kPa) at 8000 feet. This is important for children with high oxygen requirements at sea level, especially if the fraction of oxygen in inspired air (FiO_2) cannot be increased readily during transportation (e.g. those breathing spontaneously on high flow oxygen or ventilated with 100% oxygen). To compensate, the cabin altitude of pressurized aircraft can be reduced to near sea level and military helicopters can fly as low as 500 feet (150 m), weather permitting.

Effects of changing barometric pressure on partial pressure of oxygen and gas volume



7

Excessive ambient noise makes communication in aircraft difficult and tiring. Auscultation with a stethoscope is usually impossible and the detection of auditory alarms is inhibited. Children and the transport team should be protected from the damaging effects of noise with helmets and ear defenders.

Motion sickness is caused by the mismatch of afferent visual and vestibular information and is made worse by excessive head movement and reading in transit. Anti-emetics (e.g. antihistamines, ondansetron) are generally effective.

Distraction by alternative stimulation (e.g. looking out of the aircraft window or at the aircraft instrumentation) combined with difficulty hearing audible alarms means that transport personnel must be particularly vigilant.

Communication
Effective communication is important at all stages of transportation. Every PICU should have a dedicated telephone 'hotline'. Referrals should be made direct from the referring consultant to the PICU consultant, who should complete a comprehensive evaluation sheet covering the pertinent aspects of the child's location, clinical condition and treatment and give advice on further management. The ambulance service is contacted to arrange transportation and the referring hospital notified of the team's estimated time of arrival. The PICU consultant remains in regular contact with the referring physician to give additional advice and to receive clinical updates that can be passed on to the transport team, in transit, by mobile telephone. Once the transport team has assessed the child, they inform the ambulance service about the expected stabilization time to facilitate scheduling of the return journey and notify the PICU staff about the child's condition, treatment requirements and expected time of arrival in the PICU. During the child's stay in PICU, staff should provide regular feedback to the referring hospital and send a formal discharge letter to all consultants involved and the patient's GP.

Resuscitation and initial referral
Referrals should be made as soon as it is evident that the child is critically ill and needs transportation to a PICU. Children compensate and appear well in the early stages of critical illness, then rapidly deteriorate when their capacity for compensation is exceeded. The main criteria for PICU referral are given in Figure 8. The referring hospital is responsible for resuscitation and stabilization until the transport team arrives (Figure 9). This should be undertaken by the most senior staff available, following accepted PALS/APLS principles, in an appropriate location in the hospital equipped for high dependency or intensive care (usually ICU, high dependency unit, theatre or theatre recovery).

Main criteria for PICU referral

Deteriorating airway
- Chest wall recession
- See-saw breathing
- Stridor

Respiratory distress
- Rate > 60/minute
- Chest wall recession
- Oxygen saturation in arterial blood (SaO_2) < 94% or partial pressure of oxygen in arterial blood (PaO_2) < 8 kPa (on high flow face mask oxygen)
- Partial pressure of carbon dioxide ($PaCO_2$) in arterial blood > 6 or < 3.5 kPa

Shock
- Heart rate > 180 or < 80/minute (< 5 years) > 160 or < 60/minute (> 5 years)
- Absent peripheral pulses
- Cold peripheries
- Capillary refill > 2 s
- Systolic blood pressure < 70 + (age in years x 2) mm Hg

Deteriorating level of consciousness

Recurrent seizures

Burns > 10%

Multiple trauma

8

Responsibilities of the referring hospital

- Optimize resuscitation with advice from the PICU staff
- Copy clinical notes for the transport team
- Obtain cross-matched blood if required
- Communicate changes in clinical condition to the PICU staff
- Consider transport arrangements for the parents

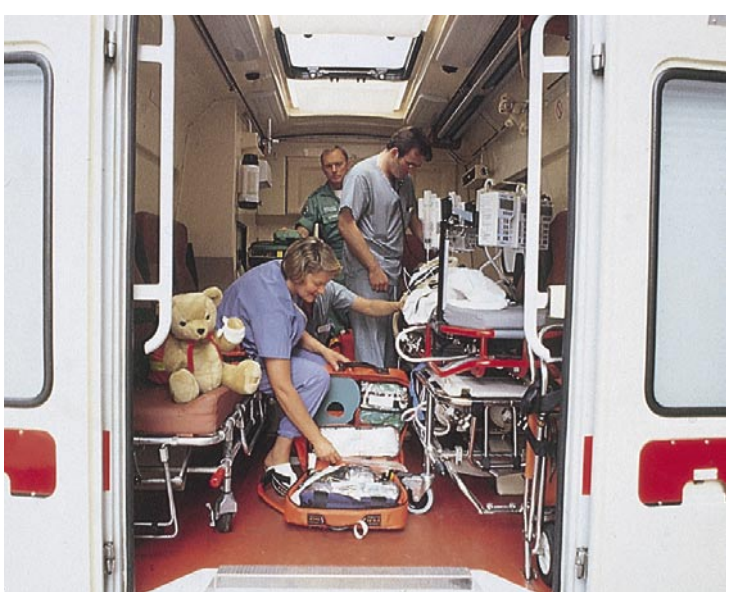
9

Stabilization
Meticulous preparation and stabilization of the child before departure minimizes the risks during transportation. This encompasses adequate resuscitation, initiation of all supportive therapies and monitoring, cessation of deterioration (ideally, improvement) in the clinical condition and pre-emptive management to avoid problems in transit. A systematic ABC approach, including assessment, optimization and preparation for transportation, of the airway, breathing, circulation, neurological status, temperature and blood glucose is useful. The child is transferred to the transport equipment to provide continuous therapy and monitoring throughout the transportation. Children must be regularly assessed to evaluate the impact of treatment and recognize further deterioration, which can be rapid.

Airway and breathing should be assessed in the context of the full clinical picture. Respiratory compromise can be the cause or result of multi-system dysfunction in children. Aspects to be clarified in the history include the speed of deterioration, duration of intubation, volume of secretions and suction requirement. Important points of examination include airway patency, level of consciousness, degree of exhaustion, and adequacy of ventilation, sedation and neuromuscular blockade. Monitoring and investigations should include oxygen saturation, capnography, airway pressures, ECG, arterial blood gas analysis and chest radiograph to confirm the correct position of a tracheal tube. The airway must be reliable before transportation. The decision to intubate can be difficult. There should be a lower threshold for intubation and ventilation for transportation than in routine PICU practice, to optimize the clinical condition before transportation. Effective tracheal tube fixation is essential and intubated children should be given sedative and neuromuscular blocking drugs throughout transportation to reduce the likelihood of accidental extubation, decrease awareness and anxiety, and facilitate controlled ventilation with the transport ventilator. All children intubated with an uncuffed tracheal tube require a gastric tube to decompress the stomach. Pneumothoraces should be drained before departure. Intermittent positive-pressure ventilation or flying at altitude can expand pneumothoraces, resulting in respiratory and cardiovascular compromise. One way flutter (Heimlich) valves should be used in preference to bottles with underwater seals for chest drains during transportation.

Circulation: hypovolaemic children tolerate transport badly. It is important that hypovolaemia (characterized by tachycardia, poor peripheral perfusion and, if severe, hypotension and acidosis) is corrected with fluid before transportation. Children with continuing haemorrhagic shock should not be transported until the bleeding has been controlled. Commencing inotrope infusions in transit is difficult so there should be a low threshold for doing this before departure. Some types of congenital heart disease require a prostaglandin infusion to sustain life by maintaining patency of the ductus arteriosus, for example interrupted aortic arch (duct dependent systemic circulation) or pulmonary atresia (duct dependent pulmonary circulation). The requirement for a central venous line and an arterial line depends on clinical condition and is not required for transport *per se*. However, non-invasive blood pressure recordings may be affected by motion artefact, can be unreliable in shocked children and are a significant drain on the battery life of the monitor. It is advisable to have at least two functioning, securely fixed intravenous cannulae because critically ill children are difficult to cannulate in transit. A urinary catheter is usually inserted and hourly urine output monitored.

Patient packaging: the difficulties of working in the confined space of an ambulance are evident in Figure 10. The child's head and tracheal and ventilator tubes should be securely fixed while ensuring easy access for airway management. Intravenous line extension tubing is useful for administering drugs or fluid without needing to move around or unwrap the child. The transport environment can be hostile (e.g. on an airport runway in mid-winter) making heat loss a problem when transporting infants who have a large surface area to weight ratio, a large head, thin skin and neuromuscular blockade preventing shivering. The use of a vacuum mattress (Figure 11), gamgee, foil blankets, chemical warming packs (which can be placed directly against the skin of an infant without causing thermal injury), a hat and warm ambient temperature within the vehicle are sufficient to maintain body temperature in infants over 1.5 kg body weight. (Babies less than 1.5 kg are usually transported by neonatal intensive care teams using a portable incubator to maintain body temperature.) All equipment, syringe pumps and the monitor must be secured and readily visible to the team while seated. Emergency drugs, fluids, airway and ventilation equipment (including a self-inflating resuscitation bag, valve and mask system) must be available immediately. A pre-departure checklist prevents accidental omissions in stabilization or inadvertently leaving equipment behind.



10 Interior of an ambulance, which provides limited space to perform procedures such as intubation or intravenous cannulation.

Baby and transport equipment packaged in a vacuum mattress. This secures the child and prevents pressure areas and heat loss. A transport incubator is unnecessary for full-term babies and infants and is heavy, complicated to operate and offers less access to the baby. **a** Head securely fixed; **b** carrying handle; **c** security straps; **d** monitor; **e** ventilator; **f** syringe pump.

11

Documentation should include a comprehensive medical, nursing and operational record from the initial telephone referral until the child arrives in the PICU (Figure 12). It should form the basis of debriefing sessions, audit and risk management.

Transport documentation

- Demographic data
- Clinical data
- Advice given by the PICU
- Treatment by the transport team
- Mode of transport, personnel and timings
- Critical incidents in transit
- Checklists
- Drug infusion and resuscitation charts
- Consent forms
- Parent information booklets

12

Critical incidents in transit
Transferring the child between trolleys, around the hospital, into and out of vehicles, with the associated switching of oxygen supplies are risk factors for critical incidents. Despite the best preparation and stabilization, children may deteriorate in transit and the transport team should be able to respond. Published series highlight the critical incidents that can occur during transportation of children, which can be classified as physiological deterioration or equipment problems (Figure 13). Transport teams should have regular audit and risk management meetings to discuss these events.

Common critical incidents during transportation of children

	Avoidable	Early recognition and treatment
Physiological deterioration		
• Hypoxia		✓
• Cardiac dysrhythmia		✓
• Hypotension		✓
• Deterioration in Glasgow Coma score		✓
• Hypothermia	✓	
• Hypoglycaemia	✓	
Equipment problems		
• Tracheal tube blockage	✓	
• Accidental tracheal extubation	✓	
• Loss of intravenous access	✓	
• Loss of monitoring	✓	
• Ventilator malfunction		✓
• Exhaustion of oxygen supply	✓	

13

During transportation the child should be reassessed regularly using a systematic ABC approach. The position, patency and fixation of the tracheal tube are confirmed. Capnography is a sensitive way of monitoring airway security in the intubated child especially during periods of maximal risk such as loading and unloading from vehicles when clinical observation is difficult. There is a high risk of tracheal tube (< 5.0 mm internal diameter) blockage by secretions, which is reduced by humidifying inspired gas using a heat and moisture exchanger and by regular tracheal suction. Adequacy of ventilation is assessed by observing chest movement, the airway pressure gauge on the ventilator and the capnograph trace. The ventilator settings, connections and oxygen source are regularly observed. The mnemonic, DOPE, is a useful method of troubleshooting (consider **D**isplacement or **O**bstruction of the tube, **P**neumothorax and **E**quipment problems). Assessment of circulation includes evaluation of heart rate, peripheral and central pulses, capillary refill, blood pressure and central venous pressure (if monitored). Intravenous access sites are inspected regularly. Neurological status is assessed by evaluating pupil size and reactivity and fontanelle pressure. Seizure activity, which is masked by neuromuscular blockade, should be suspected if tachycardia, hypertension or pupil dilatation occur suddenly. Body temperature and blood glucose in babies can fall during transportation and should be measured regularly.

Caring for the parents
The distress to parents caused by the critical illness of their child is extreme and is exacerbated by the news of transportation to a different hospital. The transport team has limited time to gain the trust and confidence of the parents, who require verbal and written information. Most transport teams have booklets for parents and some have websites containing this information. The transport team should explain the need for transportation and the risks involved. Parents often want to accompany their child during transportation. Considerations include the available space within the vehicle, the distance to be travelled, availability of alternative transport and the severity of illness of the child. It is usual for a parent to accompany a conscious child. If the parents are not travelling with their child, alternative transportation should be arranged.

Special considerations
Occasionally it is impossible to stabilize a child before transportation because of an unstable surgical pathology such as intracranial haemorrhage. The severity and urgency of the situation should be addressed during the initial referral telephone call and a decision made whether the referring hospital should expedite transportation to the PICU or whether the transport team should collect the child. Occasionally the child is so severely ill that stabilization is impossible or futile and the child dies. This is distressing for all concerned but should be considered before attempting to transport an unstable child. Cardiac arrest or death occurring in transit is uncommon. The duration of attempted resuscitation and whether to proceed towards the PICU or return to the referring hospital should be decided in discussion with the referring consultant and the PICU consultant. Occasionally it is appropriate to divert to another hospital *en route*. ◆

FURTHER READING

Paediatric Intensive Care Society. *Standards for Paediatric Intensive Care Including Standards of Practice for the Transportation of the Critically Ill Child*. Bishop's Stortford: Saldatore, 1996.

Recommended course
Paediatric and Infant Critical Care Transport Course, Leicester Royal Infirmary. Course Director Dr P W Barry.

Systemic Analgesics in Children

David Fell

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Systemic analgesics are used to treat acute or procedural pain, postoperative pain and chronic painful conditions. They can be divided broadly into opioids or non-opioid analgesics (e.g. non-steroidal anti-inflammatory drugs – NSAIDs, tramadol; or paracetamol).

Opioids

Opioids are either synthetic compounds or derived from opium (opiates) and have affinity for and activity at μ, κ and δ opioid receptors.

Pharmacokinetics: opioids may be administered intravenously, intramuscularly, subcutaneously or orally. Conscious children dislike intramuscular injections and this route should be used only intraoperatively. Gastrointestinal absorption after oral administration involves hepatic first-pass metabolism, and bioavailability (e.g. morphine – 20%, codeine – 60%) determines effectiveness.

The volume of distribution of morphine at steady state is similar throughout infancy, childhood and adulthood, despite differences in body water distribution. Opioids are bound to plasma albumin and α_1-acid glycoproteins, the concentrations of which are lower in infants and neonates than in adults; thus, more free drug is available to receptors.

Metabolism takes place in the liver microsomal system, and phase I metabolism, for example, dealkylation (morphine and fentanyl), demethylation (pethidine), deacetylation (diamorphine) precedes phase II metabolism (conjugation). Morphine is conjugated to morphine 3-glucuronide and morphine 6-glucuronide. Conjugation is immature in early infancy, but sulphation can occur during the neonatal period. Glucuronidation, however, matures at about 3 months. As metabolism matures with age, the half-life of morphine decreases while total clearance increases to a maximum at 2–3 years. Renal function also matures during the first year and excretion is limited during this period until adult values are reached at 2–3 years. Smaller bolus doses and infusion rates should be prescribed in infants less than 6 months of age.

Opioids can be classified according to their duration of action (Figure 1). Initial redistribution determines the short clinical action of fentanyl; in higher doses (10 μg/kg) its terminal half-life is apparent.

Terminal half-life of commonly used opioids

Drug	Terminal (β) half-life
• Morphine	2.5 hours
• Pethidine	3.4 hours
• Diamorphine	1–4 hours
• Codeine	1–4 hours
• Methadone	25–45 hours
• Fentanyl	3–6 hours
• Alfentanil	1–3 hours
• Remifentanil	9.5 minutes

1

Side-effects and toxicity: side-effects of opioids include respiratory depression, sedation, nausea, vomiting, pruritus, urinary retention and stasis of gastrointestinal smooth muscle leading to delayed gastric emptying or intestinal paralysis and constipation.

Untreated respiratory depression has serious consequences in children. It occurs as a result of μ_2 receptor activation, is dependent on plasma concentration and occurs equally with all opioids at equianalgesic doses. Opioids shift the ventilatory response to carbon dioxide line to the right and decrease the slope of the line. Ventilatory rate is reduced, but in children the ventilatory depth also decreases, and somnolence supervenes. Naloxone, a μ receptor antagonist, can be used to reverse opioid respiratory depression and 10 μg/kg should be prescribed whenever opioid infusions or patient-controlled analgesia (PCA) are used, to be given if needed.

Nausea and vomiting are less common in children less than 2–3 years of age compared with teenagers, but the consequences (e.g. dehydration, electrolyte imbalance, delayed oral nutrition) are more severe. Postoperative nausea and vomiting (PONV) are associated with certain procedures (e.g. strabismus surgery, ENT procedures, orthopaedic, dental, penoscrotal or gastrointestinal surgery), but more especially with use of opioid analgesia which can cause vestibular stimulation as well as stimulation of the chemoreceptor trigger zone. Preventing PONV with intravenous anti-emetics at the end of surgery (e.g. with intravenous ondansetron, 100 μg/kg, or cyclizine, 1 mg/kg) is preferable to treating established PONV. Children are more susceptible to the extrapyramidal side-effects of anti-emetics than adults; therefore, anti-emetics with differing mechanisms of action should be given for any additional treatment. Combination therapy with dexamethazone may prove successful in the future. Rectal prochlorperazine, 5 mg, is also useful for treating established PONV in children.

Morphine is the most commonly used opioid in children. Dose–response curves for children are not established, but recommended doses are based on considerable experience in children (Figure 2). Preoperative use of morphine (e.g. in a child with acute abdominal pain) can relieve pain and assist diagnosis. Intravenous morphine may be administered in conscious children in increments of 20–50 μg/kg. Intraoperatively, 100–150 μg/kg i.v., provides morphine loading before postoperative use of PCA or intravenous infusions. Morphine causes histamine release

Recommended doses of opioids in children

Drug	Intravenous bolus	Intravenous infusion	Patient-controlled analgesia	Oral	Subcutaneous
• Morphine	50–150 μg/kg	10–30 μg/kg/hour	20 μg/kg bolus + 4–5 μg/kg/hour background	300 μg/kg	100–150 μg/kg
• Pethidine	1–1.5 mg/kg	–	–	–	1–1.5 mg/kg
• Diamorphine	25–50 μg/kg	12.5–25 μg/kg/hour	–	600 μg/kg	–
• Codeine	n/r[1] (1–1.5 μg/kg i.m.)	n/r	n/r	0.5–1 mg/kg	–
• Fentanyl	1–10 μg/kg	–	–	–	–
• Alfentanil	10–15 μg/kg	–	–	–	–
• Remifentanil	n/r	0.25 μg/kg/minute	–	–	–

[1] n/r – not recommended.

2

Pethidine is metabolized to norpethidine, which can cause excitation or convulsions in children. It has greater lipid solubility than morphine and a slightly shorter duration of effect. At equianalgesic doses it has a respiratory depressant effect similar to that of morphine. There are few indications for the use of pethidine instead of morphine.

Diamorphine (diacetylmorphine) has greater lipid solubility than morphine and undergoes rapid phase I metabolism in the liver to monoacetyl morphine and morphine. Diamorphine is sometimes given by intravenous infusion, 12.5–25 μg/kg/hour, to children in intensive care. Systemic use of diamorphine intraoperatively or postoperatively provides little advantage over morphine.

Codeine is a μ receptor partial agonist with a ceiling effect for analgesia. It has a high oral bioavailability (60%) and a rapid onset (20 minutes) after oral administration. A proportion of codeine is converted by the liver to morphine, and genetic variation results in absence of this action in about 10% of individuals. Intravenous use is contraindicated because of cardiac depressant effects. Codeine is a potent cough suppressant, and inhibition of gastrointestinal motility may cause constipation. In children, codeine is used during tonsillectomy (e.g. 1–1.5 mg/kg i.m.) or following neurosurgery. In combination with paracetamol it is an effective mild oral analgesic with morphine-sparing effects superior to paracetamol alone.

Fentanyl is a short-acting opioid with a potency 100 times that of morphine. It is lipid soluble, and has a rapid onset and short duration of action in low doses (e.g. 1 μg/kg). Its terminal half-life is greater than that of morphine in high doses (e.g. ≥ 10 μg/kg), and clearance is higher than in adults. Side-effects of intravenous fentanyl include bradycardia (as a result of central sympathetic depression) and chest wall muscle rigidity, which responds to neuromuscular blockade. Fentanyl may be used in children by intravenous bolus injection for analgesia for short surgical procedures, or as part of a balanced technique for major surgery where postoperative ventilation is considered.

Alfentanil is an ultra-short-acting opioid with moderate lipid solubility and a short half-life. Clearance in children is higher than in adults and volume of distribution is lower. An intravenous bolus, 10–15 μg/kg, provides analgesia for short surgical procedures (e.g. anal dilatation) without residual effect.

Remifentanil is a synthetic ultra-short-acting opioid with a unique mode of metabolism. It is a piperidine derivative with a side chain that undergoes rapid metabolism by RBCs and plasma esterases. Kinetics in infants and children are similar to those in adults. Its rapid metabolism and short half-life dictate its use by intravenous infusion intraoperatively. A loading dose is not recommended in children and the initial dose of 0.25 μg/kg/minute is lower than in adults. The infusion is then adjusted according to response. Remifentanil causes no histamine release but leads to rapid apnoea and can cause chest wall muscle rigidity. The intravenous line must be dismantled or flushed carefully when the infusion is discontinued to avoid even small residual volumes of remifentanil being inadvertently injected by subsequent infusions. Adequate 'follow on' analgesia with other opioids or regional analgesic techniques must be ensured because of its short action.

Postoperative opioid administration

Intravenous infusion – a loading dose of intravenous morphine is given intraoperatively and the intravenous delivery system maintains a therapeutic blood concentration of the drug – the so-called 'analgesic corridor'. The initial rate of infusion is set at 20 μg/kg/hour for children, but lower in infants and neonates, with a range of 10–30 μg/kg/hour (Figure 2).

The intravenous infusion should be given through a dedicated cannula. Alternatively, a non-return valve can be included in the line to prevent retrograde infusion of morphine into another infusion line.

Morphine infusions may be used in the ICU for sedation during mechanical ventilation or for children breathing spontaneously after surgery for whom PCA is inappropriate. Breakthrough pain can be treated with a bolus injection of morphine, 20 μg/kg, after suitable assessment and evaluation of the child's discomfort. Concurrent monitoring of vital signs during morphine infusions is important.

PCA has been employed successfully both postoperatively and for other acute pain control in children as young as 4 years, but a realistic target age is 5–6 years. The PCA system should be explained to the child preoperatively. The importance of only the child pressing the demand button should be stressed, but they may be encouraged to do this by parents or nurses. A loading dose of morphine should be given intraoperatively. A dedicated intravenous cannula is attached via a non-return valve to a delivery system. Figure 3 lists the essential practical components of the technique. A bolus dose of morphine, 20 μg/kg, is an optimum dose, with a lockout period of 5 minutes and a maximum 4-hourly delivery of 400 μg/kg. If morphine, 1 mg/kg, is diluted in 50 ml saline, then 1 ml contains 20 μg/kg which is used as a standard volume bolus.

In contrast to the case in adults, younger children will benefit from a background infusion rate of 20% of the bolus dose (4 μg/kg/hour).

Nurse-controlled analgesia is advocated by some, but the rate of background infusion is closer to that of a constant rate infusion (20 μg/kg/hour) and the nurse demands equate to a 'top-up' intravenous bolus.

Subcutaneous administration – bolus subcutaneous administration may be used to avoid a painful needle injection. A small-gauge (23 SWG) intravenous cannula is inserted during general anaesthesia beneath the skin of the chest, abdominal wall or deltoid area. When covered with a transparent dressing, this provides a suitable means of painless administration postoperatively. Morphine, 100–150 μg/kg, is used. Alternatively, subcutaneous infusions can be attached via a delivery tube to a syringe pump containing morphine, 1 mg/kg in 20 ml saline solution. Infusion of 0.4 ml/hour results in a dose of 20 μg/kg/hour. Subcutaneous PCA can be used with a demand bolus of 0.4 ml (20 μg/kg) of the above solution with a lockout of 5 minutes.

Requirements for safe use of intravenous morphine infusions

- Clear labelling and prescription
- Lockable syringe pump
- Infusion pump < 80 cm above patient
- Dedicated intravenous cannula
- Antisyphon or one-way valve in line
- Regular pain and side-effect monitoring
- Prescription for naloxone (10 μg/kg) available
- Patient-controlled analgesia for those over 5 years
- No intracranial pathology

Monitoring during opioid treatment: it is important to monitor pain, respiratory frequency, sedation, pulse oximetry and side-effects in patients receiving opioid analgesia. Pain evaluation (see page 138) using a system appropriate to the age of the patient should be recorded on the patient's chart along with pulse rate and arterial blood pressure. Respiratory frequency is age-dependent and, though a potentially poor indicator of respiratory depression in some age groups, is important to monitor during sleep. The thresholds for alert according to age are given in Figure 4. A simple sedation score can be charted with other 'vital signs'.

Respiratory rate and age

Age	Threshold respiratory rate (breaths/minute)
• < 6 months	20
• 6 months–2 years	16
• 2–10 years	14
• > 10 years	12

4

Non-opioid analgesics

Tramadol is a synthetic codeine derivative which is a racemic mixture. Delta tramadol has opioid μ receptor affinity and both delta and laevo tramadol inhibit monoamine uptake. The active metabolite (O-demethyl tramadol) has similar pharmacokinetics in children and adults, and a half-life of 6.4 hours. Tramadol, 2 mg/kg i.v., given intraoperatively results in less respiratory depression in children than pethidine, 1 mg/kg, and provides postoperative analgesia. It may have a role in paediatric day- case anaesthesia for minor to moderate surgery. Initial fears of intraoperative awareness in adults with tramadol have subsided with modern techniques. Tramadol should be avoided in epileptic patients because seizure activity has been reported following rapid intravenous injection.

Ketamine is an N-methyl-D-aspartate receptor antagonist which is useful in subanaesthetic doses as an analgesic. Ketamine, 0.5 mg/kg i.v., may be given intraoperatively to provide analgesia equal to that of morphine. Recovery may be slower. Anaesthetic doses can cause severe emergence phenomena that are attenuated with concomitant use of a benzodiazepine (e.g. midazolam, 0.5 mg/kg). Analgesic doses of ketamine produce fewer side-effects, but can cause catecholamine stimulation. Ketamine is useful in children undergoing burns dressings and skin grafts and intramuscular ketamine, 0.5 mg/kg, can be given during tonsillectomy.

Paracetamol is an acetanilide derivative. It is an inhibitor of cyclo-oxygenase in the CNS and has no peripheral anti-inflammatory effects. In children, oral or rectal paracetamol is widely used to control pain of mild or moderate intensity and its side-effects are minimal. An intravenous preparation, propacetamol, has been available in Europe for some time but is not available in the UK. Propacetamol is acetylparaminophenol diethyl aminoacetic ester, which is hydrolysed in vivo by esterases and converted to paracetamol. Propacetamol, 1 g, is equivalent to paracetamol, 500 mg.

Oral paracetamol is absorbed from the small intestine and results in peak blood concentrations after 30–60 minutes. Rectal absorption is slower because of a two-stage process of suppository dissolution and rectal absorption, and peak plasma concentrations are reached only after 1.5–4 hours. Paracetamol is unbound to plasma proteins and undergoes hepatic phase I n-oxidation and phase II conjugation with glucuronide, sulphate and glutathione. Sulphation is an important pathway of excretion in babies and children, indicated by lower glucoronide: sulphate ratios (Figure 5). Its half-life is 1.5–3 hours across age groups despite differences in the way it is conjugated.

The pharmacodynamics of paracetamol in children have undergone recent re-evaluation. Recommended traditional doses of paracetamol of 10–15 mg/kg are for its antipyretic effect, and associated blood concentrations are about 10–20 mg/litre. However, analgesic blood concentrations of paracetamol exceed this value, and are achieved only at higher doses. Initial loading doses are required followed by a maintenance (4-hourly) dose (Figure 6). Provided a maximum dose of 90 mg/kg/24 hours is not exceeded, toxic effects are uncommon and may not occur until 120 mg/kg/24 hours.

Paracetamol exists in palatable preparations in syrup form, and soluble paracetamol may be used in older children. Discrete suppository sizes demand an approximation of doses for rectal use. Contraindications to the use of rectal suppositories include anorectal pathology or surgery and patient preference. Preoperative paracetamol has been advocated before day-case or dental surgery. During anaesthesia, rectal paracetamol can be administered after parental and patient consent obtained preoperatively. Suppositories are best given immediately after induction of anaesthesia to allow time for absorption and for adequate therapeutic blood concentrations to be present on waking. Postoperative oral paracetamol can be given after return of gastrointestinal function, or rectal doses can be continued.

Paracetamol conjugation – glucuronide:sulphate ratios

Age	Glucuronide:sulphate
Neonate	0.34
3–9 years	0.75
12 years to adult	1.6–1.8

5

Paracetamol doses for analgesia

	Oral (mg/kg)	Rectal (mg/kg)
Loading dose	20	30–40
Maintenance dose (4-hourly)	15	20
Maximum dose in 24 hours	90	90

6

NSAIDs

NSAIDs are chemical derivatives of acetic acid, propionic acid, anthranilic acid or oxicams with anti-inflammatory, antipyretic and analgesic properties. NSAIDs are often used in inflammatory arthritis, and only a few (ibuprofen, mefanamic acid, diclofenac, piroxicam) have dose recommendations for children. However, some drugs have been used to control acute postoperative pain in children and can significantly decrease postoperative opioid requirements.

NSAIDs reversibly block the action of cyclo-oxygenase on arachidonic acid released at injured cell membranes and inhibit peripheral prostaglandin production. This mechanism also accounts for the side-effects of NSAIDs (i.e. exacerbation of asthma, peptic ulceration, renal impairment, platelet function inhibition). There are few side-effects in children when NSAIDs are used for acute pain relief, but short-acting NSAIDs (flurbiprofen, diclofenac, ibuprofen) are preferred to medium-acting or long-acting drugs. Contraindications include renal immaturity (e.g. in infants), actively treated asthma and coagulation defects.

Absorption from the gastrointestinal tract is rapid because NSAIDs are weak acids. Rectal administration results in comparable, but delayed, plasma concentrations. There is little first-pass metabolism, and oral bioavailability is high (55–80%). NSAIDs are bound to plasma proteins and have a low volume of distribution; they undergo hepatic metabolism and conjugation. Pharmacokinetics of NSAIDs used for juvenile rheumatoid arthritis indicate no differences from those of adults. NSAIDs are 'opioid-sparing', and reduce morphine requirements after major surgery.

Diclofenac is short acting (terminal half-life about 1 hour). It may be given orally or rectally using an acute dosing regimen of 1–2 mg/kg 8-hourly. Acute postoperative pain (e.g. after day- case herniotomy, orchidopexy or minor surgical procedures) can be anticipated by rectal administration intraoperatively after obtaining appropriate parental and patient consent. After tonsillectomy, diclofenac may be associated with bleeding, but is probably safe in a single dose.

Ibuprofen has weak anti-inflammatory properties, low potency, and fewer side-effects than other NSAIDs. It has a short half-life (1–4 hours). As a sole analgesic after surgery, its potency is insufficient, but it is useful for mild postoperative pain and after opioid requirements have declined following major surgery. Regular oral doses (4–6 mg/kg) of up to 40 mg/kg/24 hours may be used.

Ketorolac has a higher clearance in children than in adults but a larger volume of distribution resulting in a similar half-life (about 6 hours). It may be used intraoperatively at a dose of 0.5 mg/kg i.v. (maximum 10 mg) to augment opioid analgesia or during minor surgery in children. After tonsillectomy, early blood loss can be significant in children given ketorolac.

Piroxicam is a long-acting NSAID with a half-life more than 30 hours. Its merit in children is that it is recommended for use in juvenile rheumatoid arthritis at a dose of 0.3–0.6 mg/kg, and it is available in a lingual melt preparation. It has been used for analgesia in dental surgery.

Paediatrics: Neonatal

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Anatomical and Physiological Development: from the Fetus through Childhood

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As the future human being develops from a single cell into the mature adult the physiology of each individual organ and the integrated systems of the body undergo many developmental changes. Although performance in the early stages may seem crude, fragile and poorly controlled, this usually reflects a stage needed to cope with the challenges of the current environment. For example, the presence of fetal haemoglobin *in utero* allows oxygen to be extracted from the placenta in a very low oxygen environment compared with that after birth. In considering developmental physiology (ontogeny) it is necessary to see fetus, preterm newborn, neonate, infant, child and adolescent as almost separate organisms that merge into each other, but with sometimes very different physiology. Moreover, different systems mature at different rates.

Birth is a stressful event but it is this stress that acts as a stimulus for initiating extrauterine physiological changes and sustaining essential functions in the newborn, such as respiration, suckling, glucose metabolism and thermoregulation. The physical stress of delivery (vaginal squeeze), loss of the nourishing placenta, and the accompanying hormonal stress response are jointly responsible for these physiological adaptations.

Cardiovascular system

Changes in the circulation at birth

During fetal life the placenta is the primary organ of oxygenation. Pulmonary vascular resistance is high and less than 10% of cardiac output passes through the lungs. The two ventricles are effectively in parallel, with the dominant right ventricle pumping about two-thirds of the combined ventricular output via the pulmonary artery, through the ductus arteriosus and into the aorta. In addition, relatively oxygenated blood from the placenta (saturation 65%) passes preferentially through the foramen ovale, left atrium and left ventricle to supply the heart, brain and upper body. Venous blood from the superior vena cava passes through the right ventricle and ductus arteriosus, supplying the lower body with blood of reduced saturation (55%). The ductus venosus shunts blood from the umbilical vein to the inferior vena cava, thus bypassing the liver and preventing desaturation of blood by the liver. This series of shunts (the ductus venosus, foramen ovale and ductus arteriosus) act to protect the brain and heart by allowing optimal oxygenation, with locally produced prostaglandin E_2 (PGE_2) maintaining patency of the ductus arteriosus.

At birth, with onset of spontaneous ventilation and loss of the placenta, the circulation changes dramatically. With the first breath, pulmonary vascular resistance falls rapidly, allowing blood to flow from the right ventricle through the lungs. As placental blood flow ceases with clamping of the umbilical cord, systemic vascular resistance rises, resulting in a reversal of right to left blood flow through the ductus arteriosus. Exposure to oxygenated blood and reduced PGE_2 production stimulates ductal constriction, with functional closure by 24 hours (a shunt murmur may be audible before closure). Histological obliteration occurs by 3 weeks in most normal term infants. Preterm babies have a higher incidence of patent ductus arteriosus, and may require medical treatment with a prostaglandin synthetase inhibitor such as indometacin (indomethacin), a cyclooxygenase inhibitor such as ibuprofen, or surgical ligation.

After the first breath, pulmonary venous blood returns to the left atrium, causing pressure in the left atrium to exceed that in the right. The valve-like foramen ovale closes, thus preventing deoxygenated blood from the right atrium crossing to the left. The ductus venosus closes passively owing to absent blood flow.

Persistent pulmonary hypertension of the newborn: although pulmonary vascular resistance is much reduced after birth, the pulmonary arteriole medial walls are muscular. If the neonate becomes hypoxic or acidotic, pulmonary vasoconstriction can lead to significant shunting through the foramen ovale and reversion to a fetal-type circulation. This condition is called persistent pulmonary hypertension of the newborn. Oxygen, hyperventilation or nitric oxide may be needed to reverse the condition, and extracorporeal membrane oxygenation has been used successfully in severe cases.

The heart as a pump

The newborn heart consists of cardiac myofibrils that are poorly organized and lack the structured architecture of the mature heart. The increased ratio of connective tissue to contractile tissue compared with adults results in limitation in myocyte contractility and ventricular compliance. In addition, calcium metabolism is immature in neonatal myocytes. Consequently, there is a relatively flat Starling curve, and while inadequate preload is poorly tolerated, overloading results in early cardiac failure. The stroke volume is relatively fixed and increases in cardiac output are achieved largely by increases in heart rate (cardiac output = heart rate x stroke volume). Conversely, bradycardias secondary to hypoxia, acidosis or cold adversely affect cardiac output. Normal heart rate at birth lies in the range 100–170 beats/minute, decreases with age, and reaches adult values by puberty (Figure 1).

Both ventricles weigh the same at birth, though the right ventricle is dominant in fetal life, possessing a thicker wall at delivery. The left ventricle enlarges rapidly after birth, and by 6 months the relative sizes of the ventricles are similar to adults. This change is demonstrated by the ECG, which shows right axis deviation at birth (up to +180°) changing to +90° by 6 months.

Normal values in childhood

Age	Blood pressure Systolic (mm Hg)	Blood pressure Diastolic (mm Hg)	Heart rate (beats/minute)
Preterm or 750 g[1]	45	25	>120
Birth	60	35	>120
Neonate	70–80	40–50	120–150
3–6 months	80–90	50–60	120–140
1 year	90–100	60–80	110–130
5 years	95–100	50–80	90–100
12 years	110–120	60–70	80–100

[1]A good rule of thumb for preterm infants is that mean arterial blood pressure is less than or equal to gestational age in weeks.

Source: British Association of Perinatal Medicine

Cardiac rhythm

Oxygen rather than atropine should be the anaesthetist's first response to bradycardia; indeed giving atropine before intubation in infants may mask bradycardias occurring as a warning sign of hypoxia.

Supraventricular tachycardia is the next most likely arrhythmia, and usually responds to vagal manoeuvres or first-line pharmacol-ogical intervention with adenosine.

Circulating blood volume

The average neonatal circulating volume is 80–85 ml/kg, falling to 75 ml/kg between the ages of 6 weeks and 2 years, and about 72 ml/kg thereafter. Infants tolerate fluid overload poorly because they are unable to redistribute or excrete extra volume. They also cope badly with sudden or massive fluid loss, such as diarrhoea and vomiting. Sinus tachycardia of 200 beats/minute or more can occur in dehydrated or septic infants. Low blood pressure is a late sign of cardiovascular compromise in young children.

Respiratory system

Airway anatomy

Infants have relatively large heads and short necks, and hyperextension compromises rather than assists visualization of airway structures during intubation. As the tongue is large and the mouth small, the insertion of an oropharyngeal airway may reduce pharyngeal obstruction in infants under 6 months of age. Infants are obligate nose breathers with narrow nasal passages, therefore any increase in secretions or airway oedema significantly compromises airflow. Resistance is proportional to 1/radius to the power of 4; according to the Hagen–Poiseuille law. Children and infants are also more prone to laryngospasm than adults.

Tonsils and adenoids, especially when inflamed, may impinge on airway patency and in severe cases cause sleep apnoea and pulmonary hypertension.

The trachea is short in infants and children (average length in a term neonate is 4 cm), and care must be taken to avoid inadvertent endobronchial intubation. A long tube intermittently stimulating the carina causes vagal effects (e.g. bradycardia), which may be marked in neonates. The main differences in airway anatomy at different ages are given in Figure 2. Appropriate endotracheal tube lengths are given in Figure 3.

Airway anatomy

	< 1 year	1–8 years	> 8 years
Upper airway	Narrow nasal passages Relatively large tongue	Tonsillar and adenoidal hypertrophy	More adult type features
Larynx	Anterior position C3–4 level	More posterior position C4–5 level	Posterior position C4–5 level
Epiglottis	Narrow, U-shape Long and thin Angled posteriorly	Wider and flattened Shorter Angled horizontally	More adult type features
Trachea	Average diameter 5 mm Narrowest point: cricoid (hence uncuffed endotracheal tube)	Average diameter 10 mm Narrowest point: cricoid (hence uncuffed endotracheal tube)	Average diameter 15 mm Narrowest point: vocal cords (hence uncuffed endotracheal tube)
Bronchioles	Average diameter 0.1 mm	Average diameter 0.15 mm	Average diameter 0.2 mm
Alveoli	Average diameter 0.075 mm	Average diameter 0.15 mm	Average diameter 0.3 mm

Recommendations for endotracheal tube length and diameter (> 1 year olds)

The Advanced Paediatric Life Support (APLS) formulae

Internal diameter (mm) = Age/4 + 4

Oral tube length (cm) = Age/2 + 12

Nasal tube length (cm) = Age/2 + 15

Lung development and the first breath

In utero the fetal lung is filled with fluid essential for lung maturation and development. The fetus makes irregular breathing movements which help the development of respiratory muscles, including the diaphragm and intercostal muscles.

As full term approaches, catecholamines and triiodothyronine (T3) stimulate the reabsorption of pulmonary fluid by reversing the chloride pump. Final reabsorption is stimulated by passage through the birth canal. This is less effective in babies born by caesarean section, often leading to transient tachypnoea of the newborn. Invasive ventilatory support is seldom required when this exists in isolation.

When newborns enter the world, somewhat hypoxic and hypercarbic, they are greeted by a barrage of sensory stimuli, resulting in the first breath, and usually followed by lusty crying. The first breath generates a negative pressure of about 50 cm H_2O, drawing in about 80 ml of air and expanding the functional residual capacity. Failure to do this efficiently results in ventilation–perfusion mismatch. The first breath initiates pulmonary vasodilatation, coinciding with the increase in systemic vascular resistance.

The bronchial tree is fully developed at birth, in contrast to the alveoli, which continue to expand in size and number, increasing the surface area of the lung up to 25 times. This partially explains why the respiratory function of infants who had severe lung damage as neonates may improve significantly with age, though some residual damage usually persists.

Surfactant: endogenous surfactant is a protein-bound phospholipid molecule produced by the endoplasmic reticulum of type 2 pneumocytes from about 26 weeks' gestation, although in inadequate amounts until 32–34 weeks' gestation. Secretion is stimulated by endogenous cortisol, β-adrenergic drugs (via the cAMP pathway), thyroid hormone, prolactin and *ex utero* by gas inhalation and alveolar distension. Surfactant acts to reduce surface tension at the air–fluid interface, thus reducing opening pressures and maintaining alveolar distension.

Extreme preterm infants are surfactant deficient, leading to the respiratory distress syndrome and often the need for ventilatory support. Studies have shown that elective intubation at birth with administration of surfactant by the endotracheal route in the first hour produces better respiratory outcomes than attempted reversal of respiratory distress syndrome once it has developed. Thus, a prophylactic dose of 4 ml/kg via the endotracheal tube should be considered in all babies born at less than 30 weeks' gestation or preterm babies under 1.5 kg.

Improvement in lung compliance following surfactant is rapid and vigilance is essential to prevent severe over ventilation and air leaks. A further dose of surfactant may be given after 6 hours if the infant's fraction of oxygen in inspired air remains above 30%, but further doses are seldom required.

Term babies may also be surfactant deficient if they suffer severe acidosis or hypoxia and secondary surfactant deficiency may occur in babies with Group B streptococcal pneumonia or meconium aspiration syndrome. Infants of diabetic mothers are vulnerable to the condition because insulin delays type 2 pneumocyte maturation and prostaglandin production, Hyperglycaemia similarly delays lung development.

The use of maternal antenatal steroids has helped to prevent respiratory distress syndrome. Two doses of intramuscular betamethasone or dexamethasone given 12 hours apart before delivery significantly reduce the likelihood of severe respiratory distress in the newborn.

Mechanics of breathing
Babies, especially preterm neonates, have extremely compliant chest walls with compressible, horizontally aligned ribs. The diaphragm is the main respiratory muscle in infancy, leading to subcostal (and intercostal) recession during periods of respiratory distress. As the infant grows in the first year of life, the percentage of type 1, slow-twitch muscle fibres that fatigue more slowly, increases from 10% to 25% (adult level). The fairly protuberant abdomen of the small child can also affect respiration by impinging on lung volumes.

Static lung volumes in infants are proportionately similar to those of adults, though alveolar ventilation is larger and closing volume is higher. During mechanical ventilation, infants require higher volumes by weight; up to 150 ml/kg/minute in neonates compared with 60 ml/kg/minute in adults. Although infants may require similar pressures to adults, they require higher rates of ventilation, mimicking normal physiology (Figure 4).

Respiratory physiology

	Neonate	Adolescent
Respiratory rate (breaths/min)	25–40	12–18
Airway compliance (ml/cm H_2O)	5	100
Airway resistance (cm H_2O/litre/sec)	30	2
Vital capacity (ml/kg)	30–35	50–55
Minute ventilation (ml/kg)	200	100
Tidal volume (ml/kg)	5–7	7–10
Alveolar ventilation ml/kg/min)	130	60
Metabolic rate (ml O_2/kg/min)	6.5	3.5
PaO_2		
(kPa)	9	12.5
(mm Hg)	68	95
$PaCO_2$ (kPa)	4.5	5.3

Control of breathing
Newborns are sensitive to changes in the partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) in arterial blood, though many other factors such as gestational and postnatal age, temperature, wake–sleep cycles and drugs all affect their responses and respiratory drive is easily lost. Preterm newborns are less responsive to increased inspired carbon dioxide than healthy term infants. Neonates react to hypoxia in a different way from older infants. In the first week of life, in well, awake babies, hypoxia produces brief hyperpnoea followed by centrally mediated respiratory depression and reduced minute volume. In the following weeks, as chemoreceptors mature, the infant develops a predominantly hyperpnoeic response to hypoxia, with apnoea and bradycardia being more ominous signs. Hypothermic babies show respiratory depression without an initial hyperpnoea response. In sleeping infants, the arousal response to hypoxia (normal in adults) is diminished, and often completely absent during rapid-eye movement (REM) sleep. Intercostal muscle activity is inhibited during REM sleep, as are the lung and chest wall reflexes responsible for determining respiratory rate and tidal volumes.

Periodic respiration, in which rapid shallow breathing alternates with apnoeas of up to 10 seconds, is normal in many infants. More prolonged apnoeas, lasting more than 20 seconds, may be associated with bradycardia and require stimulation or even bag-and-mask ventilation. In preterm babies, apnoeas usually respond to oral xanthines (e.g. caffeine, theophylline), though occasionally continuous positive airway pressure is needed until central chemoreceptors mature. Apnoeas may also have non-respiratory causes such as gastro-oesophageal reflux, seizures, sepsis or intracranial haemorrhage.

Fluid homeostasis

Body fluid composition changes with age, gender and amount of adipose tissue. Neonates have a higher percentage of total body water than older children, with a relatively higher extracellular to intracellular fluid ratio. This makes them particularly sensitive to fluid loss and dehydration. Fluid output depends on metabolic rate, urine, stool and insensible losses. These are high in small infants, particularly when under radiant warmers or phototherapy lights.

Normal fluid shifts occur in the first few days of life. Up to 5% of body weight shifts from the extracellular to the intracellular compartment, with excess fluid being excreted. This results in loss of up to 10% of birth weight in the first week, usually regained by day 10. Careful attention to fluid replacement is essential in infants and small children, particularly when starved perioperatively. The APLS formula for intravenous maintenance fluid calculations is:

- 4 ml/kg/hour for the first 10 kg of body weight
- + 2 ml/kg/hour for the second 10 kg of body weight
- + 1 ml/kg/hour for each subsequent kg of body weight.

Preterm babies need extra fluid because of their high surface area to body weight ratio; often more than 200 ml/kg/24 hours.

Renal function

The first nephrons form in the embryo during week 5 and are functional from week 8, reaching their full complement by week 36. After this there are no new nephrons; the existing nephrons grow in size and cell number.

Renal blood flow comprises 5% of cardiac output at birth, but as renal vascular resistance falls with time, this increases to 20% by 1 month of age, with increased flow to cortical areas. The glomerular filtration rate (GFR) escalates logarithmically in the first 2 years of life. Nonetheless, infants remain ill-equipped to handle massive water loads, and common neonatal problems such as hypoxia, hypothermia and low-output states may all compromise GFR. Because of this renal immaturity, levels of renally excreted drugs (e.g. aminoglycosides) should be measured regularly and doses adjusted accordingly.

In the mature kidney, water is reabsorbed in the proximal convoluted tubule with glucose, amino acids, phosphate, sodium and bicarbonate. Water is also absorbed more distally under the influence of antidiuretic hormone (ADH), with sodium reabsorbed under the influence of aldosterone in exchange for excreted potassium and hydrogen ions. Infants have immature renal tubular systems with a relative inability to handle solute loads, notably sodium and glucose. They have difficulty excreting sodium in the first week of life, and trouble reabsorbing it thereafter. Preterm neonates tend towards hypernatraemia, often reflecting fluid deficit and increased fluid requirement. After the first month of life, the reference ranges for sodium (135–145 mmol/litre) and potassium (3.5–5.5 mmol/litre) for different age groups vary little.

Preterm infants are unable to effectively excrete hydrogen ions or retain bicarbonate as compensation for acidosis; indeed bicarbonate levels remain lower on average in those under 5 years compared with older individuals (18–25 compared with 23–26 mmol/litre).

Phosphate levels are high in those less than 1 year old, with the highest levels in preterm infants (up to 2.65 mmol/litre). This is optimal for bone growth and prevention of metabolic bone disease; this level drops to about 1.5 mmol/litre by adolescence.

Calcium homeostatic mechanisms are sluggish in preterm infants. Calcium levels must be adjusted for albumin level and temperature and pH should also be considered when interpreting calcium levels.

Measures of renal function on the first day of life reflect maternal values, with more accurate results obtained from day 2 onwards. Urea levels change with age from 0.7–6.7 mmol/litre in term and preterm newborns, 1.8–8.2 in those aged 1–52 weeks, 2.1–6.4 in those 1–13 years to 2.9–7.5 in those over 13 years. Creatinine levels in preterm infants are 100 μmol/litre on day 2, 80 on day 7, and 50 on day 28. In term infants they are 70 on day 2, 45 on day 7, and 30 on day 28. They are 50 μmol/litre until 1 year of age. In those aged 1–9 years they are 35 and 75 in those over 9 years.

Hepatic function and metabolism

During intrauterine life, the fetus receives glucose via the placenta for growth, deposition of stores and maintenance of basal metabolic rate. Fetal glucose regulation is independent of maternal hormonal control and in the case of placental insufficiency endogenous fetal glucose production occurs. The fetus also utilizes ketone bodies and lactate.

At birth, following placental separation, the infant must find alternative energy sources. Aerobic metabolism is rapidly replaced by anaerobic metabolism. Fat from adipose tissue stores and from feeds becomes the key substrate. Plasma insulin levels drop while catecholamine and glucagon levels rise rapidly stimulating glycogenolysis (in heart muscle, liver and brain), gluconeogenesis (in liver from alternative energy sources such as ketones, fatty acids and lactate), lipolysis and ketogenesis.

In the immediate postnatal period, glucose remains the main metabolic substrate for most organs, except for the brain which may prefer lactate. Later in the neonatal period, ketones are preferred to glucose for cerebral metabolism. The neonatal brain uses ketones more efficiently than older brains do.

If establishment of enteral feeding is slow, hypoglycaemia may occur. Neonates may be asymptomatic at blood glucose levels below 2.5 mmol/litre, or they may appear jittery, lethargic, sweaty, or apparently 'septic'. Changes in auditory evoked potentials on EEG are demonstrable at blood glucose levels of 2.5 mmol/litre and less.

Prolonged hypoglycaemia must be avoided, by cup feeds or intravenous dextrose if necessary. An initial intravenous bolus of 10% dextrose, 5 ml/kg, should be given over 1–2 minutes, checking the blood glucose response soon after. If a dextrose infusion is required to maintain the blood glucose above 2.5 mmol/litre, 10% dextrose at the physiological rate of 3 ml/kg/hour (i.e. 5 mg/kg/minute) is given. The use of 50% dextrose in not recommended because rebound hypoglycaemia may occur and sudden osmotic fluid shifts in the brain predispose to cerebral oedema.

Infants at risk of hypoglycaemia include preterm infants, small (2.5 kg) or large (over 4 kg) babies, infants with intra-uterine growth retardation caused by lack of subcutaneous fat and muscle wasting, infants of diabetic mothers and cold or asphyxiated babies. Septic babies may demonstrate hypoglycaemia, but hyperglycaemia may also be an early warning sign of sepsis in ill preterm neonates.

Older children may also be prone to hypoglycaemia when unwell. Any child with acute neurological symptoms should have their blood glucose level checked urgently, with 10% dextrose, 5 ml/kg i.v., given as a bolus if levels are below 3.5 mmol/litre.
Few normal children have very low blood sugars even when extremely unwell. Inherited metabolic disorders may be unmasked by illness and are worth considering especially if hypoglycaemia is associated with a metabolic acidosis.

Feeding
Breast milk is the feed of choice for the first 4–6 months of life because it has immunological benefits and is more easily handled by the immature gut. Newborns have enzymes for the breakdown of carbohydrates such as sucrase, lactase, maltase and isomaltase, but amylase and proteases develop after 3 months of age, reaching adult levels by 2 years. Introducing solids too early is poorly tolerated, often causing diarrhoea.

Bilirubin
During intrauterine life, the fetus excretes fat-soluble unconjugated bilirubin via the placenta and maternal liver. There is a physiological rise in bilirubin soon after birth, owing to an increased bilirubin load and immaturity of the hepatic enzymes. The peak occurs on days 3–4, owing to immature oxidation–reduction reactions (phase I), with levels dropping in the second week of life as conjugating enzymes needed for glucuronidation mature (phase II). This drop takes longer in preterm babies. Lower treatment thresholds for phototherapy are used in preterms, because the blood–brain barrier is less developed and the risk of kernicterus or bilirubin encephal-opathy (damage to basal ganglia, auditory and occulomotor pathways) is higher than in term infants at similar bilirubin levels. Phototherapy works by detoxifying bilirubin and promoting its excretion by non-conjugatory means (e.g. urinary excretion).

Factors that may exacerbate physiological jaundice include polycythaemia or haemorrhage (due to increased red cell breakdown and turnover), hypoalbuminaemia (reduced protein binding), dehydration and breast feeding.

Drug excretion
Infants handle hepatically excreted drugs differently from older children and adults because of immature enzyme systems and the difference in blood supply to the liver. Infants receive a higher proportion of their hepatic blood supply from the portal vein than from the hepatic artery. Any increase in intra-abdominal pressure (e.g. post-abdominal surgery) reduces clearance of hepatically excreted drugs such as morphine or fentanyl.

Thermoregulation
Infants lose heat more readily than older children or adults because of their higher surface area to body weight ratio and relative paucity of subcutaneous fat. Heat loss occurs by evaporation, radiation, convection and to a lesser extent, conduction, as well as by insensible losses (e.g. through respiration). Newborns should be nursed in a thermoneutral environment, at an ambient temperature that minimizes oxygen consumption and heat loss. Preterm infants in the first week of life have particularly thin skin and high evaporative losses of heat energy and water (skin matures as a function of post-natal age). They therefore require higher ambient temperatures and humidity.

Unlike older children and adults who generate heat involuntarily by shivering, newborns rely on non-shivering thermogenesis to increase their basal metabolic rate. This is a function of their unique brown fat, present in the first few weeks of life as an adaptive, protective entity. These specialized adipose cells are situated around the kidneys and adrenals, in the mediastinum and around the scapulae. They are abundant in mitochondria and have a rich blood and autonomic nerve supply. Noradrenaline in sympathetic nerve endings stimulates the hydrolysis of triglycerides to fatty acids and glycerol, resulting in oxygen consumption and heat production. The resting metabolic rate is high in newborns, reaching a maximum of 50 kcal/m^2/hour by 3–6 months, then levelling off.

CNS
The newborn brain is immature, and though most responses are reflex or instinctive, it is extremely sensitive to hypoxia, hypercarbia and metabolic derangements, especially hypoglycaemia. Any such insult may cause jitteriness, seizures, acute collapse or chronic neurological deficit. Neonates have relatively impaired cerebral autoregulation of blood flow, and sudden fluctuations in blood flow can be extremely harmful. Preterms, in particular, have friable blood vessels in the germinal matrix and periventricular area, with intraventricular haemorrhage occurring easily. Obsessive attention to PaO_2 and $PaCO_2$ is essential in ventilated babies because hypocarbia, hypercarbia and hypoxia are all detrimental to newborn brains. Paradoxically, despite this ‘fragility’, infant brains are more plastic than those of older children or adults, and if an injury is moderately severe but not devastating, recovery may be better than expected, with different parts of the brain apparently taking over the functions of damaged areas.

Pain pathways
Nociceptive pathways and their neurophysiological responses are present even in extremely preterm infants. At 6 weeks’ gestation the dorsal horn cells in the spinal cord are forming synapses in the developing sensory neurons. These grow peripherally, reaching the skin of the limbs by 11 weeks, the trunk by 15 weeks and the remaining skin and mucosal surfaces by 20 weeks. The term neonate has at least as many peripheral nerve endings as an adult. Specific neurotransmitter vesicles are developing by 13 weeks, with completion by 30 weeks.

From week 24 the neurons start to mature biochemically, with production of glial-specific proteins and enzymes. Gyral formation and dendritic growth in the cerebral cortex begin at week 28. The newborn brain weighs about 350 g, increasing in size dramatically over the first 4 years of life to about 1000 g. This is largely due to the processes of myelination and dendrite formation, which is most rapid in the first 6 months of life.

The nerve tracts for nociception are fully myelinated to thalamic level by 30 weeks, with myelination of the thalamocortical tracts by 37 weeks. This lack of myelination does not imply lack of function; indeed the lack of inhibitory pathways increases rather than decreases afferent nociceptor transmission in the spinal cord. In other words, neonates may display hypersensitive responses to unpleasant stimuli because they lack the maturity in their inhibitory pathways needed to dampen down the response.

Auditory and visual evoked responses, though immature, are present by 28 weeks, and positron emission tomography scans have shown that increased glucose uptake, and thus increased cerebral metabolism, is highest in sensory areas of the fetal brain.

These factors lead to the conclusion that even extreme preterms experience pain and discomfort, though interpreting its expression may be difficult for the observer. Noxious stimuli such as heel pricks, generally produce physiological changes in variables such as heart rate and blood pressure and alter facial expression and behaviour. These changes may be of assistance in scoring the severity of neonatal pain and discomfort, as changes can be objectively measured when local anaesthetic or other analgesic measures are used. There is evidence that newborns may develop hypersensitivity and hyperalgesia to repetitive painful stimuli. Fitzgerald suggested that infants born at 26 weeks' gestation show a flexion withdrawal response to painful stimuli and although they are not cortically equipped to experience the unpleasant emotional aspect of pain, it is likely that this same sensitivity is true of a 26 week fetus *in utero*. Inadequate analgesia in newborns may cause long-term behavioural effects. It has been shown that circumcised infants display exaggerated pain responses months later following vaccination. These responses could be attenuated by the use of local anaesthetic agents, suggesting the existence of a pain memory even in very young infants.

Use of appropriate sedation and analgesia in infants, especially neonates, requires careful planning and consideration. In neonates, the pharmacodynamic susceptibility to opioids increases with decreasing gestational age, with changes in the number and type of opioid receptors. It is difficult, however, to separate true receptor-based or effector-based sensitivity from the effects due to selective distribution to the brain following administration.

Influence of age on the delivery of drugs to the brain
Lipid-soluble drugs (e.g. fentanyl) are redistributed rapidly out of the central compartment at a rate depending on cardiac output, regional blood flow, presence of shunts, protein binding, sequestration within peripheral tissues and membrane permeability of the drug. The neonatal brain receives a much higher proportion of cardiac output than does the adult brain. As a result, lipid-soluble drugs enter the CNS rapidly, reaching effectively high peak levels at effector sites (biophase). Offset is much slower than in adults because of slow peripheral uptake. (The brain forms 50% of the vessel-rich group in neonates, compared with only 25% in adults, resulting in drugs remaining in the CNS for longer.) This, together with immature elimination systems, leads to an overall increased drug half-life. The elimination half-life of fentanyl may thus be extended to 15 hours in neonates, as opposed to the normal 3–4 hours in adults. This should be remembered when using fentanyl in ventilated newborns close to the time of planned extubation, because failure to wean sedation sufficiently early may lead to delayed or failed extubation, with its associated increased morbidity. Delivery of morphine into the biophase may also be enhanced in newborns and young infants compared with older individuals owing to immaturity of the blood–brain barrier.
As a water-soluble drug, however, onset is still slower than fentanyl, making it a less appropriate drug to use for neonatal intubation.

Fentanyl is most useful peri-intubation for rapid ablation of the stress response and intense analgesia at the time of surgery, or for treatment and prevention of pulmonary hypertension during induction of anaesthesia. Morphine is more appropriate as an infusion drug postoperatively, particularly in ventilated patients, however, tolerance develops rapidly in neonates.

Hormonal changes
Noradrenaline (released from sympathetic nerve terminals) and adrenaline (produced by the adrenal medulla) are elevated in the first week of life. Together with cortisol (from the adrenal cortex), they regulate the perinatal adaptation of major systems, including changes in the cardiovascular system and circulation, structural lung maturation and surfactant production by type 2 pneumocytes, smooth muscle activity (and thereby pulmonary and systemic vascular resistance), energy production and temperature control. A sharp rise in thyrotropin-stimulating hormone (TSH), T3 and thyroxine (T4) just before delivery assists in respiratory control, regulation of metabolic rate and development of β-adrenergic receptors in the myocardium, thus improving contractility of maturing myocytes. Preterm infants have lower levels of cortisol, adrenaline and noradrenaline in cord blood compared with term infants, though baseline levels in unstressed babies, irrespective of gestation are similar. This implies an inability of preterm infants to cope with stressors such as hypoxia, acidosis or the birth process itself.

Haematology

Erythropoiesis
Early erythropoiesis in fetal life begins in the yolk sac during the first few weeks following conception. From the fifth week of gestation the liver is the predominant site of erythropoiesis, though minimal red cell production occurs in the bone marrow from week 9. Shortly before birth, the erythroid cells enter the bone marrow, and erythropoiesis continues there.

Haemoglobin
Newborn blood volume is about 80 ml/kg (and up to 20% higher in preterms). Neonates are relatively polycythaemic with a normal haemoglobin of 18–19 g/dl and haematocrit of 0.6 at term, depending on the timing of cord clamping.

At birth, 70–90% of haemoglobin is fetal haemoglobin (HbF). This has a much higher affinity for oxygen than adult haemoglobin (HbA), and it therefore carries more oxygen but releases it to the tissues less readily (see Figure 1, page 70). Polycythaemia improves oxygen delivery up to a point, although haematocrits greater than 0.65–0.7 increase the risk of hyperviscosity and associated sludging with microthrombi formation and organ hypoperfusion.

As HbF is gradually replaced by HbA by 3–6 months of age, the haemoglobin drops to about 8–9 g/dl. This drop occurs more quickly and to lower levels in preterms. These are normal values in this age group and though ‘top-up’ blood transfusions or prophylactic erythropoietin may be needed in sick, ventilated or oxygen-dependent infants, this is not the case in well babies even before surgery. This physiological anaemia makes preterm infants prone to postoperative apnoea and they are more likely to require positive pressure or ventilatory support after surgery.

The most common haemoglobinopathies are sickle cell disease and β-thalassaemia major; both disorders of b-chains and consequently appearing after 3–6 months of age as HbF levels fall and HbA levels rise.

Coagulation
The coagulation system in newborns differs from that in older children and adults. Haemorrhage occurs more often than thrombosis and most disorders are acquired rather than hereditary. Preterm or ill infants are more prone to coagulopathies than healthy term babies and often develop disseminated intravascular coagulopathy in response to hypoxia or sepsis. Thrombocytopenia is common in the first week of life, but recovery is usually spontaneous.

Haemorrhagic disease of the newborn is unique to the newborn and is caused largely by deficiency of vitamin K dependent clotting factors. Vitamin K crosses the placenta poorly, and neonates have immature livers that absorb fat, and therefore fat-soluble vitamins, poorly. Breast-fed infants are at higher risk because formula milks are supplemented with Vitamin K.

The condition manifests as early (in the first 48 hours), classic (days 2–6) or late (up to 6 months of age) haemorrhagic disease, with gastrointestinal bleeding, oozing from the umbilical stump and mucosal surfaces or severe bleeding into the CNS. Treatment is with fresh frozen plasma, intravenous vitamin K and blood transfusion as required. Prophylaxis is by administration of vitamin K soon after delivery, either intramuscularly (1 mg for those over 2 kg; 0.5 mg for those under 2 kg) or orally. If a breast-fed baby receives oral Vitamin K, further doses are recommended on days 3 and 7 of life, and then monthly until 3 months of age. An alternative oral regimen would be 2 mg on days 1, 10 and 28 of life. ◆

FURTHER READING

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Age-related Pharmacology

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Children differ from adults in the way they respond to drugs. These differences became apparent during the 1950s following a number of therapeutic disasters such as an increase in kernicterus among newborns treated with sulphonamides and fatal cardiovascular collapse in infants treated with chloramphenicol. Research into these conditions revealed that the responses of babies and children to drugs are determined by a large number of factors that change rapidly and independently during development. This article relates those factors to the developmental pharmacology of commonly used anaesthetic drugs.

Factors affecting responses in babies and children

Pharmacokinetic factors affect absorption, distribution and elimination.

Cardiac output per kg is higher in babies and children than in adults. This means faster circulation times, therefore drugs are distributed to and from their site of action more rapidly.

Plasma protein binding limits the amount of free drug available to interact with tissue receptors. In the neonate, the concentrations of plasma proteins (e.g. α_1-acid glycoprotein) are decreased and their affinity for drugs reduced.

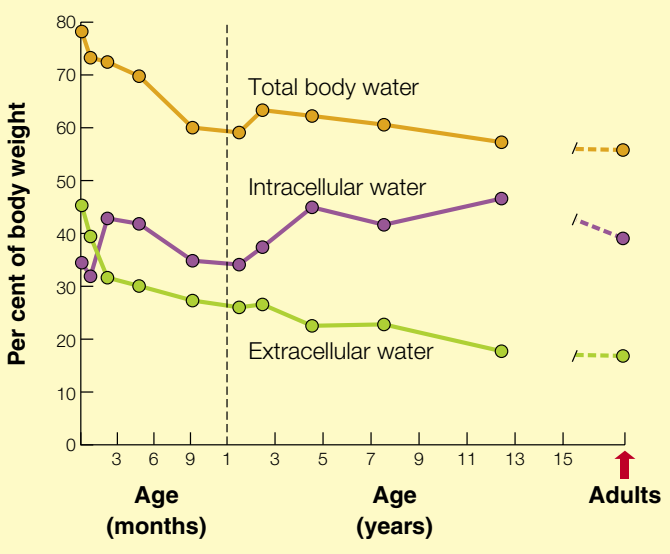
The blood–brain barrier may be immature in newborns, resulting in a greater uptake of partially ionized drugs such as morphine.

Body water compartments vary with age (Figure 1). The reduction in extracellular fluid volume in the first year of life has a profound effect on the volume of distribution of highly ionized drugs such as muscle relaxants.

Drug metabolism – the liver is the principal organ of drug metabolism. The activity of enzymes catalysing these reactions is reduced in infants leading to an increase in the duration of action of some drugs (e.g. morphine and aminosteroidal muscle relaxants).

Excretion – drugs and their metabolites are excreted mainly by the kidney. Both glomerular filtration rate (GFR) and tubular secretion rate are low at birth, reaching adult levels by 5 and 7 months, respectively.

Variation in body water compartments with age



Source: Friss-Hansen B *et al. Pediatrics* 1961; **28:** 169–81.

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Pharmacodynamic factors: the interaction between a drug and its receptor can be influenced by developmental changes in receptor number, type, affinity and availability of ligands. Such changes have been implicated in the neonate's sensitivity to non-depolarizing muscle relaxants and susceptibility to opioid-induced respiratory depression.

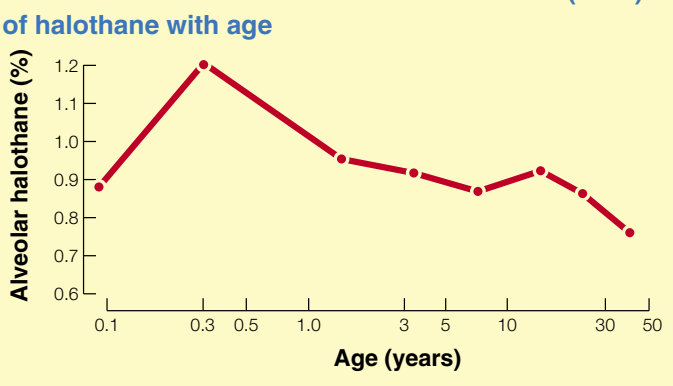
Inhaled anaesthetics

Uptake and elimination of inhaled anaesthetics occur more rapidly in babies and children than in adults owing to increased ventilation in relation to functional residual capacity, an increase in cardiac output in relation to body weight and reduced solubility of inhaled anaesthetics in blood. The increased rate of uptake in infants correlates with more rapid induction of anaesthesia and earlier development of cardiovascular side-effects. The minimum alveolar concentration (MAC) of inhaled anaesthetics varies with age, being generally lower in neonates and adults than in infants and young children.

Halothane has a sweet, non-pungent odour allowing smooth induction and maintenance of anaesthesia. Induction is rapid owing to its relatively low blood solubility and high potency. About 20% of halothane is metabolized in the liver, mainly by oxidation. Metabolism appears to be an important factor in the aetiology of halothane hepatitis, which occurs in 1 in 10,000–30,000 of exposed adults. By contrast, halothane hepatitis is rare in children and there have been no fatalities.

In neonates, the MAC of halothane is 0.9%, increasing to a maximum of 1.2% at 1–6 months, thereafter declining to 0.76% in the adult (Figure 2). The lower MAC of halothane in neonates compared with infants may be related to immaturity of the CNS. The higher MAC in infants compared with older children may reflect an increase in brain water.

Variation of minimum alveolar concentration (MAC) of halothane with age



Data from: Lerman J *et al. Anesthesiology* 1983; **59:** 421–4 and Gregory G A *et al. Anesthesiology* 1969; **30:** 488–91.

2

Halothane anaesthesia is associated with hypotension and bradycardia. Neonates and infants are susceptible owing to a reduction in active tension of the myocardium, reduced compliance of the ventricles and relative under-development of sympathetic innervation. Treatment consists of giving atropine, 20 μg/kg i.v. or i.m.

Isoflurane has an irritant odour, making it unsuitable for induction of anaesthesia. The rate of metabolism is about one-hundredth that of halothane (0.2%) and there have been no reports of hepatotoxicity in children. At 32 weeks' gestational age the MAC of isoflurane is about 1.3%, while at 32–37 weeks it is 1.4% increasing to about 1.6% at term and 1.9% at 1–6 months. It then declines to 1.2% in adults.

Isoflurane and halothane produce similar reductions in blood pressure in infants and children, though heart rate is either unchanged or increased with isoflurane. In contrast with halo-thane, the reduction in arterial blood pressure during isoflurane anaesthesia appears to be mainly the result of decreased peripheral resistance rather than myocardial depression.

Sevoflurane has a slightly pungent but not unpleasant odour, allowing rapid, smooth induction of anaesthesia. The MAC of sevoflurane is 3.3% in neonates, 2.5% in infants and children aged over 6 months and 2.0% in adults. The cardiovascular responses to sevoflurane are similar to those of halothane.

Concerns with sevoflurane include its relatively high rate of metabolism (2%), its chemical instability with soda-lime and high levels of agitation in children during recovery (67–69%). In view of the latter, some authors recommend restricting the use of sevoflurane in children to induction of anaesthesia.

Desflurane has a pungent ethereal odour, making it unsuitable for induction of anaesthesia. However, by virtue of its low blood solubility, recovery after desflurane anaesthesia is faster than that after halothane or sevoflurane. The MAC of desflurane is 9.2% in neonates, 9.9% in infants aged 6–12 months, thereafter declining to 6.0% in adults. The haemodynamic responses to desflurane are similar to those reported for halothane, metabolism is negligible (0.02%) and the drug is stable with soda-lime. Desflurane may be a useful maintenance agent for low-flow anaesthesia in infants and children.

Nitrous oxide: the low MAC of nitrous oxide gas (105%) precludes its use as a sole anaesthetic, but it is a useful adjunct to potent volatile anaesthetic agents during induction and maintenance of anaesthesia. Low blood solubility results in rapid uptake and elimination, and there is little biotransformation. Premature and sick neonates may not tolerate the cardiovascular effects of nitrous oxide, in which case air may be substituted. The main contraindications to nitrous oxide are the presence of air pockets within the body and the need for a high inspired oxygen tension.

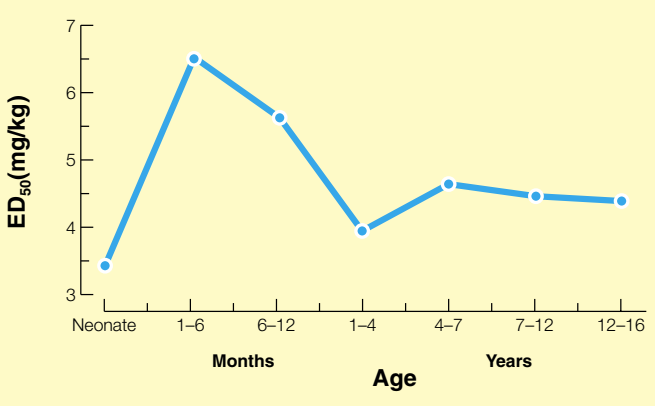
Intravenous anaesthetics

Intravenous anaesthetics are highly lipid-soluble substances that produce hypnosis in one arm–brain time when injected intravenously. Rapid recovery occurs predominantly by redistribution. Induction doses vary with age in a similar manner to the MAC of volatile anaesthetics.

Thiopental (thiopentone): plasma protein binding of thiopental (thiopentone) is reduced in neonates, so that the fraction of unbound drug is almost twice that in older children and adults. The elimination half-time is also over three times longer in newborns compared with older children; however, as recovery occurs predominantly by redistribution, the duration of effect of an induction dose should not be significantly prolonged.

The ED_{50} sleep dose of thiopental (thiopentone) varies with age (Figure 3). For smooth induction of anaesthesia using thiopental (thiopentone), neonates require 4–5 mg/kg, infants 7–8 mg/kg and children 5–6 mg/kg. The reduced requirements in neonates can be explained by a decrease in plasma protein binding. The increased requirements in infants and children compared with adults (usual dose 4 mg/kg) may be a result of their large cardiac output, which reduces the concentration of thiopental (thiopentone) arriving at the brain. Induction doses of thiopental (thiopentone) may be reduced by up to 50% by sedative premedication. The most important side-effects of thiopental (thiopentone) are respiratory and cardiovascular depression.

Variation in the ED_{50} sleep dose of thiopental (thiopentone) with age



Sources: Westrin P *et al. Anesthesiology* 1989; **71:** 344–6 and Jonmarker C *et al. Anesthesiology* 1987; **67:** 104–107.

3

Methohexitone has a shorter distribution half-time than thiopental (thiopentone), which is reflected in a shorter recovery time. The usual dose is 1–2 mg/kg for infants and children. The respiratory and cardiovascular effects of methohexitone are similar to those of thiopental (thiopentone). In addition, methohexitone may cause muscular twitching and hiccough due to CNS excitation.

Propofol: the distribution half-time of propofol is less than that of thiopental (thiopentone) but similar to that of methohexitone; accordingly, the recovery time after propofol is similar to that after methohexitone. Because of its prompt recovery characteristics and anti-emetic effects, propofol has largely displaced methohexitone as the induction agent of choice for outpatients.

Average induction doses of propofol are 4 mg/kg for infants and 3 mg/kg for children. The average infusion dose of propofol in children is 10 mg/kg/hour. This is about twice the rate required for adults (5 mg/kg/hour) and reflects a greater plasma clearance of propofol in children.

The respiratory and cardiovascular effects of propofol appear to be greater than those of thiopental (thiopentone). Pain on injection with propofol can be minimized by adding lidocaine (lignocaine), 20 mg, to each 200 mg of propofol.

Opioid analgesics

In the past, opioids were avoided in neonates and young infants because of their increased susceptibility to respiratory depression. This susceptibility may be due in part to increased penetration of the CNS by opioids, reduced drug elimination and changes in the proportions and affinities of opioid receptors in early infancy.

Morphine remains the most commonly used opioid for the management of severe pain in children. It is metabolized mainly by conjugation with glucuronide in the liver. Hence, deficiency of microsomal enzymes may be responsible for prolongation of its clinical effect in infants aged less than 6 months.

A regimen consisting of a loading dose of 100 μg/kg followed by a maintenance dose of 25 μg/kg/hour provides excellent intraoperative and postoperative analgesia in children aged over 6 months. Reduced doses are required in infants aged less than 6 months. A single dose of 25 μg/kg usually provides adequate intraoperative and postoperative analgesia in neonates undergoing relatively brief (45 minute) procedures. After longer surgery in neonates, postoperative analgesia may be supplemented with a continuous infusion of morphine, 5–10 μg/kg/hour. All infants aged less than 6 months receiving morphine infusions require high dependency nursing and respiratory monitoring.

Fentanyl is a highly lipid-soluble, synthetic opioid with a rapid onset of action. It is usually administered in a dose of 1–2 μg/kg at the start of anaesthesia followed by further bolus doses as clinically indicated, or continuously infused at 1 μg/kg/hour. After a dose of 1–2 μg/kg, its duration of action should be short in all age groups (20–30 minutes), being terminated predominantly by redistribution. After higher doses, repeated doses or an infusion, its effect may last for several hours and is terminated predominantly by elimination. Fentanyl may produce chest wall rigidity and bradycardia.

Naloxone is used to antagonize opioid-induced respiratory depression. The recommended dose is 5–10 μg/kg i.v. In view of its relatively short duration of action a supplementary dose of 10 μg/kg i.m. may be co-administered. Severe opioid overdose may require a much larger initial dose of naloxone followed by an infusion.

Muscle relaxants

Neonates and infants appear to be sensitive to non-depolarizing relaxants and resistant to depolarizing relaxants. Sensitivity to non-depolarizing drugs may be due to a reduction in acetylcholine in immature motor nerves. As this sensitivity is almost exactly countered by an increase in the volume of distribution (extracellular fluid volume), the clinical dose of non-depolarizing relaxants is unaffected by age. However, the elimination of aminosteroidal relaxants is delayed in infants with a resulting increase in their duration of action. The increased requirements for succinylcholine in babies and children may be the result of an increase in its volume of distribution (extracellular fluid volume).

The muscle relaxants described below are variously classified as ultrashort (less than 8 minutes), short (8–20 minutes) or intermediate (20–50 minutes) clinical duration drugs, where clinical duration describes time to 25% recovery of control twitch height after a 2 x ED_{95} dose. Rapid onset is defined as a time to maximum twitch depression of 1–2 minutes.

Succinylcholine is unique in having both a rapid onset and an ultrashort duration of action. In view of its side-effects, its use is reserved for emergency intubation or where immediate securing of the airway is necessary. Following 2–3 mg/kg in infants and 1–2 mg/kg in children, 100% block occurs within 1 minute with 25% recovery in about 5 minutes. Laryngospasm can be relieved in under 1 minute with succinylcholine, 4–5 mg/kg i.m., and full recovery occurs in about 20 minutes. As elimination of succinylcholine depends on hydrolysis by plasma cholinesterase, a deficiency in this enzyme may result in prolonged block.

Atracurium is a benzylquinolium diester that undergoes spontaneous degradation at body pH and temperature in a process known as Hofmann elimination. Although the volume of distribution of atracurium (extracellular fluid volume) is greater in infants compared with older children, this is accompanied by an increase in plasma clearance so that recovery rates are comparable in all age groups.

Following a standard intubating dose of 0.5 mg/kg, 100% block occurs in 1–2 minutes with 25% recovery in 29–36 minutes. Adverse effects relate mainly to histamine release, most commonly resulting in a rash along the course of the vein. Occasionally, the rash may be accompanied by more serious histamine-mediated effects such as hypotension, tachycardia or bronchospasm.

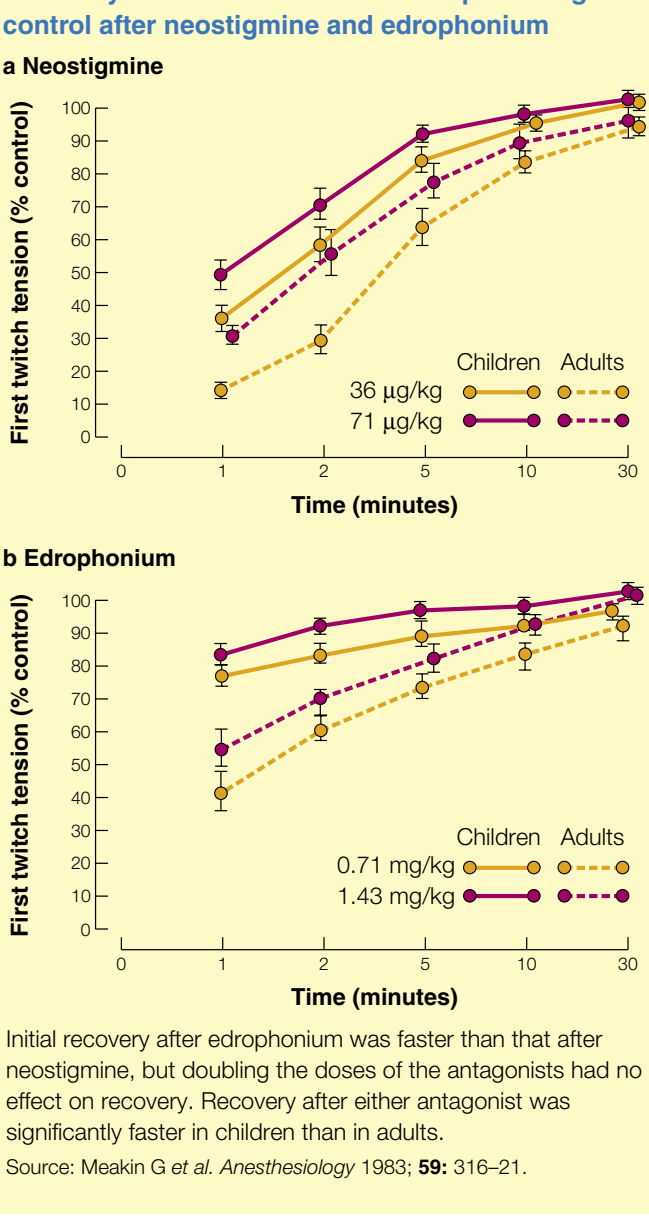
Mivacurium has a structure similar to atracurium but a shorter duration of action due to its metabolism by plasma cholinesterase. Following 0.2 mg/kg in infants and children, onset of complete block occurs in 1–2 minutes, while 25% recovery of twitch occurs in 8–9 minutes. As with atracurium, the absence of prolonged activity in infants compared with children may be due to an increase in plasma clearance. Histamine-releasing properties are similar to those of atracurium. The duration of action of mivacurium may be greatly prolonged in infants with plasma cholinesterase deficiency.

Rocuronium (*r*apid *o*nset *curonium*) is an aminosteroidal relaxant similar to vecuronium, but having a more rapid onset of action (due to its reduced potency), stability in solution and an intermediate duration of action in both infants and children. It has virtually replaced vecuronium in clinical practice.

The onset and duration of action of rocuronium, 0.6 mg/kg, have been determined in infants and children. While there was no difference in time to maximum block between the groups (64 versus 78 seconds), recovery of T1 to 25% of control was much slower in the infants than in the children (41.9 versus 26.7 minutes). Increased duration of action in infants is typical of aminosteroidal relaxants and may be due to slower elimination by the liver. In view of its intermediate duration of action, rocuronium should be used in place of succinylcholine for rapid- sequence induction only when no difficulties with the airway are anticipated.

Antagonism of muscle relaxants: in the presence of 10% recovery of twitch height, neostigmine, 35 μg/kg, or edrophonium, 0.7 mg/kg, will provide maximal antagonism in all age groups (Figure 4). For convenience, and to provide a margin of safety, neostigmine, 50 μg/kg, or edrophonium, 1 mg/kg, are usually given. Atropine, 20 μg/kg, or glycopyrrolate, 10 μg/kg, should be co-administered to counter any muscarinic effects.

Recovery of first twitch tension as a percentage of control after neostigmine and edrophonium



Initial recovery after edrophonium was faster than that after neostigmine, but doubling the doses of the antagonists had no effect on recovery. Recovery after either antagonist was significantly faster in children than in adults.

Source: Meakin G *et al. Anesthesiology* 1983; **59:** 316–21.

Local anaesthetics

Local anaesthetics are well tolerated by babies and children in whom they are often used to provide intra- and postoperative analgesia. Drugs of the amide type are used most often. Plasma protein binding of these drugs is reduced in infants, increasing the risk of toxicity. Total body clearance is also reduced in infants, which in conjunction with an increase in the volume of distribution leads to a prolonged elimination half-time. Accordingly, single doses of local anaesthetics should be kept strictly within the maximum recommended, and infusion doses reduced in the very young.

Bupivacaine is commonly used for wound infiltration and nerve blocks in infants and children. Its main advantage is its long duration of action (up to 8 hours following a single injection). Its toxic effects are similar to those of other local anaesthetics, though bupivacaine has a narrower safety margin between CNS and cardiovascular effects. Bupivacaine is particularly dangerous if cardiac effects occur, because dissociation from the myocardium is slow. For this reason, bupivacaine is not recommended for intravenous regional anaesthesia.

The maximum recommended dose of bupivacaine (plain or with adrenaline (epinephrine)) as a single injection is 2.5 mg/kg. The maximum recommended infusion rate is age dependent: less than 4 months, 0.2 mg/kg/hour for less than 48 hours; over 4 months 0.4 mg/kg/hour.

Ropivacaine is a new amide local anaesthetic with a chemical structure resembling that of bupivacaine. Compared with bupivacaine, ropivacaine offers a wider margin of safety, with lower potential for CNS and cardiovascular side-effects, and less motor block. The clinical indications, dose and duration of action of ropivacaine are similar to those of bupivacaine. ◆

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Anaesthesia for Specialist Surgery in Infancy

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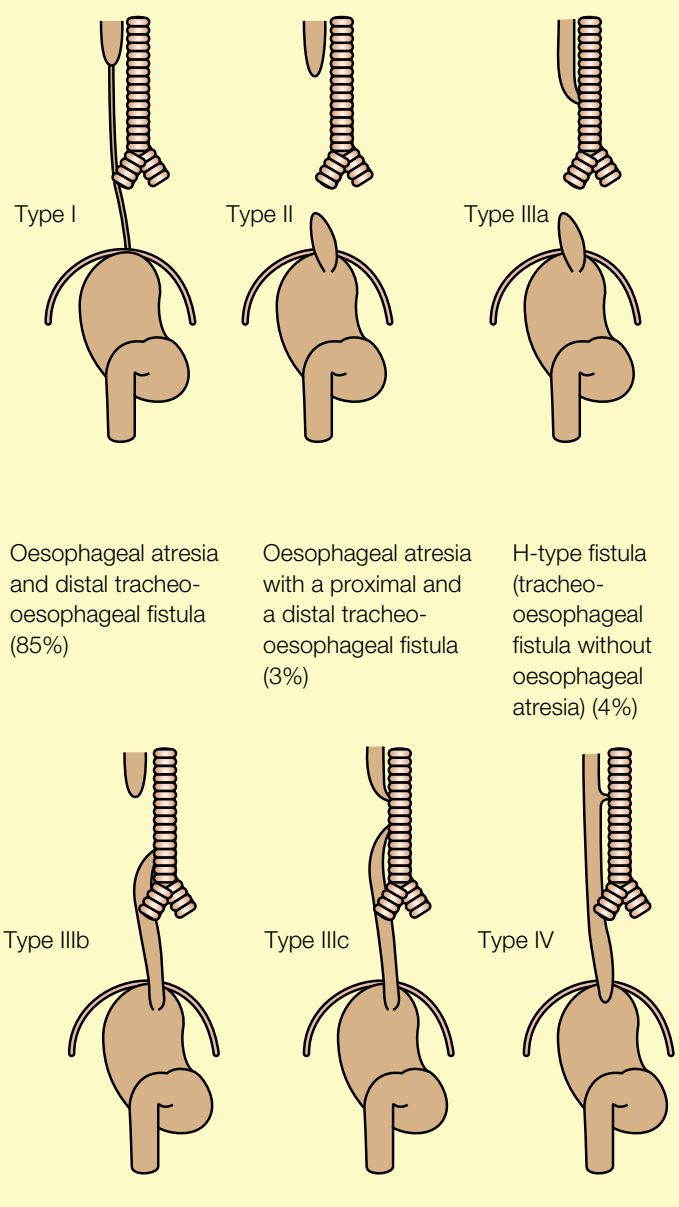
Oesophageal atresia and/or tracheo-oesophageal fistula

Oesophageal atresia is usually associated with a fistula between the oesophagus and trachea (Figure 1). Occasionally a tracheo-oesophageal fistula occurs without oesophageal atresia (an 'H-type' fistula). A fistula, if present, usually lies on the posterior wall of the mid (60%) or distal (33%) trachea.

Classification of tracheo-oesophageal fistula and/or oesophageal atresia



Isolated oesophageal atresia (7%) – either with obliteration (type I) or atresia of the oesophagus (type II)

Oesophageal atresia with a proximal tracheo-oesophageal fistula (1%)

Oesophageal atresia and distal tracheo-oesophageal fistula (85%)

Oesophageal atresia with a proximal and a distal tracheo-oesophageal fistula (3%)

H-type fistula (tracheo-oesophageal fistula without oesophageal atresia) (4%)

1

Presentation: oesophageal atresia may be suspected antenatally because of maternal polyhydramnios or characteristic ultrasound findings (small or absent gastric bubble, little intestinal fluid). After delivery, these babies characteristically drool saliva and cough, splutter or become cyanosed with feeding. The diagnosis is confirmed when a gastric tube cannot be passed into the stomach, appearing 'curled up' in the upper oesophageal pouch on radiography. Air in the stomach confirms a fistula. Contrast studies are contraindicated because of the risks of pulmonary aspiration. 'H-type' fistulas often present late, usually with recurrent ventilatory distress or chest infections.

Preoperative assessment and preparation: oesophageal atresia is often associated with prematurity, intrauterine growth retardation or other anomalies (Figure 2), which should be identified before surgery. Soiling of the lungs and pulmonary infection are the main preoperative risks. Aspiration can be reduced by nursing the baby 'head up' and continuously draining the upper pouch using a large suction catheter. Surgery is usually not required immediately and pulmonary function, hydration and plasma electrolytes should be optimized first. Antibiotics and chest physiotherapy are indicated for aspiration or pulmonary infection.

Congenital anomalies associated with oesophageal atresia with or without a fistula

	Comments	Action
• Prematurity	Affects about 33%	
• Congenital heart disease	Affects 20–50%, of which half are major lesions (e.g. Fallot's tetralogy, coarctation)	Obtain cardiological opinion and echocardiograph preoperatively
• Cleft lip and palate		
• Concurrent syndrome	VATER/VACTER sequence (Vertebral, Anal, Cardiac, Tracheo-Esophageal, Renal abnormalities) 13%	Examine plain abdominal radiograph Obtain cardiological opinion and echocardiograph preoperatively
—	CHARGE syndrome (Colombomata – a congenital anomaly of the eye, Heart disease, choanal Atresia, growth and developmental Retardation, Ear abnormalities and deafness) 6% Retrognathia common and intubation may be difficult	Obtain cardiological opinion and echocardiograph preoperatively Choanal atresia may cause significant ventilatory distress Plan strategy for difficult intubation if babies have CHARGE syndrome and retrognathia
• Other complex abnormalities of the airway	Potentially fatal anomalies (e.g. tracheal agenesisor stenosis, laryngeal atresia) are uncommon but associated with tracheo-oesophageal fistula with oesophageal atresia (but not H-type fistulas)	

2

Specific anaesthetic considerations

Leakage of gas through the fistula may cause preferential ventilation of the stomach during intermittent positive-pressure ventilation (IPPV), compromising pulmonary ventilation and causing gastric distension (with the risks of pulmonary aspiration or diaphragmatic splinting). Clinically, however, this is seldom a problem and most anaesthetists use a gaseous or intravenous induction, facilitating tracheal intubation with a non-depolarizing relaxant. Because of the rare association with other significant airway abnormalities, some prefer to insert the tracheal tube while the baby breathes spontaneously, anaesthetized with a volatile agent. 'Awake intubation' is seldom used because it is difficult, distressing for the baby and associated with significant oxygen desaturation. Leakage through the fistula is reduced by acurate positioning of the tracheal tube (see below) and using the lowest possible inflation pressure.

Positioning the tracheal tube – most fistulas lie posteriorly in the mid or low trachea. Commonly, the tube is positioned with the bevel facing forwards, so the tip occludes the fistula while allowing ventilation of both lungs. In practice, the anaesthetist often inserts the tube 'too deep', slowly withdrawing it until both lungs are ventilated. Because the tip then lies low, inadvertent bronchial intubation during surgery is more likely. Bilateral air entry should be confirmed after intubation and whenever the baby is re-positioned.

Nitrous oxide may distend the stomach, compromising ventilation, and is best avoided.

Fluids – two intravenous cannulas are advisable, though significant bleeding is uncommon. Third-space losses can be replaced with suitable colloid (about 5 ml/kg/hour).

Monitoring – a precordial stethoscope may help to detect bronchial intubation or attempted ligation or compression of a major airway.

Surgical technique: primary repair of oesophageal atresia and/or tracheo-oesophageal fistula is an extrapleural procedure through a right thoracotomy. The baby lies in the left lateral position with the upper arm abducted against the head. Oxygen desaturation commonly occurs during surgery because of lung compression, airway kinking and V:Q mismatch. The lungs are usually ventilated by hand using a T piece because the pulmonary compliance changes continuously and it is easier to detect sudden airway obstruction, and to coordinate ventilation with the surgeon's activity.

During surgery the proximal oesophagus is identified by distending the upper pouch with the large suction catheter. When the anastomosis is almost complete, a smaller nasogastric tube is advanced to act as a stent and is then carefully secured.

A primary repair may be impossible with a 'long gap' between the proximal and distal oesophagus. The surgeon then usually fashions a feeding gastrostomy, draining the upper pouch with either an oesophagostomy or a suction tube, until definitive repair is feasible.

Anaesthetic technique depends on the intended postoperative care. Some clinicians routinely paralyse and ventilate the lungs of all babies after oesophageal atresia repair. Others do this only in those with 'long gaps' or associated significant anomalies. Epidural block provides excellent analgesia, allowing early extubation, and probably improving outcome. In those electively ventilated, an opioid anaesthetic technique (e.g. fentanyl, 20–100 μg/kg in increments) is appropriate.

Postoperative complications are common (Figure 3).

Complications after repair of a tracheo-oesophageal fistula in a neonate

	Comments	Treatment
• Tracheomalacia	Common at the fistula site. Affects about 25%. Presents with a 'seal like' cough, stridor and variable degree of ventilatory distress, which becomes worse after anaesthesia or when upset. Improves with age	
• 'Death attacks' or 'dying spells' (episodes of severe airway obstruction causing cyanosis, bradycardia and apnoea)	These spells usually occur in babies aged 2–3 months during or shortly after feeding. The cause is probably compression between the aorta/innominate artery and the oesophagus of the area of tracheomalacia	Aortopexy (suspension of aortic arch from posterior sternum) required in about one-third of babies with tracheomalacia
• Gastro-oesophageal reflux	A common association. May cause ventilatory distress and be difficult to distinguish from tracheal compression. Associated with pulmonary aspiration	May require fundoplication
• Oesophageal stricture	May cause pulmonary aspiration	May require repeated dilatation
• Abnormal oesophageal peristalsis	A common association. May cause dysphagia	
• Recurrent fistula	Affects about 13%	
• Anastomotic leak	Particularly after primary repair of a 'long gap'	Risk in association with a 'long gap' probably reduced if the baby is paralysed and its lungs ventilated mechanically postoperatively

3

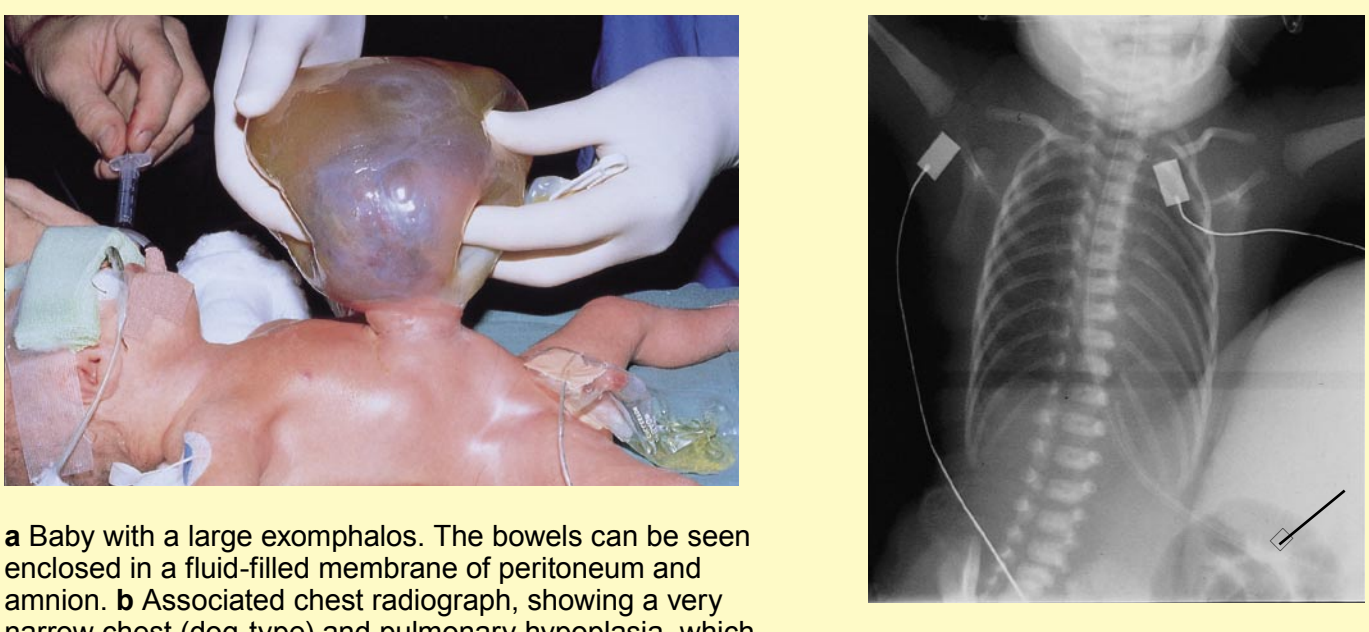
Gastroschisis and exomphalos

Gastroschisis and exomphalos have different embryological aetiologies causing herniation of abdominal contents through a defect in the abdominal wall. Their features are compared in Figure 4. Exomphalos is associated with serious congenital abnormalities. 60% of fetuses are therapeutically or spontaneously aborted (those with the most complex problems), therefore survival rates for live births are now higher. In the absence of other significant anomalies, a small exomphalos enclosed in a sac causes little disturbance. A large ('giant') exomphalos (Figure 5) or gastroschisis produces large amounts of fluid and heat loss. Preoperative assessment and management are summarized in Figure 6.

Comparison of gastroschisis with exomphalos

	Gastroschisis	Exomphalos (omphalocoele)
• Incidence (of live births)	1/5000–1/10,000	1/30,000
• Bowels	Often thickened, shortened, damaged, and enclosed in thick fibrous peel. Complications include intestinal atresia, stenosis, ischaemia, perforation, malrotation or volvulus	Usually normal structure and function, though other gastrointestinal abnormalities (e.g. malrotation, imperforate anus) can occur
• Abdominal wall defect	Lateral to the umbilicus, usually small and on the right side. Bowels not enclosed with a membranous sac	Midline defect (through the umbilical ring) often large. Bowels enclosed within a membranous sac of amnion and peritoneum
• Associated congenital anomalies	Uncommon	Common (but most fetuses with complex anomalies recognized antenatally are aborted; see Figure 6)
• Prematurity	33%	33%
• Intrauterine growth retardation	60%	37%
• Determinants of outcome	State of the bowel	Associated anomalies
• Survival (of live births)	90%	80% (but 60% of fetuses aborted)

4



a Baby with a large exomphalos. The bowels can be seen enclosed in a fluid-filled membrane of peritoneum and amnion. **b** Associated chest radiograph, showing a very narrow chest (dog-type) and pulmonary hypoplasia, which may be associated with ventilatory failure. Extra-abdominal alimentary gas shadows (arrowed).

5

Preoperative assessment and management of a baby with gastroschisis or exomphalos

	Comments	Action
• Identify associated congenital anomalies	Associated anomalies common in (congenital heart disease 25–35%; exomphalos Beckwith-Wiedemann syndrome 10%; chromosomal abnormalities, especially trisomy 13 or 18, in 10%), but not in gastroschisis	For exomphalos, obtain preoperative cardiological opinion and echocardiograph and check blood glucose regularly
• Recognize and treat ventilatory insufficiency	Large exomphalos associated with poor lung growth and pulmonary hypoplasia (see Figure 5b)	Consider mechanical ventilation
• Assess shock, reduce fluid loss	In gastroschisis or a large exomphalos, large volumes of fluid are often sequestrated within the bowel lumen Gastroschisis or ruptured exomphalos associated with greater evaporative losses because the bowels are not enclosed in a membranous sac	Site two intravenous cannulas and give warmed colloid, 20 ml/kg. Give further boluses of fluid according to clinical signs
• Reduce heat loss and prevent hypothermia		Wrap the bowels in a sterile polythene bag or 'cling film'. Nurse baby in a 'thermoneutral environment'
• Reduce bowel distension and the risk of aspiration		Pass a nasogastric tube and leave on 'free drainage'
• Prevent damage to the bowel or its blood supply		Wrap the bowels in a sterile polythene bag or 'cling film' Position a large exomphalos carefully to prevent kinking of the blood vessels. Sometimes best to lay the baby in the lateral position
• Prevent infection	Infection is a risk in gastroschisis or a ruptured exomphalos because the bowels are not enclosed in a membrane	Give prophylactic antibiotics. Wrap the bowels in a sterile polythene bag or 'cling film'

6

Specific anaesthetic considerations
Pulmonary aspiration of gastric contents – see bowel obstruction below.

Nitrous oxide is contraindicated because it causes bowel distension, which can prevent abdominal closure.

Intra-abdominal pressure – primary repair is preferable because infection rates are lower. Although a small exomphalos causes few problems, reducing a large gastroschisis or exomphalos may produce unacceptable increases in intra-abdominal pressure with serious clinical effects (Figure 7). If pressure is excessive, the surgeon sutures a silastic silo around the defect to enclose the bowels in a protective bag. The bowels are gradually returned to the abdomen over several days, after which the abdomen is closed. The decision to defer closure is often made indirectly (Figure 8), but some clinicians measure intravesical or intragastric pressures, deferring closure if these exceed 20 mm Hg.

Clinical effects of excessive intra-abdominal pressure

	Cause	Clinical features
• Hypoperfusion of intra-abdominal organs	Decreased venous return, reducing cardiac output Compression of aorta	Acute renal failure Bowel infarction Acidosis Ischaemia of the legs
• Decreased pulmonary compliance	Increased intra-abdominal pressure	'Stiff lungs' Hypoxia, hypercarbia, acidosis

7

Features supporting delayed closure of a gastroschisis or exomphalos

Significant discrepancy between abdominal cavity and volume of herniated organs
- Small abdominal cavity and/or large herniation of intra-abdominal contents
- Marked dilatation or oedema of bowels (particularly in gastroschisis)

Abdominal skin tension and perfusion (at attempted closure)
- Tense abdominal wall
- Dusky appearance

Altered cardiovascular variables (at attempted closure)
- CVP rise greater than 4 mm Hg
- Significant hypotension or tachycardia

Impaired ventilation (at attempted closure)
- Significantly decreased pulmonary compliance
- Hypoxia
- End tidal carbon dioxide tension > 50 mm Hg (6.7 kPa)

Significant associated anomalies (e.g. pulmonary hypoplasia)

8

Technique – postoperative muscle paralysis and IPPV are usual after repair of a moderate or large exomphalos or gastroschisis to optimize ventilation and reduce intra-abdominal pressure. An opioid anaesthetic with a low concentration of volatile agent and full muscle paralysis is common. For a small exomphalos, light general anaesthesia combined with epidural analgesia may facilitate early extubation.

Congenital diaphragmatic hernia

The diaphragm normally forms by 10 weeks' gestation. If proper development fails, abdominal viscera may enter the chest through the hernia (usually on the posterolateral aspect of the left hemi-diaphragm), impairing lung development (particularly ipsilaterally) and causing pulmonary hypoplasia and abnormal capillary growth.

Specific anaesthetic considerations
Associated congenital abnormalities, particularly cardiac, are common.

Ventilatory failure is a result of pulmonary hypoplasia, which is not corrected by urgent repair. These babies should be stabilized and pulmonary function optimized preoperatively.

Severe pulmonary hypertension and worsening hypoxia often develop after a 'honeymoon period'. The babies are initially treated preoperatively with muscle relaxation, tracheal intub-ation, hyperventilation, and a high fractional concentration of oxygen in inspired gas (FiO_2). However, excessive inflation pressures may further damage lungs or cause a pneumothorax and more complex ventilatory support (e.g. extracorporeal membrane oxygenation (ECMO), nitric oxide) may be necessary. Babies occasionally have surgery before weaning from ECMO.

Bleeding – if babies are receiving ECMO, bleeding may be severe because they will be heparinized.

Technique – anaesthesia is usually a continuation of intensive care. Additional analgesia is often provided with fentanyl, 20–100 μg/kg, in 10 μg/kg increments.

Necrotizing enterocolitis

Necrotizing enterocolitis is characterized by intramural air and bowel wall necrosis, sometimes leading to perforation. It has a mortality of 10–30%. 90% of affected babies are preterm (generally those who have survived the immediate post-natal period). The aetiology is multifactorial and incompletely understood. The three factors usually implicated are intestinal injury, primary ischaemia and substrate (usually formula milk) within the lumen of the bowel.

Presentation: the early stages are indistinguishable from sepsis and treatment is initially supportive with appropriate fluids, inotropes, antibiotics and IPPV. Ventilation is often compromised by splinting of the diaphragm (secondary to abdominal distension) and apnoea is common. About 50% require surgery, usually babies with more severe disease who are systemically ill (Figure 9). They should be rapidly, but carefully, resuscitated before surgery. Some very small premature babies may be too ill for laparotomy, in which case the surgeon may simply insert an intraperitoneal drain (under local anaesthetic) to drain the necrotic material.

Clinical features of severe necrotizing enterocolitis

Cardiovascular instability
- Hypotension, bradycardia
- Hypovolaemia (secondary to sequestration into dilated bowels, haemorrhage or ascites)

Respiratory failure and respiratory acidosis
- Severe apnoea
- Impaired ventilation because of abdominal distension

Haematological failure
- Thrombocytopenia
- Neutropenia
- Disseminated intravascular coagulation

Abdominal signs
- Abdominal distension and tenderness, ileus, blood per rectum
- Bilious vomiting, peritonitis, perforation

Others
- Metabolic acidosis
- Temperature instability

Specific anaesthetic considerations
Cardiovascular instability and haemorrhage – these babies may be septic and are often unstable. They have large intraoperative fluid requirements because of bleeding and third-space losses, often needing more than 100 ml/kg fluid during surgery (including platelets and fresh frozen plasma). In severely affected infants, cardiac function is poor, leading to reduced organ perfusion, decreased urine output and metabolic acidosis. Hypotension often occurs when the abdomen is opened. The anaesthetist should establish adequate venous access with two relatively large cannulas. Monitoring of intra-arterial and central venous pressures is essential. Because of associated coagulopathy, the central venous line may be best inserted using a formal surgical technique. The intraoperative course is often stormy and a second anaesthetist may be helpful. Inotropic support may be required.

Friable liver capsule – the liver capsule is often distended and can bleed profusely at laparotomy. Hepatic distension has been attributed to over-zealous resuscitation and venous engorgement.

Citrate toxicity – infusing blood products containing citrate (e.g. fresh frozen plasma) at a rate greater than 1 ml/kg/minute may produce citrate toxicity, hypocalcaemia and refractory hypotension. Ionized calcium should be measured, and, if low, corrected with intravenous calcium chloride 10%, 0.1 ml/kg, given over about 30 minutes through the central line.

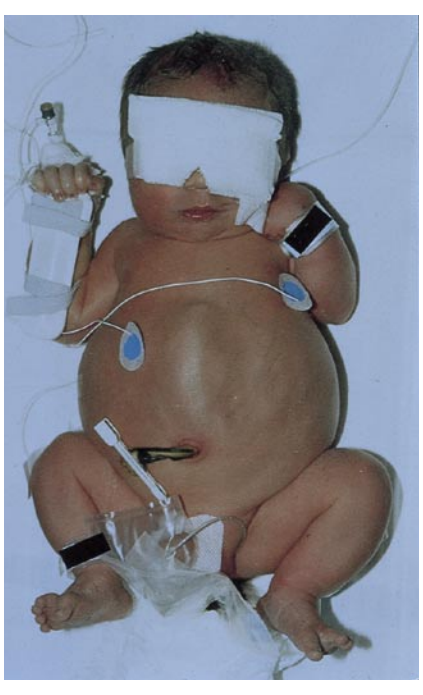
Nitrous oxide is absolutely contraindicated because of intra-mural air and the risk of intestinal perforation. It also significantly depresses cardiovascular function (60% nitrous oxide has as much effect as 0.6 minimum alveolar concentration (MAC) of halothane).

Technique – intubation and ventilation are usually part of the supportive care before surgery. Anaesthesia can be maintained with a low inspired concentration of a volatile agent in oxygen or air. Regional techniques are contraindicated because of coagulopathy and/or bacteraemia. Fentanyl, 10–50 μg/kg (in divided doses), provides analgesia, reducing the physiological stress of surgery. Alternatively, ketamine, 4 mg/kg/hour, can be infused.

Postoperative care: aggressive intensive care (including IPPV, meticulous management of fluid balance, and, often, inotropic support) are required. Morphine infused continuously provides sedation and analgesia.

Bowel obstruction

Babies presenting with bowel obstruction soon after birth are usually well and easily resuscitated. Others may be dehydrated and have significant acid–base and electrolyte abnormalities, which should be corrected preoperatively. Ventilatory function is more easily impaired compared with adults (Figure 10) because babies have relatively horizontal ribs and are mainly diaphragmatic breathers. Pulmonary function may be further compromised by aspiration of gastric contents.



10 Abdominal distension can easily cause respiratory compromise in a baby.

Preoperative assessment
Associated anomalies are common in newborn babies (Figure 11).

Fluid and electrolyte resuscitation is vital. Dehydration should be assessed clinically (Figure 12). Hypovolaemia produces cool peripheries, tachycardia and slow capillary refill (over 2 seconds). Blood pressure is a poor indicator of shock and does not fall until 25% of circulating blood volume has been lost.

Coagulopathy is common in unstable, septic babies.

Congenital causes of bowel obstruction and their associations

Condition	Incidence	Clinical features	Associated abnormalities	Specific anaesthetic considerations
Obstructed inguinal hernia			Prematurity. Low birth weight	Large aspiration risk
Duodenal atresia or obstruction	1/6000–1/20,000	Copious and forceful vomiting within days of birth (may be bile stained) 'Double bubble' on abdominal radiograph	Prematurity. 33% have Down's syndrome. May be caused by malrotated caecum compressing the duodenum with Ladd's bands	
Meconium	1/20,000	No passage of meconium after 48 hours. Meconium may be 'milked out' at laparotomy or bowel resection may be required. Perforation can lead to severe peritonitis with large fluid shifts and blood loss	Presenting sign in 15% of children with cystic fibrosis	Avoid prophylactic atropine because of thick secretions Humidify gases intra- and post-operatively
Hirschsprung's disease	1/5000–1/10,000	Caused by lack of parasympathetic ganglia in rectal mucosa, producing a functional obstruction. Vomiting and abdominal distension usually within 48 hours of birth, but may occur much later. Diagnosed by mucosal biopsy	Uncommon	
Imperforate anus		May be low with small defect may end above levator muscle. Genitourinary fistulas common with high defects	VACTER (Vertebral, Anal, Cardiac, Tracheo-Esophageal atresia, Radial abnormalities and other limb abnormalities)	Obtain cardiological opinion and ECG preoperatively
Volvulus		May involve all of small bowel owing to malrotation. May present with obstruction and bloody stools		
Mucosal cyst	Rare	May cause obstruction or intussusception		

Clinical assessment of dehydration

Degree of dehydration (% of body weight lost) as fluid	Mild (5%)	Moderate (5–10%)	Severe (> 10%)
Decreased urine output	+	+	+
Dry mouth	+/–	+	+
Decreased skin turgor	–	+/–	+
Tachypnoea	–	+/–	+
Tachycardia	–	+/–	+

Data taken from: Advanced Paediatric Life Support. London: BMJ Books, 2001.

Specific anaesthetic considerations
Preventing pulmonary aspiration of gastric contents – there may be a significant residual volume in the stomach immediately before anaesthesia. The risks of pulmonary aspiration are reduced by aspirating the nasogastric tube carefully (with the baby lying in several positions) and using a rapid-sequence induction. Cricoid pressure is effective in babies, but may make intubation difficult if applied incorrectly.

Nitrous oxide worsens bowel distension and is contra-indicated.

Invasive monitoring (central venous and arterial pressure) is indicated for sick or unstable babies and a central line if intravenous nutrition is required postoperatively.

Technique – sick babies can be managed as for necrotizing enterocolitis. For stable babies, light general anaesthesia combined with epidural analgesia often allows early extubation.

Intussusception

Intussusception usually affects boys aged 5–9 months who may become very sick. A portion of bowel (usually the ileo-caecal valve) 'telescopes' into the next, causing obstruction, bloody diarrhoea and often vomiting. Generally, intussusception can be reduced with a barium enema, but 25% require surgery, sometimes including bowel resection.

Bleeding and fluid loss can produce significant anaemia, electrolyte abnormalities and shock, which should be corrected preoperatively. Other anaesthetic considerations are similar to those for bowel obstruction.

Pyloric stenosis

Pyloric stenosis most commonly affects first-born males. The circular muscles of the pylorus become thickened, inhibiting passage of gastric contents into the duodenum. Babies classically present with projectile vomiting and a palpable tumour. The diagnosis is often made by ultrasound. Pyloric stenosis has no specific associations with other congenital anomalies.

Pathophysiology: Cl^-, H^+ and water, and smaller amounts of Na^+ and K^+, are lost causing dehydration, metabolic alkalaemia, and hypochloraemia. Initially, the kidneys attempt to compensate by excreting bicarbonate with Na^+ and K^+. Later aldosterone (released in response to hypovolaemia) conserves Na^+, causing paradoxical aciduria, worsening alkalaemia, and renal loss of K^+. Plasma Na^+ and K^+ concentrations are usually normal at presentation (despite marked loss of total body K^+). Cl^- concentration falls (usually to 80–85 mmol/litre) once plasma bicarbonate exceeds 30 mmol/litre.

Preoperative assessment and preparation: babies with established vomiting are dehydrated and have significant electrolyte and acid–base disturbances. Pyloric stenosis is not an emergency and affected babies should be resuscitated before operating.

Dehydration should be assessed clinically (Figure 12) and corrected over 24–48 hours. Intravenous water and sodium chloride are the mainstay of treatment.

Electrolyte and metabolic disturbances – major electrolytes and acid–base abnormalities are corrected by rehydration with normal saline in addition to maintenance fluids. Apnoea lasting for over 15 seconds occurs in alkalotic babies with pyloric stenosis; it may be potentiated by general anaesthesia. Surgery should be delayed, therefore, until plasma electrolytes and pH are normal. Cl^- concentration is a useful guide to adequate resuscitation, but alkalosis persists until the Cl^- is at least 105 mmol/litre. In dehydrated babies, total body K^+ is low, despite a normal plasma concentration, and 20 mmol/litre should be added to the intravenous fluids.

Reducing the volume of gastric contents – a nasogastric tube should be inserted preoperatively and aspirated regularly.

Anaesthesia and surgery: pulmonary aspiration should be prevented by suctioning the nasogastric tube immediately before anaesthesia and using a rapid-sequence induction (see bowel obstruction, above). Anaesthesia can be maintained with a volatile agent (e.g. desflurane) in oxygen and nitrous oxide/air, using a relatively short-acting drug (e.g. atracurium) for muscle relaxation. Adequate analgesia can be provided with wound infiltration and regular paracetamol.

During the operation, the surgeon makes a small incision in the right upper quadrant, and then splits the circular muscles of the pylorus. Sometimes the anaesthetist is asked to inject air through the nasogastric tube to check that the pyloric mucosa remains intact.

Inguinal herniotomy

Inguinal hernias are common in babies born prematurely (30% of those with a birth weight less than 1000 g). Surgery should not be delayed unreasonably because of the risks of incarceration and bowel infarction. An incarcerated hernia should be managed as for bowel obstruction. Healthy, term infants generally have small, unilateral hernias and can be admitted for day surgery if they are older than 50 weeks' postconceptional age. Light general anaesthesia (using sevoflurane followed by desflurane) combined with caudal or ilioinguinal block is commonly used.

Ex-premature babies often have large bilateral hernias. The anaesthetic plan must take account of the specific implications of prematurity.

Ventriculo-peritoneal shunt

In the neonate, hydrocephalus is usually 'obstructive' and caused by clot debris (after intraventricular haemorrhage) or an Arnold-Chiari malformation (commonly associated with spina bifida). The slow accumulation of CSF in the ventricles destroys brain tissue and dilates the skull. CSF is commonly drained with a ventriculo-peritoneal shunt inserted into a cerebral ventricle and passed subcutaneously along the chest wall into the abdomen.

Specific anaesthetic considerations

Intracerebral pressure remains relatively normal if CSF accumulation is gradual because the cranial bones are unfused. Acute rises in intracranial volume, however, increase pressure because the dura is tough and relatively inelastic. If the baby has significant neurological signs or symptoms preoperatively, the ventricles can be 'tapped' under local anaesthetic to reduce the intracranial pressure before inducing general anaesthesia.

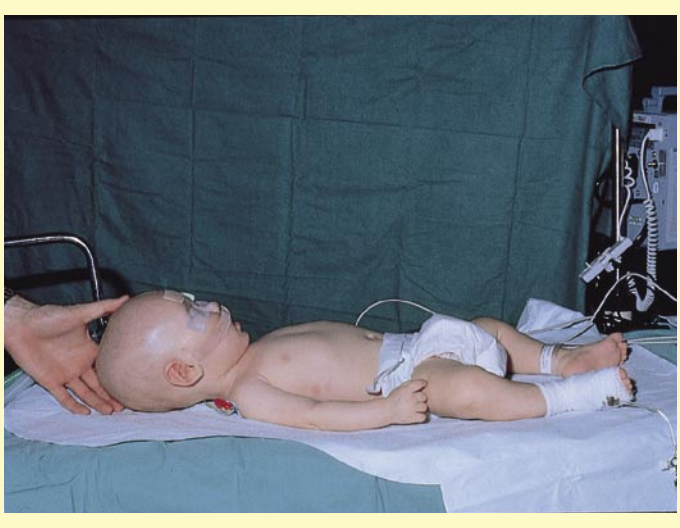
Prematurity is commonly associated with intraventricular haemorrhage.

The large head flexes the neck, which may make intubation difficult (Figure 13).

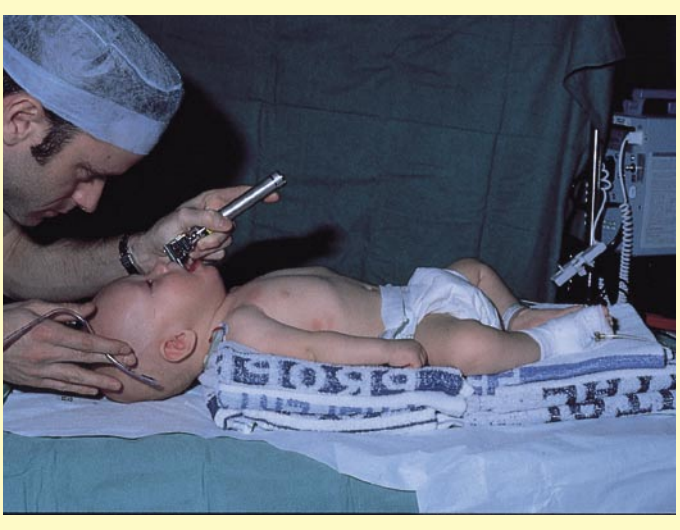
Heat loss from the large, exposed head may be significant and can be minimized by using a radiant overhead heater.

Bleeding is usually minimal, but blood should be available in case an epidural vein is damaged.

Technique depends on the child's condition. Inhalational induction is relatively contraindicated because of the increased intracerebral pressure associated with high concentrations of volatile agents and spontaneous breathing. Babies with preoperative symptoms generally improve after CSF drainage and most are extubated immediately after surgery.



a The large head in hydrocephalus flexes the neck making intubation difficult.



b This can be improved by raising the baby's body on a towel, which brings the head into a neutral position.

Postoperative care: analgesia is provided by regular paracetamol and wound infiltration with local anaesthetics. Non-steroidal anti-inflammatory drugs are contraindicated because of renal immaturity in babies less than 6 months.

Myelomeningocoele (spina bifida)

Myelomeningocoele results from failed fusion of the vertebral arches with variable loss of neural function below the lesion. It is commonly associated with hydrocephalus. There is a high risk of infection because the CNS is covered only by dura, pia and arachnoid mater and surgery is indicated within the first days of life.

Specific anaesthetic considerations

The position during intubation must not damage the sac. The baby can be laid either partially or completely on one side or supine with padding beneath the thorax, lower pelvis and head, leaving an adequate gap for the sac.

Position for surgery – the baby lies prone during surgery. The chest and pelvis must be supported to allow free abdominal movement and the tracheal tube position confirmed carefully after positioning the baby.

Latex allergy in later life is common and many hospitals provide a latex-free environment for anaesthesia and surgery from the outset.

Bleeding can be substantial with large lesions, and difficult to assess because blood is mixed with CSF. Good intravenous access must be obtained and blood cross-matched. ◆

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Managing Pain in Babies

Deborah Duce

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It is now generally accepted that neonates (the first 28 days of life) and infants (the first year of life) have cortical awareness of pain, and may have increased nociception owing to incomplete development of inhibitory pathways.

Importance of controlling pain
It has been argued that even if neonates and infants feel pain they do not remember it, and therefore the consequences of inadequate analgesia are unimportant. However, neonates who have undergone circumcision without analgesia or anaesthesia have higher behaviour pain scores and cry for longer when immunized at 4 or 6 months of age compared with other infants. In addition, ex-preterm babies who have undergone multiple painful procedures have an increased incidence of somatization (the reporting of symptoms that cannot be explained by, or are in gross excess of, physical findings) in later childhood. It is also possible that untreated pain in the neonate may result in a detrimental structural and functional reorganization of the developing nervous system.

Assessment
Assessing pain is a complex, multidimensional entity, especially in infants who are incapable of articulating feelings. In clinical practice, it can be carried out by a nurse experienced in pain management using simple sedation scores and pain scales. Many different scoring systems have been developed, none of which is ideal and many of which have not been validated. Most scoring systems use a combination of changes in observed behavioural and physiological variables (see *Anaesthesia and Intensive Care Medicine* **1:4:** 138). The ideal pain scoring system is easy and quick to use, distinguishes well between pain and other forms of distress, gives reproducible results and does not cause discomfort. It is important to repeat measurements at regular intervals to assess response to therapeutic interventions. The following two systems are in widespread use.

The CRIES neonatal scoring system is an acronym for five variables with scores of 0 to 2 for each (Figure 1). It has a maximum pain score of 10 and a minimum of 0. It is commonly used for neonates, is easy to remember and use, and has been validated down to the age of 32 weeks' postconception. However, it does not distinguish well between pain and distress (a common problem with all systems for this age group), and increased oxygen requirement can be caused by many factors other than pain. It also involves blood pressure measurement, which can be distressing for the neonate.

CRIES neonatal scoring system used to assess postoperative pain in babies

	0	1	2
Crying	No	High pitched	Inconsolable
Requires oxygen for SpO_2 > 95%	No	< 30%	≥ 30%
Increased vital signs pressure	Heart rate and blood pressure above preoperative values	Heart rate or blood pressure increased but not greater than 20% of preoperative levels	Heart rate or blood increased by over 20% of preoperative levels
Expression	None	Grimace	Grimace/grunt
Sleepless	No	Wakes at frequent intervals	Constantly awake

1

The Objective Pain Scale (OPS) has been validated for use in neonates and infants. It scores five behavioural and physio-logical signs of distress (Figure 2), is easy to use and reliable.

Objective Pain Scale

Observation	Criteria	Points
Blood pressure	± 10% preoperatively	0
	10–20% preoperatively	1
	20–30% preoperatively	2
Crying	Not crying	0
	Crying but responds to care	1
	Crying and unresponsive to care	2
Moving	None	0
	Restless	1
	Thrashing	2
Agitation	Patient asleep or calm	0
	Mild	1
	Hysterical	2
Body language	Patient asleep	0
	Mild pain (cannot localize)	1
	Moderate pain (can localize)	2

2

Techniques of postoperative pain management

Simple analgesia
Paracetamol is the most widely used analgesic in this age group because of its well-established safety profile. It is effective as sole analgesia after minor procedures, and as an adjuvant to opioid or local anaesthetic techniques for more painful procedures. The route of administration and dose have been widely discussed. Absorption is variable following rectal administration and the immaturity of hepatic glucuronidation in neonates may increase the risks of toxicity. The drug should be given 1–2 hours preoperatively to be effective at the time of surgery. Current recommended doses are given in Figure 3.

Paracetamol dosing in healthy children

Age	Oral initial dose (mg/kg)	Rectal initial dose (mg/kg)	Maintenance oral/rectal dose (mg/kg)	Maximum daily dose (mg/kg)	Duration at maximum dose (hours)
Preterm	20	20	15	60 (40 in 28–32 weeks)	48
0–3 months	20	20	15	60	48
> 3 months	20	40	15	90	72

3

Non-steroidal anti-inflammatory drugs (NSAIDs) are not recommended for neonates because they are vulnerable to the side-effects of impaired renal perfusion and fluid retention. Ibuprofen is the only NSAID licensed for use in infants over 7 kg for the treatment of postoperative pain; it is given orally at 30–40 mg/kg/24 hours in divided doses.

Opioids
Codeine and morphine are the mainstays of opioid therapy in neonates and infants because there is more extensive clinical experience and published data about them than other opioids, not because they are more effective. Neonates and infants are vulnerable to the same opioid side-effects as older children. Neonates are at particular risk of convulsions and myoclonic jerks with morphine. There are similar incidences of respiratory depression, constipation and pruritus at all ages, but nausea and vomiting are less common in infants and neonates.

Codeine is indicated for the treatment of mild-to-moderate pain. Its duration of action is 4–6 hours and it has good oral bioavailability. Codeine is metabolized mainly by conjugation to codeine-6-glucuronide and partly biotransformed by demethylation to morphine and norcodeine; morphine may be responsible for the analgesic actions of codeine. The glucuronidation pathway is immature in preterm babies and neonates; this leads to an increased half-life of the drug and proportionally higher serum concentrations. Codeine given at therapeutic doses in combination with other sedative agents in cold remedies has resulted in fatal intoxication in infants and it should be used with caution in this age group. The recommended postoperative oral or rectal dose is 1 mg/kg given 8 hourly in neonates and 6 hourly in infants. Higher peak plasma levels are achieved with the intramuscular route when compared with rectal administration but with an equal duration of action. A single intramuscular injection is commonly given intraoperatively with further doses given orally or rectally. It should not be given intravenously because it causes histamine release and hypotension.

Morphine is used for severe postoperative pain. Neonates and infants metabolize morphine differently from adults. The half-life decreases and the clearance increases with age, with values approaching those of an adult by 2 months. However, there is large interpatient variability in opioid metabolism, which may be exaggerated by surgery and critical illness. These differences may lead to accumulation of morphine with infusions or repeated doses and it should be used only in neonates given high dependency care.

Morphine can be given by the same routes as in adults though intramuscular injections are seldom used. The intravenous route by infusion or nurse-controlled analgesia (NCA) is the most common in neonates and infants. Data comparing the efficacy and complication rates of the two regimens are limited, but NCA is more popular with nursing staff; the overall morphine consumption is similar.

NCA involves the use of programmable syringe pumps that provide a background infusion of morphine and allow nurses to give bolus doses regulated by a lockout time. Although morphine infusions provide constant plasma concentrations, the rates used for NCA are inadequate for the fluctuations in pain occurring postoperatively. Bolus doses can therefore be administered if necessary by a trained nurse. A lockout time of 20 minutes between boluses is recommended. Because of the variability in morphine metabolism in babies under 2 months and the increased risk of respiratory depression, background infusions are not recommended in babies weighing less than 5 kg, except those ventilated postoperatively. Recommended doses are given in Figure 4.

Recommended maximum doses of morphine in babies

Route	Preterm	Term	Infant
I.v. bolus	4 µg/kg 2 hourly	15 µg/kg 2 hourly	40 µg/kg 2 hourly
Infusion	2 µg/kg/hour	7 µg/kg/hour	20 µg/kg/hour
I.v. nurse controlled analgesia	Not recommended No background	10 µg/kg bolus 4 µg/kg/hour infusion	20 µg/kg bolus background
Epidural	Not recommended	Not recommended	30 µg/kg 8 hourly

4

All babies should have a pain chart with hourly recording of vital signs, pulse oximetry, sedation and pain scores. The results of these observations should guide emergency measures, administration of boluses, or review by the pain team and a change in the NCA programme. When supervised by a pain service, NCA has a 1% incidence of respiratory depression.

Prescriptions for naloxone in the event of respiratory depression together with a threshold respiratory rate for its administration should be included on the same drug chart as the NCA prescription. The intravenous naloxone dose is 2–4 µg/kg which may be repeated at 2 minute intervals.

Local anaesthetic techniques
Data are limited on the absorption, distribution and metabolism of local anaesthetics in neonates and infants, but they are more vulnerable to toxicity and accumulation. There are several reasons for this. Concentrations of the plasma proteins α_1-acid glycoprotein and albumin are lower in babies less than 3–6 months of age, and further reduced in preterm neonates. These proteins bind amide local anaesthetics and reduced binding increases the concentration of free drug and the potential for CNS and cardiovascular toxicity. Hepatic metabolism by dealkylation and hydroxylation (the degradation pathways for amide local anaesthetics) is slower in young babies. Elimination half-lives are therefore prolonged in this age group, increasing the risk of accumulation with infusions or repeated doses. Smaller doses with increased dose intervals are recommended.

Lidocaine (lignocaine) and bupivacaine are well established for use in children (Figure 5). There are few data about the use of ropivacaine and levobupivacaine in this age group. They have similar properties to bupivacaine, but may prove safer and supersede it in clinical practice.

Dose of lidocaine (lignocaine) and bupivacaine for regional analgesia

	Lidocaine	Bupivacaine
Neonate (up to 44 weeks' postconceptional age)	3 mg/kg 4 hourly	2 mg/kg 6 hourly
Infant (over 44 weeks' postconceptional age)	4 mg/kg 4 hourly	2.5 mg/kg 6 hourly

5

Topical application of local anaesthetic has limited use for postoperative pain, though *Emla* (eutectic mixture of local anaesthetics) has been used for neonatal circumcision, and is recommended for use before a range of painful procedures such as venous and arterial puncture, lumbar puncture, and subcutaneous or intramuscular injections. It should be applied 60 minutes before a procedure is started. Concerns have been raised over an increased risk of prilocaine toxicity in neonates and preterm infants. Neonates have a thinner stratum corneum layer of the skin, allowing increased absorption of prilocaine and hence higher plasma levels. They also have reduced activity of the methaemoglobin reductase enzyme which converts methaemoglobin to haemoglobin. In practice, though methaemoglobin levels are raised they remain below toxic levels, however caution is advised with repeated doses. Maximum doses are given in Figure 6.

Maximum dose and application area for Emla assuming intact skin and normal hepatic and renal function

Age	Body weight (kg)	Maximum *Emla* dose (g)	Maximum area
30–37 weeks	Mean 1.9	0.5	Unspecified
Over 37 weeks	More than 2.5	1	Unspecified
1–3 months	Up to 5	1	10 cm^2
4–12 months	5–10	2	20 cm^2

6

Wound infiltration and peripheral nerve blocks are a valuable supplement to general anaesthesia, providing analgesia well into the postoperative period. Bupivacaine is the local anaesthetic of choice because of its long duration of action. The safe dose varies according to the site of administration. Peripheral nerve blocks are particularly suitable for surface and peripheral surgical procedures, and are widely used for day case surgery. They avoid the problems of central blocks but carry the risk of intraneural injection and subsequent nerve damage. Commonly performed peripheral nerve blocks include penile, ilioinguinal, axillary, intercostal and femoral (see *Anaesthesia and Intensive Care Medicine* **1:4:** 132). Blocks should be sited and working before skin incision to allow an opioid-free and low volatile anaesthetic technique; this leads to more rapid emergence from anaesthesia.

Central blocks: the epidural space can be accessed via the thoracic, lumbar and sacral intervertebral spaces and the sacral hiatus (caudal epidural). The use of epidural analgesia improves outcome in adults and may do so in babies, with benefits from improved respiratory function, reduced postoperative apnoea, and attenuation of the neuroendocrine stress response to surgery. Retrospective studies show reduced mortality and less need for postoperative ventilation in neonates having diaphragmatic hernia repair with epidural analgesia, and reduced hospital stay in children having Nissen's fundoplication with epidural analgesia. Prospective studies are required to demonstrate this benefit. Complications from epidurals in this age group include convulsions related to bupivacaine toxicity and venous air embolism. Technical problems resulting from the use of finer bore catheters (e.g. catheter occlusion, disconnection, leakage round the epidural site) lead to premature discontinuation in about 10% of infusions. The incidence of neurological complications is low.

Caudal epidurals are increasing in popularity in babies. A single dose of local anaesthetic may be given or a catheter threaded to the desired level and an infusion commenced. A single dose caudal can provide analgesia for surgery below the umbilicus and a catheter may be threaded up as high as T6 for upper abdominal or thoracic surgery. The potential hazards of accessing the epidural space at spinal cord level (the spinal cord extends to L3 in neonates) have led to many centres using caudal catheters rather than thoracic or lumbar approaches. Threading caudal catheters is most successful in neonates and infants under 5 kg and is made easier with styletted catheters. The catheter position can be confirmed by fluoroscopy which has the side-effect of radiation exposure to the patient, or by using a metal styletted catheter and nerve stimulation guidance.

The sacral hiatus is usually easy to identify in this age group and can be found using the same anatomical landmarks as in adults. In neonates, the dural sac may extend as low as S3–4 making accidental dural puncture more likely. For this reason, a technique using a cannula that is threaded over the needle as soon as the membrane is pierced is commonly used. Recommended doses of local anaesthetic for epidurals are given in Figures 7 and 8. A block from L5–S5 is suitable for penile surgery (e.g. circumcision, hypospadius repair), a T9–S5 block is adequate for herniotomy or orchidopexy. A single dose provides analgesia for up to 4–6 hours. The resultant immobility in the early postoperative period is not a problem in infants. Clonidine and ketamine have been used successfully in combination with local anaesthetics to prolong the duration and improve the quality of caudal block in older children. Data about their use in children under the age of 1 year are limited.

Volumes of bupivacaine for caudal, lumbar and thoracic epidural analgesia

Injection site	Dose
Caudal	*L5–S5 block:* 0.25% bupivacaine, 0.5 ml/kg *T9–S5 block:* 0.25% bupivacaine, 1.0 ml/kg (volume to be made up with normal saline once safe dose limit reached)
Lumbar	0.25% bupivacaine, 0.75 ml/kg
Thoracic	0.25% bupivacaine, 0.5 ml/kg

7

Infusion rates of bupivacaine for epidural analgesia

Age	Infusion rate (mg/kg/hour)
Preterm/neonate (up to 44 weeks' postconceptional age)	< 0.2
Infants (44–56 weeks' postconceptional age)	< 0.25
Infants (56 weeks' postconceptional age)	< 0.4

8

Lumbar and thoracic epidurals provide analgesia for abdominal and thoracic surgery, and have been used in babies as small as 900 g. Lumbar catheters may also be threaded into the thoracic region. In some centres, lumbar or thoracic approaches are preferred to caudal catheters because it is easier to keep the entry site clean postoperatively. Studies have shown increased bacterial colonization in caudal as compared with lumbar catheters, but there is little evidence to suggest a difference in clinical infection rates between the two sites.

A loss of resistance to saline technique is recommended for identifying the epidural space because of the potential for venous air embolism and reports of patchy blocks if air is used. A smaller gauge needle and catheter are used. The size of catheter used varies, but the following is suggested: 20 G needle with 24 G catheter for babies under 2 kg, 19 G needle with 23 G catheter for babies 2–10 kg, 18 G needle and 21 G catheter for larger babies. The finer the catheter the higher the technical difficulties threading it into the epidural space. The depth from skin to epidural space is not predictable by weight in neonates and infants under the age of 6 months but can be as little as 3 mm; in older infants it is about 1 mm/kg. Recommended doses of bupivacaine are given in Figure 8. Adding opioids is not recommended in neonates because of concerns about respiratory depression. They may be used in older infants if they are nursed in a high dependency setting.

Infants with epidural catheters postoperatively should be nursed on wards with nursing staff trained in their management and complications. Infusions are usually discontinued 24–72 hours after surgery. Standardized forms should be used for recording pain and sedation scores, respiratory rate, vomiting, urinary retention and pruritus, with instructions for treating these complications should they occur. The infants should be assessed at least daily by a member of the pain team and the epidural site inspected with each change in nursing shift.

Spinal anaesthesia can provide analgesia into the early postoperative period and is widely used. When used without supplementation it reduces the incidence of postoperative apnoea in former preterm infants compared with general anaesthesia. It can be used as sole anaesthesia for lower abdominal, lower limb and urological procedures lasting less than 90 minutes. Limitations of the technique include a variable success rate with a significant requirement for additional sedation, a second spinal injection or conversion to general anaesthesia. Bupivacaine, 0.3–0.6 mg/kg, tetracaine (amethocaine) or lidocaine (lignocaine) are used. Central blocks in young children do not cause the haemodynamic changes seen in adults, but the reasons for this are unclear. ◆

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Principles of Anaesthesia for Babies

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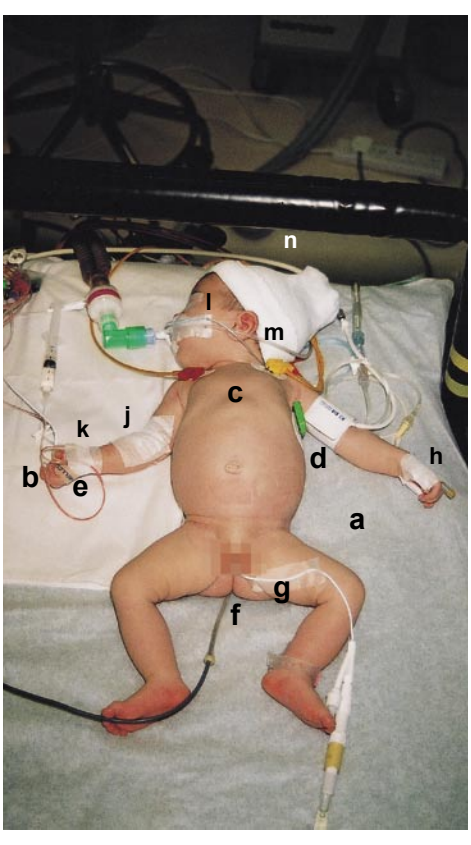
Successful outcomes in babies requiring surgery (Figure 1) demand that anaesthetists, surgeons and intensivists work together to ensure the best possible patient care before, during and after the operation. Complex surgery should be carried out in specialized centres. If minor and intermediate procedures are undertaken elsewhere, it is essential that all involved are appropriately trained and have continuing experience managing babies.



1 A baby prepared for surgery:

a covered warming matress; **b** peripheral perfusion assessed from the hand;

c ECG electrode; **d** non-invasive blood pressure cuff; **e** pulse oximeter probe; **f** rectal (core) temperature probe;

g urinary catheter measures urine output;

h intravenous access in hand;

j supplementary intravenous access in right antecubital fossa; **k** right radial (preductal) arterial catheter; **l** nasogastric tube;

m oesophageal stethoscope; **n** bar lifts the surgical drapes and allows the anaesthetist access to the airway.

Preoperative preparation

Environment

Temperature: once anaesthesia has been induced the infant's response to cold is suppressed. The operating theatre should be warmed to 24–25°C before the infant arrives. A water or air mattress should be heated to 40°C and covered with flannelette. Servocontrolled overhead radiant heaters are helpful in main-taining body temperature but must be used strictly in accordance with the manufacturer's recommendations (e.g. position a safe distance from the baby's body surface and monitor skin temperature to avoid hyperthermia. Other useful measures include warming intravenous and skin preparation fluids, and ensuring that anaesthetic gases can be warmed and humidified.

Equipment

The anaesthetic machine should incorporate the facility to deliver air in situations in which nitrous oxide is contraindicated and hyperoxia undesirable (e.g. gastroschisis, bowel obstruction).

Breathing systems – anaesthetic circuits for babies should be light, have minimal resistance and dead space, and be adaptable for spontaneous, assisted or controlled ventilation. The T piece system designed by Ayre and modified by Jackson Rees is the most widely used, though the circle absorber semi-closed system can be adapted for babies by incorporating smaller diameter breathing tubes.

Ventilators for babies should have a low internal compliance and be able to deliver small tidal volumes and rapid respiratory rates. Inspiratory flow rates and the inspiratory:expiratory (I:E) ratio should be adjustable so that peak airway pressure is kept low. Suitable ventilators can be either pressure or volume cycled. With the former, suitable settings for term babies include a fresh gas flow of 2–3 litres/minute, I:E ratio of about 1:1.5, positive end-expiratory and peak airway pressures of 5 and 20 cm H_2O, respectively, and a ventilatory rate of 30–40/minute. If volume cycling is used, a tidal volume of 10 ml/kg at a rate of 30–40/ minute is appropriate. Preterm babies (born before 37 weeks' gestation) are prone to pulmonary barotrauma; the risks are reduced by using lower peak airway pressures and faster ventilatory rates, often with an I:E ratio of 1:1.

Laryngoscopes – the larynx is higher (C4) and more anterior in babies than in adults and a laryngoscope with a straight blade (e.g. Seward or Robertshaw) provides a better view than one with a curved blade. The epiglottis is large and floppy and often obscures the larynx unless lifted by the tip of the laryngoscope blade (for which the straight blade was specifically designed).

Monitoring equipment – a complete range of monitoring equipment of suitable size for babies must be available.

Face masks are generally used for brief periods only in babies, but should provide a good fit and have a low dead space. Oral airways are not widely used.

Tracheal tubes – a cuff limits the diameter of tube that can be used and increases the risk of trauma, particularly to the cricoid mucosa, therefore, uncuffed tubes are preferred. Recommendations for the diameters and lengths of tubes for babies of different postconceptional ages are given in Figure 2, but a range of sizes should be available.

Laryngeal mask airway (LMA) – the incidence of airway complications associated with the LMA in babies is high, but it is useful if intubation is difficult. The seal achieved may not be adequate to permit controlled ventilation.

Drugs – both anaesthetic and emergency drugs should be drawn up before anaesthesia is commenced, either in finely graduated 1 ml syringes or suitably diluted in 2 or 5 ml syringes. All air bubbles should be removed to minimize the risk of air embolus.

Approximate diameter and length of oral tracheal tubes in babies

Postconceptional age (weeks)	Internal diameter (mm)	Length (cm)
< 30	2.0–2.5	7–8
30–40	2.5–3.0	8–9
> 40	3.0–3.5	9–10

2

The baby

History – even in very young babies, considerable information will have accumulated by the time of the anaesthetist's visit. This should be obtained from the parent(s) and health centre staff. Attention should be paid to birth history, gestational age at delivery and age at surgery, which is usually expressed as postconceptional age.

Trends in blood pressure and heart rate, body weight, fluid intake and output, laboratory measurements, radiographic appearances and the extent of any respiratory support required are normally available and are helpful to plan the anaesthetic technique and to anticipate problems. Knowledge of recent or current drug therapy is also important.

Physical examination – the anaesthetist should make a brief assessment of the baby's overall condition and carefully examine the individual body systems. Many surgical conditions presenting at birth are associated with other congenital anomalies, particularly congenital heart disease. Overhydration or hypovolaemia can be detected by assessing skin turgor, anterior fontanelle tension and liver size. Peripheral vasoconstriction (delayed capillary refill time) may indicate either hypovolaemia or acidosis. Jaundice is usually self-evident, but anaemia and cyanosis can be difficult to detect. Pulmonary function is also less easily evaluated than in older children and adults, but impending respiratory failure may be identified by nasal flaring, tachypnoea, chest wall recession, grunting respiration or apnoeic spells. Airway anatomy should be assessed so that potential difficulties with tracheal intubation can be anticipated.

Homeostasis – the minimum laboratory data required for most babies aged less than 44 weeks' postconceptional age includes a full blood count, blood urea and serum electrolytes, blood glucose and calcium, coagulation profile and urine specific gravity. Any abnormalities should be corrected preoperatively. If significant blood loss is expected during surgery, the infant should have blood typed and cross-matched. Body temperature should be normalized. Estimated blood volume, allowable blood loss and maintenance fluid requirements should be calculated.

Fasting – to prevent hypoglycaemia or dehydration, babies having elective or non-urgent surgery should not be starved excessively. Recommended fasting periods are generally shorter than in children (2 hours from clear non-particulate and non-carbonated fluids, 4 hours from breast milk and 6 hours from infant formula or other milk).

Coagulation – stores of vitamin K are low at birth and bleeding can occur because of depletion of factors II, VII, IX and X. Vitamin K partially reverses hypothrombinaemia rapidly and 0.5–1.0 mg is usually injected intramuscularly at birth. It is important for the anaesthetist to check that this has been given to newborns needing surgery.

Premedication – sedative premedication is not used in babies. However, many anaesthetists give an anticholinergic drug at induction to reduce secretions and protect against bradycardia. Atropine, 20 μg/kg i.v., is the most widely used drug.

Transfer to the operating theatre

Risks are minimized if the baby is accompanied to theatre by experienced personnel. Transfer should be in an incubator or an isolette with overhead heater to reduce heat loss. Any treatment in progress (e.g. intravenous fluid or drug infusion, respiratory support) and appropriate monitoring should be continued using battery-operated infusion pumps and portable equipment.

Anaesthesia

The anaesthesia plan

The anaesthetist must choose between spontaneous and controlled ventilation for maintenance of anaesthesia – it is acceptable for healthy infants to breathe spontaneously for minor procedures. Controlled ventilation should be employed when using a circle system for infants. An analgesic plan for both intra- and postoperative periods should be formulated and its potential side-effects considered. Drugs and techniques in common use are summarized in Figures 3 and 4. Intraoperative monitoring requirements must be decided in advance because access to the baby may be limited once surgery commences.

Drugs used for perioperative pain control in babies

Opioids	
• Morphine	Clearance prolonged in babies Beware respiratory depression
• Fentanyl	Well tolerated haemodynamically Care with dosing if baby is expected to breathe spontaneously postoperatively
• Alfentanil	Rapid onset, short duration of action, minimal accumulation
• Remifentanil	Ultra-short acting May be used intraoperatively by continuous infusion
• Codeine phosphate	Relatively safe; never give i.v.
Local anaesthetics	
• Lidocaine (lignocaine)	Short acting, seldom used
• Bupivacaine	Cumulation in babies after 6–12 hours if given by continuous infusion
• Levobupivacaine	May be safer than bupivacaine
Paracetamol	Useful for minor pain
Non-steroidal anti-inflammatory drugs	Seldom used, renal maturation still occurring

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Administration of drugs used for perioperative pain control

Opioids	
• Intravenous bolus injection	Often used intraoperatively
• Intramuscular injection	Avoid if possible
• Oral	May be useful in weaning from lengthy intravenous infusion
• Per rectum	Codeine most often used
• Continuous intravenous infusion	Widely used for postoperative analgesia in ventilated infants and those nursed in high dependency areas Respiratory monitoring required
• Epidural infusion	Synergistic effect when added to local anaesthetics Risk of delayed respiratory depression
• Nurse-controlled analgesia	Becoming popular, using patient-controlled analgesia devices
Local anaesthetics	
• Wound infiltration	Can be useful
• Peripheral nerve blocks (e.g penile, ilioinguinal)	More difficult to perform than in older children
• Single-shot central block (e.g. caudal)	Action may be prolonged by clonidine or ketamine
• Intrathecal block	May be used alone for short procedures, especially in ex-preterm babies
• Epidural infusion (e.g. caudal, lumbar, thoracic)	Complication rate relatively high in babies If used alone, lack of sedation may be a problem despite good analgesia
Paracetamol	
• Oral or rectal	Use reduced doses in babies

4

Induction of anaesthesia
Intravenous access should be established before induction, preferably in a vein that the anaesthetist can check to ensure patency during surgery (e.g. the back of the hand). The anaesthetist must ensure that access to an injection port will be easy once the baby is draped so that volume expanders can be given conveniently during surgery. The dead space of the line between injection port and cannula should be minimal. Basic monitoring (ECG and pulse oximetry) should be applied. The induction technique depends on the age, size and physical status of the infant, the relative risk of regurgitation, and the personal preference of the anaesthetist.

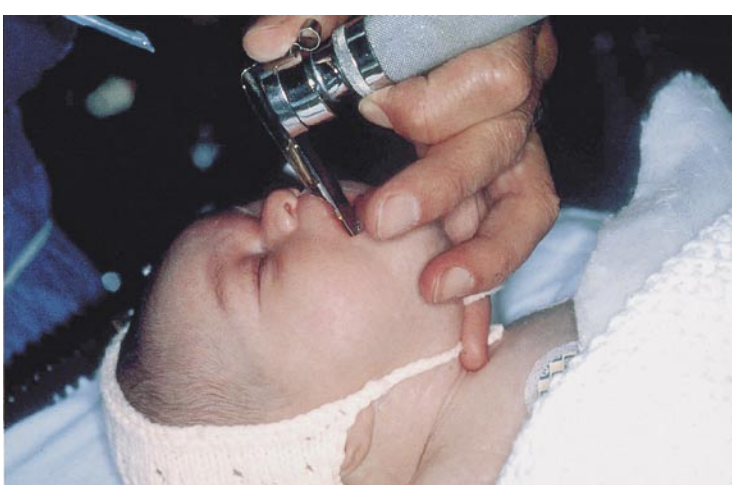
Intravenous induction – thiopental (thiopentone) sodium is the most widely used agent in infants. The induction dose (ED_{50} 3.4 mg/kg) is lower in neonates less than 14 days of age than in older babies. Experience with propofol is limited; the induction dose in infants aged 1–6 months is 25% more than that in older children. Propofol is more effective than thiopental (thiopentone) in obtunding the hypertensive response to intubation and recovery is faster. It also suppresses pharyngeal and laryngeal reflexes to a greater degree, and this has been used to facilitate LMA insertion or intubation when there is a need to avoid muscle relaxants. However it is not currently licensed for use in children below 3 years of age. Ketamine has a profound analgesic effect and is associated with greater cardiovascular stability than many other anaesthetic drugs. However, its metabolism is delayed in infants.

Inhalation induction remains popular. For many years, halothane was the most widely used volatile anaesthetic in babies. Sevoflurane is now advocated by many because it provides rapid induction with minimal airway irritation or cardiovascular effects. Induction time with sevoflurane is shorter than with halothane in older children but not in babies. Sevoflurane causes more respiratory depression than halothane in babies and young children. Desflurane, enflurane and isoflurane are unsuitable for inhalation induction because of their irritant effects on the airway. Nitrous oxide is used as a carrier to supplement volatile anaesthetics, reducing the concentration required and minimizing cardiovascular depressant effects. However, it is more soluble in blood than is nitrogen, and inhalation and diffusion of the gas causes an increase in the volume of compliant spaces. Therefore, air should be used as the carrier gas in babies with congenital diaphragmatic hernia, lobar emphysema or necrotizing enterocolitis.

Tracheal intubation
Babies should be intubated and ventilated for most surgical procedures because of their limited respiratory reserve. Most anaesthetists recommend giving a muscle relaxant (e.g. succinylcholine, 2 mg/kg, or atracurium, 0.6 mg/kg) after induction of anaesthesia to facilitate tracheal intubation. Awake intubation is seldom used because it is distressing and may be associated with intraventricular haemorrhage in preterm babies.

In babies, the epiglottis is long and floppy and should be displaced anteriorly from behind with the tip of the laryngoscope blade to aid visualization of the larynx. The view is often improved by application of cricoid pressure by either the intubator or an assistant (Figure 5). If difficulty is encountered, use of an atraumatic (but rigid) bougie can also be helpful but care should be taken to ensure that the tip of the bougie does not protrude significantly beyond the tip of the tracheal tube to reduce the risk of laryngeal or tracheal perforation.

The optimal diameter of tube is the largest that will pass easily through the glottis and subglottic region and will allow a slight leak when 20 cm H_2O positive pressure is applied. Once satisfactory positioning has been confirmed the tube should be taped securely. The anaesthesia circuit must be carefully positioned and supported.



5 A straight laryngoscope blade inserted from the right-hand side of the mouth keeps the large tongue out of the way of the intubator. A finger placed on the skin over the larynx pushes the anterior and tilted laryngeal entry in a posterior direction to give a good view and easier insertion of the tracheal tube.

Thanks are extended to Andrew R Wolf for the use of this photograph.

Maintenance of anaesthesia
Although it is acceptable for healthy babies to breathe spontaneously during anaesthesia for minor operations, prolonged anaesthesia in spontaneously breathing babies is associated with airway closure, atelectasis and increasing alveolar–arterial oxygen tension gradient.

Manual ventilation using the Jackson Rees modification of Ayre's T piece is used at times, especially when there is doubt about the adequacy of ventilation or pulmonary compliance is changing rapidly (e.g. during repair of an oesophageal fistula). Most paediatric anaesthetists revert to hand ventilation if there is any concern about the adequacy of chest wall movement or possible obstruction of the tracheal tube.

Mechanical ventilation helps to ensure adequate gas exchange and leaves the anaesthetist's hands free. Both end-tidal carbon dioxide concentration and peak airway pressure are more easily controlled. Because the amount of ventilation lost by compression of the ventilator tubing and leakage around the tracheal tube in babies is significant, readings of volume observed on a ventilator bellows are relatively meaningless. The adequacy of ventilation must be judged by auscultation, chest movement and end-tidal or arterial carbon dioxide tensions. Inspired gases should be warmed and humidified. Passive heat and moisture exchangers (HMEs) are satisfactory in most cases. Active systems such as heated water-bath humidifiers are more effective in preventing hypothermia but require the use of a servomechanism to control the temperature of the water heater.

Traditionally, halothane was the most widely used agent for maintenance of anaesthesia in babies. However, isoflurane, sevoflurane and desflurane all offer improved cardiovascular stability along with more rapid recovery. They are usually combined with 50% oxygen in air or nitrous oxide. Atracurium is an attractive neuromuscular blocking agent because its metabolism is independent of hepatic and renal function. Vecuronium should be considered long-acting in babies. Mivacurium is shorter-acting and the onset of block is more rapid in younger patients. Rocuronium causes more neuromuscular depression and has a longer duration of action during halothane anaesthesia in infants less than 2 years of age than in older children.

Termination of anaesthesia
If a volatile agent has been used during maintenance of anaesthesia it should be discontinued before the end of surgery. Residual muscle relaxation is reversed by neostigmine, 60 μg/kg, combined with atropine, 20–30 μg/kg, or glycopyrollate, 10 μg/kg. Controlled ventilation is continued with 100% oxygen or with oxygen in air until spontaneous respiration returns. Babies should not be extubated until fully awake and breathing adequately. Postoperatively they should be nursed in a warmed environment or under a thermostatically controlled radiant heater.

Monitoring
The condition of the anaesthetized baby can deteriorate rapidly with little warning. Therefore careful and continuous monitoring is essential. Figure 6 lists the minimum equipment required.

ECG electrodes designed for infants should be used. The advent of neonatal non-invasive monitors and appropriately sized cuffs has made blood pressure measurements easier. Pulse oximetry allows close observation of changes in heart rate and oxygen saturation, and reduction of inspired oxygen concentration to the minimum required to maintain adequate oxygenation (important in very preterm babies). At least one central temperature should be monitored. The precordial or oesophageal stethoscope remains valuable and is considered essential by many. It allows continuous monitoring of respiration, heart rate and rhythm, and also the intensity of heart sounds (the latter becoming muffled with hypovolaemia).

The anaesthetist should supplement monitoring with clinical observation. Assessing peripheral perfusion or palpating a peripheral pulse may prove difficult because of limited access. Even with oximetry, a light should be available to assess skin colour and perfusion. Chest wall movement should be observed continuously if possible. It should be possible to gain access to the tracheal tube.

Minimum monitoring for anaesthetized babies

- ECG
- End tidal carbon dioxide
- Non-invasive blood pressure monitor
- Pulse oximeter
- Core temperature probe
- Precordial or oesophageal stethoscope (considered by many to be essential)

6

Additional monitoring should comply with the Association of Anaesthetists' guidelines. If either the infant's physical status or the type of surgery necessitates continuous monitoring of blood pressure or regular arterial blood gas analysis, a suitable vessel should be cannulated with a 22 or 24 G cannula. The right radial artery is usually preferred because it is representative of preductal blood flow. The hand is secured with slight extension at the wrist. The fingertips are left exposed so that any peripheral ischaemic changes can be observed. Fibre-optic light sources and Doppler devices may assist in identifying the course of the artery. Cannulation is accomplished by direct entry at an angle of 15–20° or on withdrawing the cannula after transfixion of the vessel. The brachial artery is an end-artery and percutaneous puncture is more hazardous.

Central venous cannulation is useful when major shifts in intravascular volume are anticipated. The right internal jugular vein is usually the simplest and safest to cannulate. The high approach at the apex of the triangle formed by the two heads of the sternocleidomastoid muscle and the clavicle is associated with the most success. The most common complication (arterial puncture) is easily recognized and usually managed uneventfully. A 4 French gauge double-lumen catheter 5 cm in length inserted using the Seldinger technique is suitable for most babies.

Monitoring cardiac output, left atrial pressure and/or pulmonary capillary wedge pressure is seldom indicated but can be performed if necessary. For babies undergoing complex cardiac surgery, intermittent use of intraoperative trans-oesophageal echocardiography is becoming common.

Fluid balance
Maintenance fluid requirements vary in the neonatal period (Figure 7) but are about 5 ml/kg/hour for fullterm babies older than 5 days of age. 10% glucose in water is the usual starting fluid; the glucose concentration can subsequently be adjusted depending on blood glucose measurements. After 24 hours, electrolytes should be added (Figure 8). Assuming there is no fluid deficit, an intravenous infusion set at the appropriate maintenance rate should be commenced before induction of anaesthesia. The composition of the fluid administered varies according to the maturity of the baby and preoperative glucose and electrolyte levels. Fluid administration must be monitored carefully. During prolonged surgery, blood glucose levels should be checked often, especially in smaller babies, and corrected if necessary. If the surgical procedure involves significant tissue trauma and/or exposure, additional fluid must be given to replace extracellular (third-space) fluid loss. Lactated Ringer's solution is suitable in most cases. The volume required is related to the type of surgery; as little as 1 ml/kg/hour during peripheral procedures, 2–3 ml/kg/hour for thoracotomy and as much as 5–10 ml/kg/hour during major intra-abdominal surgery. There are few published data on the relative merits of crystalloid and colloid solutions in newborn surgery, and while concerns have been expressed about the cost:benefit ratio of the use of albumen (4: 5 or 20%), it remains widely used as a safe and effective volume expander. Because of the relatively high haematocrit at birth, red-cell replacement is seldom needed in newborn babies. The need for transfusion can be determined more accurately from serial haematocrit measurements than by other methods; blood loss can be extremely difficult to measure accurately. Haematocrit should be maintained at 35–40%.
When required, the blood used should be as fresh as possible. Adequacy of volume replacement can be assessed by monitoring blood pressure, central venous pressure, peripheral circulatory state and urine output (at least 1 ml/kg/hour).

Daily maintenance fluid requirements in newborns

Day	Volume (ml/kg)
1	50–80
2	80–100
3	100–120
4	120–150

7

Daily electrolyte requirements in mmol/kg

Sodium	2–4
Chloride	2–4
Potassium	1–3
Calcium	0.5–1
Magnesium	0.25
Phosphate	2–3

8

Day-case anaesthesia for babies
The lower age limit for day-case management depends on several factors including postconceptional age. Healthy fullterm babies may safely be scheduled for minor surgery as outpatients within a few days of birth provided that access to inpatient care is available should it become necessary. Preterm or ex-preterm infants are at increased risk of postoperative complications (e.g. apnoea). Most anaesthetists will not consider day-case management for these babies at less than 50 weeks' postconceptional age or even older if the infant still exhibits lung disease. ◆

Resuscitation of the Newborn

Jonathan Wyllie

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In the UK, about 650,000 babies are delivered each year and mostmake the transition to extrauterine life without problems. A fewrequire assistance in establishing adequate respiration and both the Royal College of Paediatrics and Child Health and the Royal College of Midwives, state that 'anybody attending a delivery should be able to deliver basic resuscitation to the baby'.

The main difference between resuscitation in adults and in children is that most adult arrests are a result of myocardial infarct or dysrhythmia, while most paediatric arrests are respiratory in origin.

Physiology

In pregnancy, the fetal lungs are net exporters of fluid. The onsetof normal labour stimulates the production of adrenaline (epinephrine) by the fetus and thyrotrophin-releasing hormone by the mother causing cells within the fetal lung to cease secretion and to begin re-absorption of fluid from the alveolar spaces.

During vaginal delivery at term, about 35 ml of fluid is expelled from the lungs by uterine contraction and passage through the birth canal. The first breath usually occurs within 60–90 seconds of clamping or obstruction of the umbilical cord. The first breaths are important in aerating the fluid-filled fetal lungs.

The healthy term baby may generate a negative pressure of between –0 and –100 cm H_2O (–3.9 and –9.8 kPa) to aerate the lungs for the first time. This pressure is 10–15 times greater than that needed for later breathing, but is necessary to overcome the viscosity of fluid filling the airways, the surface tension ofthe fluid-filled lungs and the elastic recoil and resistance of thechest wall, lungs and airways. These powerful chest movementscause fluid to be displaced from the airways into the circulation.

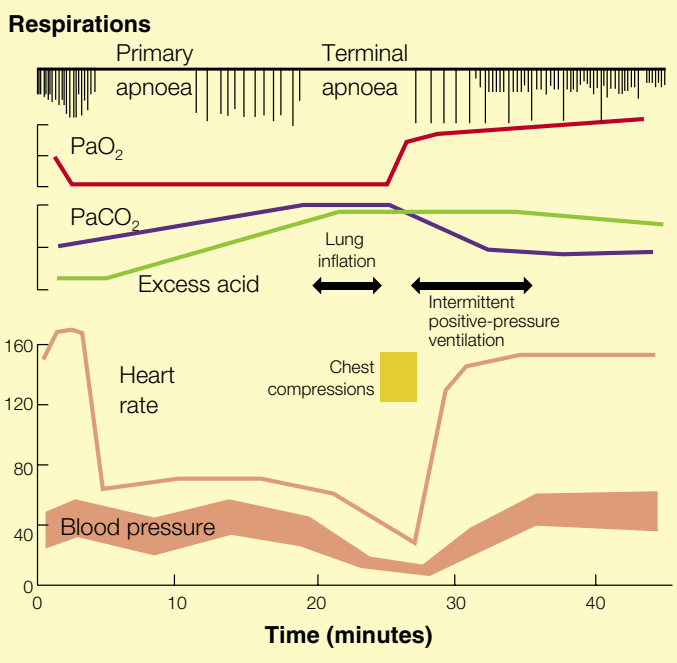
In a 3-kg baby, about 100 ml of fluid is cleared from the airways following the initial breaths, a process aided by full inflation and prolonged high pressure on expiration (i.e. crying). Delivery by section before the onset of labour may slow the clearance of pulmonary fluid from the lungs and reduce the initial functional reserve capacity. Lung inflation and alveolar distension release mediators that affect the pulmonary vasculature, reducing pulmonary resistance and increasing oxygenation.

Pathophysiology

Understanding of the pathophysiology of fetal hypoxia is based on pioneering animal work by Geoffrey Dawes, Kenneth Cross and others in the early 1960s.

When the placental oxygen supply is interrupted, the fetus initiates breathing movements. Should these fail to provide an alternative oxygen supply, the baby loses consciousness. If hypoxia is prolonged, the respiratory centre can no longer initiate breathing and stops functioning, usually within2–3 minutes (primary apnoea: Figure 1). Babies have several automatic reflex responses to such a situation. Bradycardia ensues secondary to hypoxia and vagal mediation, but peripheral vasoconstriction and an increased cardiac stroke volume usually maintain blood pressure. After a period of primary apnoea, primitive spinal reflexes initiate gasping breaths, similar to Cheyne-Stokes respiration. These deep spontaneous gasps are easily distinguishable from normal respirations because they occur 6–12 times per minute and involve all accessory muscles in a maximal inspiratory effort. If hypoxia continues, this activity eventually ceases (terminal apnoea; Figure 1). The time taken for such activity to cease is longer in the newborn (up to 20 minutes) than in later life.

Physiology of acute hypoxia and resuscitation in the newborn



PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood.

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1

The circulation is almost always maintained until all respiratory activity ceases. This circulatory resilience is a feature of all newborn mammals at term, largely because of the reserves of glycogen in the heart. Therefore, resuscitation is relatively easy if undertaken before respiratory activity has stopped. If the circulation is still functioning then, once the lungs are aerated, oxygen is carried to the heart causing an increase in heart rate. Oxygenated blood then flows to the brain and recovery is rapid.

Once gasping ceases, the circulation starts to fail owing to the combined effects of hypoxia and acidosis and these infants may need more extensive resuscitation.

General care of the newborn

Most mature babies breathe or cry within 90 seconds of birth and few need resuscitation, even after an operative delivery. However, every newborn should be assessed at birth. Because of their small size and relatively large surface area, babies become cold very quickly. Evaporation and convection are the most important routes of heat loss for the newborn, and so the baby should be dried and wrapped in a pre-warmed towel and protected from draughts.

Resuscitation (Figure 2)

Newborn life support

Remove any wet cloths, dry the baby and cover

↓

Initial assessment at birth
Start the clock or note the time
Assess: colour, tone, breathing, heart rate

↓

If not breathing

↓

Control the airway
Head in the neutral position

↓

Support the breathing
If not breathing give five inflation breaths
(each 2–3 seconds' duration)
Confirm a response – increase in heart rate or visible chest movement

↓

If there is no response:
• double check head position and apply jaw thrust
• give 5 inflation breaths
• confirm a response – increase in heart rate or visible chest movement

↓

If there is still no response:
• use a second person (if available) to help with airway control and repeat inflation breaths
• inspect the oropharynx under direct vision and repeat inflation breaths
• insert an oropharyngeal (Guedel) airway and repeat inflation breaths
• Consider intubation
• Confirm a response – increase in heart rate or visible chest movement

↓

When the chest is moving
Continue with ventilation breaths if no spontaneous breathing

↓

Check the heart rate
If the heart rate is not detectable or slow (less than about 60 beats/minute) and not increasing

↓

Start chest compressions
First confirm chest movement – if not moving return to airway
3 chest compressions to 1 breath for 30 seconds

↓

Reassess heart rate
If improving – stop cardiac compressions, continue ventilation if not breathing
If heart rate still slow, continue ventilation and chest compressions
Consider venous access and drugs

At all stages consider whether help is required
In the presence of meconium, remember:
• screaming babies have an open airway
• floppy babies have a look

Reproduced with the permission of the Resuscitation Council (UK).

2

Equipment: all healthcare staff working in the maternity department should be familiar with the equipment available for the resuscitation of babies.

Preparation: if there is time, introduce yourself to the parents, study the obstetric notes and prepare the resuscitation equipment and area. Wash your hands and put on gloves.

Drying, covering and assessing: whatever the problem, first ensure the cord is securely clamped, then dry the baby (removing any wet towels) and cover the baby with dry towels. Drying the baby provides stimulation and allows time to assess the baby's colour, tone, breathing and heart rate. Reassess these observations about every 30 seconds throughout the resuscitation process. Consider and reconsider whether help is required and, if so, ask for it immediately.

A healthy baby is born blue but has good tone, cries within a few seconds of delivery, has a good heart rate (usually about 120–150 beats/minute) and rapidly becomes pink. A less healthy baby is blue at birth, has poor tone, may have a slow heart rate (less than 100 beats/minute) and may not establish adequate breathing by 90–120 seconds. An ill baby is born pale and floppy, not breathing and with a slow or very slow heart rate. The heart rate is best judged by listening to the chest with a stethoscope – palpating the cord does not necessarily give an accurate heart rate.

Airway: for a baby to breathe, the airway must be open. The bestway to achieve this is to place the baby on his back and to supportthe head in the neutral position. Most newborn babies have a relatively prominent occiput, which tends to flex the neck and obstruct the airway if the baby is supine. This can be avoided by placing some support under the baby's shoulders. If the baby is very floppy it may also be necessary to apply jaw thrust.

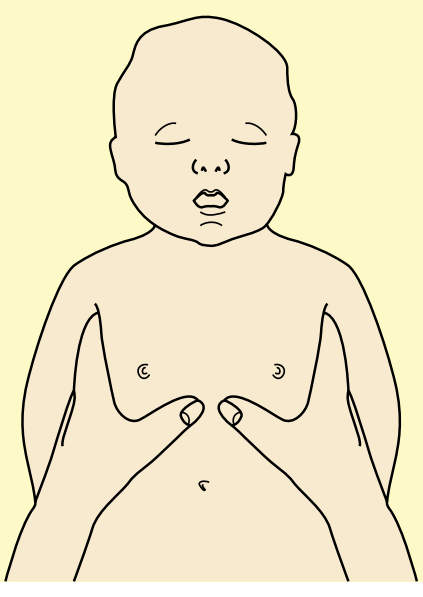
Breathing: if the baby is not breathing adequately by about 90 seconds consider giving five inflation breaths. Until this point, the baby's lungs have been filled with fluid. Lung aeration therefore requires sustained application of pressures of about 30 cm H_2O for 2–3 seconds for about five breaths – these are 'inflation breaths'. The heart rate usually increases in response to inflation breaths. If it does, assume the chest has been inflated successfully. If the heart rate increases but the baby does not start breathing for himself, continue to provide regular breaths at a rate of about 30–40 per minute until he starts to breathe on his own. If the heart rate does not increase following inflation breaths, then the chest is not inflated or the baby needs more help. It is most likely that inflation of the chest has failed. To ensure the lungs are inflated consider the following while checking for chest movement.

- Is the baby's head in the neutral position?
- Is jaw thrust required?
- Is a longer inflation time needed?
- Is a second person's help with the airway required?
- Is there an obstruction in the oropharynx (laryngoscope and suction)?
- Consider an oropharyngeal (Guedel) airway.
- Consider intubation.

If, following five inflation breaths, the heart rate remains slow or absent despite good chest movement, consider chest compressions. Make certain that breaths are being delivered because neither chest compression nor drugs will work without oxygenated blood.

Chest compressions: almost all babies needing help at birth respond to successful lung inflation with an increase in heart rate and the onset soon after of normal breathing. However, in some cases, chest compressions are necessary. In babies, the most efficient method of delivering chest compressions is to grip the chest in both hands such that the thumbs of both hands can press on the sternum at a point just below an imaginary line joining the two nipples and with the fingers over the spine at the back (Figure 3). Compress the chest quickly and firmly to reduce the antero-posterior diameter of the chest by about one-third. The currently recommended ratio of compressions to inflations in newborn resuscitation is 3:1.

Hand encircling technique for infant chest compression



3

Drugs: in a few babies (perhaps 1/1000 births), inflation of the chest and effective chest compressions are insufficient to produce an effective circulation. In these babies, drugs may be helpful. Drugs are needed only if there is no significant cardiac output despite effective lung inflation and effective chestcompression. They are listed in Figure 4 and are usually given viaan umbilical venous line. The place of drugs in the resuscitation of babies less than 28 weeks' gestation remains controversial.

Records should be clear and factual, noting the timing and sequence of events (Figure 5).

Drugs used in resuscitation of babies

Drug and dose	Route
Adrenaline (epinephrine)	
First dose, 10 μg/kg (0.1 ml/kg of 1:10,000 solution)	Via umbilical venous line
Second dose, 30 μg/kg (0.3 ml/kg of 1:10,000 solution)	Possible via tracheal tube but unproven at birth
Sodium bicarbonate,1–2 mmol/kg 2–4 ml/kg of a 4.2% solution	Via umbilical venous line
10% Glucose, 2.5 ml/kg	Via umbilical venous line

4

Records to be kept during resuscitation of the newborn

- When were you called, by whom, and why?
- The time you arrived, who else was there, and the condition of the baby on your arrival
- What you did, when you did it, and the timing and details of any response from the baby
- Assessment of the baby at birth
- The baby's heart rate at birth and when it first exceeded 100 beats/minute
- Whether gasping respiration preceded the onset of rhythmical breathing, when gasping started and how long it lasted
- When the baby started to breathe evenly, regularly and effectively 30–60 times per minute (even if gasping still occurred intermittently)
- The date and time of writing your entry and your signature

5

Special cases

Meconium: 'meconium stained liquor' is seldom a major problem in resuscitation, though it may cause problems for continuing care. Hypoxia *in utero* in the infant approaching term (over 37 weeks), leads to gut vessel vasoconstriction, increased peristalsis and a relaxation of the sphincters. This can result in passage of meconium *in utero*. In addition, fetal hypoxia, if severe, may lead to gasping and aspiration of meconium into the trachea before birth.

After delivery, meconium can cause problems if it obstructs the airway. Combined with asphyxia it causes a multi-organ problem, which is relatively uncommon in the UK. The original insult is the cause of this rare, but significant, problem. Slight coloration of liquor with meconium is not significant.

Prematurity: babies born prematurely are smaller, more likely to get cold and have fewer reserves than term babies. They may also be deficient in surfactant. Surfactant reduces alveolar surface tension and prevents alveolar collapse on expiration. Initial inflation pressure should be less (20–25 cm H_2O) to avoid lung damage, but if this pressure is inadequate it may need to be increased.

Congenital abnormality: most abnormalities are detected antenatally and only orofacial abnormalities (e.g. micrognathia, cleft lip and palate) and occasionally diaphragmatic hernia cause problems at resuscitation. The latter may be one of the few indications for intubation.

Prognosis

After resuscitation, parents will want to know the likely outcomefor their baby. Following any significant resuscitation the mostsenior person present should discuss events with the parents.

The prognosis for the full-term baby subjected to sudden acute asphyxia is usually good, provided the episode does not last for long. Most babies resuscitated from primary apnoea have no sequelae secondary to the resuscitation. Many babies who start to breathe again regularly within 20 minutes of the circulation being restored recover completely, but it is rare for a baby who is still gasping after 30 minutes to recover.

The prognosis for the preterm baby of less than about 34 weeks'gestation subjected to severe acute anoxia is less predictable. This is because of the risk of secondary intraventricular haemorrhage or periventricular intracerebral haemorrhage and/or infarction, after even a relatively brief asphyxial episode, especially in the period immediately before and after birth.

The effects of chronic hypoxia are also difficult to predict, but a reasonably clear idea of the extent of the problem should be obtainable within 36–48 hours of the original chronic asphyxial insult. A mild short-lasting state of hyperexcitability usually carries a good prognosis even if there is seizure activity, but moresevere symptoms can be associated with permanent handicap.

If no cardiac output has been established after 15 minutes, then the outcome is dire and consideration should be given to ceasing efforts. This should be a team decision; led by a senior person and with involvement of the parents. ◆

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Contact: Resuscitation Council (UK).
Website: www.resus.org.uk
E-mail: enquiries@resus.org.uk
Telephone: 020 7388 4678.

Special Considerations for Anaesthesia in the Premature Baby

Peter M Crean

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Babies are considered premature if born before 37 weeks' gestation and represent 6% of births. 7% of newborns weigh less than 2500 g. Babies weighing less than this are referred to as low birth weight (LBW) and those below 1000 g as extremely low birth weight (ELBW). ELBW babies constitute 0.5% of live births. Neonatal intensive care units (NICU) mainly cater for babies less than 28 weeks' gestation. Many of these babies are critically ill and can develop respiratory distress syndrome, life-threatening infections, intraventricular haemorrhage, heart failure or necrotizing enterocolitis.
In many premature infants scheduled for surgery, the conduct of anaesthesia is an extension of neonatal intensive care management. For this reason an understanding of the basic principles of neonatal care is essential.

Respiratory system

During fetal life the bronchial tree grows by dichotomous branching to produce 16 to 25 generations that form the future airways. Structures then develop by branching and budding to form respiratory bronchioles by 24 weeks' gestation, at which stage extrauterine survival is possible. Production of surfactant begins at about this time, though surfactant concentrations may remain inadequate until 36 weeks' gestation. The neonatal lung contains few alveoli, but alveolar growth accelerates after birth and continues until 8 years of age. Respiratory difficulties are common in preterm infants (Figure 1).

Respiratory difficulties in premature infants

- Deficiency of pulmonary surfactant leading to respiratory distress syndrome
- Risk of aspiration because of poor gag and cough reflexes, uncoordinated suck and swallow
- Compliant chest wall and weak respiratory musculature resulting in less efficient ventilation
- Periodic breathing and apnoea because of immaturity of the respiratory centre in the medulla

1

Respiratory distress syndrome

Respiratory distress syndrome is caused by surfactant deficiency and mainly affects the premature infant. The incidence is inversely related to gestational age and affects 90% of infants born at 26 weeks' gestation. Surfactant is produced by type 2 alveolar cells and, by reducing surface tension, prevents alveolar collapse at end-expiration. Deficiency of surfactant leads to reduced lung volumes, decreased lung compliance and ventilation/perfusion abnormalities. In severe cases, this results in hypoxaemia, tachypnoea and a mixture of metabolic and respiratory acidosis. Medical treatment includes oxygen delivered through a headbox, continuous positive airway pressure, mechanical ventilation and exogenous surfactant. In babies with severe respiratory distress syndrome, surfactant replacement therapy reduces mortality and morbidity and decreases complications such as pneumothorax and pulmonary interstitial emphysema. It is also beneficial when used prophylactically in babies of less than 30 weeks' gestation.

Anaesthesia may cause low lung volumes and ventilation/perfusion mismatch. The combination of immature structural development, disease and anaesthesia increases the chance of hypoxia and an anaesthetic technique based on mechanical ventilation with the use of positive end-expiratory pressure should avoid this complication. The risks of oxygen toxicity and barotrauma should also be considered during anaesthesia and the goal should be to maintain adequate oxygenation and ventilation, with the minimum oxygen concentration and peak inspiratory pressure necessary. Occasionally, surgery is required in infants suffering from respiratory distress syndrome and advice about optimal ventilator settings should be sought from a neonatologist. However, during anaesthesia with muscle relaxation, peak inspiratory pressures often need to be increased above preoperative values.

Chronic lung disease

Chronic lung disease is defined as a need for supplemental oxygen in babies of a postconceptional age of 36 weeks or term (postconceptional age = gestational age at birth + postnatal age). It is becoming more common as increasing numbers of immature babies survive. It develops in 25–30% of babies following treatment with intermittent positive-pressure ventilation on the NICU and in 5–10% of all babies less than 1500 g. Affected infants have continued oxygen requirement, indrawing, wheezing, cyanotic spells and right heart failure.

Subglottic stenosis

Acquired subglottic stenosis is a rare complication of long-term intubation in premature babies and is related to the number of intubations. Less than 1% of ventilated babies require a tracheostomy. Surgery to split the cricoid cartilage is an alternative.

Cardiovascular system

The premature infant is at greater risk of cardiovascular compromise during anaesthesia and surgery than the term infant. The fetal heart has fewer contractile units with more connective tissue than that of the infant, resulting in poor diastolic function and a decreased responsiveness to changes in intracellular calcium. The left ventricle is less compliant and cardiac output depends more on heart rate than in the term infant. Premature babies have small absolute blood volumes, therefore relatively minor blood loss during surgery can rapidly lead to hypovolaemia, hypotension and shock. Autoregulation is not well developed in premature babies and the heart rate may not increase with hypovolaemia. Also, anaesthesia blunts the baroreflexes in premature infants, further limiting the ability to compensate for hypovolaemia.

Patent ductus arteriosus

Physiological closure of the ductus arteriosus usually occurs 10–15 hours after delivery and depends on a complex process involving raised partial pressure of oxygen in arterial blood and falling prostaglandin levels. As gestational age increases, the muscular wall of the ductus becomes more sensitive to these stimuli so the ductus of a term infant tends to close more effectively than that of a premature infant. In term babies, permanent closure with obliteration of the duct lumen may take several weeks. Delayed ductus closure is more common in premature infants, occurring in 20–40% of those less than 1000 g. The clinical features are given in Figure 2.

Signs of a patent ductus arteriosus

- Bounding pulses
- Active precordium
- Loud systolic or continuous murmur at left sternal edge
- Widened pulse pressure
- Metabolic acidosis
- Apnoea

2

Congestive heart failure with pulmonary hypertension may develop in some infants, producing a large left-to-right shunt that leads to severe recurrent apnoea, intractable metabolic acidosis and the need for prolonged mechanical ventilation. Initial treatment includes fluid restriction and diuretic therapy, which may control symptoms until spontaneous closure occurs, usually at a postconceptional age of 40 weeks. However, in severely affected babies who remain in congestive heart failure and are 'ventilator dependent', surgical closure of the duct should be considered. Indometacin (indomethacin), a prostaglandin synthetase inhibitor, should be tried first. However, it is relatively common for a patent ductus arteriosus to reopen following a course of indometacin (indomethacin), especially in babies less than 1000 g, often during an episode of sepsis. Further courses of indometacin (indomethacin) are worth considering, but if severe symptoms persist, surgical ligation may be necessary. Babies with a patent ductus arteriosus, managed by chronic fluid restriction and diuretic therapy, are at increased risk of hypotension during anaesthesia.

Intraventricular haemorrhage

Intraventricular haemorrhage is common in ELBW babies and occurs in 25–30% of babies less than 1200 g; the incidence reduces with increasing gestational age. In the premature infant, the cerebral vessels are supported by a loose lattice-work of connective tissue. Under certain conditions (e.g. asphyxia), there is a loss of autoregulation of cerebral blood flow. With hypoxia, hypertension occurs and cerebral flow is not kept constant when the arterial pressure increases. Under these circumstances, bleeding can occur from capillaries in the germinal plate and blood may rupture into one or both lateral ventricles. The prognosis depends on the extent of haemorrhage with a high risk of disability if the brain parenchyma is involved.

Intraventricular haemorrhage during anaesthesia should be preventable. Abrupt fluctuations in cerebral blood flow, cerebral blood volume and cerebral venous pressure play a role in its development, therefore values should be maintained at normal levels during anaesthesia. Arterial and central venous pressures should remain constant, and rapid fluid administration, hypoxia and hypercarbia should be avoided.

Retinopathy of prematurity

In retinopathy of prematurity, marked retinal vasoconstriction occurs, which may be followed by new vascular proliferation. This leads to fibrosis, scarring and retinal detachment. Oxygen therapy is a main cause of its development but the duration and extent of high oxygen tension required are unknown. During anaesthesia, the lowest inspired oxygen concentrations should be used while avoiding fluctuations in oxygen saturation. Babies developing retinopathy of prematurity are usually born very prematurely and often have associated medical problems. By the time laser therapy for retinopathy is considered, the baby may be many weeks old and, although extubated, may have developed chronic lung disease requiring low flow oxygen therapy. An alternative to tracheal anaesthesia is ketamine sedation, which may be carried out in the NICU under full monitoring. Postoperative apnoea in these infants is discussed below.

Necrotizing enterocolitis

Necrotizing enterocolitis is an inflammatory condition that may affect the large and small bowel; about 90% of cases occur in premature infants. These babies are often very sick, requiring aggressive intensive care; 50% require surgery. Perioperative management is discussed on page 84.

The former premature infant

Inguinal hernia occurs most often in babies born before 32 weeks' gestation with a birth weight of less than 1250 g. Repair of inguinal hernia is the most common surgical operation in these babies. The operation is usually performed when the infant has been weaned from mechanical ventilation, has grown and is medically stable. This often corresponds to the time when the baby is ready to be discharged home from the NICU. Infants born prematurely are more at risk of developing complications after anaesthesia and surgery; the most serious being apnoea.

Postoperative apnoea

Although the incidence of apnoea has been reported to be as high as 81%, most investigators have found that 20–30% of otherwise healthy premature infants undergoing inguinal hernia repair under general anaesthesia develop one or more apnoeic episodes in the postoperative period. Babies are at risk of apnoea for the first 12 hours postoperatively.

Predisposing factors

Gestational age and postconceptional age – the incidence of apnoea is inversely related to gestational age and is less common when postconceptional age is more than 43 weeks. However, apnoea can occur as late as 55–60 weeks' postconceptional age.

Weight – infants born small for gestational age are less likely to develop apnoea. These infants undergo significant intrauterine stress, which can induce accelerated maturation and may offer protection against postoperative apnoea.

Anaemia – premature infants experience a decrease in haemoglobin level, which reaches its lowest level at 1–3 months of age. This is known as the 'physiological anaemia of prematurity' and is usually benign and self-limiting. Former premature infants with anaemia (Hct < 30%) are particularly vulnerable to postoperative apnoea, even up to a postconceptional age of 60 weeks.

Anaesthesia: all general anaesthetic agents, including ketamine, can cause postoperative apnoea. The methylxanthines, aminophylline and caffeine, have been used for many years for the treatment of apnoea of prematurity. Caffeine, 10 mg/kg, given at induction of general anaesthesia, reduces the incidence of postoperative apnoea.

Regional anaesthetic techniques are popular for former premature infants undergoing inguinal hernia repair. These babies can be managed successfully with spinal, caudal or combined spinal/caudal block for surgery. Regional techniques without sedation have been reported to have a reduced incidence of postoperative respiratory complications and may be more suitable than general anaesthesia in the very young.

Recommendations

- Former premature infants must be carefully observed following anaesthesia and surgery.
- Infants less than a postconceptional age of 60 weeks should be managed only as in-patients.
- The age at which these babies outgrow this anaesthetic risk is ill-defined and must be made on an individual basis taking into account factors such as growth, development and co-existing medical problems.
- If possible, surgery in otherwise healthy premature infants should be delayed until the infant's respiratory control mechanism is more mature. This corresponds to a postconceptional age of 44–46 weeks.
- In younger infants, measures should be taken to minimize respiratory problems in the postoperative period.
- Surgery should be delayed in anaemic infants and feeds supplemented with iron until the haematocrit is at least 30%. If surgery cannot be delayed, anaemic infants must be closely observed in the postoperative period. ◆

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Pain

Anaesthesia
and intensive care medicine
on CD-ROM

Anatomy, Physiology, Pharmacology and Psychology of Pain

Mick Serpell

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Pain is not simply a biological response, it is a complex interaction that involves sensory, emotional and behavioural factors, and its definition and treatment must include all these aspects. The International Association for the Study of Pain (IASP) defines pain as 'an unpleasant sensory and emotional experience associated with potential or actual tissue damage'. It is a fundamental component of the stress response to injury and therefore needs to be managed to improve patient recovery and minimize complications (Figure 1).

Pathophysiological associations of pain

- Neurohumoral alterations at site of injury[1]
- Alteration in synapses and nociceptive processing at the dorsal horn of the spinal cord[1]
- Neuroendocrine
  – increased catabolic: cortisone, glucagon, growth hormone, catecholamines
  – decreased anabolic: insulin, testosterone
  – increased plasminogen activator inhibitor (increased coagulation)
- Sympathoadrenal via adrenal gland and lateral horns of spinal cord

All of the above result in the following clinical effects

- Misery, anxiety, depression, sleep disturbance
- Increased blood pressure, heart rate and vascular resistance, increased cardiac ischaemia
- Cough inhibition (pneumonia), hyperventilation (respiratory alkalosis)
- Ileus, nausea, vomiting
- Urinary retention, uterine inhibition
- Restlessness, increased oxygen consumption
- Immobility, increased incidence of pulmonary thromboembolism

[1]Can lead to persistent pain states

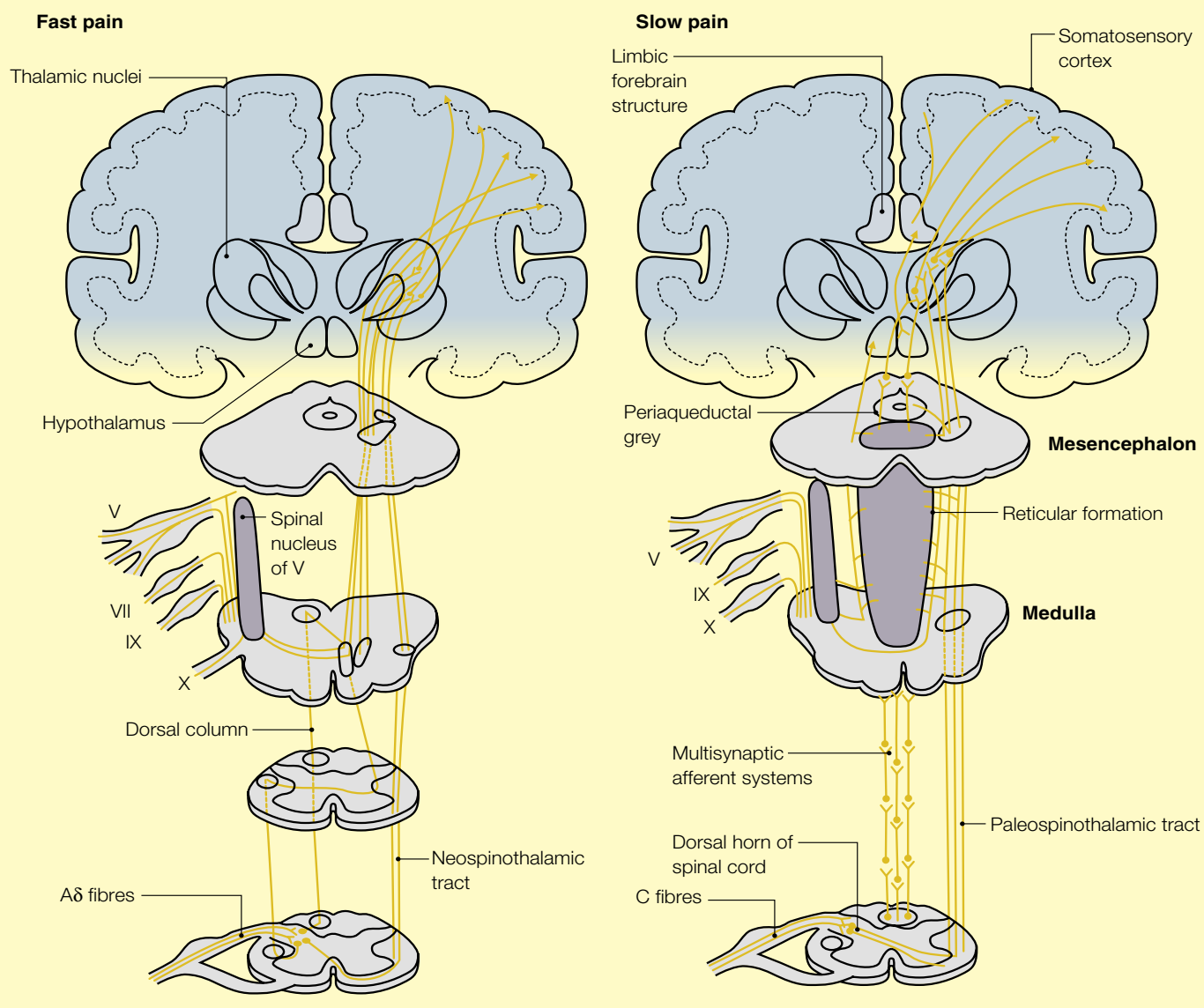
1

Anatomy
Pain can no longer be viewed in terms of a simple pathway transmitting traffic from the periphery to the cortex. Although these pathways exist, the system is adaptable and dynamic. Nociception is transmitted and modulated at three levels; the peripheral nociceptor, the dorsal horn (spinal), and supraspinal (brain) levels.

Somatic pain

Physiological pain
Physiological pain, also known as first or 'fast' pain is a protective event that enables the organism to localize pain rapidly and accurately and withdraw from the stimulus in order to avoid or reduce tissue damage. It is produced by stimulation of high-threshold thermo/mechanical nociceptors and is transmitted by fast conducting Aδ fibres (Figure 2). The Aδ primary afferent enters the dorsal horn of the spinal cord and synapses at laminae I, V and X. Conduction continues along the secondary afferent fibres via the neospinothalamic tract which is monosynaptic as it ascends to the posterior thalamic nuclei. From there it synapses with tertiary afferents to the somatosensory postcentral gyrus at the cortex. If this short-duration stimulus does not result in tissue damage, the pain disappears when the stimulus stops.

Spinal and supraspinal pathways of fast and slow pain



Source: Bonica JJ. *The Management of Pain,* 2nd ed. Philadelphia: Lea & Febiger, 1990: 72.

2

Pathophysiological pain
Pathophysiological pain, sometimes called second or 'slow' pain, is responsible for the delayed pain sensation that occurs after tissue injury, which encourages tissue healing by eliciting behaviour to protect the damaged area. This is the type of pain that occurs after surgery, trauma and inflammation, and which doctors endeavour to manage in the clinical setting. It originates from stimulation of the high-threshold polymodal nociceptors (free endings) present in all tissues. The nociceptors respond to mechanical, chemical and thermal stimuli and are transmitted via slow-conducting C fibres, which synapse at laminae II and III (substantia gelatinosa) of the dorsal horn. Secondary afferents ascend cranially via the paleospinothalamic tract which is polysynaptic as it ascends to medial thalamic nuclei. It has collaterals that also project to the midbrain, pontine and medullary reticular formations, the periaqueductal grey and the hypothalamus, where they synapse on to neurons that project to forebrain limbic structures (Figure 2). This system is primarily involved with reflex responses concerned with respiration, circulation and endocrine function. They also engage descending modulatory systems. Spinoreticular tracts and spinomesencephalic tracts also supply afferent impulses. All are involved in producing the emotional and behavioural response to pain.

In addition to the two types of nociceptors mentioned above, there are 'silent' or 'sleeping' nociceptors. They are present in the skin and visceral organs and account for about 15% of C fibres. They become active only under inflammatory conditions when they may respond spontaneously or become sensitized to other sensory stimuli.

Visceral pain

Visceral pain is less well understood than somatic pain. There are functional differences between the two systems. The density of visceral nociceptors is less than 1% compared with somatic afferents and the cortical mapping of visceral afferents is also less detailed. Visceral pain is poorly localized, diffuse and often in the midline; exceptions are joints and the mesentery.

The qualitative nature of the pain is also different because the viscera are sensitive to distension. Afferent fibres respond in a graded fashion to intensity of stimulation rather than to individual stimulating modalities. Visceral pain exhibits spatial summation in that if a large area is stimulated, the pain threshold is lowered; this does not occur in cutaneous nociception.

Visceral pain can also be referred to a site away from the source of stimulation. It is often segmental and superficial, and frequently shows hyperalgesia (bladder pain can produce these effects in the peri-anal S2–4 dermatomes).

Neuropathic pain

Injury of nerve fibres can lead to abnormal functioning of the nervous system. Complete destruction, for example if a nerve is severed, usually results in complete loss of sensation and muscle power. Partial damage, which may occur after physical trauma (crush injury or surgery) or medical conditions (diabetes and shingles), can result in the preservation of gross motor and sensory function but produce subtle abnormalities such as altered temperature sensation, unusual or unpleasant feelings or even pain. This altered function occurs because the overall activity of the nervous system results from the balance between excitatory and inhibitory components. Partial damage often leads to increased activity of the nerve fibres. Treatment is aimed at suppressing the hyperactivity of the abnormal nerves.

Physiology and pharmacology

Peripheral level
Most pain originates from tissue damage. The release of inflammatory mediators from tissues, immune cells and sympathetic and sensory afferent nerve fibres results in an 'inflammatory soup' bathing the nociceptors (Figures 3 and 4). These chemicals sensitize the high-threshold nociceptors so that they can be activated by low-intensity stimuli. This results in sensitization at the site of injury or 'primary hyperalgesia'.

Some mediators act directly on ion channels in the membrane (protons and serotonin (5-HT)) but most bind to membrane receptors and act via regulatory intermediates (G-proteins and second messengers) to produce changes in membrane ion channels or enzymes. These inflammatory mediators also interact to form a complex process of events, which not only changes the short-term function of sensory afferent fibres but can also alter gene transcription. This can result in long-term alterations in intracellular biochemistry, receptor and transmitter production, which in effect changes the phenotype and behaviour of the neuron.

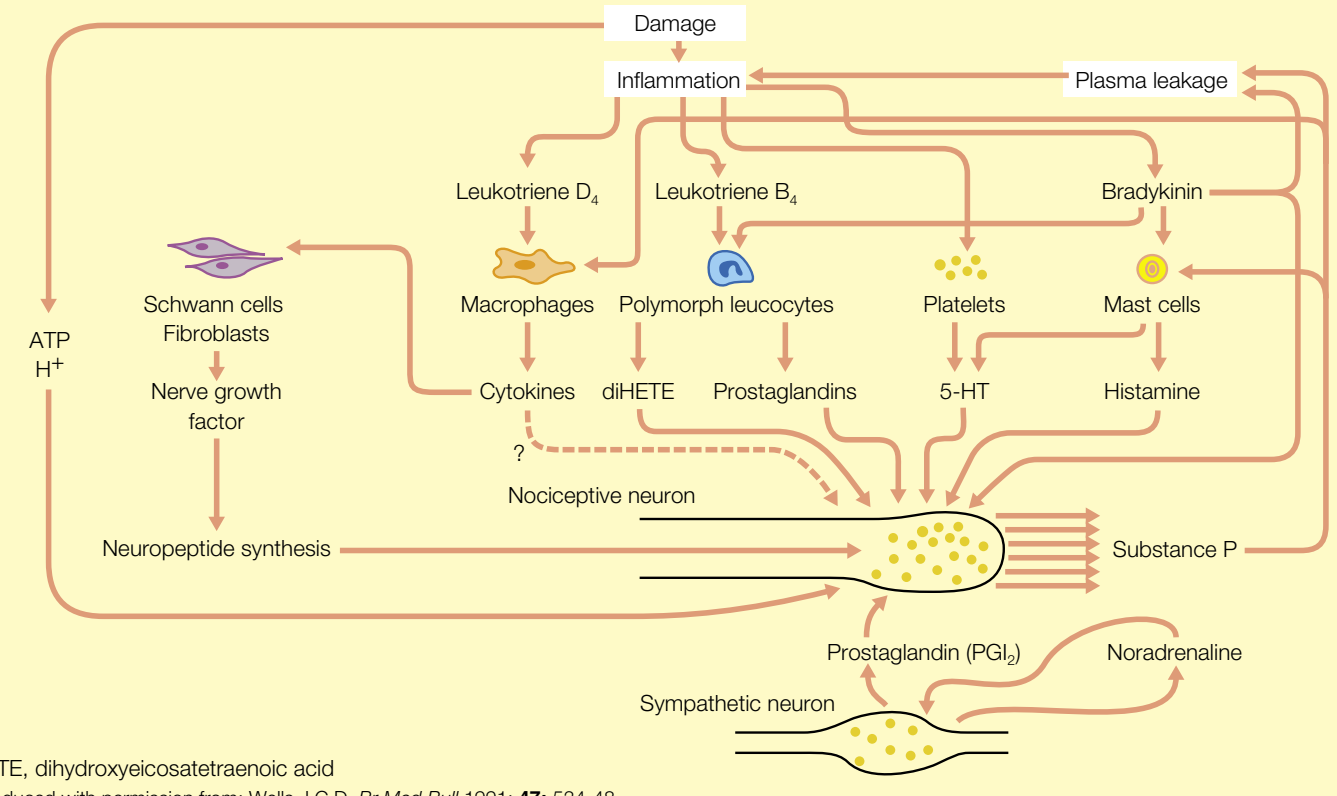
There are many potential pharmacological targets in the periphery (Figure 3). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin production and are among the most common analgesic drugs used. Other targets being explored are bradykinin, substance P and nerve growth factor. Drugs blocking the action of histamines, adenosine and nitric oxide have not proved clinically useful.

Common inflammatory mediators and their effect on the primary afferent fibre

	Comments
Activate	
Potassium (K^+)	
Serotonin (5-HT)	
Bradykinin	Most potent endogenous alogenic substance known acts at the bradykinin 2 (B2) receptor
Protons (H^+)	Stimulate same receptor as capsaicin
Histamine	
ATP, Adenosine (A)	Cause pain via A2 receptor, A1 receptor analgesic
Sensitize	
Prostaglandins	Inhibited by cyclo-oxygenase (COX) inhibitors, inhibition of COX-2 accounts for the analgesic and anti-inflammatory effects
Leukotrienes	
Cytokines	Secreted from immune cells, stimulate interleukin synthesis
Nerve growth factor	Increases production of neuropeptides
Neuropeptides	Substance P, neurokinin A and B and calcitonin gene-related peptide released from sensory afferent nerves
Noradrenaline	
Nitric oxide	Sensitizes nociceptors to bradykinin
Reactive oxygen species	

3

Peripheral inflammatory mediators



diHETE, dihydroxyeicosatetraenoic acid

Reproduced with permission from: Wells J C D. *Br Med Bull* 1991; **47:** 534-48.

4

Spinal level

The dorsal horn of the spinal cord is the site where complex interconnections occur between local excitatory and inhibitory interneurons and the descending inhibitory tracts from the brain. The second-order neurons are of two types, some are nociceptive specific, located in the substantia gelatinosa, responding selectively to high-threshold nociception. Others are wide dynamic range (WDR) neurons or convergent neurons located in deeper laminae (V and VI) responding to a wide range of input, both nociceptive and non-nociceptive.

The gate-control theory was proposed in 1965 by Melzack and Wall to explain the variable and non-linear relationship between injury and response to pain. They proposed that primary nociceptive cells synapsed with a WDR neuron (called a T cell in the original hypothesis) which carried the impulse to higher centres. This T cell could also be excited by Aβ fibres, depending on the configuration and intensity of firing, thus proposing a hypothesis for mechanical allodynia (painful response to non-painful stimuli). Crucial to this theory was the presence of an inhibitory interneuron in the substantia gelatinosa, that prevented activation of the T cell. This interneuron could be activated by Aβ fibre firing and inhibited by the small nociceptor fibres (Aδ and C fibres). The theory proposed that pain would be 'gated-out' by stimulating the large Aβ fibres in the painful area. This is the working mechanism behind transcutaneous electrical nerve stimulation (TENS) in pain control.

However, this theory does not explain the presence of secondary hyperalgesia, which is the result of the following three spatiotemporal characteristics.

- Radiation – the area of pain enlarges past the receptive field of the primary nociceptive afferent (usually less than 1 cm^2) through recruitment of WDR neurons at caudal and rostral levels. This is termed 'secondary hyperalgesia' because it occurs outside the area of injury as opposed to 'primary hyperalgesia'.
- After response – the pain response outlasts the peripheral impulses that evoke it (hyperpathia).
- Slow temporal summation – the intensity of the pain increases if the stimulus is repeated (every 3 seconds or faster) despite the stimulus remaining at the same intensity.

These three phenomena result in a widened receptive field that exhibits exaggerated responses to noxious stimulation and increases the spontaneous discharge rate. In general, this situation is temporary and resolves with tissue healing. However, if significant tissue injury has occurred or there is nerve injury, the nervous system may dysfunction permanently and produce a chronic pain state.

Neurotransmitters at the dorsal horn

Multiple neurotransmitters play a role in the transfer of nociceptive information in the dorsal horn. The mediators fall into two categories; excitatory amino acids (EAAs) and neuropeptides. These transmitters activate the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and neurokinin 1 (NK-1) receptors to produce ionic depolarization of the cell. They both also activate a metabotropic receptor, which results in the production of secondary cellular messengers that prime the N-methyl-D-aspartate (NMDA) receptor to be activated. As a result, the EAAs and neuropeptides can stimulate the NMDA receptor, resulting in sustained depolarization. This receptor is pivotal to the maintenance of spinal cord hyperalgesia and therefore is a strong potential target for analgesia. NMDA receptor antagonists such as ketamine or memantine reduce allodynia and hyperalgesia but because they act on all four subtypes of the receptor, side-effects of hallucinations, sedation and amnesia are troublesome. Therefore, development of selective NMDA antagonists is required if they are to be acceptable for clinical use.

Many other neuropeptides are involved in the nociceptive process described above. Some enhance nociception, such as substance P acting at the NK-1 receptor, neurokinin A and B, cholecystokinin (CCK), calcitonin gene-related peptide (CGRP), bombesin and vasoactive intestinal peptide (VIP). Other neuropeptides are antinociceptive such as somatostatin, galanin, γ-aminobutyric acid (GABA) and glycine. These are all promising potential targets for modulation but at present there are no useful agents available for clinical use.

Currently the main form of clinical management aimed at the spinal cord level includes local anaesthetic agents and opioids. The former produce nonspecific conduction blockade of neuronal tissue though the concentration of drug can be titrated to produce a mainly analgesic effect. The opioid drugs are specifically analgesic and act on receptors that can be pre- or post-synaptic, however their predominant action is at the more numerous pre-synaptic sites. All the endogenous opioids (enkephalin, endorphin, dynorphin A) are rapidly inactivated by peptidases, therefore administration of exogenous opioids (morphine, fentanyl) is the most commonly practised technique. The opioid receptors are subject to plasticity, being down-regulated by CCK and reduced in number following nerve injury. The effects of opioids can be potentiated by α_2 agonists and NMDA antagonists and these agents may be better given in combination.

α_2-adrenergic agonists include endogenous noradrenaline, involved in the descending inhibitory pathways, or exogenous clonidine and dexmedetomidine. The latter two can be given systemically or by epidural. They offer the advantage of analgesia without the risks of respiratory depression, addiction, nausea and vomiting induced by the opioids. However, their use is limited by side-effects such as sedation, bradycardia and hypotension. Cholinergic agonists seem to enhance noradrenergic-mediated analgesia and neostigmine has been used with some beneficial effect.

CCK differs from the other nociceptive neuropeptides by indirectly antagonizing the effect of opioid μ agonists at the receptor. The amount is increased in neuropathic pain and decreased in inflammatory pain. This may explain the relative opioid resistance and sensitivity, respectively, of these two pain syndromes. Antagonists to CCK are not useful analgesics on their own but could enhance the effects of opioids. They may also be useful in tolerance and addiction and clinical trials are under way.

Midazolam produces segmental spinal analgesia probably via the benzodiazepine receptor which, once activated, forms a complex with the GABA receptor. Benzodiazepines also react with the opioid receptors, but further studies are needed to determine their potential role.

Supraspinal level

The supraspinal organization and function in nociception is largely unknown. However, it is commonly agreed that the perception of pain is associated with changes in activity of the thalamus, primary and secondary cortex and particularly the anterior cingulate cortex.

Various regions of the brain are involved with descending inhibition. These pathways originate at the level of the cortex and thalamus, and are mediated via relay stations in the brain stem such as the periaqueductal grey, nucleus raphe magnus and locus coeruleus subcoeruleus complex.

The inhibitory pathway descends the spinal cord via the dorsal columns and terminates at the dorsal horn where neurotransmitters noradrenaline, 5-HT and the endogenous opioids are released to provide antinociception. All three receptors (μ, δ, κ) play a role in the ascending pathways but the μ and δ receptors are mainly responsible in the descending component.

Noradrenaline and 5-HT synthesis and release are increased by the action of opioids and they in turn enhance the action of opioids. This may be the mechanism by which tramadol and the antidepressants work as analgesics. GABA and acetylcholine appear to be other mediators.

Psychology

Pain always has physical and psychological components. The gate-control theory was suggested to account for some of the clinical observations made about pain. For example, the observations that pain sometimes occurs without apparent cause or does not occur despite obvious injury (e.g. wounded soldiers on the battlefield), or often persists after tissue healing or fails to respond to appropriate treatment. The theory proposed that there were mechanisms in the spinal cord (see above) that increased or decreased pain signals. An example of this is the placebo response whereby an inert treatment can produce good pain control. The converse is the nocebo response in which pain can be experimentally induced despite there being no nociceptive stimulus, only a suggestion of one.

The pain experience and amount of suffering depends on many psychological parameters such as anxiety, past experience, the meaning to the patient of the pain, injury or illness, their beliefs about treatment and medications (e.g. fear of dependence, addiction, tolerance, organ damage) and self-management strategies. This applies equally to acute and chronic pain. Pain services should screen patients to address any critical psychological issues as an integral component of medical management.

One of the most commonly used techniques is cognitive behavioural therapy, in which the patient is trained to behave differently towards the pain experience by a combination of preparatory information, diaphragm breathing, muscle relaxation, guided imagery and/or hypnosis, leading to greater self-control.

Motivation and positive attitudes can be just as important to pain control and recovery, as illustrated by the phrase 'People who have something better to do don't suffer as much' (W E Fordyce, 1988).

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Assessment of Acute and Chronic Pain

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Why assess pain?
Effective control of pain requires accurate assessment. Pain is a subjective, private experience and must be made 'visible' through measurement and assessment.

Who should assess pain?
Pain is a subjective experience, therefore the patient is the most reliable assessor. Health professionals and family members can help but health professionals tend to underestimate the level of pain a patient is experiencing and family members tend to overestimate. Some patients (e.g. infants, children, the mentally impaired) are less able to communicate their pain experience. In these cases, more responsibility passes to health professionals and carers to adapt the assessment accordingly.

What to measure and assess?
The essence of pain measurement is to assign a value to pain. This can aid the overall assessment. Pain can be measured only indirectly using one of three strategies: what a patient reports about their experience (self-report); the way a patient reacts in response to pain (behavioural measures); and how the body responds to pain (physiological and biological measures).

Patient self-report is the most reliable and valid measure of pain in the clinical situation. Self-report in conjunction with appropriate measurement tools, history and examination, produces comprehensive assessment. This process requires clear communication. Those involved should have some idea of the potential barriers to communication, including: under-reporting by patients, under-assessing by health professionals or carers, language and cultural differences, impaired hearing or cognition, incorrect attitude and knowledge deficit in health professionals.

Behavioural observations have been used extensively in animal studies to infer the presence of pain. The same principles can be applied to neonates and pre-verbal children (e.g. observation of facial expression, movements, quality of cry, and sociability). However, scales relying on behavioural observations depend on context, because they are often based on patterns of behaviour during specific procedures or circumstances.

Physiological and biological measures: physiological measures include heart rate and blood pressure. Heart rate may increase in the presence of pain but alone it is not a reliable indicator of pain. At best, physiological parameters improve the discriminatory power of other measures. Some biological changes (e.g. endocrine responses) occur in association with pain, but are not used clinically.

Acute and chronic pain

Pain is a multidimensional experience that includes physical, psychological and spiritual factors. In the acute setting it may be sufficient to acknowledge the patient's anxiety and fear, attempt to reassure them and provide an explanation. The pain intensity is assessed with an expectation of a return to normality. Concentrating on the measurement of pain intensity using unidimensional scales (Figure 1) is the norm and is usually, but not always, sufficient.

In a patient with chronic pain, depression, interference with activities of daily living or interpersonal relationships, or fears regarding the future may cause more distress, suffering and disability than the pain itself. In such a situation, concentrating on pain intensity alone is inadequate. Multidimensional tools (Figure 2) look at factors in addition to pain intensity.

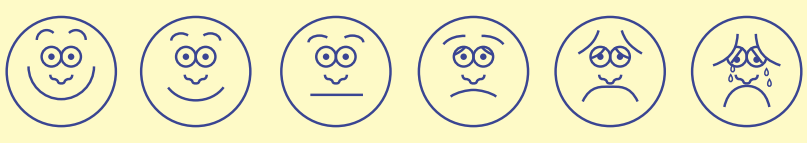
Unidimensional measures of pain intensity

Verbal rating scale
The patient rates the pain verbally (e.g. none, mild, moderate or severe)

Numerical rating scale
The patient rates pain on a scale typically from 0 (no pain) to 10 (severe pain)

Visual analogue scale
The patient indicates intensity of pain on a line typically 10 cm long marked from 'no pain' at one end to 'severe pain' at the other end. The pain is then scored in cm or mm, often with a sliding marker to aid measurement

Faces scale
The child indicates which face represents how much pain they have. Clearly this may measure other factors such as general distress rather than pain exclusively



1

Multidimensional tools for pain assessment

McGill Pain Questionnaire (MPQ)
Descriptive words are grouped into sets containing between two and six words. The words are in ranked order with a numerical score. There are 20 sets grouped into sensory, affective, evaluative and miscellaneous

Wisconsin Brief Pain Inventory (BPI)
Measures intensity and relief of pain, psychological distress, and functional impairment

Memorial Pain Assessment Card (MPAC)
A brief measure that uses 100 mm visual analogue scales to characterize pain intensity, pain relief and mood. Plus a further 8-point verbal rating scale to further characterize pain intensity

2

How to assess acute pain
Pain intensity is the main focus of acute pain, therefore it is usually, but not always, appropriate to concentrate on the biomedical model. Pain intensity is assessed from the patient's report usually aided by unidimensional measures (Figure 1).

History, examination and investigations should be tailored to the underlying cause of the pain. However, what appears as an obvious source of pain may not be what the patient is reporting. A patient who has had a laparotomy may have pain from several sites, such as the throat from tracheal intubation, the bladder from a urinary catheter, or the chest from myocardial ischaemia. Assuming the wound is the problem may lead to inappropriate treatment.

Scoring tools: the verbal rating scale (Figure 1) is a category scale. It makes a minimal demand on the patient and can be applied to individuals with some mental impairment. It is commonly used in the postoperative period, often with a score attributed to each descriptor (e.g. 0 no pain, 1 mild pain, 2 moderate pain, 3 severe pain). However, it is not a ratio scale because the increase from mild to moderate pain is not necessarily the same as the increase from moderate to severe.

Figure 3 shows an example of a postoperative pain chart using a verbal rating scale. The pain score, on movement, is plotted against time, with analgesic interventions noted. Documenting pain on movement, deep breathing or coughing helps to ensure that analgesics are used to aid appropriate mobilization and rehabilitation. The chart renders the pain and the response to analgesics 'visible'.

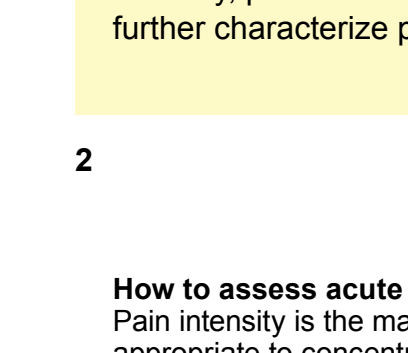
Moderate or severe pain requires analgesic interventions to be considered with reassessment. Consistent scores of no or mild pain allow progressively longer assessment intervals. There is a score 's' for sleeping. It is usually inappropriate to awaken a patient to determine pain intensity.

The numerical rating scale asks the patient to score their pain as a number whereas the visual analogue scale asks them to indicate a point on a line. Both scales are anchored at either end with descriptors, which can be altered to measure other variables such as anxiety.

The visual analogue scale is a ratio scale and is widely used in research as well as in clinical practice. A sliding marker is often incorporated, which the patient moves to the appropriate point on the line. On the reverse side, there is a scale in cm or mm that can be read off directly. These scales require more patient understanding, although, with appropriate explanation, they can be used by children as young as 5 years.

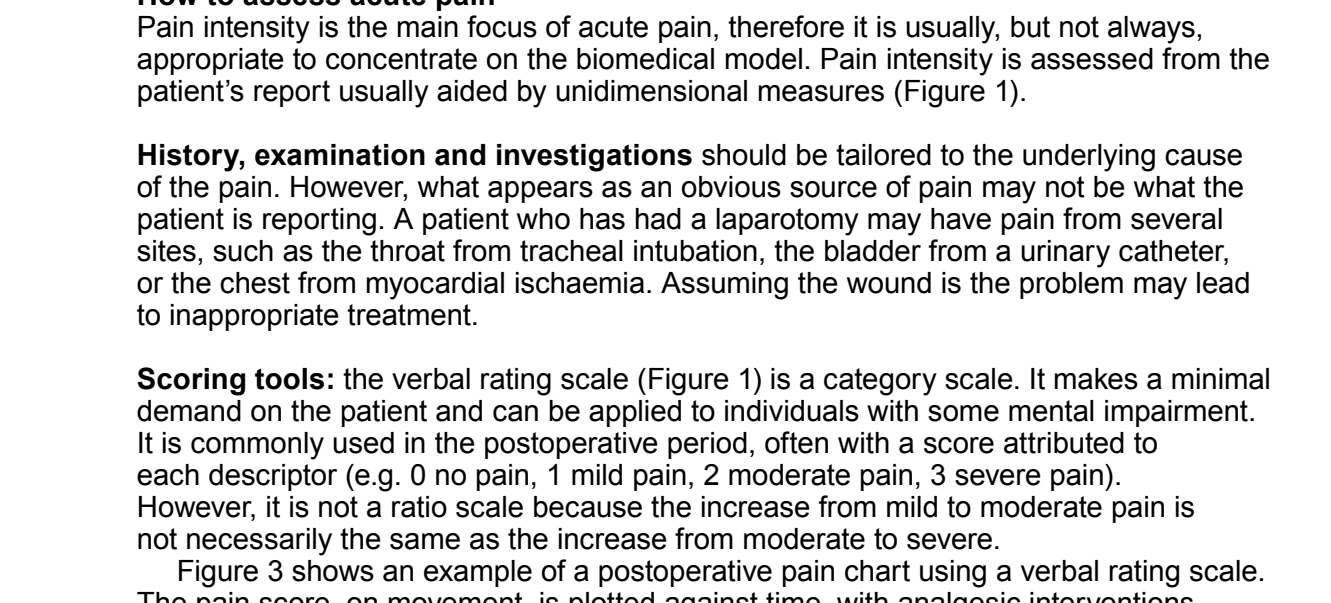
Typical pain assessment chart used in the postoperative setting

Pain score guidelines



Ask the patient: 'When you move, which of the following words best describes your pain?'

	Score
Sleeping	S
None	0
Mild pain	1
Moderate pain	2
Severe pain	3



Drug reactions and contraindicated drugs (e.g. NSAIDs) _____

3

Children: the assessment of pain in children is discussed in elsewhere in *Anaesthesia and Intensive Care Medicine*

Comparing scoring tools: mild pain corresponds to a score of less than 30 mm on a visual analogue scale ranging from 0 mm (no pain) to 100 mm (worst possible pain), moderate pain is 31–54 mm and severe pain above 55 mm.

The exact method of assessment and choice of scale is pragmatic. The choice depends on general circumstances and individual patients. However, pain intensity and its response to treatment is usually the focus.

How to assess chronic pain
In the patient with chronic pain, pain intensity is only one of many areas that require assessment. There is only a moderate correlation between pain intensity and the patient's disability, distress and suffering. Classically the domains involved are:

- sensory-discriminative (the nature, location, intensity and temporal aspects)
- affective-motivational (comprising emotions and their arousing, compelling nature to escape and avoid)
- cognitive-evaluative (how the person perceives, interprets and relates to pain).

The inclusion of psychological and social variables is described as the biopsychosocial model.

Multidimensional scoring tools: many tools are available to aid assessment of the various domains. This suggests that no single one is ideal for all situations. Some are designed for specific applications, others to assess specific aspects of a problem and some may be of use to one practitioner and not to another. Three of the more commonly used multidimensional tools (measuring more than one domain) are outlined in Figure 2.

The McGill Pain Questionnaire (MPQ) attempts to assess the multidimensional nature of pain. Scores can be obtained for the sensory, affective and evaluative descriptors as well as a total. Body diagrams allow different pain sites to be documented. The MPQ has been widely used, with versions in many languages. It takes time to complete, though a short form is available (SF-MPQ).

The Wisconsin Brief Pain Inventory (BPI) is widely used across different cultures. Numerical rating scales indicate the intensity of pain in general, at its worst and at its least and at the time of assessment. A percentage scale quantifies relief from current therapies. A body diagram allows the patient to indicate the areas involved. Seven questions, using a numerical rating scale, determine the degree to which pain interferes with general activity, mood, walking, work, relations with other people, sleep and enjoyment of life. The BPI is self-administered and easily understood.

The Memorial Pain Assessment Card (MPAC) is the briefest of the three tools outlined. The mood scale, which is correlated with a measure of global psychological distress, depression and anxiety, is considered to be a brief measure of global symptom distress.

Continuing records – asking the patient to maintain a continuing record of pain scores and other variables such as activities and sleep pattern is of great value. A patient's recall of how they were feeling days or weeks earlier varies depending on their mood and perceived pain at the time of questioning.

History, examination and investigations: a detailed history should include the medical complaint, treatments and any interaction with other health workers. It is important to gauge the patient's overall expectations because these may differ from what is felt to be realistic. The focus should then move to wider issues including their social, financial and employment situation, as well as physical and functional limitations.

Physical examination is essential as a baseline, to document the present medical condition, and to exclude other pathology. However, the absence of findings does not infer the absence of pain, because the correlation between somatic findings and pain is poor. The findings from physical examination should be added to the information gathered from assessment, with appropriate weighting. Concentrating on examination and the biomedical model may detract from assessment of the other relevant domains.

Investigations may be useful to assess the underlying disease process and to exclude other pathology. Recent advances have allowed the imaging of different parts of the brain involved in pain processing. At present, however, investigations have little clinical role in assessing chronic pain.

Multidisciplinary assessment: ideally, assessment of a chronic pain problem involves a multidisciplinary team approach. Health professionals from different backgrounds, possessing different skills, contribute to holistic assessment and management. The make-up of such teams is variable and depends on circumstances and resources. Typical teams include a physician, nurse, psychologist and physiotherapist.

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Control of Acute Pain in Postoperative and Post-traumatic Situations

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Historical perspective

During the late 1980s there was mounting concern about the treatment of acute pain. In the UK, this concern culminated in the setting up of a joint working party by the Royal College of Surgeons and the College of Anaesthetists. Their report on *Pain after Surgery* was published in 1990. The report cited papers dating back 40 years that revealed postoperative pain was badly treated, with up to 75% of patients reporting moderate to severe pain. The reasons for the poor treatment are based on inadequate and inappropriate education, poor organization and infrastructure, and other institutional issues. The report highlighted the low priority given to postoperative pain in the ward routine, the lack of education among medical and nursing personnel and the failure to provide responsible personnel to manage postoperative pain. Recommendations for improvement are listed in Figure 1.

Recommendations of Joint Colleges' Working Party Report, 1990

- A named responsible consultant with appropriate training in pain management
- Development of an interdisciplinary approach to all areas of pain management
- Continuing education of clinical staff; challenge traditional attitudes
- Continuing audit and performance appraisal
- Introduction of a scoring system to enable formal, regular assessment and recording of pain in all patients
- The provision of trained staff, equipment and facilities
- Introduce new techniques and improve use of existing techniques
- Encourage research and innovation
- Development of Acute Pain Teams

1

Progress during the 1990s
The past 10 years have seen some advancement in our understanding of the physiology of acute pain and the introduction of some new analgesics, but improvements in the quality of acute pain management have tended to focus on using existing drugs and techniques more effectively. These efforts centre on the introduction of patient-controlled analgesia (PCA) and epidural infusion analgesia, and challenge traditional thinking with improved programmes of education for clinical staff and the introduction of regular assessment and scoring of pain. In the UK, progress has been patchy, with several examples of good practice in the development of dynamic Acute Pain Teams contrasting with many hospitals where little has changed. A report from the UK Audit Commission in 1997 on provision of anaesthesia and associated services identified Acute Pain Teams in only 57% of hospitals. Studies continue to report significant levels of poorly treated pain in acute hospital patients.

More recently, the Royal College of Anaesthetists outlined guidelines for pain management services. It is of interest to note that their recommendations differ little from those of the 1990 report though there is an emphasis on integration of acute and chronic pain services.

Two other recently published guidelines relate their findings and recommendations to best available evidence. *Acute Pain Management – Scientific Evidence* from the Australian National Health and Medical Research Council (NHMRC) emphasizes the multidisciplinary approach to the treatment of acute pain and highlights many areas of acute pain outside the postoperative period requiring the services of the Acute Pain Team. In the UK, the Royal College of Anaesthetists recently issued guide-lines on the use of non-steroidal anti-inflammatory drugs (NSAIDs).

The Acute Pain Service

An anaesthesia-based multidisciplinary team approach to acute pain relief was first described by Ready in Seattle, USA. This has been developed in the UK and Wheatley and his colleagues from York District General Hospital have described one of the better examples of such an Acute Pain Service.

Various models of acute pain service delivery have been described. Generally, they come under the auspices of the anaesthesia department. In some services, the Acute Pain Team is predominantly nurse based while others are physician orientated; there are advantages and disadvantages for each. National or local resources determine which model is optimal in a given setting. UK hospitals have largely adopted the anaesthetist-based service with dedicated specialist nurse input.

Generally, analgesics are under-prescribed by doctors, under-delivered by ward nursing staff and under-demanded by patients. This results from a long-term deficit in the education of healthcare staff over many years, with what little effort there was on education about pain control under-emphasizing the benefits of good analgesia, while exaggerating the adverse effects of analgesic drugs and techniques. One of the factors inhibiting improvements in acute pain control is the requirement for extra resources. Improvements in postoperative pain control have been demonstrated following the sequential introduction of a staff education programme, pain scoring and a more proactive regimen for administering intramuscular morphine. Further, though less dramatic, improvement was seen when the more expensive ‘high-tech’ interventions, such as PCA and epidural infusion analgesia were added.

Rationale for treating postoperative pain

Pain should be treated on humanitarian grounds, though this can be difficult to prove in terms of evidence-based medicine. It is also difficult to measure patient satisfaction. However, effective postoperative pain relief is fundamental to good quality patient care and is a legitimate therapeutic goal. There is increasing evidence relating good postoperative analgesia to reduced clinical morbidity. Some authorities suggest that there may be economic benefits associated with enhanced patient well-being and early rehabilitation.

The aim of postoperative pain relief is to provide subjective comfort in addition to inhibiting trauma-induced nociceptive impulses that induce autonomic and somatic reflex responses to pain. The physiological changes brought about by pain result from activation of both central and peripheral nervous systems. Bradykinin and other peptides produce the pain, tissue oedema and hyperaemia associated with the peripheral inflammatory response. Effective analgesia may modify these responses, and may reduce the stress response to surgery.

Pain induces stress hormone responses, with activation of cytokines, adhesion molecules and coagulation factors. These responses result in numerous physiological changes promoting catabolism, sympathetic activation, hypercoagulability and immunosuppression. Hypertension, tachycardia and increased cardiac work are among the adverse cardiovascular effects of acute pain, which may compromise precarious myocardial oxygen balance in the ‘at-risk’ cardiac patient. The respiratory effects of unrelieved pain can result in significant reductions in respiratory function including the reduced ability to cough and clear secretions. Treatment of acute pain results in better cardiovascular stability, decreased respiratory complications, less gastrointestinal upset and quicker mobilization after surgery.

Less readily observed, but no less harmful, are the psychological effects of pain. Two recent guidelines stress the importance of preparing the patient psychologically for surgery and the positive value this has on patient well-being. Psychological effects may interact with physical parameters, leading to a vicious cycle of anxiety, pain and sleeplessness. This is a role that probably requires expansion in the future and would be appropriately managed by the Acute Pain Team.

There is now a significant body of opinion suggesting that effective pain control reduces the incidence of chronic post-surgical and traumatic pain.

Pain assessment

To treat pain effectively its severity must be measured (see page 428). Several scoring systems and methods are available (Figure 2). In UK wards, the observer rating generally meets with greater acceptance. Pain must be assessed at rest and during activity to allow appropriate function. Frequent pain scoring drives analgesic management and improves pain management. Many studies confirm that clinical staff underestimate patients’ pain levels unless a formal scoring system is used. Introduction of universal pain charting is facilitated by incorporating the scoring into the general observations chart.

More information on patient well-being can be obtained if a sickness scoring system and a sedation score are used in conjunction with the pain score. The sedation score is thought to be a better indicator of respiratory depression than the respiratory rate.

Pain assessment tools

- Verbal rating scale – different descriptions are used to rate the patient's pain (i.e. no pain, mild pain, moderate pain, severe pain, worst possible pain)
- Visual analogue scale – uses a 10 cm line rated from ‘no pain’ at the left to worst possible pain on the right and requires the patient to mark their pain on this line. The score is the distance from the ‘no pain’ point to the patient’s estimate
- Verbal numerical rating scale – requires the patient to rate their pain from 0 (no pain) to 10 (worst possible pain)
- Observer rating is carried out by the nurse looking after the patient – pain is rated 0, 1, 2 or 3, corresponding to no pain, mild, moderate and severe pain. This scale mixes rest and movement in its assessment, and its scientific validity can be criticized, however it provides useful language for clinical staff and has been shown to correlate well with visual analogue scale scoring
- Complex multidimensional methods – applicable to research but too cumbersome for routine use
- Inferential methods (e.g. respiratory rate or depth, cardiovascular response) are unreliable

2

Therapeutic options

In most cases, acute pain is managed solely with drugs. New drug advances have tended towards the development of agents with a better safety profile or a novel delivery route rather than more analgesic efficacy. There is increasing use of multi-modal analgesic strategies in which several analgesics are used in combination to maximize efficacy and minimize side-effects.

Opioids
Opioids are the first-line treatment for severe postoperative pain in most patients. Their use must balance the efficacy of analgesia against the occurrence of side-effects. Individual opioid requirements vary. In adults, age rather than weight has been shown to be a better predictor of opioid requirement. Morphine requirements after abdominal surgery vary by a factor of 30.

Common side-effects of opioids include sedation, pruritus, nausea, vomiting, slowing of gastrointestinal function and urinary retention. Respiratory depression, hypoxia, dysphoria, hallucinations, miosis and muscle rigidity also occur. Most side-effects are dose dependent.

Adequate doses of opioids are often withheld because of traditions, misconceptions, ignorance or fear. Both doctors and nurses fear addiction and respiratory depression, but addiction is not a problem with opioid use in severe pain. For safe and effective use the dose of opioid should be titrated to the desired effect while minimizing side-effects.

Intramuscular opiates: the dose should be based on the patient's age and medical condition, though absorption varies with muscle mass and blood flow. There is a 30-fold variation in morphine requirements after abdominal surgery, therefore a conventional regimen is unlikely to be effective in many patients. The onset of analgesia following intramuscular morphine begins after about 20 minutes with a peak effect at about 60 minutes. Injections should be given in the context of an algorithm that takes account of pain scores and potential side-effects. One such algorithm permits repeat injections on an hourly basis subject to satisfactory respiratory and sedation parameters.

Intravenous opiates: intermittent intravenous bolus doses of morphine allow titration to effect, though care must be taken not to 'overshoot'. The peak effect of intravenously injected morphine is reached at about 15 minutes and most of the effect by 5 minutes. Thus incremental titration with a 1–2 mg bolus each 5 minutes generally represents the best compromise between rapid pain relief and safety. Continuous infusion may be used to avoid peaks and troughs in pain relief. Reliable infusion devices, frequent assessment and monitoring with adjustment of infusion rates and bolus dose administration are essential for optimum safe analgesia. In UK practice, this level of care may not be achievable in a general ward setting.

Intravenous PCA allows patients to adjust the level of analgesia to their own level of comfort and tolerance of side-effects. PCA requires sophisticated infusion devices, adequate preoperative instruction, and an understanding of and ability to activate the device. PCA use has been shown to provide better patient satisfaction and improved ventilation than conventional routes of administration. Background infusions in adult patients increase the amount of opioid delivered and increase the risks of side-effects without improving analgesia.

Peripheral effects of opioids: opioid receptors are synthesized in the dorsal root ganglion and are transported centrally in C-fibre afferents to become presynaptic receptors. In the presence of inflammation, peripheral axonal transport of opioid receptors also occurs. Therefore, it might be expected that local application of opioids may have an analgesic action in damaged tissue, however, recent meta-analyses have not demonstrated significant clinical effects attributable to peripheral receptors, except perhaps in the knee joint.

Tramadol
Tramadol is a synthetic analgesic with minimal sedation, respiratory depression, gastrointestinal stasis or abuse potential. It is a weak μ agonist but it has important non-opioid spinal and CNS effects via norepinephric and serotonergic pathways. It has both opioid and non-opioid analgesic properties. The disadvantages of its use are its relative expense and the side-effects of dizziness, nausea, sedation, dry mouth and sweating. Efficacy shows a clear dose response increasing up to 150 mg, but at this dose there is a high incidence of side-effects.

NSAIDs
NSAIDs do not relieve severe pain when used alone but they are valuable in multimodal analgesia because they decrease the opioid requirement and improve the quality of opioid analgesia. They have the benefit of improved analgesia without sedation or respiratory depression and are of particular use in day case surgery, or in combination with other drugs for more major surgery.

The use of NSAIDs is limited by their side-effects, which are an extension of their pharmacological actions. Both NSAIDs and aspirin act by preventing prostaglandin production through inhibition of the cyclo-oxygenase system. New-generation NSAIDs have a more selective effect on cyclo-oxygenase 2 (COX-2), which is associated with trauma-related inflammation, and less effect on COX-1 which relates to gastrointestinal and renal prostaglandin production. These selective COX-2 inhibitors are associated with fewer gastrointestinal side-effects though they may have a similar incidence of renal and liver toxicity.

The Royal College of Anaesthetists published evidence-based guidelines on the perioperative use of NSAIDs in 1998; the key recommendations are described in Figure 3.

There is little evidence to suggest that one route of NSAID administration is superior unless fast onset is required when an intravenous preparation should be used. They are more effective when prescribed regularly and provide a useful adjunct to opioid therapy.

Recommendations of Royal College of Anaesthetists guideline on perioperative NSAID use

- NSAIDs are not sufficiently effective as the sole agent after major surgery
- NSAIDs alone are often effective after minor or moderate surgery
- NSAIDs often decrease opioid requirement
- The quality of opioid-based analgesia is often enhanced by NSAIDs
- NSAIDs increase bleeding time and some studies have shown increased blood loss

Oral analgesics
Paracetamol is effective for mild-to-moderate pain because it is analgesic and antipyretic. It is thought to act by inhibiting cyclo-oxygenase enzyme in the CNS, while sparing peripheral prostaglandin production. It is rapidly absorbed from the gut, and peak plasma levels are achieved 30–60 minutes after administration. The dose must be reduced in renal and hepatic impairment. The active component, acetoaminophen, has been introduced in some European countries. Paracetamol may be given rectally if the oral route is unavailable.

Paracetamol is more effective when combined with other compounds such as codeine, dihydrocodeine or dextropropoxyphene. Numerous different compound preparations are available. Care should be taken to avoid paracetamol overdose by mixing these compound preparations.

Relative efficacy of commonly used oral drugs and intra-muscular morphine: relative analgesic efficacy can be expressed in terms of the number needed to treat (NNT); that is the number of patients who need to receive the active drug for one to achieve at least 50% relief of pain compared with placebo over a treatment period of 6 hours. For analgesics to be considered effective they require an NNT of 2–3 or less. Because the comparison is with placebo, the NNT represents the analgesic effect over and above placebo. The total percentage of patients experiencing effective pain relief will be correspondingly greater. Of 100 patients treated with an analgesic with an NNT of 2, 50 would be expected to gain more than 50% pain relief because of the intrinsic analgesic effect of the drug. However, another 20 would be expected to gain a similar reduction in pain score owing to the placebo effect. Thus, 70 of the 100 patients would get at least 50% pain relief. In addition, others would get less than 50% relief. In many circumstances this would also represent a useful clinical effect. Caution must be exercised when interpreting such results. Figure 4 shows the relative efficacy of some common analgesics. The results have been gleaned from many meta-analyses of hundreds of clinical trials in thousands of patients. Its apparent simplicity hides the vast resource and expertise required to produce it. On the other hand, the results must be interpreted with caution because they may hide effects such as non-standardization in the pain being treated.

Relative efficacy of common analgesics

	Number needed to treat
Paracetamol, 1 g	4.6
Paracetamol, 1 g + codeine, 60 mg	3
Codeine, 60 mg	18
Dihydrocodeine, 30 mg	10
Tramadol, 50 mg	8.9
Tramadol, 100 mg	4.8
Tramadol, 150 mg	2.9
Diclofenac, 50 mg	2.3
Diclofenac, 100 mg	2.1
Ibuprofen, 200 mg	5.5
Ibuprofen, 400 mg	2.9
Ibuprofen, 600 mg	1.8
Morphine, 10 mg (single i.m. dose)	2.9

Local and regional analgesia
Simple methods include the use of topical agents such as *Emla* (eutectic mixture of local anaesthetics) or *Ametop* to provide surface analgesia. Infiltration of the operative site is well established in paediatric surgery but is of limited benefit after major surgery.

In a comprehensive qualitative systematic review of wound infiltration, 26 randomized trials were reviewed. Unequivocal benefits were reported for hernia surgery only. In other groups (e.g. hysterectomy, cholecystectomy) results were equivocal or clinically insignificant.

Nerve blocks, with or without the use of catheters, may be used for the surgical procedure or as a form of postoperative analgesia. Coexistent sympathetic blockade may be problematic or advantageous. Motor block is less troublesome with some of the newer local anaesthetic agents (e.g. ropivacaine, levobupivacaine).

Epidural infusions have the potential to improve postoperative analgesia and reduce adverse physiological changes associated with surgery. Postoperative epidural analgesia can significantly reduce the incidence of pulmonary morbidity. When combined with active convalescence, epidural analgesia may improve overall outcome. Uncommon, but important, risks relate to catheter insertion (neurological injury) and the potential for life-threatening complications (intravascular or subarachnoid injection of large doses of local anaesthetic). These factors must be considered to determine the risk:benefit ratio for each patient.

It is generally recommended that, where possible, epidurals should be placed in the awake patient. Aspiration and test doses should be used to detect subarachnoid or intravascular placement. The catheter should be placed as close as possible to the level of dermatomes affected by the surgical incision. Patients must be closely supervised with an anaesthetist readily available for advice and management of occasional life-threatening complications.

Postoperative epidural infusions may be of local anaesthetic alone or combined with opioids. Epidural analgesia, particularly when both local anaesthetic and opioids are used in the infusion, reduces postoperative morbidity and mortality. Epidurals are discussed in more detail elsewhere.

Adjuncts to drug therapy

Simple methods of pain relief include splinting or immobilizing painful areas. The application of cold compresses occasionally has a role. Transcutaneous electrical nerve stimulation (TENS) is largely in-effective for acute postoperative pain relief. Acupuncture is used particularly in Chinese medical practice. Few randomized trials exist to support the efficacy of acupuncture postoperatively.

Many factors influence the perception of pain, including past experience, personality, cultural background, anxiety and fear. Coping strategies and the ability to control events may modify the pain experience.

Relaxation training, procedural information, cognitive coping methods and behavioural instructions have been shown to improve pain scores and reduce consumption of analgesics.

Specific patient groups

Opioid tolerance and addiction
Tolerance describes the decrease in efficacy of a drug as a result of its previous administration. This is manifest as a high requirement for opiate analgesia and relative resistance to side-effects. Patients taking chronic opiate therapy require significantly increased doses of opiate in the acute situation. If the oral route is available, chronic oral opiates should be continued with parenteral supplementation as required. Intravenous PCA with frequent review of settings can help to define opiate requirements. Every opportunity should be taken to use non-opioid alternatives as adjunct or sole therapy. Surgical review is warranted if opioid requirements appear to increase rapidly, in order to rule out any surgical complication.

Addiction is unlikely following the use of opioids for postoperative pain in opioid naïve patients. When treating patients with opioid dependence or addiction it is important to realize that pain-scoring systems are unreliable. It is essential to obtain a measure of the opioid problem and to work out a management plan to return the patient to oral medication as soon as possible, using a long-acting opioid if appropriate. Patients on a methadone programme may require a slow reduction of their opioid doses and continuing assistance for total withdrawal after resolution of the acute episode. In patients still using opioids, PCA may be advantageous because it allows the use of high doses of opioids and may reduce confrontation with staff members. Background infusions are a reasonable method of delivering the patient's daily requirement. Non-opioid therapies should be considered, either as adjuncts to opioids or as alternatives, and epidural infusion analgesia may be valuable after major surgery. In the reformed addict there is significant onus on clinical staff to avoid re-establishing dependency. Patients in this category presenting for major surgery are a particular challenge but every effort should be made to avoid opiates without subjecting the patient to unrelieved pain.

Elderly patients
Pain management in the elderly should recognize their generally reduced reserve and high incidence of concomitant disease and polypharmacy. Pain assessment may be complicated by a background painful disease state, cognitive impairment and altered pain responses. NSAIDs should be used with caution because the elderly have an increased incidence of gastric and renal toxicity. Co-administration of a proton pump inhibitor should be considered if gastric ulceration is of particular concern. Opioid drugs are effective analgesics in the elderly. Patients experience a higher peak and longer duration of pain relief but they are also more sensitive to sedation and respiratory depression, probably as a result of altered drug distribution and excretion. Opioid dose titration should take into account analgesic effects and side-effects, including an awareness of possible cognitive impairment. Use of PCA should ensure careful titration of the initial dose, avoidance of accumulation by not using background infusions, and setting a longer lockout period. Regional techniques may be associated with cognitive impairment from high blood levels of opiate, when standard bolus and infusion doses are used, orthostatic hypotension from sympathetic blockade and clumsiness from partial motor or sensory anaesthesia may also occur. When regional techniques are used the dose of any opioid should be reduced accordingly.

Children
The assessment of pain in children requires modification of pain scoring systems. Preparation of the patient starts at home, psychological support may decrease fear and anxiety of surgical procedures. Familiarization with equipment and procedures preoperatively enhances the use of PCAs postoperatively. The presence of parents or carers in the anaesthetic room decreases postoperative pain and reduces adverse psychological sequelae.

Drug therapy is the mainstay of postoperative analgesia in children, but non-drug modalities may be useful. Analgesia should be given by the least painful route and regular assessment of analgesic efficacy is required. It has been clearly demonstrated that children as young as five can understand the principles and workings of PCAs.

Trauma patients
Various studies have shown that analgesia in the Accident and Emergency Department is often inadequate. Appropriate techniques are listed in Figure 5. All patients require formal assessment of pain.

Various groups require special attention; it is important to reduce the distress associated with analgesic administration in children. Insertion of an intravenous cannula allows rapid control of pain and repeated doses can be given by subcutaneous cannula to avoid repeated intramuscular injection. In the elderly, an increased frequency of adverse drug interactions warrants cautious treatment.

It was traditionally thought that pain relief masked the clinical signs of pathology, but early administration of opioids to patients with an ‘acute abdomen’ does not reduce the detection rate of serious pathology and may facilitate it.

The Acute Pain Team may make a significant contribution to the continuing management of trauma patients. The use of intercostal blocks or epidural infusion may significantly reduce pulmonary morbidity after chest trauma.

Patients with multiple injuries who are initially managed with sedation and ventilation in the ICU require considerable effort in the management of analgesia during the early stages of recovery.

Analgesia in the Accident and Emergency Department

Local anaesthetics
Used in the form of wound infiltration or nerve blocks, such as femoral nerve block for a fractured neck of femur

Entonox
An inhaled 50:50 mixture of oxygen and nitrous oxide, which may be of some use for minor procedures

Opioid analgesics
Best used intravenously with careful titration of the dose. The intramuscular route may be used, but caution is required if tissue perfusion is less than optimal

Non-opioid analgesics
Generally inadequate in severe pain but non-steroidal anti-inflammatory drugs (NSAIDs) are of value in certain conditions (e.g. renal and biliary colic) or as an adjunct to opioid therapy

Physical methods
Fracture stabilization with splints, plaster and early recourse to operative fixation if indicated

Burns
Burn pain has been underestimated and inadequately treated. The belief that third degree burns are painless is fallacious, because damaged nerve endings may result in neuropathic pain. Inadequate pain management may lead to exacerbation of the hypermetabolic state and may increase the incidence of psychological disturbances in the form of depression or post-traumatic stress disorder.

Provision of analgesia deserves high priority in patients with acute burns; analgesia improves cooperation allowing clearer assessment of burns and other injuries. Careful titration of intravenous opiate followed by PCA or intravenous infusion for maintenance is required. Standard pain scoring may require modification in these patients.

During the healing phase adequate background analgesia must be supplemented by intense analgesia for incident pain related to procedures, mobilization and physiotherapy. Again PCA is useful for background pain while a variety of techniques including peripheral nerve blocks, ketamine, benzodiazepines, *Entonox*, regular paracetamol and NSAIDs are useful for incident pain.

Future developments

The future of acute pain management lies in better education of healthcare staff, universal introduction of pain scoring and improved use of existing facilities. The challenge lies in disseminating knowledge and expertise to ensure that best practice is adopted universally.

Novel concepts such as early postoperative restoration of function and ‘fast track’ surgery require further exploration. This approach may have economic benefits in terms of reduced hospital stay, reduced convalescence, and shorter absences from work and other social benefits. The use of effective pain control in facilitating this seems obvious, but the reasons why these results have not been widely replicated remains to be determined.

A further area of evolution in UK practice is the issue of nurse prescribing, which like other aspects of traditional demarcations between health professionals is likely to come under scrutiny.

The developments of evidence-based medicine and systematic review have many applications in pain management. There is room for increased cooperation between acute and chronic pain clinicians and several national trends and initiatives will lead to greater integration.

The development of more sophisticated methods of defining quality and patient satisfaction relating to pain management will allow us to test new pain therapies and innovations in a meaningful way.

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Implantable Technology for Pain Management

John Hodkinson

John Hodkinson is Consultant in Anaesthetics and Pain Management at Furness Hospital, Cumbria, UK. He qualified from Manchester University and trained in anaesthesia and pain management in Manchester, Liverpool and New Zealand. He is Director of the Morecambe Bay Trust Pain Management Programme and Neuromodulation Service with research interests in both specialist units.

Implantable devices for managing chronic pain by neuro-modulation evolved from spinal regional anaesthesia. Their use was assessed by the European Federation of Chapters of the International Association for the Study of Pain in 1998 and a consensus from this task force stated 'Neuromodulation procedures offer a non-destructive reversible alternative to the treatment of severe chronic pain where less invasive therapies and/or neurodestructive procedures are not effective or contraindicated.'

The procedures involve stimulation of the peripheral nerve, spinal cord, deep brain or motor cortex and drug delivery by the intraspinal or intracerebroventricular route. They should be performed in Pain Treatment Centres by a multidisciplinary team trained in patient selection and education, behavioural and psychological assessments and therapy, surgical implantation of the devices and continuous aftercare.

General selection criteria
Patients are suitable for an implantable device if other conservative or interventional (surgical) treatments have failed and there is no intention of pursuing those routes. The patient must give informed consent, have a realistic expectation of the outcome and a high degree of cognitive motivation.

Patients are unsuitable if they have a severe coexisting medical disease, a major psychiatric disorder or illness-seeking behaviour, poor understanding, social support and compliance, or if they abuse drugs.

Neuromodulation by stimulation

In 1965, Melzack and Wall demonstrated the gate control theory of pain. According to the theory, electrical stimulation of large diameter low threshold Aβ proprioceptive sensory nerve fibres causes suppression of small diameter high threshold Aδ and C sensory fibre activity within the dorsal horn of the spinal cord. Antidromic and summation loops are involved following stimulation of the peripheral nerve, spinal cord, deep brain and motor cortex. Stimulation of the spinal cord also influences sympathetic and parasympathetic activity with an autonomic response. Neuromodulation within the CNS by stimulation is governed by the gene–peptide link and the release and reuptake of neuropeptides within groups of wide dynamic range neurons, particularly of the dorsal horn. Release of vasoactive peptides influences peripheral vascular tone and myocardial perfusion. The types of stimulation required for each clinical group are listed in Figure 1. Specific selection criteria for the most commonly treated conditions are given in Figure 2.

Patient selection by clinical group

Site of lesion	Clinical group
Peripheral nerve	
• Peripheral nerve lesion	Trauma, incision, amputation, stump pain
• Complex regional pain syndrome (CRPS)	
Spinal cord	
• Mixed neuropathic nociceptive	Chronic mixed spinal pain, failed back syndromes
• Peripheral nerve lesion	Entrapment, trauma, amputation
• Neuralgias	Post-herpetic
• Plexopathies	Traumatic avulsion, post-radiation
• Radiculopathies	Cervical, lumbar disc, osteoarthritis
• Myelopathies	Spinal cord incomplete lesion, injury
• Polyneuropathies	Diabetes, post-chemotherapy
• CRPS	CRPS type 2
• Refractory angina	Occlusive coronary artery disease, syndrome X
• Peripheral vascular disease	Atherosclerosis, vasospastic, Raynaud's disease, Buerger's disease, CRPS type 1
Deep brain	
• Thalamic nuclei	Trigeminal neuralgia, post-herpetic neuralgia, stump or phantom pain, spinal cord lesion, post-stroke pain
• Periventricular, aqueductal grey matter	Chronic mixed failed back, neuropathic pain
Motor cortex	
• Neuropathic	Post-herpetic neuralgia, cluster headache, post-stroke, phantom pain

1

Specific selection criteria for spinal cord stimulation

Chronic low back pain
- Failed conservative therapies
- Pain experienced correlates with observed pathology
- No further surgical intervention indicated
- Drug habituation has been treated
- Psychological evaluation clearance
- No contraindications (e.g. sepsis, coagulopathy)
- Successful trial screening

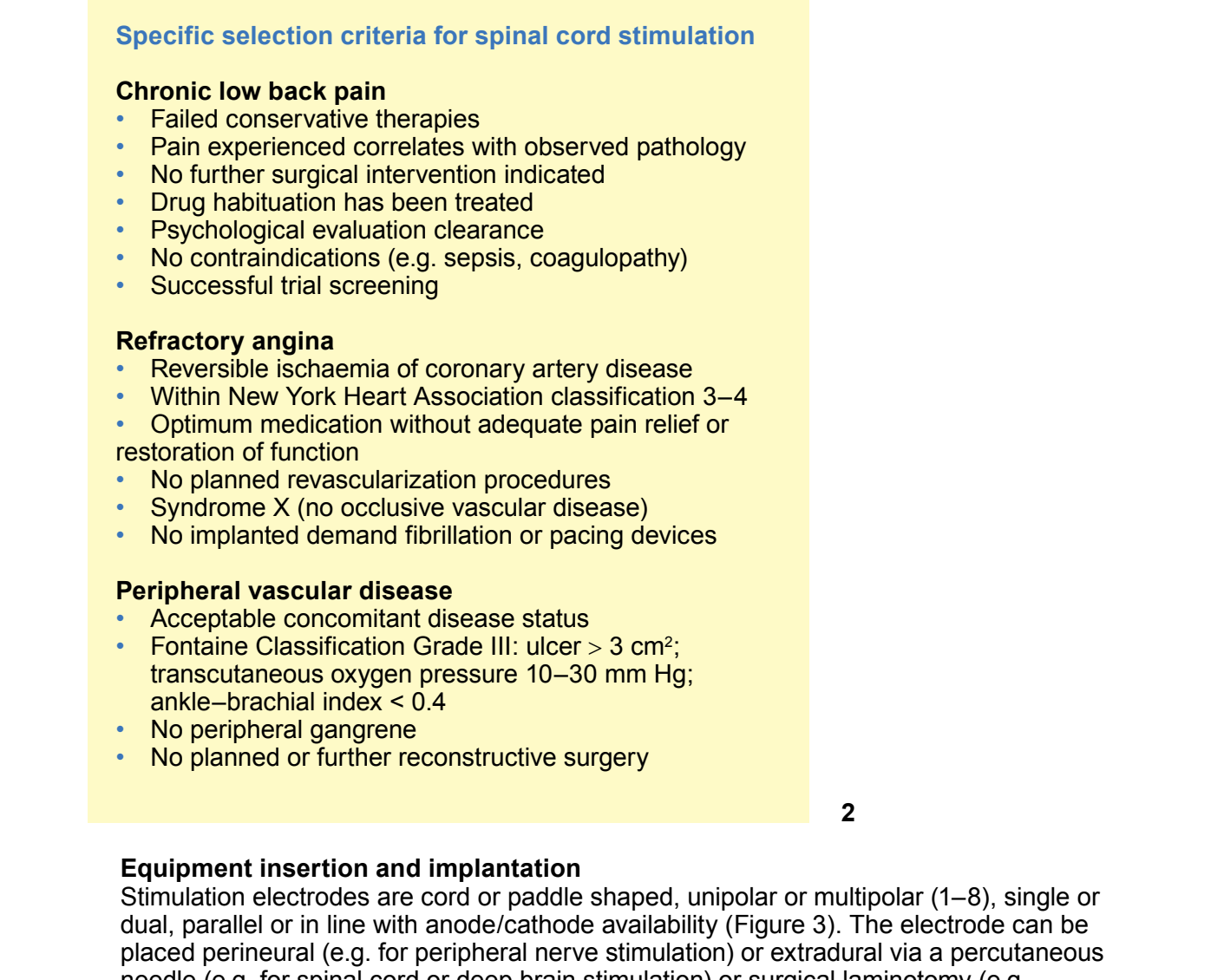
Refractory angina
- Reversible ischaemia of coronary artery disease
- Within New York Heart Association classification 3–4
- Optimum medication without adequate pain relief or restoration of function
- No planned revascularization procedures
- Syndrome X (no occlusive vascular disease)
- No implanted demand fibrillation or pacing devices

Peripheral vascular disease
- Acceptable concomitant disease status
- Fontaine Classification Grade III: ulcer > 3 cm^2; transcutaneous oxygen pressure 10–30 mm Hg; ankle–brachial index < 0.4
- No peripheral gangrene
- No planned or further reconstructive surgery

2

Equipment insertion and implantation
Stimulation electrodes are cord or paddle shaped, unipolar or multipolar (1–8), single or dual, parallel or in line with anode/cathode availability (Figure 3). The electrode can be placed perineural (e.g. for peripheral nerve stimulation) or extradural via a percutaneous needle (e.g. for spinal cord or deep brain stimulation) or surgical laminotomy (e.g. spinal cord stimulation) or craniotomy (e.g. motor cortex stimulation). Computer-aided stereotactic imaging and cortical mapping are used to guide the placement of deep brain and motor cortex stimulation. Electrode placement for spinal cord stimulation uses continuous fluoroscopy and evoked sensory stimulation (paraesthesia) as experienced by the patient at the time of placement. Figure 4 lists the common electrode placement sites. A trial period of stimulation precedes implantation of the pulse generator, which is usually placed in the abdominal wall within a subcutaneous pocket with a hardwire connection lead to the electrode through a percutaneous tunnel. An aseptic technique with broad-spectrum antibiotic prophylaxis for *Staphylococcus* is used.

Spinal cord stimulation



3

Electrode placement for stimulation

	Stimulation mapping
Spinal cord stimulation	
• Chronic mixed low back pain	D9–L1
• Chronic mixed neck pain	C2–D1
• Angina chest wall pain	C7–D2
• Peripheral vascular disease of arm	C6–D1
• Peripheral vascular disease of leg	D11–L1
Deep brain stimulation	
• Central pain	Periaqueductal and periventricular Thalamic projections
Motor cortex stimulation	
• Central pain	Broca motor cortex projections

4

There are a variety of implantable programmable devices activated by internal battery or transcutaneous radiofrequency induction, operated by the patient using a hand set (Figure 3). Operation parameters vary widely, some commonly used ranges are amplitude 2–7 volts, frequency range 30–50 Hz (motor cortex or deep brain stimulation), 50–85 Hz (spinal cord stimulation), 100–150 Hz (peripheral nerve stimulation), and a pulse width of 200–500 microseconds. Various waveform, operational and cycling modes are available and combinations of stimulation arrays within multipolar channels. Interesting effects of concentrated stimulation ('sweet spot') can be achieved by anode/cathode variation across the dorsal columns with parallel dual electrodes. Follow-up evaluation is essential. Usage guidance is provided by audit of patient experience and demand and reprogramming of parameters is often required. Fully internalized battery-operated electronic systems are reprogrammed by transcutaneous computerized telemetry.

Complications
Wound infection occurs in 5% of cases and 3% of implants require removal. Epidural abscess or haematoma may require surgical decompression.

Electrode migration occurs in 35% of cases and 23% require re-implantation. Electrode fracture occurs in 5%, and discomfort at the implantation site occurs in 13%.

Other complications include seroma formation of the pocket, a foreign body immune response causing allergic phenomena either local to the implant or systemically, and CSF leakage.

Failure of the implantable device can occur through technical failure or battery failure. Batteries commonly last for 2–6 years depending on usage and power delivery.

Neuromodulation by implantable drug delivery systems

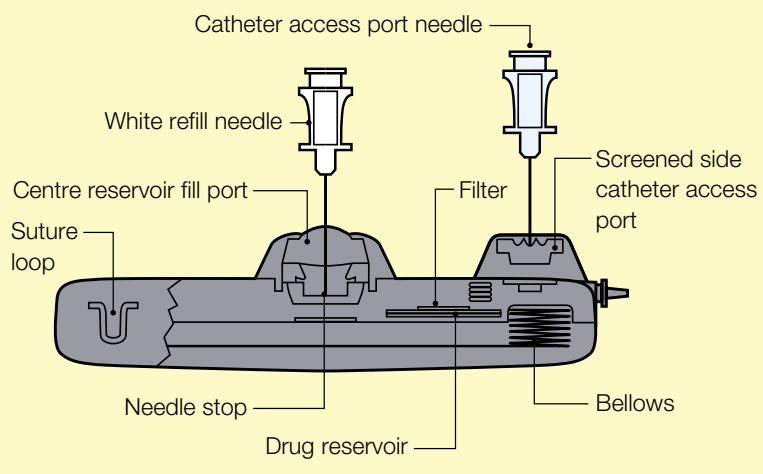
Delivery routes are intraspinal (extradural or intrathecal) and less commonly intracerebroventricular. The general indications for use are a failure of conventional treatments including stimulation, or if the oral and systemic administration of analgesic drug(s) at appropriate dose as recommended by the World Health Organization ladder does not control pain or is associated with unmanageable side-effects. A good response to a screening trial and life expectancy over 3 months is necessary. The types of pain treated include somatic, visceral, neuropathic and mixed. The clinical distribution includes failed back syndrome (42%), cancer (32%), complex regional pain syndrome (5%), post-herpetic neuralgia (5%), peripheral nerve injury (3.7%), multiple sclerosis (2.1%), spinal cord injury (1.4%) and others (8%).

Equipment, insertion and implantation

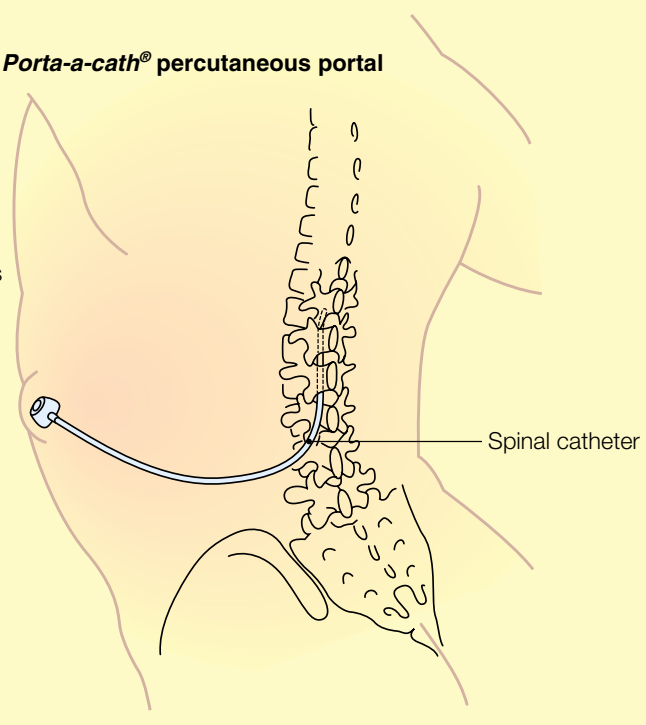
A trial epidural, intrathecal or intraventricular catheter is percutaneously inserted using an aseptic technique. Dose reductions of up to 300:1 are achieved in some cases. When titration to effect and pain control are acceptable, reinsertion of a long-term indwelling silastic catheter is performed percutaneously, tunnelled and connected to the implanted delivery device. An aseptic technique and broad-spectrum antibiotic prophylaxis is essential for the trial and implant procedures and the immediate aftercare period. The various systems used include a subcutaneous portal for continuous or bolused treatments via needle access (*Porta-a-cath*), or totally implantable pumps consisting of a primed chamber with a reservoir manually operated by patient palpation for refill and delivery of a fixed volume and dose (*AlgoMed*). The *IsoMed* is fully internalized with a primed reservoir under pressure giving constant flow delivery, and the *SynchroMed* has a primed reservoir with a battery-operated, electronically programmable, constant flow pump. All the devices are accessible percutaneously for priming the pump or reservoir, changing the drug or concentration and for a test bolus, sometimes through a separate portal (Figure 5). Drugs in common use include opioids (e.g. diamorphine, morphine, hydromorphone, fentanyl, sufentanyl, buprenorphine), local anaesthetics (e.g. bupivacaine) and α_2-agonists (e.g. clonidine). Combinations of opioid drugs, local anaesthetic and α_2-agonists are used synergistically for their dose-sparing effect, though all drugs have an analgesic property and can also be used separately.

Implantable drug delivery systems

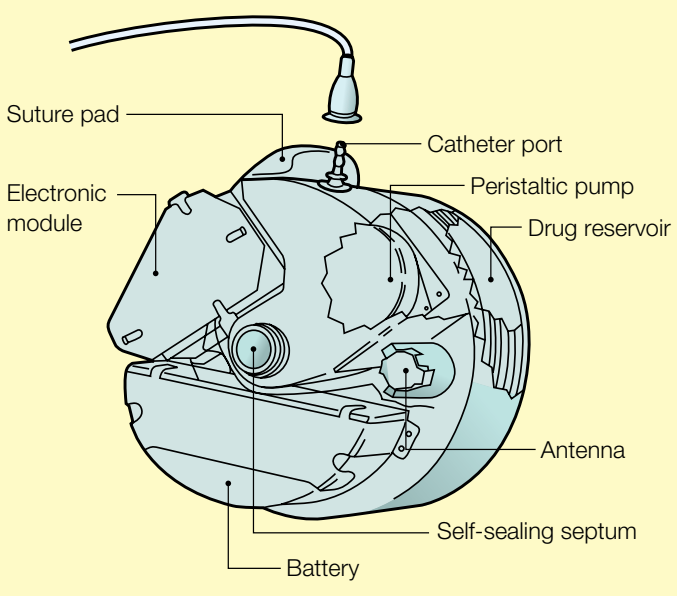
***IsoMed*® pressure chamber continuous delivery pump**



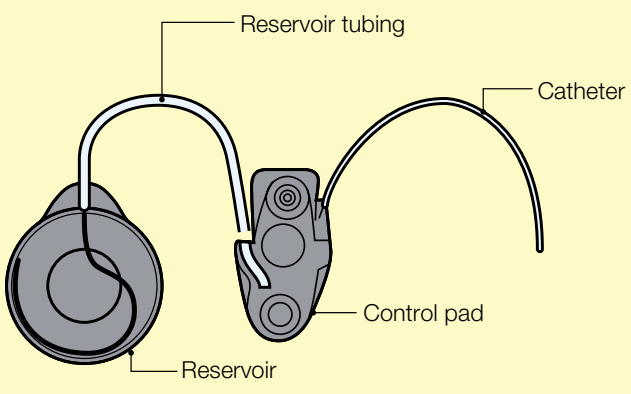
***Porta-a-cath*® percutaneous portal**



***SynchroMed*® programmable infusion system pump**



***AlgoMed*® manual peristaltic pump**



The devices require continual patient monitoring, re-priming, dosage re-adjustments or re-programming of battery-operated devices, which can be performed by transcutaneous computerized telemetry.

Complications

Complications can occur with surgery or the implantation procedure as described above. Drug overdose, tolerance and postural hypotension may occur. Side-effects of the drugs include constipation, micturition disturbance, nausea, vomiting, dysfunction of sexual potency and libido, pruritus, sweating, oedema, weakness, weight gain and nightmares. Catheter complications include migration of catheter tip, fibrosis at the delivery site and nerve root irritation. Mechanical or electrical failure of the pump device can also occur.

Clinical efficacy stimulation and pumps

Data on clinical efficacy are derived from personal and clinical practice supported by case reports and internal audit. Patient series longtitudinal data and retrospective non-randomized and randomized controlled trials have been performed, and repeated measures of sensory, psychological and qualitative dimensions show improvement of quality of life with less social dependence. The usual measurement tools and outcome predictors are visual analogue scores and psychometric questionnaires. Implantable devices are cost-effective because they reduce hospitalization and the use of medication. ◆

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Inhalational Analgesia

Mick Serpell

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The advantage of administering analgesic agents via the respiratory tract is that it is a non-invasive method of achieving high plasma levels.

Analgesic agents that have a low blood-gas solubility coefficient produce analgesia of rapid onset and equally rapid elimination. These are the ideal requirements for managing intermittent and short-term pain problems. The requirements are that the substance must be either a gas, volatile substance or aerosolized. Many different agents have been used in this way, but the one most commonly used employs nitrous oxide (laughing gas); one of the earliest anaesthetic agents (Figure 1).

Most inhalational agents are anaesthetic agents used at sub-anaesthetic doses. Although the technique is inherently safe because the patient self-administers the drug, it is sometimes possible to receive an overdose resulting in depressed consciousness. Therefore care must always be taken, and the technique is contraindicated if there is no one present skilled in airway management.

Inhalational analgesics

Agent	Comments
Entonox	Nitrous oxide (N_2O) mixed with oxygen in a 50:50 mixture
Trilene	Trichloroethylene 0.35–0.5% in air. Administered via a temperature compensated *Emotril* or *Tecota* drawover vaporiser. Central Midwives Board withdrew approval for use in 1984. Slow onset owing to high blood–gas solubility coefficient, slow recovery owing to accumulation and therefore use was limited to less than 6 hours
Methoxyflurane	Methoxyflurane 0.35% in air. Administered via the Cardiff Inhaler. Even higher blood-gas solubility than Trilene, therefore slow onset and recovery. Excessive exposure can lead to 'high output renal failure'. Restrict use to less than 2 minimum alveolar concentration (MAC) hours (MAC 0.16)
Isonox	Isoflurane 0.2–0.75% in *Entonox.* The lower concentrations of isoflurane produce less drowsiness
Isodesox	Desflurane 1%, isoflurane 0.25% and oxygen 60% in nitrogen produced inferior analgesia but significantly less hypoxia than intravenous analgesia with fentanyl and midazolam

1

Nitrous oxide

Nitrous oxide is a weak anaesthetic agent (minimum alveolar concentration (MAC) 105) but a good analgesic. *Entonox* is a 50:50 mixture of nitrous oxide and oxygen and comes in a pre-mixed blue cylinder. Both substances are in the gaseous form but nitrous oxide can liquefy if the cylinder is cooled to –7° C. The cylinder would then initially deliver a high oxygen-containing mixture, but eventually hypoxic pure nitrous oxide would emerge. If accidentally exposed to low temperatures, the cylinder must be warmed up and agitated to ensure thorough mixing of the gases. The gas is administered through a demand valve that is activated by an inspiratory effort of–3 to –5 cm H_2O.

Since the mid 1930s, *Entonox* has been popular in the labour suite as a form of patient-controlled analgesia because it can be self-administered through a mask or mouthpiece. Onset of analgesia occurs within 30 seconds, peaks in 40–120 seconds and dissipates rapidly after discontinuation. For this reason, it is very useful for intermittent pains such as labour contractions and renal colic, or procedural pain such as change of burns dressing, removal of chest drains, insertion of cardiac pacemakers or oocyte recovery. The side-effects of *Entonox* are listed in Figure 2.

Side-effects of *Entonox*

- Drowsiness, nausea
- Augments the effects of respiratory depressant drugs
- Excitability
- Diffuses rapidly into and increases air-containing cavities (i.e. could exacerbate pneumothorax, blocked sinuses, air embolism)

Prolonged and excessive exposure may lead to

- Inhibition of B_{12} coenzyme, methylcobalamin, which results in depression of haematopoietic cell proliferation in bone marrow
- Megaloblastic anaemia, leukoplastic anaemia
- Myeloneuropathy resembling subacute combined degeneration of the spinal cord
- Environmental pollution

2

Other volatile anaesthetic agents

Other volatile anaesthetic agents used for analgesia (Figure 1) include isoflurane and desflurane. They are suitable because they have a low blood-gas solubility coefficient and therefore rapid onset and are the least metabolized of all the volatile anaesthetic agents. Owing to the fact that they are mixed with at least 50% oxygen, desaturation occurs less frequently compared with intravenous analgesic methods. Nitrous oxide produces analgesia for experimental pain in humans but isoflurane does not seem to exhibit any specific effects on pressure, heat or cold induced pain. Isoflurane may produce clinical analgesia by its potent hypnotic and sedative properties.

Opioid drugs

Opioid drugs can also be administered by inhalation. Butor-phanol, 1 or 2 mg, delivered intranasally by a metered dose spray pump relieves pain within 15 minutes after dental impaction surgery. Fentanyl can also be administered intranasally with good short-term effect. The drugs are principally absorbed systemically via the highly vascular nasal mucosa although there may be some direct central absorption through the cribriform plate to the brain.

Alternatively, fentanyl and morphine have been given in an aerosolized form for pulmonary absorption. Fentanyl, 100–300 µg, administered either in the intravenous or aerosol form, produced similar plasma concentrations of rapid onset. These non-invasive and transportable techniques have strong potential for field and domicillary use, and for patient-controlled analgesia without the need for intravenous cannulae.

Environmental exposure

The recommended upper limits for environmental exposure of inhalational agents averaged over an 8 hour period are 100 parts per million (ppm) for nitrous oxide and 50 ppm for isoflurane. These values are more stringent in North America, where for example the values are 25 ppm for nitrous oxide and 2 ppm for other halogenated agents. Inhalation analgesia will undoubtedly cause some pollution due to leakage round the mask, but this can be minimized by using a well-fitting face mask and an operational scavenging system. One group recorded 85 ppm for nitrous oxide in a maternity unit without scavenging and could not identify any significant haematological effects.

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Management of Severe Pain in Advanced Cancer

Alison C Mitchell

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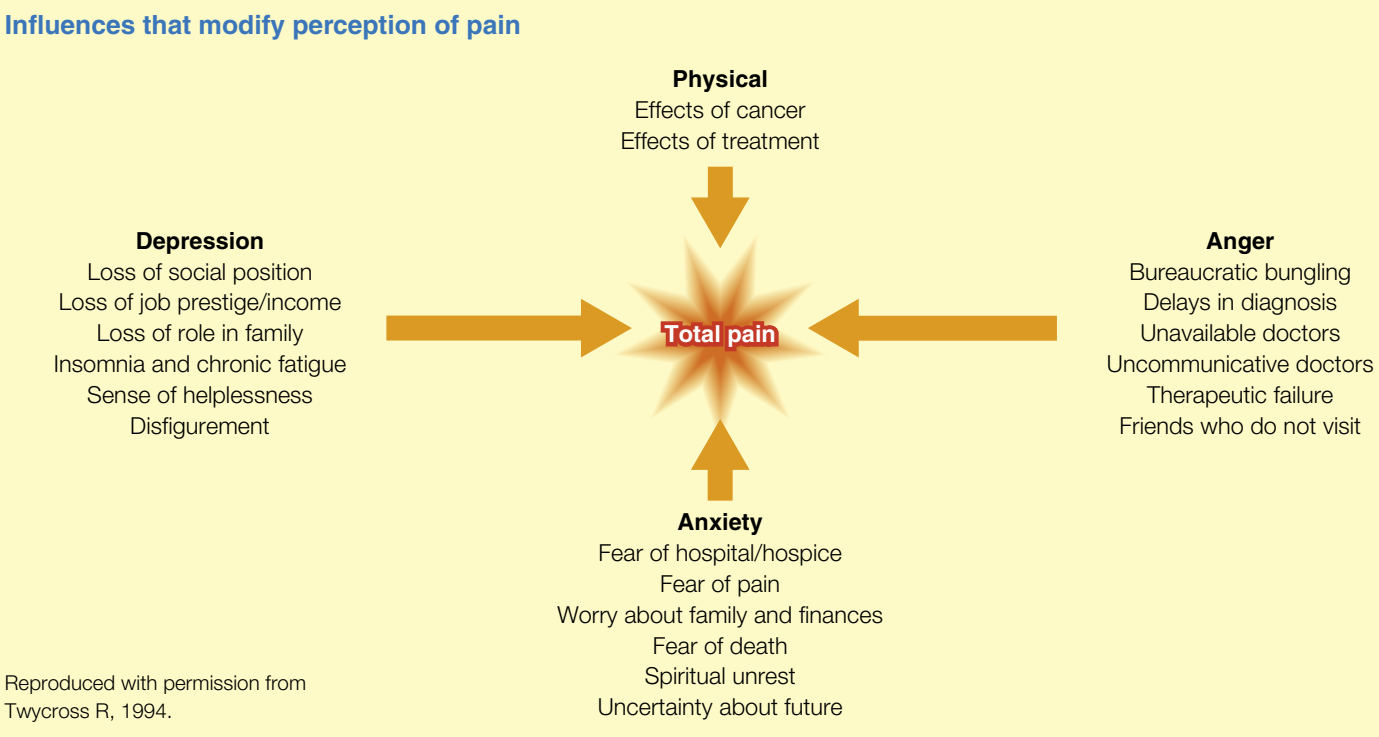
Worldwide there are estimated to be 17 million patients living with cancer. One-third of these patients who receive anti-cancer treatment will experience pain. In patients with advanced disease, more than two-thirds experience pain, and symptom management becomes the principal aim of treatment. In this group of patients, more than 80% can experience pain relief with regular oral analgesia, if a systematic approach to pain management is adopted.

Pathophysiology
Pain in advanced cancer can be caused by a variety of patho-physiological mechanisms. These can be divided into three main groups.

- The pain can be associated directly with the tumour itself. Metastatic bone disease, nerve compression or infiltration and visceral infiltration are the most common causes of pain from direct tumour involvement.
- The pain can be related to the anti-cancer treatment. This group includes pain secondary to surgical intervention, chemotherapy and radiotherapy.
- The pain is unrelated to the cancer or cancer treatment.

The pain experienced by cancer patients is multidimensional (Figure 1) and recognizing this is essential for effective pain management. The spiritual, psychological and social aspects of the patient's suffering must be addressed along with the physical symptoms, or the pain may continue unrelieved.

Influences that modify perception of pain



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Evaluation of pain
A careful history and examination of the patient are essential to determine the most likely cause of the pain (Figure 2). Two-thirds of patients with advanced cancer have two or more distinct pains, and these should be dealt with individually. It is vital to take a detailed history of the analgesic medications that have been tried and a measure of their effectiveness. This will include details of the dose used, whether it was taken on a regular or 'as required' basis, over what period and any side-effects experienced. It may be appropriate to order further investigations to elucidate the cause of the pain.

Evaluation of pain in cancer (WHO, 1994)

- Believe the patient's report of pain
- Initiate discussions about pain
- Evaluate the severity of the patient's pain
- Take a detailed history of the pain
- Evaluate the psychological state of the patient
- Perform a careful physical examination
- Order and personally review any necessary investigations
- Consider alternative methods of pain relief
- Monitor the results of treatment

2

Pain relief in advanced cancer requires a multidimensional and often a multiprofessional approach (Figure 3). It may be appropriate to try to modify the pathological process with surgery, chemotherapy or radiotherapy.

Pain management in advanced cancer

Examination

Explanation
- Reduces psychological impact of pain

Modification of disease process
- Surgery
- Chemotherapy
- Radiotherapy
- Hormone therapy

Analgesia
- Non-opioids
- Opioids
- Adjuvant drugs

Non-drug pain-relieving procedures
- Physical
  - TENS (transcutaneous electrical nerve stimulation)
  - Heat pads
  - Acupuncture
- Psychological
  - Relaxation techniques
  - Cognitive behavioural therapy
  - Psychodynamic therapy

Modification of pain pathway
- Peripheral nerve blockade
- N-methyl-D-aspartate (NMDA) receptor blockade
- Neurolytic procedures
- Neurosurgery

Lifestyle modification
- Immobilization
- Walking aids
- Wheelchair
- Hoist

3

Drug treatment

Morphine remains the strong opioid of choice for the treatment of cancer pain. However, newer synthetic opioid analgesic drugs may be more appropriate in individual patients.

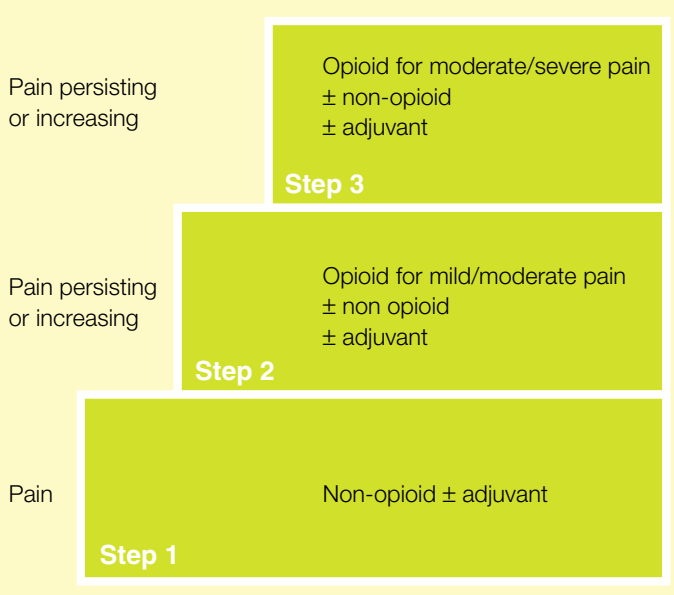
Over 80% of patients with advanced cancer can achieve complete pain control by application of six basic principles for cancer pain relief set out by the World Health Organization (WHO).

By mouth – morphine and several other strong opioid preparations are effective orally and should be taken orally for as long as gastric absorption is unimpaired. This allows patients control of their own medication.

By the clock – analgesia should be prescribed at regular intervals and not on an 'as required' basis because this necessitates that the patient must be in pain before requesting a further dose of analgesia. If the analgesia is given on a regular basis the drug plasma concentration remains relatively stable and the patient experiences more constant pain relief.

By the ladder – the WHO recommended titration of analgesic strength to severity of pain is shown in Figure 4. As the pain increases so should the strength of the analgesia prescribed, with appropriate use of adjuvant analgesia. If a step 2 analgesic drug given regularly does not provide adequate analgesia, it is not appropriate to change to an alternative step 2 drug; a step 3 drug should be commenced.

WHO analgesic ladder



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Individual treatment – there are no standard doses for opioid drugs. The 'right' dose for a patient is the dose that relieves that patient's pain.

Supervision – the response to analgesic treatment should be monitored carefully to achieve a balance between therapeutic benefit and unwanted side-effects.

Adjuvant drugs fall into three groups, secondary analgesic drugs, psychotropic medication, and drugs to combat predictable opioid side-effects (Figure 5). A laxative is nearly always necessary and an anti-emetic is required in up to 50% of patients when commencing strong opioid analgesia.

Adjuvant drugs

Secondary analgesic drugs
- Corticosteroids
- Anticonvulsants
- Antidepressants
- N-methyl-D-aspartate (NMDA) receptor antagonists
- Membrane stabilizing drugs

Psychotropic medication
- Anxiolytic agents
- Night sedation

Drugs to counteract adverse effects of analgesics
- Laxatives
- Anti-emetics

5

Dose titration
It is important to titrate the dose of opioid required to the individual patient. This can be achieved by starting a regular dose of a short-acting formulation of morphine (either tablets or elixir). An appropriate starting dose for patients stepping up from a regular step 2 analgesic is morphine, 10 mg every 4 hours. The patient should also be prescribed a dose equivalent to that of the regular 4-hourly morphine to be given as often as needed between the regular doses of morphine. This makes allowance for the occurrence of 'breakthrough' pain.

After 24–48 hours, the patient and the analgesic requirements are reassessed and the regular and breakthrough doses of morphine adjusted. Generally the dose of morphine (both regular and breakthrough) is increased by 25–30% at each dose adjustment, though this will be guided by the number of breakthrough doses of analgesia that the patient has required. By titrating the dose of morphine against the effect, the various factors that contribute to the variability in dose are accounted for. These include the type and severity of the pain, any psychological component of the pain and individual variations in pharmacokinetics.

Once the patient has achieved good analgesia and requires a maximum of two breakthrough doses of morphine in 24 hours, it may be appropriate to convert to a long-acting morphine preparation. These are available as slow-release preparations either as a once daily dose lasting 24 hours or a twice daily preparation lasting for 12 hours.

Opioid side-effects
The common side-effects of strong opioid analgesics are well recognized and predictable (Figure 6). The initial side-effects of nausea and vomiting, drowsiness, delirium and unsteadiness tend to wear off after the first few days, but they may reappear temporarily after a dose escalation. Patients should be warned about the potential side-effects and given appropriate medication to counteract them. Occasional side-effects include sweating, myoclonus and urinary retention.

Adverse effects of opioid analgesics

Common initial
- Nausea and vomiting
- Drowsiness
- Unsteadiness
- Delirium (confusion)

Common continuing
- Constipation
- Nausea and vomiting

Occasional
- Dry mouth
- Sweating
- Pruritus
- Hallucinations
- Myoclonus

Rare
- Respiratory depression
- Psychological dependence

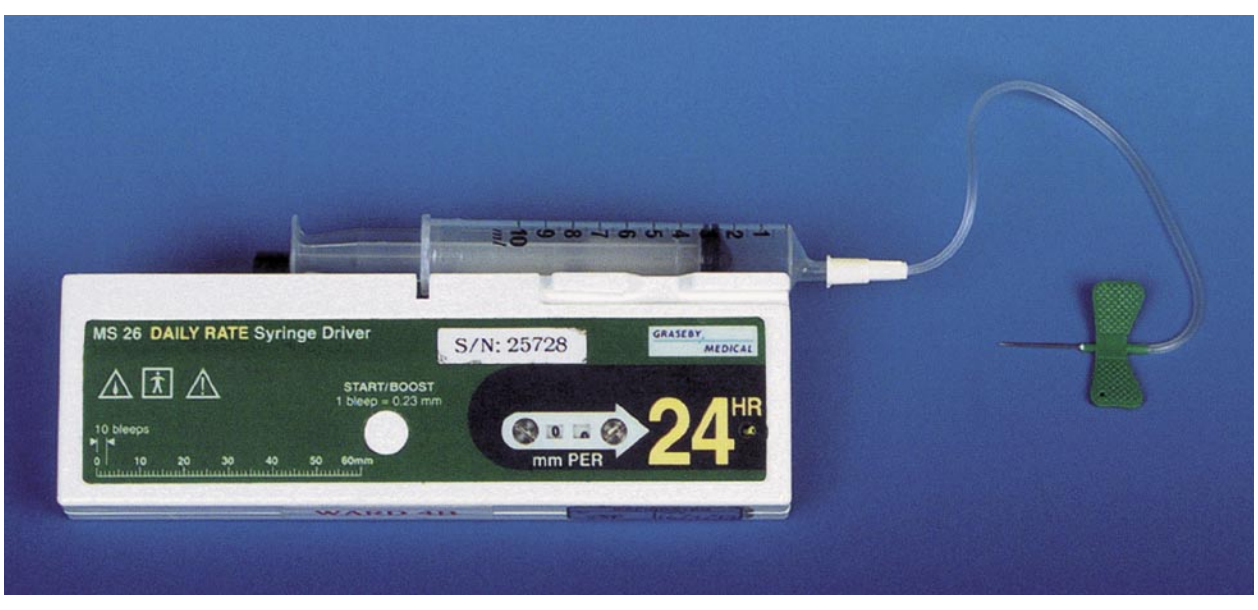
6

In particular, it is important that patients are not dehydrated while taking morphine because impaired renal function increases and prolongs the therapeutic and adverse effects of this drug.

Nausea and vomiting occur in 33–50% of patients taking oral morphine. In most patients, this resolves after the first few days of use, but for a few it may persist and be difficult to control. Suitable anti-emetics are metoclopramide, 10–20 mg q.d.s., or haloperidol, 1.5 mg at night. They can be given subcutaneously using a syringe driver if vomiting persists.

Constipation and a dry mouth continue for the duration of opioid treatment. Laxatives should be given prophylactically and should include a stool softener (e.g. docusate sodium, glycerol) and a peristaltic stimulant (e.g. bisacodyl, senna). Dry mouth should be dealt with by maintaining good oral hygiene and ensuring adequate hydration either orally or parenterally by the intravenous or subcutaneous route.

Alternative routes of administration
It may be necessary to use an alternative route of administration if the oral route becomes difficult or impossible. Morphine can be delivered rectally in suppository form at a dose equivalent to that taken orally. However, it may be more convenient to convert directly from the oral route to the subcutaneous route using a portable syringe driver (Figure 7). This delivers a continuous infusion of the required drug (usually morphine or diamorphine). The relative potency of the opioid delivered increases when it is given parenterally. Therefore the 24-hour dose of oral morphine should be divided by two to reach an equianalgesic dose of subcutaneous morphine, and by three to reach the equianalgesic dose of diamorphine.



7 Portable syringe driver.

The transdermal route can also be used to deliver fentanyl in patients unable to take oral medication.

Patient-controlled analgesia can make effective use of the intravenous route, particularly when the patient can anticipate the pain (e.g. dressing changes).

Opioid alternatives to morphine
In patients with opioid-sensitive pain who cannot tolerate the side-effects of morphine, it may be appropriate to try an alternative strong opioid. As these vary in potency in relation to the equianalgesic dose of morphine, care is essential. For patients who have had good pain control the starting dose of the new drug should be reduced to 50–75% of the equianalgesic dose to allow for incomplete cross-tolerance. If pain control was poor on the previous regimen, the starting dose of the new drug can be about 75–100% of the equianalgesic dose.

Hydromorphone is a synthetic morphine congener that is about seven times more potent than morphine. It is available in oral quick-release and long-acting preparations as well as parenterally.

Oxycodone is a synthetic derivative of thebaine. It is twice as potent as oral morphine. It is available in oral quick-release and long-acting preparations.

Diamorphine is a semi-synthetic analogue of morphine. It is classified as a pro-drug because it is biotransformed to 6-acetylmorphine and morphine to achieve its analgesic effect. It is delivered parenterally, and in this form is about three times as potent as oral morphine.

Transdermal fentanyl is a semi-synthetic opioid, which is released gradually from self-adhesive patches. The patch is changed every 72 hours. There is a slow onset of effect because it takes 12–24 hours to reach steady plasma fentanyl concentration. There is an equally slow decline in plasma drug concentration when the patch is removed. It is therefore suitable only for patients with stable pain.

Opioid responsiveness
Opioid responsiveness is not an all-or-nothing phenomenon, but a continuum. Not all pains respond well to opioid analgesia. Although a therapeutic trial of opioids should be given, bone pain, visceral pain and neuropathic pain are less likely to respond completely to opioids. Radiotherapy should be considered if the pain is caused by a bone metastasis. It can often be given as a single treatment, and results in partial or complete pain relief in over 80% of patients.

Neuropathic pain
Neuropathic pain in advanced cancer usually results from either nerve compression or infiltration. The pain may be in a neurodermatomal distribution, and the patient may complain of a 'shooting' or stabbing sensation. There is an area of altered sensation, and the pain does not respond well to opioid analgesia. If the pain is thought to be secondary to nerve compression, a corticosteroid is the drug of choice. If the pain is thought to be secondary to nerve infiltration, then the anticonvulsant gabapentin can be tried. Gabapentin is a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). The dose of gabapentin should be titrated up gradually. The principal limiting side-effect of gabapentin is drowsiness.

Other classes of drug useful in neuropathic pain are antidepressants, antiarrhythmics, and the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine. It is important that these adjuvant analgesic drugs are tried in conjunction with regular analgesia following the WHO analgesic ladder (Figure 4).

It may be appropriate for some patients to consider a nerve-blocking procedure if the pain is localized to the distribution of a single nerve. Commonly used nerve blocks include intercostal nerve blocks for chest wall pain and coeliac plexus blocks for pain secondary to pancreatic carcinoma.

Opioids, local anaesthetics, and other adjuvant drugs for neuropathic pain (e.g. ketamine) can be given spinally using the epidural or intrathecal route. A successful local anaesthetic nerve block reduces the afferent input to the dorsal horn of the spinal cord, and reduces the amount of opioid analgesia required by the patient. If opioids are given spinally the dose required reduces (e.g. diamorphine 100 mg s.c = 10 mg epidurally = 1 mg intrathecally). ◆

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Medico-legal Aspects of Pain

Charles Pither

Charles Pither trained as an anaesthetist and has been working full time in pain management for 5 years. His particular interest is the treatment of chronic benign pain by interdisciplinary approaches. He has been providing medico-legal reports for 8 years.

The pain specialist professionally encounters the legal system in three circumstances.

- The practitioner is the subject of legal action or censure as a result of negligence or malpractice.
- The practitioner is requested to provide a medical report for litigation purposes.
- The practitioner is undertaking the treatment of patients involved in litigation.

This article focuses on the latter two aspects.

The legal system

The legal system has its own rules and language. Experienced lawyers function in ways better understood by their colleagues than by outsiders. The point you feel most strongly about in a case may not be the point the solicitor is most interested in. Interacting with the legal system involves learning its language and recognizing that it knows best. Doctors who fail to appreciate this can become frustrated when lawyers do not listen to them. The best approach is to listen to what the lawyers want and do your utmost to provide it – save your fascinating point for your medical friends. It is helpful to remember that you are an outsider, but nevertheless providing the court with something it cannot do without.

In civil law, the legal system works on likelihood not on certainty. Thus the burden of proof is not 'beyond reasonable doubt', but 'on balance of probabilities'. Herein lies a conceptual leap for the medical mind: your view need not be proven if it is the most likely explanation. Doctors are interested in rarities and small print; lawyers are interested only in winning the case. This can be harsh and at times disconcerting, but it is crucial to remember it when writing medical reports.

Medical reports

You may be requested to write a medical report about one of your patients as their treating physician or as an expert witness. In either case your report will have to conform to the civil procedure rules as modified following the recommendations of Lord Woolf in 1999 (Figure 1). These changes aim to speed cases through the courts by active management and encourage communication between experts. In all cases, the medical report is directed to the court, which implies a lay readership, thus the use of complex medical terms is to be avoided. Although you will have been instructed to prepare the report by a firm of solicitors, you are not preparing the report for them, but for the court. It is implicit in this arrangement that the expert is impartial. As treating physician, the court will respect the position you hold in your hospital, whatever your grade, but to be accepted as an expert witness the court requires a copy of your curriculum vitae and it should be included with your report.

Important aspects of a medico-legal report as proposed by Lord Woolf

The report is addressed to the court

In your report you must

- State your qualifications
- State the sources of material instructions on which you base your report
- Give references and provide literature where used to support your arguments
- Say who carried out any tests or investigations referred to
- If a range of opinion is expressed this must be summarized and reasons given for your own opinion
- Conclude with a summary
- Contain a final statement saying that you understand your duty to the court and have complied with it
- Conclude with the statement of truth 'I believe the facts I have stated in this report are true and that the opinions I have expressed are correct'

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The court is interested in two main aspects of the case, often dealt with separately:

- liability and causation
- condition and prognosis.

It is often the case that the former is not in dispute but the latter cannot be agreed. Pain clinicians are not commonly asked to provide medical reports on their patients, compared with, for example, orthopaedic surgeons. In simple factual medical reports the essence is clarity and certainty. Reports need not be long-winded; simple explanations suffice, especially when the diagnosis is not in doubt. For example, if you performed various nerve blocks on a patient who developed a clear-cut complex regional pain syndrome following a wrist fracture, it is important to state clearly that in your view, this is the condition from which the patient is suffering. Reasons why you believe this (for example, in terms of matching up to internationally agreed criteria) are important. Similarly, a brief sentence or two explaining the condition is in order but complex explanations of the putative dysfunctions within the CNS are unnecessary. If a reference is appropriate, as in the above case, a photocopy of the paper should be included with the report.

In musculoskeletal pain syndromes, such as whiplash injury and low back pain, the situation is more complicated, not least because the diagnostic systems are more arbitrary. In many ways the legal system is overly simplistic about diagnosis. For an award of damages to an individual, something must have happened to them in the form of an injury or the development of a diagnosable medical condition. Cases run into difficulty when doctors either cannot agree on what condition the person has, or it is disputed whether they have a condition at all. Doctors may not be satisfied by the term 'whiplash-associated disorder' in a medical meeting, finding it nonspecific and not representing a clear pathological entity. However, the diagnosis may have considerable utility in court especially when accompanied by a referenced learned paper on the subject. All the court has to do is to decide whether the person in question has this condition and then act accordingly. Your task as treating doctor or expert is to help them make that decision.

Most plaintiffs with claims relating to chronic pain are also depressed, anxious or both. They may also have a post-traumatic stress disorder. Psychiatric consequences of an accident are no different from other injuries and can be compensated for. If a clear medical diagnosis is difficult to identify it can be helpful to invoke a DSM IV diagnosis such as 'somatoform pain disorder' or pain disorder with psychological factors. The ubiquitous term 'chronic pain syndrome' can also be useful. I have never been cross-examined on the point that this term is no longer recognized by the International Association for the Study of Pain.

Joint reports

Under the Woolf rules, experts are now appointed jointly by solicitors for both the plaintiffs and defendants, to avoid the previous lunacy of two groups of experts producing opposing reports. In time this will simplify matters but there are still many cases in the system with two sets of experts. In this situation, the Woolf recommendations allow the experts to produce a joint report. This can be interesting and can help to resolve difficult cases. It can also serve to demonstrate the differences in approach between different specialties.

Those interested in learning more about writing medical reports within clinical practice or as an expert witness should consider attending one of the courses organized by the BMA and others. The Pain Society has a special-interest group on the legal aspects of pain.

The question of fees always arises and is usually the first thing on the mind of the specialist asked to provide a report. Guidelines are published by the BMA, and other bodies have recommended fees. If in doubt ask a colleague.

The treatment of patients involved in litigation

The old dictum that the symptoms of people involved in litigation resolve with settlement has been challenged. Numerous studies have examined the fate of plaintiffs following the award of compensation and shown that, contrary to the enduring opinion of Henry Miller, subjects are not 'cured by a verdict' and do not make a speedy return to function once the case is settled. This is not to say that seeking compensation does not influence function and outcome. Several studies have demonstrated adverse outcome in subjects pursuing compensation. Without doubt, seeking compensation is stressful, prolonged and causes individuals to become expert in rehearsing the wrongs done to them. Furthermore, the more disabled they are and the greater their suffering the more they stand to gain. The biopsychosocial model is in essence a multivariate system and thus it would be surprising if these effects did not have an influence on disability and distress. What is more surprising is that these effects are seldom reversed once the award has been made, suggesting that the physical and mental influences are not feigned but become reality for the sufferer. The effects are not as prominent if compensation is paid in the form of regular payments rather than a lump sum, which supports the concept of 'no fault' workers' compensation schemes that do not require fault to be proven in an adversarial system.

A common question is whether patients involved in litigation should be treated vigorously in pain management centres before resolution of the case. The answers are conflicting. Much anecdotal information supports the notion that patients can and do make positive changes even in the face of litigation and thus withholding treatment is harsh and ethically questionable, especially because it is difficult to predict which patients will make changes. The author's recommendation is to ensure a multidisciplinary assessment before treatment in order to maximize the chance of detecting those for whom the award is more important than the restoration of quality of life.

However, there is often an impetus from the solicitors to obtain all possible treatment for the patient in an effort to 'mitigate the loss'. The interests of the solicitor are often to close the case rather than to maximize the patient's rehabilitation potential. In fact the reverse may be true, because the worse the plaintiff is, the more work the solicitor has to do, the larger the settlement will be, and the larger the potential fees. ◆

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Neurobiology of Chronic Pain States

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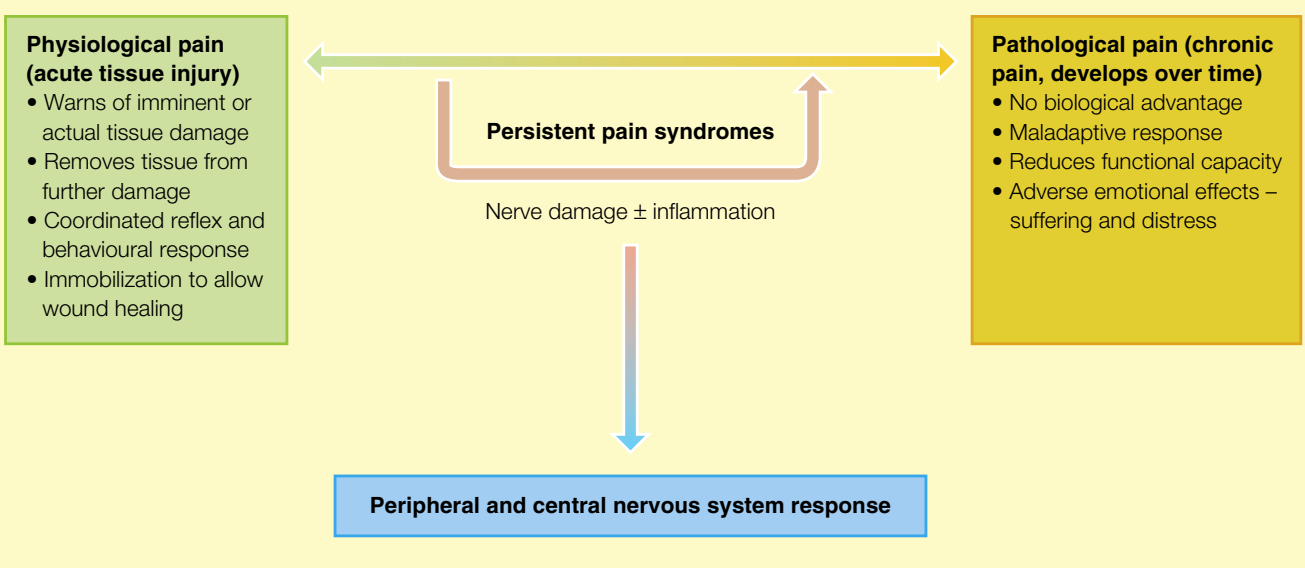
This article focuses on the sensory systems involved in pain perception, but other aspects play a significant role in the experience of pain, particularly in chronic pain conditions. Woolf differentiated between acute, 'physiological' pain and chronic 'pathological' pain (Figure 1). The prevalence of chronic pain is about 30%. Persistent post-surgical pain may occur in 5–10% of patients, with certain procedures being particularly high risk. For example, post-amputation pain occurs in about 75% of patients, while about 30–40% of patients suffer from persistent pain problems after thoracotomy, mastectomy or cholecystectomy.

Many changes in the peripheral and central nervous system contribute to the development and maintenance of pain. The challenge to clinicians is whether improved understanding of neurobiology can be translated into prevention or more effective treatment of chronic pain.

Figures 2 and 3 outline the pathways involved in pain processing. In chronic pain, particular and specific changes in the nervous system can be detected, depending on whether nerve damage or a continuing inflammatory response is the main component of the syndrome. In addition, recent studies indicate that cancer pain may also cause unique and characteristic alterations in the nervous system.

Differences between acute and chronic pain



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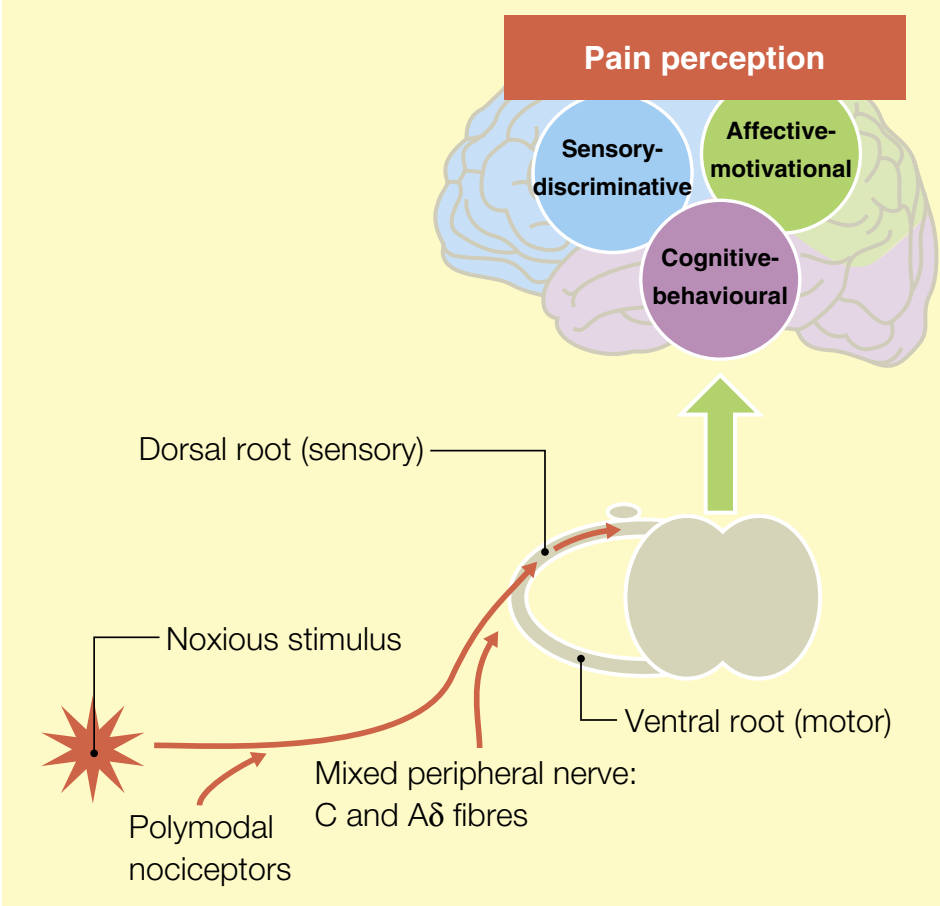
Pathways involved in pain processing



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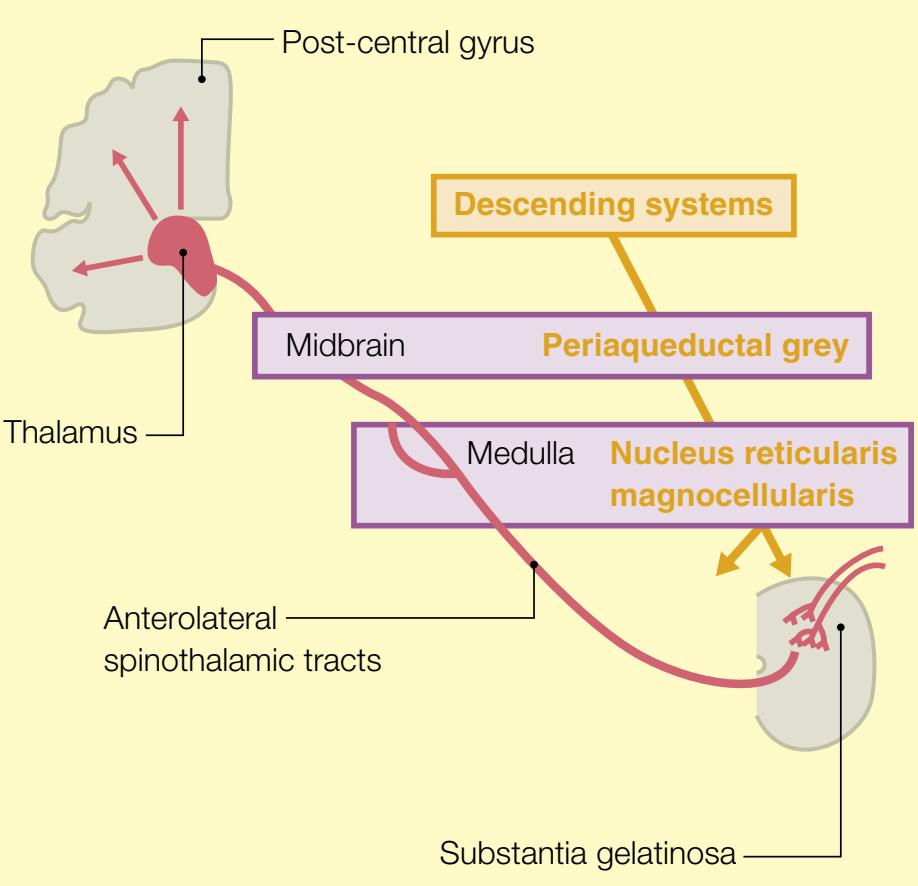
Central pain pathway



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Peripheral alterations

Following nerve injury, two major changes may occur peripherally in primary sensory neurons: alterations in the electrical response properties and alterations in the chemical nature of the neurons.

Electrical properties

Spontaneous activity: normally, a particular high-threshold peripheral stimulus (e.g. pin prick) is required to activate peripheral nociceptors. Neuronal sodium channel permeability then increases, resulting in action potential generation and propagation. After nerve injury, action potentials arise spontaneously at sites distant from peripheral nociceptors, in the absence of any peripheral stimulation. These spontaneously arising action potentials, or 'ectopic discharges', can originate from the nerve injury site, and more proximally, at the cell bodies themselves, in the dorsal root ganglia. The type of sodium channel involved in the generation of these ectopic discharges (the $Na_v1.3$ tetrodotoxin-sensitive channel) is normally found only during development, but reappears after nerve injury. Animal models and clinical microneurographic work have shown that the rate of ectopic discharges may be related to the severity of spontaneous pain.

Evoked activity: normally a high-intensity peripheral stimulus initiates action potentials in nociceptors and these are propagated centrally along small myelinated Aδ fibres and unmyelinated C fibres. The initiation of action potentials stops when the stimulus has ceased and mechanical stimulation of the sensory axon distant from peripheral nociceptors does not generate action potentials. In contrast, after nerve injury, there may be continued action potential generation, termed 'after discharges'. There may also be a change in the pattern of action potential firing, with prolonged bursting discharges. Further impulses may be initiated at the nerve injury site, which may become mechanosensitive after injury.

In response to peripheral nerve injury, there is a clear trend towards increased and altered electrical input into the spinal cord, which has lost the close link to the stimulus-encoded input that is normally found. This increase in primary afferent drive is likely to contribute to the changes that occur in the spinal cord.

Chemical properties

Peripherally synthesized substances that are transported centrally by primary afferent fibres play an important role in neuronal homeostasis. Glial cells (e.g. Schwann cells) are also likely to be involved in this process. Damage to peripheral axons interferes with retrograde transport of peripherally derived chemicals. Substances such as neurotrophins seem to play a major part in maintaining the 'primary afferent phenotype', the characteristic pattern of neurotransmitters produced by primary afferent neurons. At least part of the stimulus for altering neurotransmitter synthesis by primary sensory cell bodies is the loss of tonically transported neurotrophins from the periphery, which act at specific receptor sites.

In addition to actions at the dorsal root ganglia, loss of retrogradely transported neurotrophins may have further effects downstream within the spinal cord. Within the dorsal root ganglia, sympathetic fibres begin to sprout and form basket-like structures around the cell bodies of primary afferent neurons. There appears to be some cross-talk between sympathetic and sensory neurons, with stimulation of sympathetic neurons generating impulses in sensory fibres.

Central alterations in the spinal cord

Extensive and persistent changes in the spinal cord after periph-eral nerve injury include anatomical changes in the 'hard-wiring' of the system, neurochemical changes and functional changes.

Anatomical changes

Large myelinated Aβ fibres, that normally terminate in laminae III/IV of the dorsal horn, begin to sprout into the superficial dorsal horn. They may make functional synaptic connections in the substantia gelatinosa (the area of the spinal cord involved in pain transmission). The formation of these new connections may be one of the mechanisms underlying allodynia, where light touch (normally transmitted by Aβ fibres) is perceived as painful.

Neurochemical changes

There are a huge number of changes in neurotransmitter production, release and receptor activation in response to peripheral injury. Some of the amino-acid and neuropeptide transmitters are considered here. The neurochemical transmitter changes affect intracellular second and third messenger systems, with substances such as nitric oxide being implicated in altering gene expression. Immediate early genes, such as *c-fos* and *c-jun* may also play a role in maintaining chronic pain via alterations in protein synthesis.

Amino acids – the balance between excitation and inhibition is altered by nerve injury. There is a tendency towards an amplification of sensory input within the spinal cord. These changes may persist after the original tissue damage has healed, with continuing alterations in central processing. Figure 4 shows the involvement of amino-acid neurotransmitters in the spinal cord.

- The main excitatory amino acid involved in pain processing is glutamate. Fast transmission of sensory information occurs via ionotropic (ion channel) receptors, such as the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. After nerve injury, or a repeated high-intensity stimulus, the voltage-dependent magnesium block of the N-methyl-D-aspartate (NMDA) receptor is lifted and subsequent release of glutamate results in increased action potential generation, involving NMDA receptor activation. Metabotropic glutamate receptors may also be involved in nociceptive processing. These are not ion channels, but are coupled to G-proteins, with glutamate binding producing intracellular changes in enzyme activation and calcium levels.
- The two main inhibitory amino acids found in dorsal horn neurons are γ-aminobutyric acid (GABA) and glycine. After peripheral nerve injury, GABA levels in the dorsal horn are decreased bilaterally. Glycine-containing inhibitory neurons in the dorsal horn may also be more susceptible to the massive neuronal discharge occurring at the time of nerve injury, resulting in preferential inhibitory cell death.

Amino acids and receptors

Excitatory receptors
Glutamate receptors
Ionotropic
- α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)
- N-methyl-D-aspartate (NMDA)
- Kainate

Metabotropic

Inhibitory receptors
γ-aminobutyric acid (GABA) receptors
$GABA_A$ (mainly post-synaptic)
$GABA_B$ (mainly pre-synaptic)

Glycine receptors

4

Neuropeptides – many neuropeptides are involved in sensory processing, and their synthesis and release alters in response to peripheral injury. Figure 5 shows some of the changes that occur in the primary sensory neuron production of neuropeptides after nerve injury.

Changes that occur in the primary sensory neurons after nerve injury

Excitatory changes
Decreased synthesis
- Substance P
- Calcitonin gene-related peptide (CGRP)

Increased synthesis
- Vasoactive intestinal peptide (VIP)
- Pituitary adenylate cyclase activating polypeptide (PACAP)
- Cholecystokinin (CCK)

Inhibitory changes
Decreased synthesis
- Somatostatin

Increased synthesis
- Galanin
- Neuropeptide Y (NPY)

5

Functional changes
After nerve injury there is an increase in spontaneous neuronal activity within the spinal cord that seems to be partly independent of peripheral ectopic discharges. It may be related to a decrease in 'descending noxious inhibitory control'. The descending pathways involved originate in the brain stem, and normally exert tonic inhibition on intrinsic spinal neurons by the release of serotonin (5-HT) and norepinephrine.

There is also an increase in the functional response evoked within the spinal cord by a given peripheral stimulus, with an increase in receptive field size and prolonged neuronal activation.

Supraspinal changes

One of the limitations of animal studies is that they focus on the peripheral and spinal cord changes in sensory processing. By combining the information gained from these studies with clinical investigations using brain-imaging techniques to examine the wider aspects of pain perception, understanding of this dynamic system can be improved.

Recent studies using indirect measures of neuronal activation have demonstrated that there are rapid and persistent alterations in cortical responses after upper limb amputation. Additionally, it appears that the greater the changes in the somatosensory map on the cortex, the greater the severity of phantom pain. The underlying mechanism for this may vary between patients. Potential mechanisms include unmasking of silent synapses and neuronal sprouting from the thalamus and within the sensory cortex itself.

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Neurosurgical Techniques in the Treatment of Chronic Pain

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Over several decades, many surgical procedures have been undertaken in an attempt to alleviate chronic pain and most have involved ablation or excision of neural tissue. However, present neurosurgical techniques based on current understanding of the pathophysiology of pain attempt to modify or modulate pain pathways.

It is sometimes possible to treat the cause of chronic pain and investigations must always be directed at this possibility. Only when treatable causes have been excluded should other treatment modalities for chronic pain be considered. Pain resulting from spinal root compression or instability pain caused by metastatic spinal disease might be treatable by direct surgical techniques.

Neuroablative procedures

Neuroablation or destruction of neural tissue has been the mainstay of surgical procedures for chronic pain but the recognition that nerve injury is often the cause of chronic pain syndromes has resulted in reluctance to induce further nerve damage. However, some neuroablative procedures remain useful in the treatment of chronic pain.

Cordotomy

Interruption of the spinothalamic tract in the anterolateral quadrant of the spinal cord abolishes nociceptive pain from the contralateral side of the body. However, this effect is not always long lasting and the procedure is mainly used in pain caused by malignant disease that proves resistant to drug treatment. There are several methods of performing a cordotomy but the most commonly used techniques are a percutaneous cervical cordotomy or an open thoracic cordotomy.

Percutaneous cervical cordotomy: under local anaesthesia, using radiological control, a lateral cervical puncture is carried out at the C1/2 level following which an electrode is placed in the anterolateral quadrant of the spinal cord. The optimal position of the electrode is verified by electrical stimulation that should produce sensory effects on the contralateral side. A thermal lesion is then created by applying a radiofrequency current to the tip of the electrode that should result in loss of pain sensation in the opposite side of the body. The percutaneous method has the advantage of being a relatively minor procedure but requires good patient cooperation and tolerance.

Open cordotomy is usually undertaken under general anaesthesia though techniques of waking the patient during the procedure to confirm satisfactory lesioning of the cord have been described. A small upper thoracic laminectomy is carried out and the anterolateral quadrant of the spinal cord is sectioned with specially designed blades.

Indications for cordotomy (Figure 1): because the analgesic effects reduce with time and there is a risk of delayed dysaesthetic pain syndromes, cordotomy is seldom carried out in patients with pain resulting from benign disease.

Indications for cordotomy

Cervical cordotomy

Indications

- Unilateral pain below C4/5

Contraindications

- Pain above C4/5
- Bilateral pain
- Axial pain
- Compromised respiratory function
- Dysaesthetic pain (?)

Open thoracic cordotomy

Indications

- Unilateral or bilateral lower limb pain due to malignant disease

Contraindications

- Axial pain
- Dysaesthetic pain
- Poor anaesthetic risk

(Loss of bladder function invariably ensues after bilateral cordotomy)

The distribution of nerve fibres in the spinothalamic tract makes it impossible to obtain pain control above C4/5. In cervical cordotomy the reticulospinal fibres responsible for spontaneous respiration are also destroyed and if carried out bilaterally there is a risk of respiratory failure. This is also the situation if there is significant lung disease on the side of the cordotomy and caution must be exercised in patients with pulmonary malignancy.

Dorsal root entry zone lesions

The superficial part of the grey matter in the dorsal horn of the spinal cord has a complex of neural networks that are thought to modulate pain pathways. Lesions have been made in the area where the dorsal root enters the spinal cord (dorsal root entry zone) in an attempt to control a variety of pain syndromes. The operation requires a laminectomy to expose the dorsal root entry zone followed by either a series of radiofrequency coagulations or an incision and diathermy of the area. Though it has been used in a variety of neuropathic pain conditions the best indication for this procedure is for pain resulting from brachial plexus avulsion.

Other neurosurgical ablative procedures

Other ablative procedures in the spinal cord that are sometimes performed include commissural myelotomy for lower limb cancer pain and cordectomy for spinal cord injury pain.

Today, few intracranial ablative procedures are carried out for chronic pain. Mesencephalic tractotomy may be an option in patients with head and neck cancer. Patients with malignant disease in whom cordotomy has failed may occasionally benefit from lesions placed in the thalamic and subthalamic sensory pathways.

Pituitary ablation, with either a percutaneous alcohol injection or a trans-sphenoidal hypophysectomy, has been undertaken for pain caused by disseminated breast and prostatic malignancy.

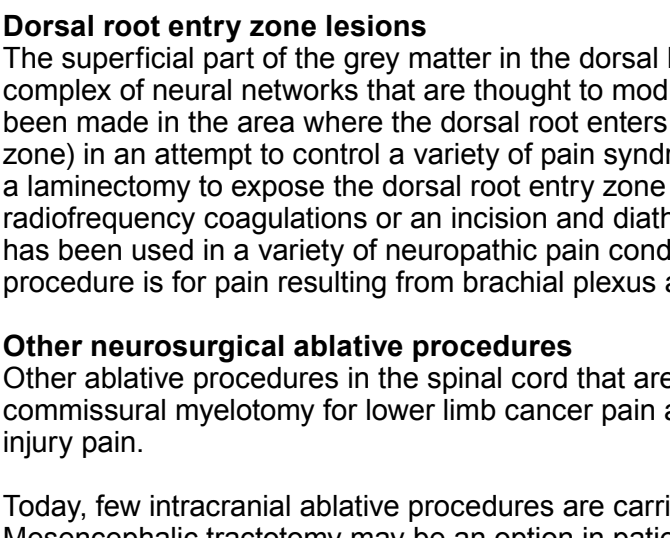
Neuromodulation procedures

The current trend in neurosurgery for chronic pain has been to replace ablative techniques with those that attempt to modulate the generation or transmission of pain impulses. The two methods that are widely used are neurostimulation and drug delivery systems.

Neurostimulation

Chronic electrical stimulation of the CNS as a method of controlling pain was introduced in the early 1970s but was handicapped by unreliable hardware. Improvements in stimulator technology have allowed this method of treatment to be widely used.

Spinal cord stimulation: previously called dorsal column stimulation, the technique was introduced in 1967 and was widely thought to be based on the gate control theory of pain proposed by Melzack and Wall. The exact mechanism of action is uncertain but the best indications for the procedure are now emerging. Refractory angina and advanced peripheral vascular disease are the best indications for spinal cord stimulation. Neuropathic pain, including the complex regional pain syndromes, is probably the most widely used indication (Figure 2). Its use in axial pain of spinal origin and in the so-called ‘failed back surgery syndrome’ is disputed, though some authors claim good results in this condition.



Reversal of autonomic changes in complex regional pain syndrome following spinal cord stimulation. Note the reduction of swelling in the left hand before (**a**) and after (**b**) spinal cord stimulation.

The outcome of spinal cord stimulation depends on rigorous assessment of patients and choice of indications. Most large series show that in carefully selected patients 60% derive 60–70% pain relief. This has to be balanced against the need for long-term supervision of the hardware along with re-operation for system failure.

Surgical methods of spinal cord stimulation – patients considered for spinal cord stimulation have to be subjected to a rigorous preoperative assessment to determine the potential benefits they may derive from the treatment. In certain patients, spinal cord stimulation could have a placebo effect and therefore assessment and evaluation by a multidisciplinary team is essential.

Before implantation of a permanent system it is usual to undertake a trial of stimulation with a percutaneously placed epidural electrode connected to an external pulse generator. The position of the electrode is adjusted so that electrical stimulation projects a sensation of paraesthesia into the painful area. A prolonged period of stimulation is then undertaken to allow careful assessment of the patient’s response to stimulation. Implantation of a permanent system should be considered only in patients who show a consistent reduction in pain levels (60–70% reduction in the visual analogue score (VAS)) in parallel with reduction in analgesic requirements and with normal activity.

A wide range of hardware is available for implantation and the choice is often based on the expertise and experience available locally. Percutaneously placed epidural electrodes have the advantage of converting a trial electrode into a permanent electrode but have the disadvantage of being prone to migration. Electrodes placed by laminotomy are less prone to migration and can give a wider area of stimulation but require a more invasive procedure.

The power source for stimulation could be a totally implantable pulse generator or a radiofrequency coupled receiver that has an external power source. The former, which is similar to a cardiac pacemaker, has several advantages but requires expensive replacements for battery depletion. Currently available systems have sophisticated electronic devices that allow the clinician and patient to alter the stimulation parameters.

Other neurostimulation techniques

- Stimulation of nerve roots or peripheral nerves is now seldom undertaken. There are a few studies on the use of electrical stimulation of the trigeminal nerve for facial pain.

- Deep brain stimulation of the periventricular grey matter or of the sensory pathways in the brain continues to be investigated as a potential target for chronic electrical stimulation for the treatment of chronic pain.

- In motor cortex stimulation a variety of methods are used to identify the motor cortex before an electrode placed extradurally over the motor cortex is connected to an implantable pulse generator. The mechanism of action remains unclear, but interest has been shown in the evaluation of motor cortex stimulation for the treatment of central pain syndromes, and particularly in central post-stroke pain.

Drug delivery systems

For a long time, anaesthetists have appreciated the use of intraspinally administered analgesia and external infusion devices have also been used in palliative care. The development of reliable implantable drug infusion devices has led to their increased use in the management of chronic pain syndromes. Electronically controlled systems allow for sophisticated external programming of infusion cycles and are being increasingly used for benign chronic pain syndromes. These systems are expensive and require careful long-term follow-up for dose adjustments and drug refills. While opioids are the most commonly used drugs a variety of other analgesics are being evaluated for intrathecal use.

Trigeminal neuralgia

Trigeminal neuralgia is probably the most common chronic pain syndrome requiring neurosurgical treatment. Surgical treatment must be considered if the pain proves refractory to drug treatment or if there is intolerance to drug treatment. The cognitive side-effects of drug treatment are often underestimated and this is particularly important in younger patients in whom a lifetime of anticonvulsant medication can be avoided by surgery.

Surgical treatment

Percutaneous neuroablative procedures: the trigeminal ganglion and rootlets can be accessed percutaneously by an entry lateral to the angle of the mouth and directed under radiological control to foramen ovale at the base of the skull. Percutaneous procedures have the advantage of being relatively minor and well-tolerated operations especially in medically compromised patients. The disadvantages are the short-lived effects with the need for frequently repeated procedures. The incidence of denervation pain syndromes (e.g. anaesthesia dolorosa) is high and they are effectively untreatable. However, these techniques are extremely useful in secondary trigeminal neuralgia (e.g. multiple sclerosis) and in physiologically compromised patients.

Radiofrequency thermocoagulation – with intermittent intravenous anaesthesia a radiofrequency electrode is inserted through the foramen ovale and the position verified by electrical stimulation. When the appropriate divisions of the nerve have been identified a radiofrequency thermal lesion is produced to damage the more sensitive pain fibres while preserving the touch fibres.

Chemical neurolysis – alcohol and phenol have now been largely replaced by glycerol for chemical neurolysis. The procedure can be undertaken under local anaesthesia and under ideal circumstances selective ablation of pain fibres can be achieved.

Balloon compression – a small arterial embolectomy catheter is placed in Meckel's cave and is repeatedly inflated to gently crush the trigeminal ganglion and lesion the pain fibres.

Other ablative procedures

Stereotactic radiosurgery – using stereotactic surgical techniques, a controlled dose of radiation is administered precisely to the trigeminal root entry zone in the brainstem. This is a relatively new procedure that is non-invasive but the long-term effects are uncertain.

Open selective rhizotomy – open section of the trigeminal nerve was previously undertaken in the middle cranial fossa but is now largely carried out in the posterior cranial fossa. Good long-term denervation can be achieved, though the risks of denervation pain syndromes are high.

Microvascular decompression: vascular compression of the trigeminal nerve at the root entry zone is now largely accepted as the main aetiological factor in trigeminal neuralgia and can be radiologically confirmed by MRI. Microvascular decompression treats the cause of the disease without inducing nerve damage. Following a retromastoid craniectomy a microsurgical exposure of the trigeminal nerve in the cerebellopontine angle is under-taken. The vascular compression is usually identified by the brainstem at the root entry zone and the offending vessel is mobilized away from the nerve. A synthetic sponge is then inserted between the vessel, the nerve and the root entry zone.

Microvascular decompression is a major neurosurgical operation with the attendant risks, but despite this it is well tolerated, even by elderly patients. Risks such as CSF leaks, infection, haemorrhage and unexpected neurological deficits remain, though the specific risks to the auditory and facial nerves can be reduced by meticulous microsurgical techniques and intraoperative neurophysiological monitoring. These risks are counterbalanced by the fact that the technique attempts to treat the cause of the condition and is associated with good long-term results. The avoidance of iatrogenic nerve damage and denervation pain syndromes is a significant advantage. ◆

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Organization of Pain Management Services

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Good administration is vital for any organization if it is to succeed in delivering the service it intends. A well-organized pain clinic will be able to deliver a high quality service efficiently. It will enable clinicians to focus on individual patients and their needs. Patients presenting with chronic pain represent a major clinical challenge because they commonly have complex clinical problems. They present with additional psychosocial problems, are demanding to treat and have often experienced significant problems during their previous encounters with the healthcare system. By creating an administrative system in which responsibilities and workload are clearly defined the staff will be able to perform more effectively and efficiently. This will engender good morale and help to attract and retain staff.

The report of the Clinical Standards Advisory Group indicated the complex nature of chronic pain and its impact on patients and their families. It outlined the lack of support and resources in many pain treatment facilities. It pointed out that psychologically based approaches could be effective but that few patients had access to such treatment. Purchasers did not seem to understand what services they were buying and were often uncertain about the potential outcome of treatment. Some regarded chronic pain as not being a high- profile problem.

Shape of the service

Pain clinics in the UK vary from single-mode treatment clinics (e.g. acupuncture clinics) to large multidisciplinary pain centres involving staff from differing specialties and professions. Most pain clinics are run by anaesthetists with support from other professions (e.g. nursing). The shape of the pain service largely depends on the case mix (Figure 1).

Typical pain clinic case mix

- Average pain history of 5 years
- Complex problems with concurrent disease
- Failure to respond to previous treatments
- High level of healthcare use (drugs, GP, accident and emergency department, specialists)
- High levels of psychological distress
- Low level of physical functioning
- Employment problems
- May be seeking compensation

1

The International Association for the Study of Pain (IASP) has published *Desirable Characteristics for Pain Treatment Facilities*. While these may be regarded as a counsel of perfection, there are a number of important points that should be applied to any pain service. The UK Pain Society endorsed these recommendations in their own document *Desirable Criteria for Pain Management Programmes*.

The skills of more than one profession are needed to help patients with such complex problems. Over the past 20 years there has been a move away from pain clinics being run entirely by anaesthetists to the development of multidisciplinary or interdisciplinary teams, usually involving nurses, physio-therapists, occupational therapists and clinical psychologists. Each profession is able to bring a different perspective to the assessment and management of patients with chronic pain problems. Thus, by assessing and treating not only the pain but also the many problems caused by the pain or concurrent to the pain, it is more likely that there will be an improvement in physical and psychosocial measures. The main aim is a reduction in pain and an improvement in the quality of life.

The treatment options available in a clinic depend on the resources, including the administrative personnel, individual clinical skills and interests, the available facilities (e.g. theatre sessions with radiography, gymnasium), links with other services (e.g. spinal services) and appropriate funding (Figure 2).

Types of service available

- Clinics (e.g. new patient, follow-up, clinical psychology, rapid referral, pre-pain management programme assessment)
- Clinic treatments (e.g. acupuncture, transcutaneous electrical nerve stimulation)
- Outpatient treatments (e.g. individual rehabilitation)
- Day case treatments (e.g. epidurals, facet joint blocks, sympathectomies)
- In-patient treatments (e.g. long-term epidurals, spinal cord stimulation)
- Pain management programme

2

Key players

It is important to identify the key players to ensure the success of a pain clinic. Apart from the patients, the key players are the referring agents (e.g. GPs, specialists), the managers of the trust or hospital unit and the purchasers of healthcare (Primary Care Groups, Health Authorities). Each of these needs to understand the nature of the service being offered to the patients, the expected outcome and the costs involved in running the service.

Regular clinical audit provides vital information for managers about case mix and outcome. It is important to explain to managers the complexity of the presenting clinical problems and the significant degree of psychological distress and disability (Figure 3). For example, most patients seen in pain clinics present with levels of distress seen in only 15% of patients attending routine orthopaedic clinics.

Data for key players

- Describe case mix in detail, including medical, psychological and physical function problems
- Argue the case for careful broad-based assessment
- Describe the (proposed) service in detail
- Highlight links with other services and departments (e.g. orthopaedic surgery, rehabilitation services)
- Outline resources needed and those currently available (personnel, time, space and facilities)
- Describe consequences (financial and clinical) of not setting up, or developing, the service

3

Without support from clinicians and local managers it is difficult to convince purchasers of the need for the service. Careful documentation with supporting evidence of benefit must be available. The links with other services should be emphasized, in particular how the pain clinic can help in the development of common clinical pathways. This should be done in collaboration with hospital and unit managers, who will often understand the current trends in purchasers' thinking and will assist in tailoring the arguments to be presented to the purchasers.

Resources

The shape of the service is often determined by the case mix. Many pain clinics develop without much planning. As a consequence they are often run on tight budgets and inadequate resources. Often there is a lack of secretarial and administrative back-up which can lead to poor delivery of service and undue stress on clinicians. Both the Pain Society and the IASP have published documents outlining resource requirements. All clinical staff must have experience in assessing and treating patients with chronic pain. Time must be made available for continuing professional development, audit and research. Figure 4 lists the essential resources required by any clinic wishing to offer a broad range of assessment and treatment options.

Potential resource needs

- Clinical personnel (physician, nurse, physiotherapist, psychologist)
- Time (each clinician should have enough time for dedicated clinical sessions, training, audit and research)
- Administrative support (business manager,audit co-ordinator, secretary, clerk)
- Premises (clinic room(s), treatment room(s), pain management programme room, office(s))

4

Organization

Good organization is achieved by making the best use of resources and playing to people's strengths. There should be a clear agreed shape of service with a clinician responsible for clinical matters. Each team member should be given a clear area of autonomy and responsibility. There must be a senior administrator to monitor workload, track patients, facilitate audit and maintain contact with purchasers. Regular meetings of the team to discuss clinical and administrative matters are essential for cohesion. Purchasers tend to pressurize clinics to see a greater number of patients more quickly, but quality of service should take precedence over quantity.

Clinical pathways: much of the treatment of chronic pain can be set out in a protocol that can be performed by non-medical staff, under the supervision of the physician. By outlining in detail both a generic patient pathway (e.g. assessment process) and syndrome-specific pathways (e.g. treatment of neuropathic pain) it is possible to ensure a high quality of service delivery and also monitor progress and outcome more successfully. Inclusion and exclusion criteria as well as a clear pathway for those patients thought to be suitable for the pain management programme should be published.

Administrative pathways are complex and need adequate investment to allow clinicians to function efficiently and effectively. Much information can be obtained by questionnaire before the clinic appointment or at the clinic. This can provide vital clinical information for triage, assessment and outcome measurement as well as providing data about case mix. Adequate resources must be allocated to record this data.

Links with other services are vital if the pain clinic is to provide a useful service. Common protocols and explicit referral criteria should be negotiated with other users of the service (e.g. orthopaedic surgery) to ensure appropriate referrals and improve the quality of service. ◆

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Patient-Controlled Analgesia

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It is impossible for a practitioner to predict the amount of analgesia required to relieve each patient's pain effectively. Patient-controlled analgesia (PCA) allows individualized pain relief according to the patient's requirements. It allows patients to administer a predetermined dose of analgesia within the constraints of a lockout period using a programmed device (Figure 1). This concept acknowledges that the patient is a good judge of the magnitude of their pain. PCA is now widely used as an alternative to intramuscular analgesia in managing postoperative and acute episodic pain.

PCA can be administered by oral, inhaled, epidural or intravenous methods. For patients with acute pain, the most commonly used form is intravenous PCA, usually delivering an opioid. Although PCA (and nurse-controlled analgesia) is appropriate for use in a paediatric setting, there are specific requirements for children. Therefore, this article discusses intravenous PCA in adults.

1 Patient-controlled analgesia machine.

Rationale and history of PCA

PCA overcomes some of the problems of traditional therapies, including variable absorption with intramuscular therapy and frequent adjustments of infusion rates with continuous infusions. Although PCA allows the patient to 'control' the administration of the drug, it may be more accurate to call it patient-assisted analgesia because it is prescribed and limited by a doctor.

Intravenous PCA was developed to address the need for an improved mode of administering standard opioids. The first demonstration of a PCA machine was in 1976 at the Welsh National School of Medicine. This became the first commercially available PCA machine 'The Cardiff Palliator'. PCA allows on-demand repetitive dosing of small amounts of opioid by the patient, followed by a lockout period during which the machine will not allow any more doses of analgesic to be given. The drive for the patient to press the button is to reduce their pain to an acceptable level. This titrates the plasma concentration of opioids around the minimum effective analgesic concentration and avoids the peaks and troughs associated with traditional intramuscular regimens. Therefore, constant plasma levels of opioid and consistent analgesia are more easily attained with PCA than with intramuscular analgesia.

The usual drug of choice for use with PCA is morphine, but other opioids such as pethidine, fentanyl and tramadol have also been used successfully.

Patient suitability

PCA is suitable for use in adults following surgery where there is a likelihood of parenteral opioid analgesia being required for 24 hours or more, or for the management of acute episodic pain such as that associated with a sickle cell vaso-occlusive crisis. Correct selection of patients is important because they have to be mentally able to understand the concept of self-administration of analgesia and physically capable of pressing the button to deliver the analgesic dose. Specially adapted handsets are available for patients with conditions such as rheumatoid arthritis for whom use of the usual handset and button may prove difficult.

Relative contraindications for PCA use are:

- patients who are abusing illicit drugs
- patients who have marked metabolic disorders such as sepsis or severe fluid and electrolyte abnormalities
- patients with end-stage renal and hepatic disease
- patients who have severe chronic obstructive pulmonary disease
- patients who suffer from sleep apnoea.

For patients in whom PCA is contraindicated, careful assessment and reassessment of analgesic requirements needs to be undertaken to ensure adequate relief is achieved and the safety of the patient is maintained. Advice from experienced healthcare practitioners regarding specialized care should be sought.

Mode of action

The patient presses the button to deliver analgesia only when they have pain or discomfort. The safety of the device depends on a negative feedback loop of which the patient is a part. This works because if the minimum effective analgesic concentration is exceeded or if the patient is very sensitive to opioids, they will become sedated and therefore will not administer any further doses until the plasma concentration of opioid has decreased to a safer level and they become less sedated. As sedation is a precursor to respiratory depression, its occurrence is therefore reduced or avoided.

Parameters

Loading dose

The loading dose is the opioid dose initially required to achieve the minimum effective analgesic concentration. The actual dose required to achieve effective analgesia is impossible to predict and varies depending on the severity of the pain and the effectiveness of the analgesia for each patient. The loading dose can be administered by pre-setting the PCA pump and allowing automatic administration, but usually the anaesthetist or nurse titrates the loading dose to the desired effect in the recovery unit. If the loading dose is omitted, patients are unlikely to obtain good analgesia because even if the demand button is pressed as often as permitted by the programme, the minimum effective analgesic concentration may not be achieved. The resultant ineffective management of pain may reduce the patient's trust in PCA and increase their anxiety, contributing to their experience of pain.

Bolus dose

The bolus dose is the quantity of analgesia the patient receives after a successful self-administration demand. It is assumed that patients will demand doses of analgesia until pain has been relieved, but the size of the bolus dose influences the patient's perception of how effective the treatment has been. If the dose is too small, the patient fails to achieve adequate analgesia. If the dose is too large, the plasma concentration gradually increases with repeated doses until it reaches a level that may cause excessive sedation and possibly respiratory depression and other opioid-related side-effects such as nausea and vomiting.

The efficacy of PCA is dependent on the skill and expertise of the prescriber. The optimal bolus dose is that which provides consistent, satisfactory analgesia without producing excessive or dangerous side-effects. This has been quoted as morphine, 1 mg, and pethidine, 10 mg, in healthy adults. In elderly or frail patients, a smaller dose is often required.

Lockout interval

The lockout interval is the time during which the machine will not administer a further dose despite further demands from the patient. The ideal interval is related to the size of the bolus dose, and it should reflect the length of time necessary for the patient to appreciate the effects of the bolus dose. The lockout interval is also determined by the pharmacokinetics of the drug and the pharmacodynamics of that drug in the patient; in particular, the length of time for the drug to reach peak plasma concentrations after intravenous bolus injection. In general, a larger bolus dose requires a longer lockout interval. If the patient has impaired drug clearance (e.g. elderly patients) a longer lockout interval is required. For morphine, peak concentration after intravenous bolus is achieved after about 4 minutes. It would be inappropriate to set a lockout time shorter than the time to achieve peak plasma concentration. Subcutaneous or epidural PCA require a longer lockout interval because the time to peak effect is longer.

The 1 mg bolus dose of morphine is best combined with a 5-minute lockout interval unless the patient is elderly or frail. The initial combination of bolus dose and lockout interval should be reassessed continually and altered if necessary for each individual patient.

Background infusion

The basis of PCA means that the patient experiences pain before demanding relief. If a drug with a short half-life is used, analgesia is rapidly achieved but the patient is required to make frequent demands for analgesia. If the patient falls asleep, they may wake up in pain, which then requires several demands, depending on the length of the lockout interval, to attain analgesia. Pharmacokinetically it might be felt that a background infusion would improve analgesia, particularly at night, by reducing the frequency of demands required to maintain the plasma concentration at the desired level. In practice, this has not been found to be the case because it neither improves the effectiveness of analgesia by PCA nor reduces the number of demands but does result in higher opioid consumption. However, a background infusion may be useful to replace the maintenance requirements in patients in whom acute pain is superimposed on existing chronic pain that necessitates the use of opioid analgesia.

The addition of a background infusion removes patient control and they will receive analgesia even if they do not need it. This reduces the inherent safety of PCA by decreasing the negative feedback element and some studies have shown that respiratory depression can occur when a background infusion is used. It is essential that patients are carefully monitored and it may be appropriate for the patient to be nursed in a high dependency or intensive care setting where the nurse to patient ratio is high. There is also the potential to programme a 4- or 24-hour dose limit, which allows only a predetermined total amount of drug to be administered within a given time. This is particularly pertinent when pethidine is used, because with repeated or high doses there is an accumulation of its active metabolite (norpethidine) which acts as a CNS stimulant. While a dose limit improves the safety of PCA when used with a background infusion, it may cause ineffective relief from pain for those patients who require large doses of analgesia.

Expectations of effect

PCA is not the panacea for all pain, but it can be beneficial in the management of acute pain. To maximize the potential of PCA, it is necessary to select patients appropriately. This technique can safely achieve no or mild pain at rest, and mild-to-moderate pain on movement for patients following straightforward intermediate or major surgery, or acute episodic pain where the anticipated pain is likely to require parenteral opioids for 24–48 hours. For patients who have had complex major surgery where the anticipated pain is likely to be severe and prolonged, it is more appropriate to select a method such as epidural infusion, provided it is not contraindicated.

The beneficial effects of PCA can be enhanced by concurrently administering additional analgesics such as a non-steroidal anti-inflammatory drug (NSAID) and/or paracetamol. These combinations can produce an additive or synergistic effect because the drugs act by different mechanisms to achieve pain relief. The opioids act on specific opioid receptors in the CNS, while NSAIDs act mainly in the periphery to inhibit the initiation of pain. Combined drug regimens may also decrease the amount of each drug required to relieve pain and thus reduce the potential for drug-related side-effects. Some acute pain services have a policy to ensure that NSAIDs and/or paracetamol are prescribed for regular administration to accompany PCA provided there are no patient contraindications. This may also avoid the troughs in analgesia that occur during the night when the patient is asleep and cannot use PCA.

Complications of PCA

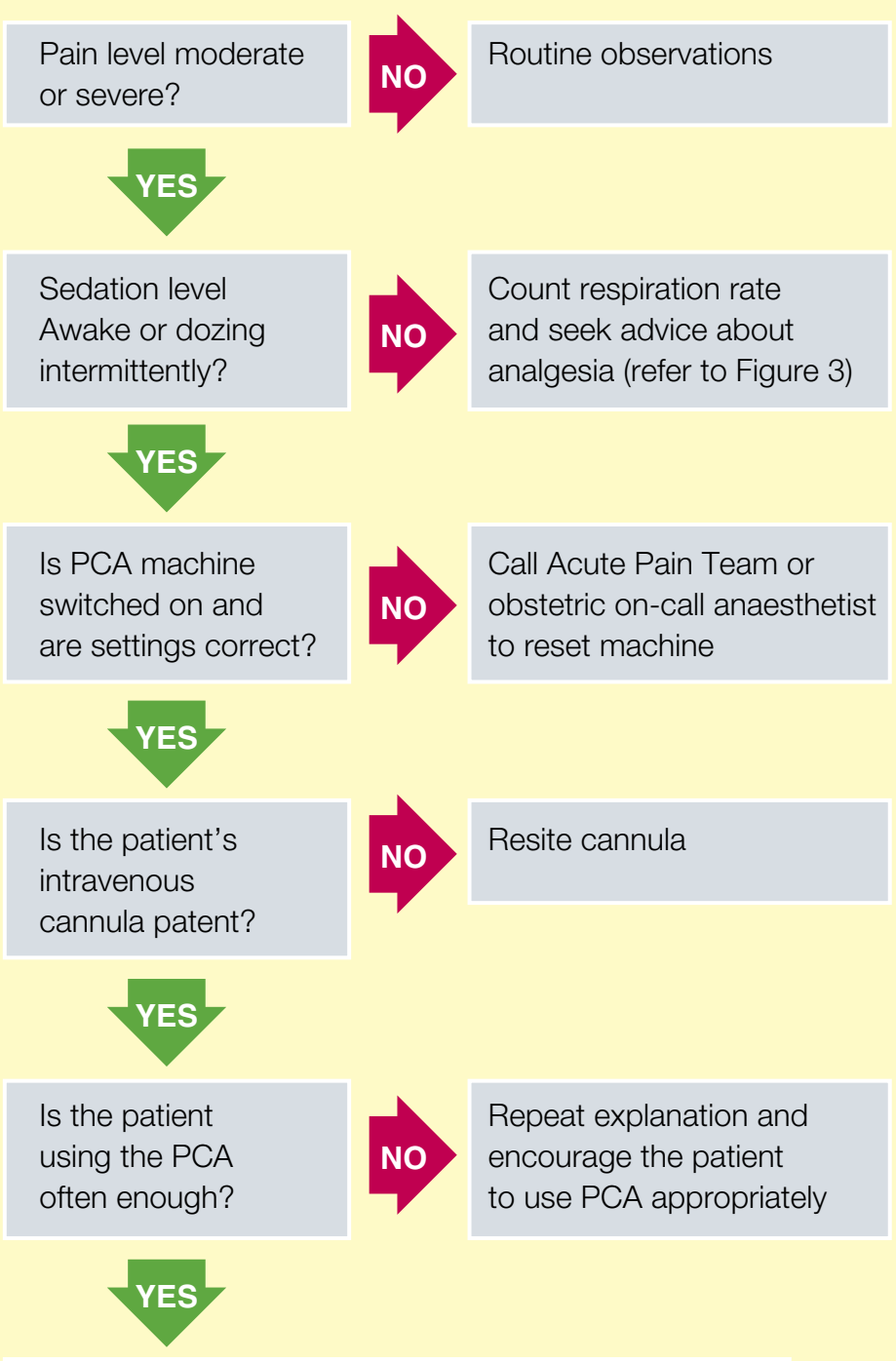
Figure 2 describes the procedure to follow if analgesia with PCA is inadequate.

Drug-related side-effects

Problems with PCA are related mainly to the drug used. The incidence of problems is comparable with other methods of parenteral opioid administration. Opioids are associated with a high incidence of nausea (up to 80%). This is probably because prophylactic anti-emetics tend not to be given routinely to patients receiving analgesia via PCA.

The respiratory depression associated with PCA is dose dependent, as with any other opioid administration. Increasing levels of sedation can alert the practitioner to impending respiratory depression. However, respiratory depression can occasionally occur in unsedated patients, therefore monitoring of all vital signs is essential to detect deleterious changes. The principle of patient control of bolus dose combined with the lockout period may protect against this complication to some extent. Other side-effects include pruritus, paralytic ileus and constipation. Figure 3 provides guidelines for medical and nursing staff to address common drug-related side-effects associated with PCA.

Procedure if analgesia with PCA is inadequate



Source: Acute Pain Service. University Hospital of Wales, Heath Park, Cardiff

2

Drug-related side-effects of PCA

Respiratory depression or excessive sedation

- If the respiratory rate drops to 10 remove PCA button from the patient, give oxygen 4 litres/minute by mask and reassess regularly
- If the SaO_2 is being recorded and falls below 94%, give oxygen at 4 litres/minute, if there is no improvement after 5 minutes seek advice from the Acute Pain Service or obstetric on-call anaesthetist
- If the respiratory rate drops below 8 and the sedation score is 2 (mostly sleeping) or 3 (difficult to waken), give oxygen at 4 litres/minute. Give naloxone, 50 μg (1 ml ampoule of naloxone contains 400 μg, dilute with normal saline to 4 ml and give in 0.5 ml (50 μg) increments until the respiratory rate increases to 12 and the patient is awake or dozing intermittently) and seek advice from the Acute Pain Service or obstetric on-call anaesthetist

Itching

Occasionally opioid drugs cause itching, particularly of the face – if this distresses the patient, treat as follows

- Change the opioid drug from morphine to pethidine or vice versa
- Naloxone, 50 μg, used with caution will reverse this side-effect without reversing analgesia – this should be reserved for very resistant, distressing pruritus
- Antihistamines: chlorphenamine (chlorpheniramine, Piriton), 4 mg, 4 hourly p.r.n. orally (max 24 mg in 24 hours), or if the patient cannot absorb tablets, 10–20 mg i.m. (max 40 mg in 24 hours)

Nausea or vomiting

- Do not stop or discourage use of PCA – pain can also cause nausea
- Give regular anti-emetic medication (see below), do not wait until the patient vomits
- If anti-emetic treatment fails, changing from morphine to pethidine or vice versa may reduce or eliminate nausea
- Give regular diclofenac plus regular paracetamol if not contraindicated. This may have an opioid sparing effect.

Anti-emetic treatment:
First choice: cyclizine, 50 mg i.v. 8 hourly p.r.n.
Second choice: prochlorperazine, 12.5 mg i.m. 6 hourly p.r.n.
Third choice: ondansetron, 8 mg i.v., one dose per 24 hours

Hallucinations may occur with morphine or pethidine – if the patient is distressed seek advice from the Acute Pain Service

Source: Acute Pain Service. University Hospital of Wales, Heath Park, Cardiff.

3

Mechanical problems

Mechanical problems such as 'syphoning', can be resolved by using anti-syphon valves. Syphoning occurs when all the contents of the syringe empty into the patient via the giving set, it is usually associated with damaged or cracked syringes and may result in overdose. Reverse flow of PCA solution into another intravenous infusion connected to the same cannula has also been reported and can lead to the patient receiving a bolus of opioid from the infusion fluid rather than from the PCA. One-way valves in the intravenous giving set can prevent this. Some pumps are susceptible to a build-up of static electricity that can reprogramme the system, and this has been reported as producing a non-fatal overdose.

User-related problems

Staff-related: misprogramming can be prevented by scrupulous protocols and ensuring the programming is checked by two nurses or doctors. Machine design could be improved to make available default settings, which could be pre-programmed; there would then be no need to programme the machine with each use, but merely to check it. Pre-filled syringes may also assist in avoiding errors in drug concentration, however, these need to be checked carefully. These changes may improve safety, but they do not allow for patients who require more individualized dosing regimens.

Patient-related: there are many reasons why patients do not use PCA to its full potential:

- they may not have been taught how to use it properly
- they have not retained the information on how to use it
- they may be confused postoperatively
- they are afraid of the side-effects associated with the drugs
- they fear addiction to the opioid drugs.

Problems can also occur if other patients, relatives or healthcare staff press the button, resulting in the administration of a dose of opioid. Also, the patient may press the PCA button thinking that it is the nurse call bell, resulting in an inadvertent opioid dose.

Requirements for PCA use

Patient education

For patients to use PCA to its maximum potential, they should be instructed in its use before surgery. It is advisable that they are given written information to support any verbal instruction. The type of information the patient may require includes:

- how to administer the analgesia
- when and how often to administer the analgesia
- what happens if the syringe runs out
- what to do if the analgesia does not work
- what the main side-effects are and how they are managed
- how safe PCA is and the risks associated with its use
- expectation of the pain after surgery and the effect that PCA should have.

Staff education

The setting up and programming of the PCA device is the responsibility of the anaesthetist or member of the Acute Pain Service initiating the treatment. However, the staff caring for the patient need to have written guidelines and protocols to standardize care and ensure safe practice. Staff will need to be educated regarding the following aspects:

- patient education
- standardized PCA regimens
- drug side-effects and their management
- changing syringes
- managing safety regarding the drugs and the PCA device
- monitoring of patients
- when to discontinue PCA.

Monitoring requirements

In the recovery area, staff will be required to assess the patient and titrate analgesia according to the patient's report of pain. PCA can be commenced once the patient is awake and able to use it. Hospitals have differing policies, but the following is recommended as safe practice. For the initial 2-hour period, pulse, blood pressure, respiratory rate, pain on movement and sedation levels should be assessed and recorded every half hour, then every 2 hours for 48 hours and 4-hourly thereafter if previous observations have been satisfactory. If observations are not satisfactory, the frequency of monitoring pain and vital signs will need to increase depending on the patient's condition. Patients who have had upper abdominal surgery or who have known pulmonary disease or who are receiving PCA with a background or concurrent infusion should have their oxygen saturation level monitored as well. If during the night, the patient is asleep and observations have been satisfactory it is acceptable to record the pulse and respiratory rate only. A recording should be entered on the sedation score chart to indicate that the patient was asleep at the time the observation was made. The amount of drug used should be recorded hourly on an appropriate chart and the infusion site checked for pain, swelling and leakage of fluid. A policy needs to be in place to advise ward staff who to contact should there be PCA-related problems.

When to stop PCA

The time for which patients require PCA following surgery is variable. On average, most patients require PCA for about 48 hours following surgery, but this differs between patients and the type of surgery. The following points should be considered before stopping PCA.

- If the patient has not reported any episodes of severe pain on movement in the previous 12 hours and the overall level of pain has reduced, the pain could be managed with weak opioid oral analgesics and/or NSAIDs if appropriate.
- If the patient is not using the device effectively, consider removing it and providing an alternative form of analgesia.
- When the patient is able to drink free fluids and has not experienced nausea and vomiting since commencing free fluids, oral analgesia can be commenced.
- If the patient is able to mobilize without being hindered by pain, PCA can be stopped.
- The amount of drug used in the previous 12 hours should be considered. The previous 12-hour PCA opioid dose must equate with or be less than the proposed maximum dose of oral analgesic substitute.
- If the patient does not want to use the PCA device to its maximum potential to effect pain relief, consider removing it and providing an alternative form of analgesia. However, discuss the patient's reasons and address any issues in order to improve compliance if possible. The patient may also be reluctant to have the PCA discontinued because they may fear the lack of control over their analgesia and the resultant increase in pain. This requires careful thought and discussion with the patient about assessment and management of their pain including the provision of appropriate alternative analgesia.

For patients using PCA to manage acute episodic pain, a careful assessment of their pain and condition should be made before stopping PCA and the following points should be considered:

- level of pain
- amount of drug used in the previous 12 hours
- patient's wishes.

Most patients require a less potent alternative form of analgesia once the PCA device has been discontinued. An initial alternative dose should be given and its effect monitored before PCA is discontinued.

FURTHER READING

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Pharmacological Treatment of Chronic Pain

Mick Serpell

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Pain mechanisms involve numerous pathways, transmitters and receptors at numerous levels (peripheral, spinal and supra-spinal). Therefore there will never be a single 'magic bullet' antinociceptive agent, but a mixture of agents working together will be required to provide optimal analgesia.

Assessment of chronic pain
It is important to identify and manage any treatable aetiology of pain in the early stages because this will reduce the chances of it developing into a chronic problem. However, by the time most patients present at a pain clinic, they have been fully investigated and the cause is either identified and untreatable, unknown or of 'trivial' significance. This reaffirms that chronic pain is not just a symptom but an illness, with a major component occurring at the microbiological level. Our diagnostic tools are inadequate to detect these abnormalities and therefore clinicians and patients are often left without a satisfactory diagnosis.

The full assessment of a patient with pain requires evaluation of the biomedical and other components. The predominant issues should be identified and managed concurrently. The disability of pain is equal to the sum of the patient's physical, emotional, environmental, social and employment problems.

Pain is classified into nociceptive, neuropathic and psychogenic types, which can be acute or chronic (Figure 1).

Characteristics of clinical pain

Nociceptive (pain due to tissue damage)
Somatic
- Site – well localized, cutaneous or deep
- Radiation – dermatomal
- Character – sharp, aching, throbbing, gnawing
- Periodicity – often constant, also incident pain
- Associations – seldom

Visceral (sympathetically innervated organs)
- Site – vague distribution
- Radiation – diffuse, can be transferred to body surface
- Character – dull, vague (cramping, squeezing, dragging)
- Periodicity – often periodic, building up to peaks
- Associations – nausea, vomiting, sweaty, blood pressure and heart rate changes

Neuropathic (pain due to injury of nerve pathway)
Site of injury
- Central – central pain (thalamic infarct)
- Mixed – plexus avulsion, post-herpetic neuralgia
- Peripheral – neuroma,nerve compression, phantom, neuralgias, painful polyneuropathy, reflex sympathetic dystrophy, causalgia

Character
- Burning, tingling, pricking, numb, cold, pressing, squeezing, itching
- Constant often with intermittent shooting, lancinating, electric shock

Psychogenic (difficult to differentiate whether secondary to or actual cause of pain)
- Anxiety, depression (30% of depressives complain of pain on initial presentation)

1

Treatment
Goals: the main goals in the management of chronic pain are to reduce the pain as much as possible, to improve maximal function and where there is remaining pain, to improve the patient's ability to cope. In the early stages, the first objective is achievable to almost complete analgesia but when patients are in the intractable phase, the latter two goals are often the only ones possible.

Principles: the general principle of treatment comprises modulation of the pain pathways; destructive procedures are seldom performed. The treatment strategies are based on managing the nociceptive and neuropathic constituents of the condition. Chronic pain is often a combination of the two constituents, though often one plays the predominant role.

A logical and ordered approach is required, which must be initiated as rapidly as possible to avoid prolonging the patients' suffering. There is evidence that rapid control of pain symptoms can reduce the development of chronic pain. Pain symptoms are managed using pharmacological techniques, regional analgesia, physical therapy and psychological therapies. There is no strong evidence that one form of therapy is more effective than another. The exact order of implementation of therapies depends on local availability, side-effect profile and the patient's preference (most patients prefer to avoid medication). Optimal pharmacological treatment for chronic pain is that the medication should be taken 'round the clock' as opposed to 'as required'. It is easier to reduce severe pain by preventive measures rather than trying to manage it once it has become established.

This article deals only with pharmacological treatments and regional analgesia but the reader should be aware of the importance of physical and psychological modes of management.

Nociceptive pain

Nociceptive pain is the most common form of chronic pain. Low back pain and degenerative or inflammatory joint pains account for most of the referrals at pain clinics. There are also a large number of chronic visceral and postoperative pains. Although pain, such as that from rheumatoid arthritis, may begin as purely nociceptive, over time there is a neurological reaction which suggests that all pains eventually become neuropathic to a degree. Therefore, it makes sense to consider the use of neuropathic-type analgesics if pain control is still suboptimal. Pharmacological treatment of nociceptive pain can be classified into systemic and local modulation.

Systemic modulation
The World Health Organization (WHO) 3 step analgesic ladder was developed in the early 1980s as a tool to manage cancer pain. Analgesics, including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), codeine and the stronger opioid drugs (with or without adjuvants) have proved successful in controlling pain in over 80% of cancer patients. However, in non-cancer pain, step 3 is seldom used to its full potential because of the reluctance of these patients to use strong opioids.

Step 1: all non-opioid analgesics are derived from three types of compounds:
- aniline derivatives (e.g. paracetamol)
- aspirin and other acidic NSAIDs
- non-acidic pyrazole drugs (e.g. phenylbutazone, dipyrone).

Paracetamol is tolerated well by most patients and when taken regularly, seems to be as effective as the NSAIDs in managing the pain of rheumatoid arthritis. There is little effect on the liver when taken at normal recommended doses (maximum dose 4 g/day). It is indicated for mild-to-moderate pain, but reduces the requirements for more potent analgesics in severe acute pain. Although this has not been tested for chronic pain it should have the same effect and be worth adding to any regimen.

Over two dozen different NSAIDs are listed in the *British National Formulary.* Although they are a heterogeneous group of drugs with several types of chemical structure and subtle differences in bioproperties, they all inhibit the cyclo-oxygenase (COX)-mediated production of prostanoids (Figure 2). This mechanism is responsible for most of the analgesic effect and the side-effects (Figure 3). These drugs are useful for musculoskeletal pain and incident (movement-related) pain. There is no definitive algorithm of which drug to prescribe first but it is logical to try in sequence two or three different NSAIDs from different groups. Patients can obtain benefits or side-effects from one drug and not from another. It is appropriate to start with the drug that has the fewest side-effects, and then move to others. Consequently, most patients try ibuprofen first, followed by voltarol or mefenamic acid.

Classification of non-steroidal anti-inflammatory drugs

Group	Drug
Enolic acids	
• Oxicams	Piroxicam
• Pyrazoles	Phenylbutazone
Carboxylic acids	
• Salicylates	Aspirin Salsalate Diflunisal Benorilate (benorylate)
• Proprionic acids	Ibuprofen Naproxen Ketoprofen Fenbufen Fenoprofen Flurbiprofen Tiaprofenic acid
• Acetic acids	Indometacin (indomethacin) Diclofenac Ketorolac Sulindac
• Fenamates	Mefenamic acid Flufenamic acid

2

Side-effects of non-steroidal anti-inflammatory drugs

Gastrointestinal
- Nausea
- Dyspepsia
- Diarrhoea
- Peptic ulceration
- Perforation
- Bleeding

Renal
- Fluid retention
- Renal failure
- Papillary necrosis
- Interstitial fibrosis

Respiratory
- Bronchoconstriction
- Pulmonary eosinophilia
- Alveolitis

Coagulation
- Reduced platelet aggregation
- Increased bleeding time

Skin
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Angioedema

Visceral
- Congestive heart failure
- Hepatitis
- Pancreatitis
- Aseptic meningitis

3

With long-term use of NSAIDs the side-effect profile increases. Annually, 65,000 patients are admitted to UK hospitals for upper gastrointestinal perforation or haemorrhage; 20% (13,000) of these problems are directly caused by NSAIDs and 20% (2,500) of these patients will die. This problem has led to the development of a new generation of NSAIDs that reduce the incidence of side-effects – COX-2 inhibitors and dextro-isomers. COX-2 inhibitors (e.g. celecoxib, refecoxib) predominantly block the action of the COX-2 isoenzyme, therefore providing analgesia while permitting COX-1 to produce the beneficial prostanoids and so reduce side-effects. Dexketoprofen is the
S(+)-enantiomer of ketoprofen and is more potent, has a faster onset of action and fewer side-effects than the racemic mixture or the laevo form. Early evidence demonstrates that the COX-2 inhibitors are safer, but are not completely without NSAID-type side-effects. Similar evidence is emerging for dexketoprofen.

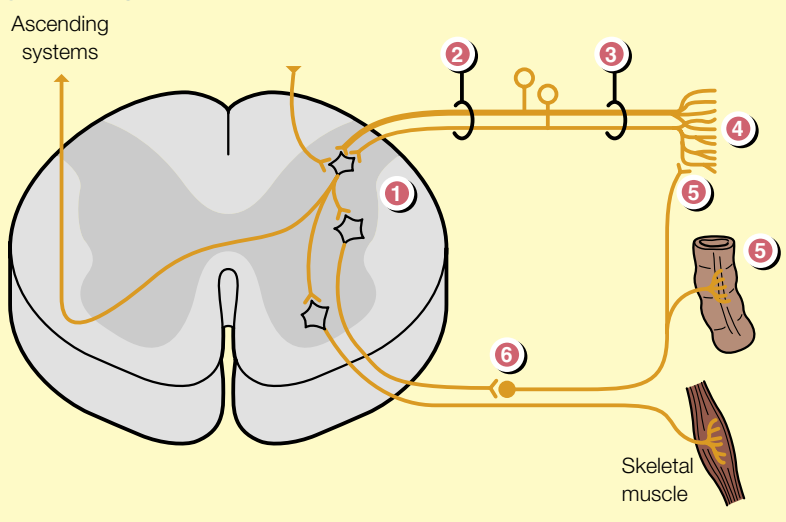
Aspirin is seldom used as an analgesic because it has a higher incidence of the side-effects listed in Figure 3. It causes irreversible inhibition of COX and therefore its effects do not subside with a reduction in plasma level but have to await production from new cellular growth, which may take several days. Phenylbutazone, the only pyrazole available in the UK, is restricted for resistant ankylosing spondylitis because of the incidence of aplastic anaemia and agranulocytosis.

Step 2: the less potent opioids (e.g. codeine, dihydrocodeine, dextropropoxyphene) are commonly used but inappropriately prescribed. Often, these drugs are not taken regularly and are usually combined with paracetamol. This limits the daily dose of opioid that can be taken because the patient is restricted to about eight tablets per day (maximum 4 g/day of paracetamol). The use of compound analgesics makes consumption simpler for the patient, but limits optimal opioid titration and is often more expensive. If the decision to use an opioid is made, then it should be titrated to an appropriately potent level to assess response. This philosophy and other aspects of step 3 of the WHO ladder are discussed elsewhere. The issue of adjuvant drugs is discussed below.

Local modulation
Local modulation uses the local application of treatments. These may be physical, such as transcutaneous electrical nerve stimulation (TENS) or acupuncture. They both have few side-effects and should be tried early. Alternatively, treatment may be pharmacological in the form of regional application of drugs.

Injection of drugs into tissue (e.g. into a myofascial 'trigger spot') or a nerve has the advantage of requiring only a small dose with a consequent low risk of side-effects. Regional analgesia can be applied to any nerve, from superficial peripheral nerves to more complex and deeper nerves that require X-ray facilities (Figure 4). They can be grouped into somatic (peripheral or cranial), sympathetic and central nerve blocks (epidural and spinal). The indications for performing a nerve block are that it can aid in the diagnosis, it sometimes gives a prognostic indicator as to how easy the pain will be to treat, it can be therapeutic and educational (to experience motor/sensory loss if a neurolytic procedure is contemplated). Nerves are injected at a peripheral site first, but if this is unsuccessful injection can be performed at progressively more central sites. While not a long-term cure, these blocks often have a beneficial response outlasting the pharmacological action of the local anaesthetic. They can provide benefit for days to weeks and can be useful in conjunction with other therapies.

Types of regional blockade performed for pain relief



1 **Pharmacological inhibition**
Using spinal or epidural block

Afferent blockade
2 Differential blockade
3 Peripheral nerve somatic or visceral

4 **Tissue/organ injection**
Periarticular
Cutaneous
Soft tissues
Viscera
Skeletal muscle

5 **Transmitter block**
Autonomic target organs

6 **Sympathetic block**

Printed with permission from Boas R, Cousins M. Diagnostic Neural Blockade. In: Cousins M, Bridenbaugh P, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain.* 2nd ed. Philadelphia: JB Lippincott, 1988.

4

The drugs used include a mixture of pharmacological agents. Local anaesthetic drugs such as bupivacaine can be used as a dilute solution (0.1%) which often blocks the pain fibres but spares most of the sensory and motor fibres. This is called an analgesic versus an anaesthetic block. Various other drugs are often used to reduce pain fibre activity such as opioids, corticosteroids, α_2-agonists (e.g. clonidine) and N-methyl-D-aspartate (NMDA) antagonists (ketamine).

Some patients ask if they can have a neurolytic block to destroy the nerve permanently. Neurolytic blocks (using alcohol, phenol, cryotherapy or radiofrequency) do not have a permanent effect. The neural system usually regenerates and adapts after 3–6 months and the pain can return or be worse with sensory dysaesthesia and deafferentation pain and motor deficits. These procedures are usually reserved for terminally ill patients who will not survive long enough to experience these complications. However, there are some conditions for which this approach is appropriate, for example neurolytic sympathetic block for small vessel peripheral vascular disease.

Occasionally a patient has symptoms that are amenable to more invasive procedures. These include implanted drug delivery systems (epidurals and spinals) and dorsal column or intracranial stimulation. More invasive treatments should be performed only in appropriately selected patients by centres experienced in such procedures.

Neuropathic pain

Diagnosis
Neuropathic pain affects 2–4% of the population. This does not include the patients with chronic nociceptive pain, mentioned earlier, who may also have a significant component of neuropathic pain. Neuropathy activates certain excitatory and inhibitory mechanisms and it is the relative over-excitability of the neural balance that determines whether pain is produced. The primary aim of treatment is membrane stabilization of the abnormal nerves. The exact abnormality probably involves several mechanisms.

Patients often find neuropathic pain symptoms difficult to describe but some of the words commonly used include burning, tingling, numb, pressing, squeezing and itching (Figure 5). It may be present constantly or intermittent with electric shooting sensations. The signs of neuropathic damage are often subtle but are usually elicited with the aid of simple tools such as a pin, cotton wool and tuning fork. Occasionally more specialized equipment is used such as von Frey hairs, thermal thresholds for temperature and pain detection, electromyography or nerve conduction velocity studies.

Signs of neuropathic damage

Negative phenomena	Positive phenomena
Sensory	
Hypoaesthesia	Hyperaesthesia, dysaesthesia, paraesthesia
Hypoalgesia	Hyperalgesia, hyperpathia, allodynia
Autonomic	
Vasodilatation	Vasoconstriction
Hypohidrosis, anhidrosis	Hyperhidrosis
	Piloerection
Motor	
Paralysis	Fasciculations, dystonia

Modified from Table 1 in *Serra J. Acta Neurol Scand* 1999; **173**: 7–11. Printed with permission.

5

The site of injury and cause of the nerve damage vary and include several pathologies. It is important to identify any treatable aetiology of pain in order to prevent progression of the disease (i.e. good normoglycaemic control for diabetic neuropathies). However, this is not always possible and treatment of pain should commence as soon as it is experienced. Although neuropathic pain can be unrelenting and difficult to treat, several options are available.

Treatment
The conventional analgesics used for nociceptive pain are often ineffective for neuropathic pain. Most of these drugs are called 'adjuvant analgesics' because their primary indication is not for pain (i.e. antidepressants, anticonvulsants, antiarrhythmics). However, many of them are used more commonly for neuropathic pain than for their approved indication. They share a common action, are usually membrane stabilizers and can suppress the excessive neuronal activity that maintains this disease process.

Currently all neuropathic pains are treated the same regardless of cause or symptoms. In the future, diagnostic criteria may identify subpopulations of patients which respond to particular drugs based on pain mechanism characteristics and physical findings. There is no evidence to support the old dictum that burning pain is more responsive to tricyclic antidepressants and lancinating pain is more responsive to anticonvulsants. At present, the general mode of drug prescription is sequential drug trials. A patient undergoes a titration of a drug to a suitable dose and for a suitable duration until they obtain greater than 50% pain relief or experience intolerable side-effects. If there is no relief, the drug is usually omitted. If they obtain partial pain relief, a second drug is usually added to the regimen. If a patient obtains benefit they can continue the medication indefinitely, though they should be encouraged to wean off gradually every 6 months or so to ensure they still require the medication.

Antidepressants: the tricyclic antidepressants are the 'gold standard' of treatment because they are the most effective and best known. The tertiary amines have more side-effects than the secondary amines; the latter can be used as an alternative if side-effects are a problem (Figure 6). They inhibit the reuptake of the neural transmitters noradrenaline and serotonin and thus potentiate the dorsal inhibitory pathway that terminates in the dorsal horn of the spinal cord.

Side-effects of antidepressants

Secondary amines
- Predominantly blocks noradrenaline reuptake (i.e. nortriptyline, desipramine)
- Less sedation than tertiary amines
- Fewer anticholinergic effects than tertiary amines
- Weight gain
- Nortriptyline is less hypotensive than the tertiary amines

Tertiary amines
- Block noradrenaline and 5-HT reuptake (i.e. amitriptyline, imipramine, dothiepin)
- Antihistamine effect – sedation
- Anticholinergic effects (dry mouth, constipation, urinary retention)
- Weight gain
- Cardiac arrhythmias – tachycardia, hypotension

Selective serotonin reuptake inhibitors
(i.e. fluoxetine, sertraline, citalopram)
No evidence that they are better than placebo

Third-generation antidepressants
(i.e. venlafaxine inhibits noradrenaline and 5-HT reuptake)
Results in less sedation and fewer anticholinergic effects
In theory, should work but only weak evidence at present

6

Amitriptyline is started at 10 or 25 mg at night and gradually increased in 10 or 25 mg increments every few days to 50–100 mg at night. Analgesic benefit may occur after 2 weeks but often requires 8 weeks. Compliance is poor because patients often experience side-effects early on without any benefit and so discontinue the medication. Also, if they have not had an adequate explanation of the rationale for an antidepressant to be used, they may think that the doctor believes their pain to be psychological in origin and may feel that they have not been taken seriously. They must be told to persevere if possible and that they will become tolerant to most of the side-effects after a few days to weeks. One in three patients will get more than 50% pain relief, an excellent result for a chronic pain condition. If amitriptyline is too problematical then a less sedating alternative such as imipramine, nortriptyline or venlafaxime is worth trying. Not all antidepressants relieve pain; the serotonin selective reuptake inhibitors (SSRIs) are not regarded as useful and are seldom used.

Anticonvulsants have been used successfully for neuropathic pain. The older drugs such as carbamazepine and phenytoin are as effective as amitriptyline. However, they produce more central side-effects such as sedation, and induce liver enzymes, which can affect the metabolism of other drugs. This is particularly important in the elderly because they often have neuropathic pain and are taking several drugs.

Carbamazepine can cause allergy, and liver and bone marrow suppression. Again, the secret is to titrate low and slow, from 100 mg t.i.d. up to 300 mg t.i.d. over a few weeks. Before taking an anticonvulsant the patient's baseline haematology and biochemistry profile should be determined.

Gabapentin is the only anticonvulsant with a licence specifically for neuropathic pain. It is increasingly being used as first-line therapy because it appears to be as effective as the other anticonvulsants and with fewer side-effects. Other drugs worth trying are lamotrigine, clonazepam, valproate and more recently topiramate.

Antiarrhythmics: lidocaine (lignocaine), 5 mg/kg, can be given intravenously as an infusion over 1 hour with cardiovascular monitoring to assess the responsiveness of the patient's pain. If it results in an improvement for several weeks or months, it can be repeated as required. If it brings improvement for a few hours or days only, give the patient oral mexilitine to maintain the effect (oral lidocaine (lignocaine) is unsuitable because it undergoes extensive first-pass metabolism). Patients must have a baseline electrocardiogram to ensure they have no underlying contraindication to mexilitine. The dose is gradually increased from 100 mg t.i.d. towards 300 mg t.i.d. but most patients experience nausea at high doses.

Topical drugs have fewer side-effects because they are not taken systemically. Pain in a small and accessible cutaneous area is suitable for topical treatment.

Capsaicin is a nerve toxin that inactivates the small pain C fibres. It needs to be applied 3–4 times daily for up to 8 weeks before it can be appraised. Capsaicin comes in two strengths, 0.075% for neuropathic pain and 0.025% for arthritic pain. The former can cause an uncomfortable burning sensation, but this often recedes after 1 week or so. However, if it is a problem, it can be mixed with lidocaine (lignocaine) gel or glyceryl trinitrate ointment or titrated up gradually from the 0.025% strength.

Topical imipramine is licensed for itch but seems promising for neuropathic pain. Lidoderm patches (containing lidocaine (lignocaine)) and topical clonidine are available only in the USA. Few neuropathic pains have a sympathetic component and therefore clonidine has only a limited role. The lidoderm patch is often used as first-line treatment in the USA.

Opioids: it used to be said that neuropathic pain was resistant to opioids, but this is not always the case. They can help one of eight patients and are always worth a trial as a last resort. Morphine is the standard drug but it may be more appropriate to try other opioids if inefficacy or side-effects occur. The reason neuropathic pain is relatively resistant to opioids is that there is an increase of cholecystokinin (CCK) in the spinal cord which acts as an opioid antagonist. One way to address this problem is with CCK antagonists such as cholycade or devacade, and clinical trials are under way.

Tramadol has a dual mode of action, it is a moderately strong opioid (equipotent to pethidine) with two-thirds of its activity caused by a mechanism similar to amitriptyline. It is a multi-modal drug in keeping with the underlying principle of current pain management strategies.

Other drugs: ketamine can be useful given alone, or to potentiate the effects of an opioid. It can be given as an intravenous or subcutaneous infusion in a dose of 0.1–0.5 mg/kg/hour. It can also be taken orally and titrated from 20 mg b.d. to 50 mg q.i.d. if required. The oral dose is impossible to predict from the parenteral dose owing to the highly variable oral bioavailability.

There is evidence that oral tizanidine, 4–16 mg/day, is beneficial; it is an α_2-agonist like clonidine.

Pain management programme
When all medical management has failed it may be time to consider a pain management programme. It should be considered earlier on if the patient is coping poorly. It is a programme that uses primarily psychological and physiotherapy techniques to help patients improve their ability to cope and function. The aim is to empower the patient to adapt and achieve as optimal a quality of life as possible. ◆

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Principles of Ethics in Pain Research

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Ethics are the rules and principles that govern proper conduct and as such may vary with time and place. Modern research ethics owe their origins to the atrocities conducted, in the name of scientific experimentation, in the concentration camps during World War II. The Nuremberg code of 1947 and more recently the World Medical Association Declaration of Helsinki (1964, revised 1975, 1983, 1989, 1996 and 2000) provide a framework of principles that guide biomedical research today.

A major theme is the conflict of interest that may develop between the rights of individual research subjects and the benefits of that research to present and future members of society. The Helsinki Declaration stipulates that 'considerations relating to the well-being of the human subject should take precedence over the interests of science and society' and that the doctor should 'obtain the subject's freely given informed consent'.

Pain research is governed by the same ethical principles that apply to all biomedical research. Patients with chronic pain may represent a vulnerable group that characteristically expresses a willingness to try new therapies, at the risk of side-effects, in order to achieve some benefit. Their relationship with the specialists caring for them may make them susceptible to pressure (not always intended) to participate in research studies and a placebo effect is well recognized. Research with the aim of expanding the scientific understanding of pain mechanisms requires careful ethical consideration if human subjects are involved. Central to the ethics of research is the free, autonomous choice to participate by the research subject. This is achieved by obtaining 'fully informed consent', guided by the principles in Figure 1.

Principles for informed consent in research

Competence
Research should be carried out only on legally competent persons unless the physical or mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. In such instances consent may be given, subject to certain restrictions beyond the remit of this article, by others with legal authority over the research subject, as for example parents on behalf of their child

Disclosure of information
The Helsinki Declaration requires that every subject must be 'adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail'

Understanding
The information should be presented in a form and language that the research subject understands

Voluntary
Research subjects should be helped to feel comfortable about saying "No" if they feel this is the right choice for them. It may be necessary to have a named other person, who is not directly involved in the study, available to discuss any issues the research subject may wish to raise

Authorization
Having fulfilled the criteria listed above the research subject should sign the consent form and be allowed to keep a copy of the information sheet

Therapeutic, non-therapeutic research and innovative treatment

Although no longer distinguished in the revised Declaration of Helsinki, it can be useful to differentiate between therapeutic and non-therapeutic research. In therapeutic research the subject may derive therapeutic benefit from the trial. In non-therapeutic research the only intention is to extend knowledge of a particular condition and it will be of no benefit to the research subject. Phase 1 drug studies, which study the toxicity of drug schedules, are examples of non-therapeutic research. Both types of research require thorough ethical examination by Local (LRECs) or Multicentre Research Ethics Committees (MRECs).

New treatments or techniques are often introduced into clinical practice without prior formal ethical scrutiny and this leads to a number of anxieties. In general, techniques that diverge substantially from normal practice, or that warrant more than minimally greater risk, or those where the intention is to acquire new knowledge that is not solely for the benefit of the patient, should be subject to ethical committee review. In all examples of innovative or non-standard therapy, ethical doctrine dictates that patients should be fully informed and consent obtained.

Randomized controlled trials

The randomized clinical trial poses a particular ethical problem for researchers. Randomization is ethical only if there is significant doubt about the best treatment for a patient volunteering as a research subject. If one treatment is perceived by the doctor to be advantageous, or otherwise inappropriate, for an individual patient, then randomization would be unethical and should not proceed. This is known as 'therapeutic equipoise'. The clinician should be indifferent to the choice of treatment because there is no body of evidence to dictate which treatment may be better. The new proposed treatment may be better, equal or worse than the established treatment. The 'double blind' technique also aids in achieving therapeutic equipoise.

There is an argument that because subjects may exclude themselves from randomized trials, the final pre-selected group is not representative of the total population, invalidating any extrapolation of results. The effect of informed consent in reducing participation may be greater when one limb of a study is a placebo group because participants may consider (correctly) that they have a 50% chance of receiving an ineffective therapy (placebo) while there is a chance that the intervention under test is effective. This may be of greater importance in pain research.

The circumstances in which it is ethical to deprive a patient of treatment need to be strictly regulated. An extreme view is that placebos should be allowed only when there is no agreed alternative treatment of greater therapeutic value than placebo. This viewpoint is becoming more widely accepted.

Problems may also develop after the study if patients wish to continue a treatment that has proved beneficial but is not yet licensed for general use.

Despite this and other concerns, randomized clinical trials remain the accepted gold standard in clinical research. Although participation in trials may appear to constitute a potentially hazardous step for the individual patient, those who participate in trials do better, even when receiving placebo or a less effective treatment, than patients not involved in the research study. This probably reflects the greater degree of monitoring, compliance to protocol and generally higher quality of care in research projects.

It is imperative that patients are asked to take part only in well-designed, scientifically sound research projects. Poorly designed research is unethical because erroneous scientific data cannot contribute to new knowledge and calculation of risk versus benefit for a particular treatment is impossible. There is also an ethical duty to publish and make available results (negative or positive) of well-conducted scientifically validated trials.

Law and medical research

In many countries, human research is conducted within a legislative framework of principles. In Britain, research, apart from that on embryos, is not governed by legislation. There is no legal requirement for research ethics committees to be established in all health districts, though it is Department of Health policy that all research carried out in the National Health Service is subject to their scrutiny. At present, a combination of general medical law (laws of consent and confidentiality), general legal provisions and a pattern of established good practice exists.

British courts have not considered how much information a research subject should be given. However, the Canadian case of *Halushka* is indicative of the approach British courts might take.

This case concerned the trial of a new anaesthetic agent in which the subject suffered a cardiac arrest when a catheter was advanced into his heart. The basis for the lawsuit was insufficient disclosure of information to enable valid consent to be obtained. The judge stated that 'there could be no exceptions to the ordinary requirements of disclosure in the case of research as there may well be in ordinary practice'.

It would thus seem that the rights of the research subject are greater than the rights of a patient receiving normal routine therapy. The standard of information offered to research subjects requires 'full and frank' disclosure of the risks involved. This standard appears to be even greater for 'non-therapeutic research'. Thus, if research is designed to test a hypothesis and thus contribute to general knowledge, the law is more likely to set limits on the risk of harm that an individual may agree to.

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Psychological Techniques in the Management of Pain

Herma F Caris

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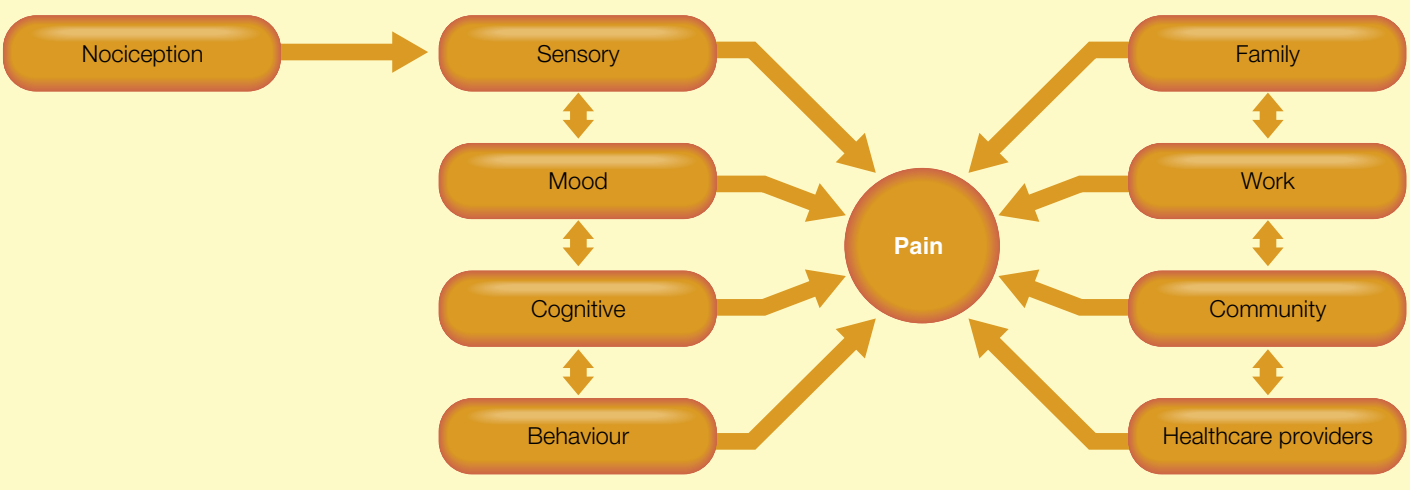
Everyone has experienced pain to some degree, but attempts to define it accurately have often been unsatisfactory. In the 1980s, the International Association for the Study of Pain defined pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage', and this definition is widely accepted. It stresses that pain can occur in the absence of a physical cause, and it emphasizes the psychological contribution to pain.

If the premise is that pain is a complex subjective phenomenon that is uniquely experienced by each individual, then psycho-logical issues such as knowledge about idiosyncratic beliefs, appraisal and coping repertoires are essential for optimal treatment planning and delivery and for evaluating treatment effectiveness.

Until the early 20th century, concepts such as the mind and the soul were thought to have no bearing on physical function and behaviour. At that time, influential writings began to appear that emphasized the importance of adopting a more integrated, holistic approach to health and illness. This culminated in the development of the gate control theory and the biopsychosocial model, which is widely applied to the study and treatment of pain.

Biopsychosocial model
The biopsychosocial model focuses on illness rather than disease. Illness is seen as a result of a complex interaction of biological, psychological and social variables. The main tenet of this model is that there is a continuing, dynamic and reciprocal interplay between these variables, which shapes the patient's perceptions and response to disease and pain. From this perspective, the diversity in illness expression is accounted for by the complex interrelationships among those variables (Figure 1).

Multidimensional model of pain



1

In the biopsychosocial model, the role of the psychologist in the treatment of pain is essential. Treatment from the biopsychosocial perspective aims to furnish patients with knowledge and techniques to improve their control over the effects of pain on their lives and to modify the sensory, affective, behavioural and cognitive facets of the pain. Ideally, pain management consists of an interdisciplinary structure (i.e. medical, physiotherapy, nursing, occupational therapy, psychology). The psychologist's initial role is to assess the patient's psychosocial functioning (current and pre-morbid), personality characteristics, motivational status, coping resources and social support. This aids interdisciplinary treatment planning. Subsequently the psychologist provides pain management treatment, when indicated, and monitors progress (Figure 2).

Role of the psychologist in an interdisciplinary pain management team

- Provides evidence-based psychological therapy to improve the patient's ability to cope with pain and the interpersonal stresses and problems arising as a result of pain
- Provides education to other team members about the psychological needs and problems of pain patients
- Assesses psychological parameters and social/ environmental factors that affect the patient's pain experience and treatment outcome
- Researches pain management
- Improves effective communication between patients and healthcare providers

2

One of the hallmarks of the biopsychosocial perspective is the concept of evolution; at different points during the evolution of the pain experience, the weighting of the biological, psychological and social variables changes. Therefore, there is a distinction between the acute phase of pain experience and the chronic state experience of pain. During the acute phase, biological factors generally predominate, but over time psychological and social factors may gradually assume a disproportionate role in accounting for symptoms and disability. Therefore the role of the psychologist is less central, yet not insignificant, in the management of acute pain than it is in chronic or persistent pain management.

Techniques for acute pain

Psychological techniques may be useful in acute pain management if standard medical techniques fail to provide the amount of pain relief desired, or if patients are intolerant of or opposed to interventional techniques.

Education
Increasing the patient's knowledge about pain and medical procedures can help to reduce the anticipation of threat or harm. Relieving anxiety often decreases reported pain. Providing education and information may act synergistically with pharmacological methods of pain relief.

Cognitive strategies
Sometimes the fears associated with pain and analgesic use are not alleviated by a simple, rational explanation of the facts. In these cases, a clinician trained in addressing the multidimensional aspects of pain (i.e. sensory, affective, cognitive, social, behavioural) will have to assist the patient. There may be some benefit in addressing some cognitive factors that can impede adequate pharmacological pain control. Maladaptive pain-specific beliefs and self-efficacy beliefs can negatively mediate pain perception and the use of coping strategies. Beliefs about the duration of pain are important. If patients can be helped to view pain in terms of discrete time duration, coping will be more adaptive and pain reduction more likely. It may also be important to address maladaptive beliefs that have sprung from past traumatic experiences involving pain or painful procedures. This process of attempting to look at pain-related issues from a different, more 'healthful' angle, can be classified as a low-level form of cognitive restructuring. Cognitive restructuring is the core of cognitive therapy, which is an essential component of chronic pain management described below.

Using positive affirmations (i.e. positive and encouraging self-statements) can also be helpful in acute pain management.

Distraction is another useful method in acute pain management. Distraction strategies can be simple, such as getting patients to focus on an interesting item in the room, a mathematical task or a story, or introducing counter-stimulation to some other part of the body. Sometimes distraction needs to be more complex. An example of the latter would be inviting the patient to imagine him/herself in an interesting, pleasant place or situation, which would verge on the strategy of formal relaxation.

Relaxation and biofeedback
Relaxation training is a systematic approach to teaching individuals to acquire awareness of their physiological responses and achieve a cognitive, an affective and a physiological sense of comfort and tranquillity.

Biofeedback is a procedure in which the therapist monitors, through a machine, the patient's bodily responses and then feeds this information back to the patient. This information enables patients to learn to exert some control over their bodily function and thus to enhance pain control.

Because relaxation therapy generally entails fewer sessions and does not require machinery, it is often chosen as the first intervention. There is a wide range of relaxation techniques; one form is not consistently superior to any other. The major forms used are progressive muscle relaxation therapy, guided imagery, autogenic training and meditation.

Hypnosis
There is usually some overlap between relaxation and hypnosis and these techniques are commonly blended as needed. Hypnosis is a state of highly focused attention during which alteration of sensations, awareness and perceptions can occur. An integral part of hypnosis is suggestion (this is not necessarily the case in relaxation). Suggestion is a way of conveying to a patient that something will be accomplished or experienced; this can be explicit or implied. In acute pain situations, where long-term coping with pain is unnecessary, hypnosis can be used to obtain relief by actively moving the patient's mind to comfort and pleasure unrelated to symptoms.

Techniques for chronic pain

Chronic pain is often demoralizing and incapacitating. Patients often develop significant symptoms of depression and anxiety if they are unable to obtain relief. Over time, a vicious cycle ensues between chronic physical pain and psychosocial dysfunction in which each condition exacerbates the other. Determining suitability for treatment is a crucial element of the psychological assessment interview. Pre-morbid psychological problems can contribute to or are aggravated by the chronic pain and may negatively interfere with a patient's ability to achieve progress. The presence of certain social or environmental factors, such as personal injury litigation or a disability claim, can potentially hamper therapeutic progress. Such factors may lead to the decision to postpone treatment or to commence treatment cautiously.

Treatment of chronic pain involves a comprehensive, holistic approach, using medication and functional rehabilitation. The objectives are for patients to learn to accept that pain is not always curable and therefore something they may have to live with, to get a better understanding of the pain, and to elevate the level of perceived control over the pain.

The following psychological techniques are essential in effective chronic pain management. All of the treatment approaches can be administered on an individual or on a group basis. Group treatment has the added value of peer support and vicarious learning. Individual therapy generally allows for greater depth.

Education
When pain is persistent or chronic, patients need to be informed of the nature and biopsychosocial background of their pain. This helps to modify any unrealistic assumptions and expectations, and enhances their motivation to engage in pain self-management. The basic building blocks of the 'psychology of pain', such as the gate control theory, learning processes and psychosocial aspects, should be explained to patients to furnish them with a sound foundation for understanding and applying self-management strategies.

Relaxation
Relaxation methods are core to the treatment of chronic pain. They are described above in the section on acute pain.

Cognitive therapy
Cognitive therapy is a structured, time-limited, problem-focused, goal-oriented and educative form of psychotherapy. It is present (rather than past) oriented, stresses a collaborative relationship between therapist and patient, and encourages active participation in the treatment by both therapist and patient. Cognitive therapy has been used in chronic pain management for 20 years. It is based on the idea that cognitions (thoughts) have a strong controlling influence on emotions, behaviour and pain experience. This approach places specifically irrational ideas about pain and suffering at the forefront and suggests that the modification of these maladaptive beliefs is the central ingredient for a more successful adaptation to a life with chronic pain. The aim is to promote cognitive restructuring, facilitating a basic change in a person's perspective, attitudes, beliefs, emotional reactions and behaviours related to the pain they are experiencing. This entails teaching patients skills for identifying, evaluating and modifying the inner dialogue they maintain with themselves, in order to change the nature of the pain experienced favourably. This requires a sound motivation to change.

Hypnosis
Long-term coping is necessary for chronic pain and so the technique of hypnosis differs from that used for acute pain. As a general rule, positive suggestions (i.e. the indication of what is felt), are more powerful than negative suggestions (e.g. the pain will disappear). The most commonly used suggestions for chronic pain relief include: creating an escape or distraction, replacing the pain with something else that is similar but hurts less or is of lesser intensity, or creating sensory transformation.

Operant conditioning
Operant conditioning is an empirically based behavioural model of learning. It finds its clinical application in behaviour therapy. In the 1960s and 1970s, Fordyce contributed greatly to the field of pain management, by introducing and highlighting the role of operant conditioning principles in the genesis and maintenance of pain behaviour problems. The theory of operant conditioning asserts that all overt behavioural responses are significantly influenced by both their consequences and the context in which they are emitted. The most fundamental paradigm within the model is that of reinforcement. Operant conditioning methods have become a fundamental part of successful pain rehabilitation, particularly in terms of increasing physical functioning. The mainstay of this approach is the targeting of behavioural excesses, as well as deficiencies, for intervention. Behavioural excesses are targeted for reduction or elimination, and for replacement by more adaptive behaviours. Behavioural deficits are targeted for remediation through shaping and positive reinforcement procedures. Operant conditioning methods are ideally used in concert with other psychological and medical treatments within an interdisciplinary team approach.

Psychodynamic psychotherapy
Most patients with chronic pain benefit significantly from the interventions described so far and they should be treatments of choice for all patients suffering from chronic pain. Occasionally, however, these treatments do not have the desired effect, or patients are assessed as unlikely to respond to such interventions. In those cases the psychodynamic approach might be a treatment option. The psychodynamic perspective (i.e. Freudian) highly values unconscious processes, especially those related to pain proneness. These processes have their origins in untoward early life experiences. These unconscious factors lie dormant until life events such as physical trauma or illness provide a theatre for expression in chronic suffering. Psychodynamic therapy is often long-term, and this may curtail its use within current healthcare systems. ◆

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Radiofrequency Lesioning Techniques in the Management of Chronic Pain

Dil Kapur

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The concept of destroying neural tissue by electrical current is not new. Direct current (DC) causes electrolysis of tissue fluids and effective destruction of nervous tissue (this is the manner in which the CNS is destroyed by the 'electric chair'). DC apparatus was used in the 1950s to perform limited neuroablative procedures, but such lesions were difficult to control and the DC was painful and hazardous to apply.

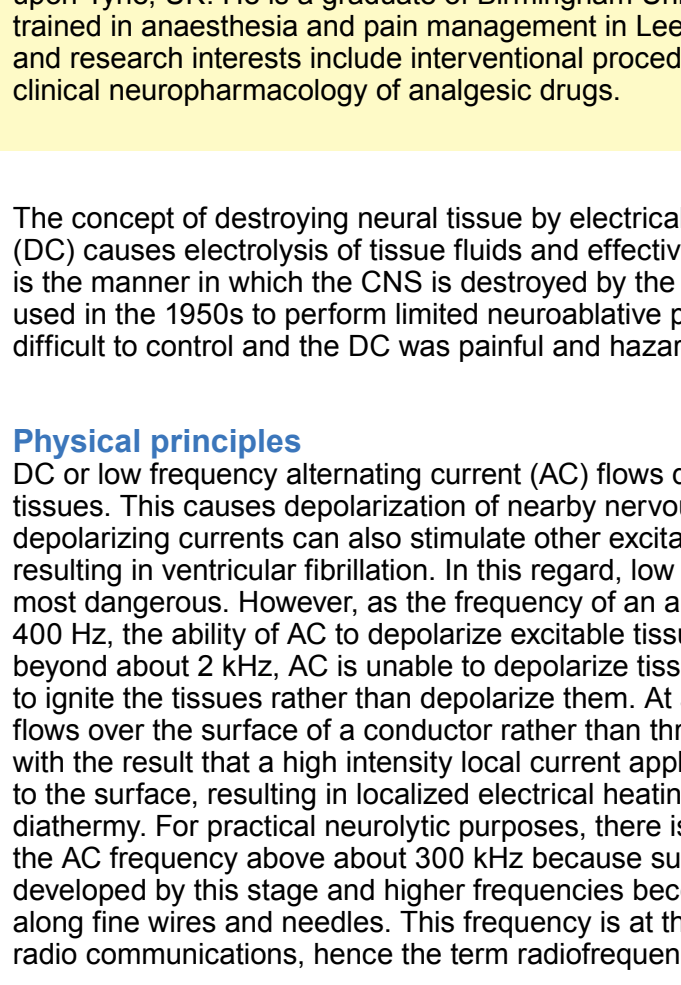
Physical principles

DC or low frequency alternating current (AC) flows directly through central bodily tissues. This causes depolarization of nearby nervous tissue and pain. Such depolarizing currents can also stimulate other excitable tissue, such as the heart, resulting in ventricular fibrillation. In this regard, low frequency AC of about 50 Hz is the most dangerous. However, as the frequency of an applied AC is increased above about 400 Hz, the ability of AC to depolarize excitable tissue decreases dramatically such that beyond about 2 kHz, AC is unable to depolarize tissues and the currents required tend to ignite the tissues rather than depolarize them. At a frequency above several kHz, AC flows over the surface of a conductor rather than through the substance of the material with the result that a high intensity local current applied to an area dissipates rapidly to the surface, resulting in localized electrical heating – this is the basis of surgical diathermy. For practical neurolytic purposes, there is little advantage in increasing the AC frequency above about 300 kHz because surface conduction effects are well developed by this stage and higher frequencies become increasingly difficult to transmit along fine wires and needles. This frequency is at the lower end of the range used for radio communications, hence the term radiofrequency (RF).

RF lesioning

Practical RF lesioning apparatus uses an RF source to apply a current to an insulated needle with an exposed tip. The needle can accommodate a close tolerance platinum thermocouple that measures the temperature generated around the uninsulated section of the needle. Control circuitry within the equipment regulates the current applied to maintain a preselected temperature, usually in the range 60–90°C. A timer regulates the duration of applied current. Modern equipment also includes devices for measuring impedance and applying low intensity stimulating currents to the needle in order to help locate nervous tissue.

An RF current applied to the needle causes a zone of heating around the uninsulated portion of the needle. It is important to remember that it is the tissue that is heated, not the needle. The heating occurs in an oblate spherical pattern and the area with minimal heating is the tip of the needle. For this reason, it is essential that the needle is placed adjacent and parallel to a nerve rather than perpendicular to it (Figure 1).



1

Heating nervous tissue above about 50°C denatures intra-cellular proteins and kills neurons. Temperatures above 65°C destroy myelin and kill axons. As a general rule, temperatures of 70–80°C are used, though lower temperatures are safer when lesioning areas of the CNS such as in spinal cordotomy.

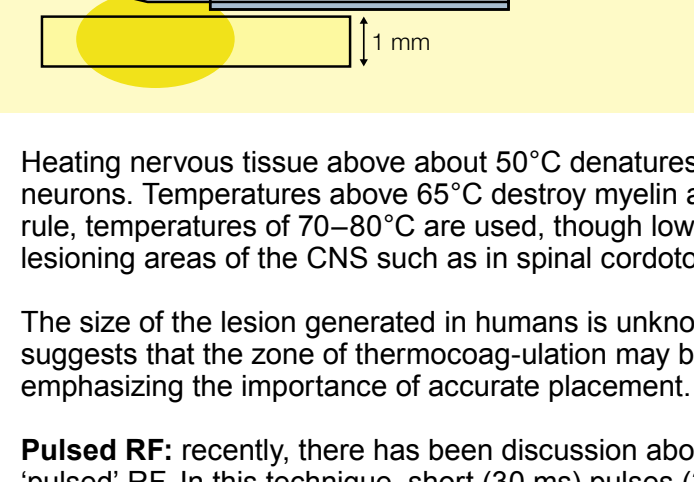
The size of the lesion generated in humans is unknown. However, *in vitro* work suggests that the zone of thermocoag-ulation may be as little as 4–6 mm in diameter, emphasizing the importance of accurate placement.

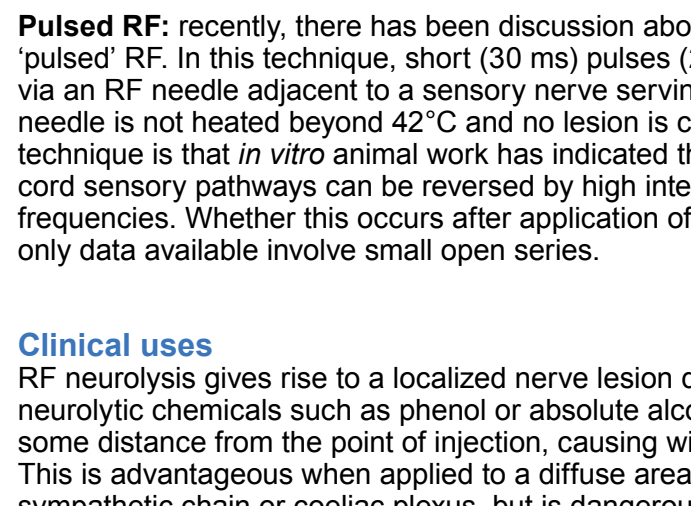
Pulsed RF: recently, there has been discussion about the technique of so-called 'pulsed' RF. In this technique, short (30 ms) pulses (2 Hz) of RF current are delivered via an RF needle adjacent to a sensory nerve serving a painful area. The tip of the needle is not heated beyond 42°C and no lesion is created. The rationale for using this technique is that *in vitro* animal work has indicated that long-term potentiation of spinal cord sensory pathways can be reversed by high intensity stimulation of Aδ fibres at low frequencies. Whether this occurs after application of pulsed RF is unknown and the only data available involve small open series.

Clinical uses

RF neurolysis gives rise to a localized nerve lesion different from that generated by neurolytic chemicals such as phenol or absolute alcohol. The latter substances spread some distance from the point of injection, causing widespread neural destruction. This is advantageous when applied to a diffuse area of neural tissue such as the sympathetic chain or coeliac plexus, but is dangerous where specific neurolysis is required and spread might cause serious morbidity. A good example of such a situation is spinal facet joint neurolysis. Figure 2 shows RF lesioning needles placed to destroy the medial branch of the dorsal ramus of the L4 spinal nerve. These nerves innervate the facet joints but lie close to the lateral foraminae carrying the main mixed spinal nerve. Application of a neurolytic chemical to this area would run a high risk of causing permanent injury to these nerves. RF lesioning on the other hand can provide a localized lesion. Moreover, the position of the lesion can be checked by electrical stimulation before lesioning. Similar considerations apply to RF lesioning procedures within the spinal cord such as cordotomy or dorsal root entry zone lesions.

Radiofrequency lesioning of the medial nerve branch at L4





The radiofrequency cannula is placed along the lateral margin of the articular pillar where it abuts the medial end of the transverse process. Note that the tip of the cannula is within 5–10 mm of the spinal nerve exiting the lateral foramen

2

Outcomes

Data from randomized controlled trials or large open series support the use of RF lesioning in the conditions listed in Figure 3. There is insufficient evidence to give recommendations about the use or safety of many of the other purported uses of RF lesioning. The greatest experience of RF lesioning is in the area of lumbar facet neurolysis. Patient selection is important because only 1–2% of patients presenting with chronic lower spinal pain have facet arthropathy. Nevertheless, within this group of patients, 70% can expect a clinically significant reduction in pain over the course of the first 6 months, though this has fallen to about 40% by 3 years. A more limited data set suggests that similar outcomes might be expected after cervical facet denervation.

Indications for radiofrequency neurolysis in chronic pain

Condition	Procedure	Evidence[1]
Lumbar facet arthropathy	Lumbar facet rhizolysis	RCT LOS
Cervical facet arthropathy	Cervical facet rhizolysis	RCT LOS
Trigeminal neuralgia	Trigeminal gangliolysis	LOS
Unilateral cancer pain (e.g. mesothelioma)	Cervical spinal cordotomy	LOS
Segmental cancer pain	Dorsal root entry zone lesion	Anecdotal
Discogenic low back pain	Pulsed radiofrequency	Anecdotal
Sympathetically maintained pain	Sympathectomy	Anecdotal

[1]RCT, randomized controlled trials
LOS, large open series (> 50 patients, more than one series)
Anecdotal, case reports, small open series (< 50 patients or only one series)

3

In many cases, RF trigeminal gangliolysis has been supplanted by brainstem microvascular decompression of the trigeminal root, but it remains an option in patients who are unfit for surgery or in whom a compressing vessel is not seen. Initial success has been reported to be as high as 90% but recurrence is common after 2–3 years and complications, while uncommon, are potentially debilitating.

Spinal cordotomy was the earliest operation performed on the CNS for the relief of pain. Percutaneous RF techniques were described in the 1960s and are now the technique of choice. Unilateral pain of a somatic origin responds best to this technique, and in conditions such as mesothelioma complete relief of pain is possible in over 70% of patients. Recurrence of pain is common beyond 1 year though some series report substantial and persisting pain relief in a minority of patients. Nevertheless, potential complications are serious and persistent, therefore this technique can be recommended only for patients with intractable cancer pain that has not responded to conventional techniques.

Complications

The safety of percutaneous RF lesioning compares favourably with many of the techniques it has supplanted and in most cases it is considerably safer. Nevertheless, it is an invasive and destructive technique and complications are well reported.

Unintentional nerve injury

Most lesioning procedures take place in close proximity to other nerve trunks or ganglia where nerve destruction could have serious effects. Both cervical and lumbar facet denervations take place close to major spinal nerves and destruction of, for example, the C6 nerve root could have serious consequences for the patient's functional status. For this reason, it is essential that the patient is awake and not heavily sedated while these procedures are performed; this allows the use of sensory and motor stimulation to confirm safe needle placement.

In procedures such as cordotomy or trigeminal gangliolysis, it is more difficult to avoid damage to adjacent neural structures. Trigeminal gangliolysis is associated with widespread loss of facial sensation in a small number of patients. Corneal anaesthesia can be particularly troublesome and potentially dangerous and occurs in about 5% of patients. Cordotomy can be associated with damage to the pyramidal tracts, even with accurate needle placement. This can result in extensive motor weakness of a hemiparetic nature. Despite this, such motor deficits often recover in a few hours; a persisting Babinski sign indicates that this is not always due to recovery of the pyramidal tracts but rather to other descending motor tracts being 'reprogrammed' to accommodate voluntary motor function.

Peripheral and central neuropathic pain

To the basic scientist, the concept of deliberately generating a nerve injury to relieve pain would seem fraught with hazard. Injured nerves have a high capacity to cause pain. All forms of nerve destruction caused by RF lesioning (or any other technique) may result in neuropathic pain, though it should be emphasized that such pain is not inevitable.

Neuropathic pain after facet joint denervation is uncommon though in some cases the pain that 'recurs' may represent neuropathic pain rather than pain from the facet joint. A number of patients may develop temporary cutaneous allodynia over dermatomes related to the facet joint sclerotome, probably representing sensory reorganization within the spinal cord, but this usually settles within 4–6 weeks.

Trigeminal neuralgia is a neuropathic pain condition and gangliolysis is associated with one of the most serious and intractable complications of neuroablative techniques, 'anaesthesia dolorosa' This is a condition in which intense pain is experienced in an area that is otherwise numb. The condition responds poorly to most pharmacological treatments and can cause great distress to sufferers. The syndrome occurs in about 5% of patients undergoing the procedure.

Cordotomy has its own spectrum of neuropathic pain states which differ from those described above. The most serious is the post-cordotomy dysaesthesia syndrome in which a large unilateral area of the patient's body develops sensations of severe pain. This complication is rare (about 1%) but other centrally generated dysaesthesias are reported after cordotomy. These usually take some time to develop, emphasizing that this technique is best reserved for patients with a short life expectancy.

Future directions

Improvements in imaging techniques have increased the scope for accurate placement of lesions using RF equipment. Two-dimensional fluoroscopy can now be of similar quality to standard radiographs. The most interesting development is the use of CT. CT-guided cordotomy is well described. Procedures such as dorsal root entry zone lesioning, commisural myelotomy and dorsal rhizotomy could all, theoretically, be performed using CT guidance but no large series exist to validate such techniques. ◆

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Regional Techniques for Acute Pain

Fergus A Millar

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The use of local anaesthetics for the treatment of acute pain can be traced to the days of the pharaohs. Hieroglyphics show that the ancient Egyptians used a topical substance to ease the pain of circumcision. Since the discovery of cocaine and the subsequent development of local anaesthetic agents, many techniques have been described for providing regional anaesthesia, some of which are suitable for providing prolonged analgesia.

Most acute pain therapy is directed at treating postoperative pain but there are a small number of acutely painful conditions in which regional anaesthetic techniques can be used to provide analgesia. Single shot local anaesthetic techniques can provide up to 18 hours of analgesia, depending on the site of injection and the length of surgery. To provide longer analgesia, a catheter must be placed to allow infusion or repeated boluses of local anaesthetic. The three main regional anaesthetic techniques discussed in this article are:

- central neural blockade (mainly epidural)
- nerve plexus blockade
- peripheral nerve blockade.

The advantages and disadvantages of regional techniques are listed in Figure 1.

Advantages and disadvantages of regional techniques

Advantages

- Potential to provide almost total analgesia at the operation site
- Avoidance of opioid side-effects
- Reduction of the stress response
- Active and passive movement is easier
- Sympathetic blockade with increased blood flow
- Reduced incidence of deep vein thrombosis and pulmonary embolism
- Reduced morbidity and mortality
- Potential reduction in hospital stay

Disadvantages

- Difficult to perform
- Central neural blockade can cause instability of the cardiovascular system
- Respiratory problems (particularly central neural opioids)
- Extra education for those providing postoperative care
- Potential neurological damage
- Morbidity and mortality from local anaesthetic toxicity
- Entry site for infection (particularly epidurals)

1

Epidural analgesia

The epidural is the most common catheter technique used for acute pain. Intrathecal catheters are available, but owing to some case reports of cauda equina syndrome and arachnoiditis, they are not widely used in the UK and are not discussed here. Epidural techniques offer the widest scope for the treatment of acute pain, from the thorax to the feet. Cervical epidurals can be used in head and neck surgery but this is not widely practised in the UK. The indications for epidural analgesia are:

- surgery (intra-operative and postoperative)
- trauma (especially fractured ribs or pelvis)
- labour pain
- acute ischaemic pain
- severe angina not controlled by conventional means (seldom used but some papers have shown a clear benefit).

Absolute contraindications are patient refusal, allergy to local anaesthesia, infection at the site of injection and lack of resuscitation equipment or skills. Relative contraindications require an assessment of the individual's risk and benefit and include, hypovolaemia, dehydration, bowel obstruction, co-existing neurological disease, coagulopathy and compartment syndrome.

The benefits of postoperative epidural analgesia are:

- effective analgesia
- reduced opioid requirement
- reduction in the stress response after surgery
- reduction in the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE)
- an earlier return to gastrointestinal function after abdominal surgery
- reduction in postoperative morbidity and mortality.

Epidural solution

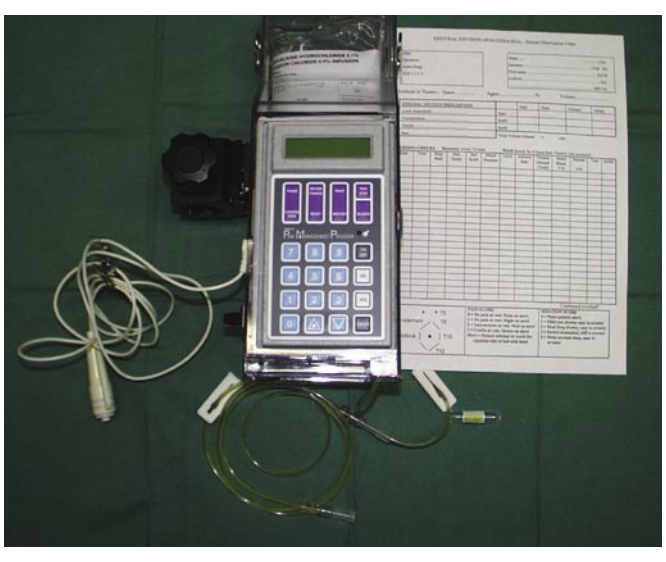
The epidural has to be correctly sited, with the catheter inserted in the middle dermatome of the actual or anticipated site of pain. The combination of local anaesthetic and opioid is the optimal way to provide epidural analgesia. The opioid reduces the amount of local anaesthesia required thereby reducing the extent of motor and sympathetic block. As analgesia and not anaesthesia is required, a weaker solution of local anaesthetic (0.1–0.2% bupivacaine) can be used. The author's current practice is to use 0.1% bupivacaine with diamorphine, 25 μg/ml. Other opioids include fentanyl and morphine. Opioids act at the substantia gelatinosa in the dorsal horn. There are pharmacokinetic differences between the commonly used opioids that result in clinical differences. The more lipophilic the opioid, the quicker the drug penetrates the dura and crosses the CSF to its site of action. Lipophilic opioids also have a quicker termination of action because they are more rapidly absorbed into the blood stream. Fentanyl is more lipophilic than diamorphine and morphine is the least lipophilic. Morphine has a slow onset but can last for 24 hours because it is slow to clear from the CSF, and is usually the drug responsible for late-onset respiratory depression. Patient monitoring must be continued for at least 24 hours. Clonidine, midazolam and neostigmine have been used but there is no product licence for these drugs. Opioids are not licensed for use in epidurals, but their use is accepted, because there is a large body of supporting evidence.

Epidural regimens

Most postoperative epidural analgesia regimens consist of establishing an effective block and maintaining it with a continuous infusion. The infusion usually consists of a weak mixture of local anaesthetic and an opioid because this mixture is additive or possibly synergistic.

There is currently some interest in using patient-controlled epidural analgesia (PCEA), particularly in obstetric units (Figure 2). The advantage of PCEA is that it allows the patient some control over their pain relief. PCEA is useful for weaning patients from epidural to oral analgesia. It is potentially a valuable research tool, because it allows more accurate comparisons between drugs and regimens. The author uses a mixture of background infusion and a bolus facility after major surgery, thus giving the patient some control although the block does not completely regress if the patient falls asleep. The bolus facility in the PCEA may increase the effectiveness of the epidural, as some research has shown bolus doses of local anaesthetic to be more effective than background infusions.

The concurrent use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) is recommended because they improve the quality of analgesia and are useful for weaning the patient off the epidural.



2 Patient-controlled epidural analgesia.

Management

The key to successful acute pain management with epidural catheters is to avoid complications (see below). The patient must be cared for in a safe environment where the staff are trained in the care and monitoring of patients with epidurals. Regular assessment of the patient is essential and the following observations are recommended: hourly measurement of blood pressure, heart rate, respiratory rate, sedation score, level of sensory block, degree of motor block, pump performance and, if appropriate, urine output and central venous pressure. This level of monitoring should be carried out for all major surgery, the only extra requirement for epidurals is sensory block height, motor block and pump performance.

Cardiovascular management: epidurals using local anaesthetics reduce preload and afterload and can cause bradycardia, resulting in reduced cardiac output and hypotension. This is complicated by the effects of major surgery and its associated fluid shifts. Prevention of these problems requires treatment of the bradycardia (block height may be too high), restoration of the preload and an increase in afterload. Fluid management for patients who have an epidural following major surgery can be difficult and therefore hourly urine volumes and central venous pressure monitoring can be helpful. Epidurals are often used to provide analgesia following major gastrointestinal surgery and this can have an impact on splanchnic blood flow. If the patient becomes hypovolaemic, splanchnic blood flow may be reduced thus compromising anastomotic blood flow. If normovolaemia is achieved, then epidural analgesia with local anaesthetic can increase splanchnic blood flow.

Respiratory management: respiratory complications of epidurals are uncommon but can be fatal. If the block extends upwards beyond C3/C4, respiratory arrest will occur. Even a high thoracic block can interfere with respiratory effort by paralysing the intercostal muscles. Epidural opioids can cause respiratory depression and arrest. The less lipophilic opioids take longer to reach the CSF, but once there, persist longer resulting in cephalad spread; if they reach the respiratory centre, respiratory depression can occur. Morphine is particularly associated with this because it is the least lipophilic of the opioids used in epidurals. Patient observation is the key to the prevention of respiratory complications: block height, sedation score and respiratory rate must be monitored. This is not foolproof and if respiratory complications occur prompt action is required: a clear airway, adequate ventilation and sufficient oxygen must be ensured. If local anaesthetic is the cause, supportive measures are required with fluids and vasopressors until the local anaesthetic action terminates. Naloxone, in small incremental doses, treats opioid-related respiratory depression.

Complications

Cardiovascular – when using local anaesthetic, there will be a sympathetic block that can result in vasodilatation, reducing preload and afterload. If the cardiac sympathetic fibres (T1–T4) are involved, this can cause bradycardia and reduced contractility. Hypotension and reduced cardiac output can then occur.

Respiratory – motor blockade of the intercostal muscles causes respiratory depression and even arrest. The innervation of the diaphragm is C3, C4 and C5. The use of opioids can cause respiratory depression. All opioids can do this, but morphine, being the least lipophilic, can cause late-onset respiratory depression (up to 24 hours following administration).

Itch, nausea and vomiting are opioid-related side-effects that can be distressing. Itch can be treated with small doses of naloxone, 20 μg i.v. Nausea and vomiting can be treated with anti-emetics.

Motor block can delay mobilization but use of weaker local anaesthetic solutions will minimize it.

Dural puncture can occur and, if not recognized, can result in extensive or total spinal block and may require cardiorespiratory support. Post-dural puncture headache can occur.

Subdural block is uncommon but can result in a total spinal.

Infection is uncommon but can result in meningitis. Strict aseptic techniques during epidural insertion are mandatory.

Epidural spinal haematoma is a rare and potentially devastating complication. It can occur spontaneously or be triggered by antiplatelet or anticoagulation therapy. It is difficult to determine the incidence following central neural blockade, but a rate of 1/150,000 for epidurals and 1/220,000 for spinals has been quoted. This risk increases if there is a haemostatic abnormality or there has been difficulty with needle insertion (87% of reported cases of spinal haematoma had one of these problems). In 75% of the reports, epidurals were used and 75% of those had a catheter inserted. In half of these the haematoma occurred following catheter removal. Tryba has published guidelines to help reduce the risk of DVT and PE (see Further Reading). The three main points are given below.

- Low dose heparin: 4 hours recommended between administration and performance of the block. A minimum of 1 hour following block before low dose heparin is given. This also applies to catheter removal.
- Low molecular weight heparins (LMWH): there is a difference between US and European doses for DVT and PE prophylaxis, and Tryba's guidelines advise the lower European doses. An interval of 10–12 hours is required after LMWH before performing epidural blockade. The recommended interval between epidural blockade and giving LMWH is 4 hours. This 4-hour interval also applies to catheter removal. It is imperative that the nursing and medical staff caring for the patient are aware of these recommendations.
- Aspirin and NSAIDs alone do not increase risk but in combination with low dose heparin or LMWH, the risk of spinal haematoma rises.

The signs and symptoms of spinal haematoma are:

- increasing motor block
- increasing sensory block
- back pain.

If spinal haematoma is suspected, an urgent CT or MRI scan and a neurosurgical opinion must be obtained. If a haematoma occurs, swift action is required to decompress the spinal cord and prevent or limit permanent neurological damage. A laminectomy is required. The person performing the block must document any difficulty with epidural placement. The patient must be cared for in an environment that allows early recognition, so education and training are vital. Epidural abscess may present in a similar fashion with the additional signs of fever and a raised white cell count. Investigation and management are similar to those for spinal haematoma.

Peripheral nerve/plexus catheters

Most local anaesthetic techniques described for the provision of anaesthesia are single injection methods. The effectiveness of the block in providing postoperative analgesia depends on the length of surgery, the type of local anaesthetic drug, the accuracy of the initial block, adjuvant drugs and the vascularity of the injection site. The placement of a catheter close to the nerve or plexus provides an opportunity to prolong the analgesia. A good understanding of nerve/plexus anaesthesia provides an excellent platform on which to develop the skills necessary for nerve/plexus catheters. The advantages and disadvantages of nerve/plexus catheters are listed in Figure 3.

Most catheter techniques are used for upper limb pain, because lower limb pain can be dealt with using epidural analgesia. However, techniques for lower limb catheters can provide significant analgesia with fewer cardiovascular complications. The indications for nerve/plexus catheters are given in Figure 4.

Advantages and disadvantages of nerve/plexus catheters

Advantages

- Extend the period of analgesia
- Localize sympathetic block
- Improve blood flow
- Reduce opioid requirement
- Fewer cardiovascular system complications

Disadvantages

- Difficult to place
- Easily dislodged
- Specialized equipment
- Source of infection
- Continuous motor block

3

Indications for nerve/plexus catheter

Indications

- Acute postoperative pain (e.g. elbow replacement)
- Trauma (beware compartment syndrome and discuss with surgeon before the block)
- Repeated painful procedures over 5–7 days (e.g. burns dressing changes)
- Re-implantation of digits, hand, foot (improved blood flow)
- Acute limb ischaemia (e.g. vasculitis, peripheral vascular disease)

Contraindications

- Infection at injection site
- Local anaesthetic allergy
- Severe coagulopathy
- Risk of compartment syndrome (discuss with surgeon)
- Inability to provide adequate care for the patient with a nerve/ plexus catheter

4

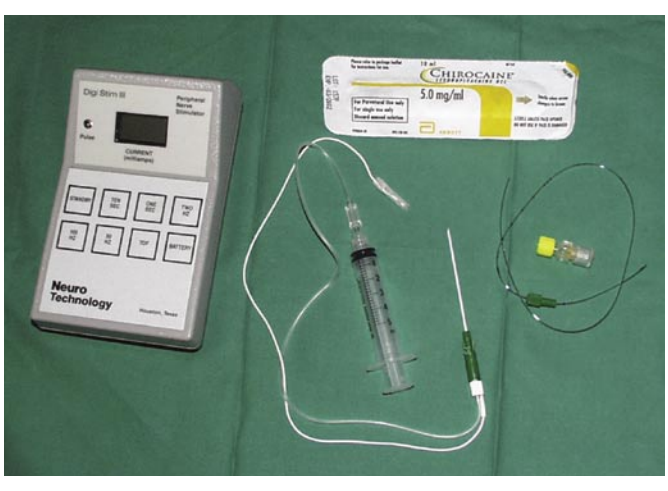
Techniques

The safety of the patient is paramount, therefore, everything required should be assembled before the procedure begins. The anaesthetist should have a dedicated knowledgeable assistant and have instant access to resuscitation drugs.

Equipment: most of the equipment required for placing a nerve/plexus catheter is readily available:

- peripheral nerve stimulator with low output (0–5 mA)
- dressing pack
- antiseptic solution
- catheter kit
- local anaesthetic agent
- syringes and needles.

Commercial kits (Figure 5) require the insertion of a cannula and then threading the catheter through the cannula. Tips to aid insertion of a nerve/plexus catheter are given in Figure 6.



5 Commercial catheter kit.

Tips to aid insertion of a nerve/plexus catheter

- Select the appropriate length of catheter kit
- Use a nerve stimulator
- Once the nerve/plexus is located, inject 2–3 ml of local anaesthetic to expand the ‘space’ around the nerve/plexus allowing easier cannula insertion
- There is a risk of exiting the nerve ‘sheath’ if the cannula is threaded too far, therefore advance it 2–3 mm at a time
- Inject 4–5 ml of local anaesthetic through the cannula (there should be no resistance)
- Thread the catheter, which should be easy, remove the cannula and inject the rest of the local anaesthetic via the catheter. Aim to thread the catheter about 2–5 cm along the nerve ‘sheath’
- Secure and dress with a sterile, transparent, occlusive dressing

6

Upper limb: the upper limb nerve supply comes from the brachial plexus C5–T1, making a cervical epidural impractical. However, it is relatively easy to perform plexus anaesthesia and insert catheters. Continuous brachial plexus block is useful for pain relief following major surgery (e.g. elbow replacement), re-implantation surgery and pain due to ischaemia (e.g. vasculitis).

Axillary brachial plexus block is the most widely used for catheter techniques. It is good for hand and forearm surgery and analgesia. Anyone who can perform a single-shot axillary block can also insert a catheter. The catheters can be dislodged despite adequate fixation.

Interscalene plexus block is good for shoulder surgery and analgesia. For successful cannulation, the angle of approach to the plexus should be more acute (the needle should point more caudad) to aid insertion of the catheter. Aim to thread 2–4 cm of catheter. Adequate fixation can be difficult.

Infraclavicular plexus block has been described with good results. The perpendicular approach to the plexus may make catheter placement difficult. Fixation of the catheter to the anterior chest wall reduces its displacement.

Lower limb: the lower limb is amenable to continuous epidural blockade and therefore the use of nerve/plexus catheters is less common. However, they do offer some advantages, particularly cardiovascular stability, preservation of motor function in the other leg and retention of urinary tract control.

Lumbar plexus – there are several descriptions of the anatomy and approach to the lumbar plexus, and they can all involve threading a catheter. The use of a nerve stimulator helps to locate the nerves. The lumbar plexus consists of lumbar roots L2–L4, but by approaching it from the L4 transverse process (as described by Alon Winnie), there may be some sciatic plexus blockade. This can be useful following hip and knee surgery.

Femoral nerve is relatively easy to block – to place a catheter, approach the nerve with the needle at 45° to the skin to aid its placement. There have been a number of studies showing significant analgesia and opioid dose reduction when femoral nerve catheters have been used following major knee surgery. By placing a catheter, there is a greater chance of blocking the lateral cutaneous nerve of thigh and obturator nerve, because the local anaesthetic is delivered further up the nerve sheath.

Sciatic nerve is more difficult to block than the femoral nerve because it is not as close to the skin. The needle must be off the perpendicular to aid catheter placement. This can be achieved using two approaches to the sciatic nerve (Labatt and Raj) to map the surface anatomy. This technique is particularly effective for analgesia after below-knee amputation and any acute pain in the foot.

Mansoor recently described an approach to the sciatic nerve that is also suitable for nerve catheters. The patient lies on their side with the leg to be blocked uppermost. A line is drawn between the ischial tuberosity and the greater trochanter, 4–5 cm from the ischial tuberosity along this line, the needle is inserted with a slight caudad angle. The nerve is encountered as it leaves the pelvis. The angled approach makes this block amenable to catheter placement.

Lower approaches to the sciatic nerve have been described and are also suitable for catheter techniques. The posterior approach via the apex of the popliteal fossa, with placement of a catheter has been described. The advantage of the lower approach is that the hamstring muscles have no motor block, so the patient can stabilize their knee and mobilize more easily. This technique is useful for foot surgery, trauma and below-knee amputations.

Common peroneal nerve and tibial nerve can be individually blocked and a catheter placed at the popliteal fossa. They are useful for foot surgery.

Drugs for nerve/plexus catheters: local anaesthetics are the main drugs used. Other drugs, especially opioids, have been used with mixed results and should be avoided. There is no generally accepted drug, concentration or delivery method for nerve/plexus catheters. Bupivacaine and ropivacaine have been used successfully. Suggested concentrations of bupivacaine range from 0.1% to 0.375% and ropivacaine 0.2%. Continuous infusions, patient-controlled top-ups and intermittent boluses have all been described. There seems to be little difference between them, with the intermittent bolus method perhaps being slightly more effective. The choice may be governed by what is practical in the particular institution. The only exception is femoral nerve catheters for total hip and knee surgery where a large intermittent bolus may be more effective. This is due perhaps to the mass of drug encouraging cephalad spread and thus achieving the Winnie 3-in-1 block. Continuous infusions are less labour intensive and usually employed. The concurrent use of NSAIDs, paracetamol and opioids is recommended because it improves the analgesic efficacy.

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Role of Opioids in the Treatment of Chronic Non-Cancer Pain

Mick Serpell

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The estimated prevalence of chronic non-cancer pain in the community is about 30% and yet only 0.2% of the general population receive prescriptions for strong opioids. This compares with chronic cancer pain for which the adoption of potent step 3 analgesics in the WHO ladder is commonly used. There is no evidence that the pathophysiological mechanisms of cancer and non-cancer pain or the severity of pain and disability resulting from them are different, and yet the two groups are treated differently. The main reasons for this seemingly irrational pharmacological approach are that doctors and patients are concerned about waning efficacy, the potential for neuropsychological impairment and the development of drug addiction. Also, patients associate opioids with cancer and impending death.

Chronic pain is a complex entity and analgesics are only part of the treatment. The goals of treatment are to reduce pain and suffering and to improve function, with the aim of enabling patients to regain their social and occupational activity and become less reliant on healthcare services.

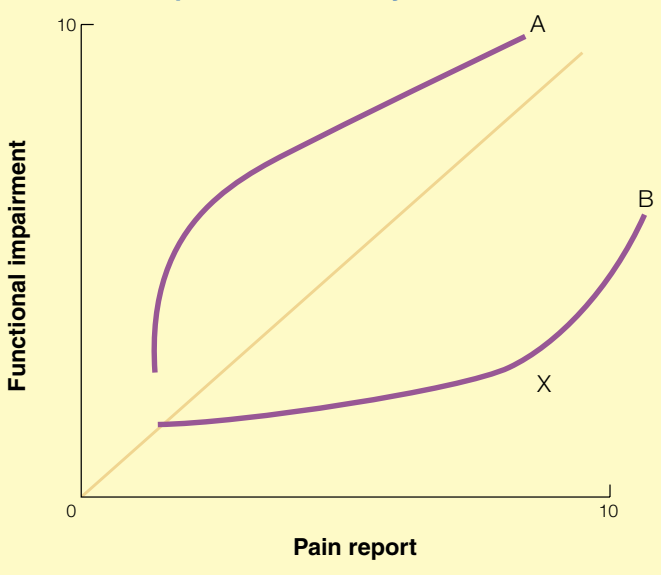
Before a treatment can be recommended, the following must be ascertained:
- is it effective – if so, how effective compared with other options?
- how safe is it?

Efficacy

The efficacy of opioids for cancer pain is widely accepted. They result in good control of pain for 80% of patients. Their use is based on empirical clinical practice and there are few randomized controlled trials.

In non-cancer pain, controlled clinical trials have demonstrated that opioids can reduce pain scores in both nociceptive and neuropathic pain types, though the former is more responsive. Only a few studies have examined psychological issues, such as functional status and quality of life, but these are the most important outcomes to measure. Patients with similar pain scores can demonstrate completely different levels of disability (Figure 1). The symptom of pain is subjective; pain is what the patient says it is. However, pain relief after an intervention is not just what the patient says it is, but what they can do. This measure allows the doctor to gauge any improvement objectively. Therefore, in an opioid trial, the level of disability from pain should be reduced as well as the severity of pain, before it can be deemed a success (Figure 2). This is the ultimate goal of pain management, and future research should address these issues.

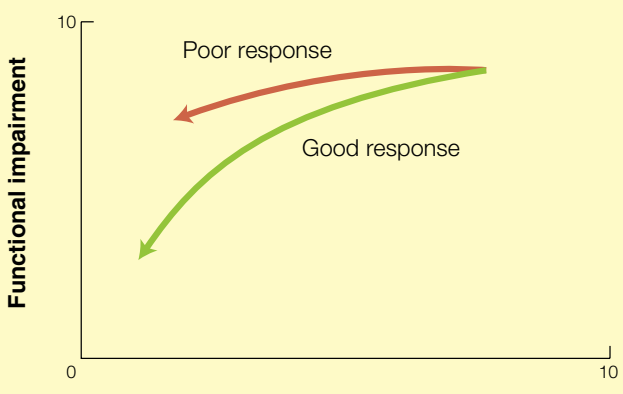
Link between pain and disability



Patient A is developing severe dysfunction (measured by Brief Pain Inventory) with a low pain score. Patient B maintains good function until severe pain is experienced at X.

1

Response to treatment of two patients with similar pain and dysfunction levels



Both patients have equal improvements in pain scores but the patient in the upper curve shows little improvement in function.

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2

In studies that assess psychological and quality-of-life issues, the success of opioids is variable. Also, only a few studies have evaluated the use of opioids for treatment periods longer than 1 or 2 months. However, some patients respond well and the task of future research must be to identify these people and determine how they can best be managed.

The efficacy of opioids compared with other drugs is harder to establish because there are no quality trials. Potent opioids are conventionally used only as a last resort, when everything else has been tried and failed. Therefore they are often first used in a relatively resistant subgroup of patients, which does not predispose to success.

Side-effects

Side-effects from opioids are the same as in cancer therapy, though most patients are outpatients and are less tolerant of treatments that impair their ability to perform at home and at work. Patients develop tolerance to many of these side-effects, though there is a significant drop-out rate (usually 30%), mainly due to CNS and gastrointestinal effects. Pain can impair cognitive function; it may also have an arousal effect and counteract the sedative effects of opioids. In patients who can tolerate opioids, there is no deterioration in cognitive function. Psychomotor performance is also maintained so the ability to drive is not diminished. Constipation is such a common problem that the prescription of regular laxatives is mandatory. Psychological addiction is often confused with drug tolerance and physical dependency, but is a separate issue.

Drug tolerance is the requirement for an escalating dose of drug to maintain the same effect. This is a form of neuroadaptation that occurs with the side-effects as well and is not a common problem because most patients who have genuinely opioid-responsive pain will establish themselves on a relatively stable daily dose. These patients often require supplementary opioids for breakthrough analgesia on some days, but they can return to, or get below, their baseline requirements on other days.

Physical dependence occurs as the body becomes accustomed to the drug. If the drug is suddenly discontinued, the body may go through withdrawal symptoms. This is a normal physiological response to chronic opioid exposure, it is not a sign of psychological dependence. It is avoided by gradual dose reduction if the opioid is to be discontinued.

Psychological dependence is drug-seeking behaviour to acquire the drug for non-medical purposes (i.e. euphoria rather than analgesia). It is characterized by a pattern of persistent dysfunctional opioid use that may consist of one or all of the following:
- adverse consequences associated with the use of opioids
- loss of control over the use of opioids
- preoccupation with obtaining opioids despite the presence of adequate analgesia.

There is only a small risk of psychological dependence in appropriately selected patients. One study looking at 10,000 patients found evidence of psychological dependence in only four patients. Prescribing guidelines have been developed to assist practitioners in selecting the appropriate patients and ensuring an acceptable risk:benefit ratio of long-term opioid therapy (Figure 3). The process of administration has to be agreed on by all parties concerned. It needs to be closely monitored and tightly controlled. In the current climate of increasing substance abuse in the general population, physicians need to be aware that the opioid drugs they prescribe may be diverted to improper uses. However, suitable patients should not be denied this option simply because of these general concerns.

Selection and management of patients for chronic opioid treatment

Selection criteria
- No previous history of drug or alcohol abuse (if so, require more careful management)
- No abnormal pain behaviour
- No impoverished social environment
- No psychotic problems
- Screening by psychologist

Management criteria
- Contract agreement between patient, GP and pain consultant
- Opioids will be discontinued if any suspicion of abuse determined by missing prescriptions or random blood sampling
- Adequate trial period of opioid, frequent reviews
- Patient must demonstrate improved function (reduced pain of secondary importance)
- Single source for opioids, once dose is established use long-acting opioids

3

Administration

The technique of opioid administration follows the same general principles as those for cancer pain. Injectable preparations should not be used for non-cancer pain because they reinforce dependency. In particular, pethidine should be avoided because it is too short acting and can accumulate as norpethidine, which is a CNS stimulant. ◆

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Role of the Sympathetic Nervous System in Pain

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The sympathetic nervous system was described about 100 years ago but its relationship with pain is still being debated. It is most commonly perceived as a component of chronic pain syndromes and cancer pain, though recent interest has looked at its role in the pathogenesis of cardiac pain.

Historical aspects

Interest in the sympathetic nervous system and pain developed in the early 1900s and over the ensuing two World Wars many patients underwent interruption of their sympathetic nervous system in the hope of providing analgesia. However, there is still uncertainty about the role of the sympathetic nervous system in pain, and the clinical benefits and hazards of its interruption.

The clinical disorders in which the sympathetic nervous system is thought to play a central part and sympathectomy is indicated are:

- complex regional pain syndrome
- abdominal cancer pain
- pelvic cancer pain
- peripheral vascular disease
- herpes zoster
- intractable angina
- erythromelalgia.

Historical points

- Silas Weir Mitchell described a syndrome of pain, hyperalgesia and trophic changes in American Civil War veterans who had sustained nerve injuries. He termed this syndrome causalgia, which means ‘burning pain’
- In the early 1900s, Leriche, a French surgeon, described patients with severe painful peripheral nerve injuries that he concluded were related to ‘wounds of the sympathetic’

Complex regional pain syndrome (CRPS)

CRPS is a disorder of unknown aetiology that usually presents in a peripheral limb following an injury, which is often minor. It can also follow surgery and may be associated with medical disorders such as stroke, myocardial infarction and several neurological disorders (e.g. syringomyelia, polio). It is a syndrome of diffuse limb pain, often burning in nature, with variable sensory, motor, autonomic and trophic changes (Figure 1).

Changes of complex regional pain syndrome

Sensory
- Allodynia
- Hypoaesthesia
- Hyperaesthesia

Autonomic
- Vascular abnormalities
- Hyperhidrosis
- Oedema

Trophic
- Shiny skin
- Altered hair growth
- Brittle nails
- Osteopenia

Motor
- Weakness
- Stiffness

If untreated the clinical picture usually has three stages:
- pain and oedema (acute)
- muscle wasting and cyanosis (dystrophic)
- bone and skin changes (atrophic).

Aetiology

The main aetiological theories of CRPS can be separated into peripheral and central components though there may be a continuum of neural events occurring throughout the CNS.

Peripheral nervous system: after partial nerve injury, injured and uninjured axons begin to express α-adrenoceptors, which render them sensitive to circulating catecholamines and noradrenaline released from postganglionic sympathetic terminals. This occurs in C polymodal nociceptors in both the resting and active states. Noradrenaline has been shown to release prostaglandins from sympathetic postganglionic neurons, which may initiate nociceptor activity. There are decreased levels of circulating noradrenaline and its metabolites in the limbs of patients with CRPS. Denervation hypersensitivity has been proposed as a mechanism involved in the generation of some of the trophic changes. Recent research has concentrated on the inflammatory aspects of CRPS and it has been shown that there are increased levels of cytokines in neuropathic pain syndromes.

CNS: nerve injury also induces the sprouting of sympathetic axons into the dorsal root ganglion where they form baskets around the cell bodies of sensory neurons and may constitute a mechanism in which sympathetic activity initiates activity in sensory fibres.

Diagnosis

The formal diagnostic criteria of CRPS as defined by the International Association for the Study of Pain (IASP) are given in Figure 2.

Formal diagnostic criteria of CRPS as defined by the International Association for the Study of Pain

- The presence of an initiating noxious event or cause of immobilization
- Continuing pain, allodynia and hyperalgesia disproportionate to the inciting event
- Evidence, at some time, of abnormal skin blood flow, sudomotor activity or oedema
- The diagnosis being excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

CRPS type 2 (causalgia) differs from CRPS type 1 (reflex sympathetic dystrophy) because a definitive nerve is involved. These diagnostic criteria have recently been re-examined and were thought to have inadequate sensitivity and specificity but no revision has yet taken place. Clinically cold allodynia is thought to be associated with sympathetically mediated pain.

The response to sympathetic blockade clinically confirms whether sympathetically maintained pain or sympathetically independent pain is present. The diagnosis of CRPS can be present even when sympathetically independent pain is present. The response to local anaesthetic sympathectomy is not a good predictor for benefit from a neurolytic procedure. Intravenous regional anaesthesia with guanethidine has been demonstrated to have no benefit over placebo. The phentolamine infusion test has been proposed as a predictor of response to sympathectomy though its validity has been questioned. Tests of autonomic function such as thermography and sweat output tests are used for research purposes.

Recently there has been interest in the use of laser Doppler as a measurement of cutaneous blood flow, reflecting sympathetic activity. Radionuclide bone scan imaging may show a diffuse uptake in affected extremities and X-rays may show periarticular osteoporosis.

Differential diagnosis: several pathologies can be confused with CRPS including local pathology (fracture, sprain), vasospasm, cellulitis, Raynaud’s disease, thrombosis and thromboangiitis obliterans.

Treatment

Early multidisciplinary treatment aimed at the initiating cause (if known) and maintaining function in the affected extremity is essential. In a critical review by Kingery most trials for the treatment of CRPS were shown to be of small size, were unlikely to be placebo controlled or double blinded or have valid statistical testing. The two treatment modalities are described below.

Local anaesthetic techniques: Hannington Kiff first described intravenous regional blockade with guanethidine in 1974. Since then, randomized controlled trials have shown it to be no better than placebo. The timing of intravenous regional blockade is contentious and some authorities believe early blockade in the acute phase of CRPS can be beneficial. The serotonin antagonist ketanserin, the anti-arrhythmic bretylium and the non-steroidal anti-inflammatory drug ketorolac have also been used for intravenous regional blockade, though their long-term efficacy is undetermined. Sympathetic blockade has never been evaluated in a placebo-controlled trial and surgical procedures have been presented only in small series. Epidural clonidine, intrathecal opiates and dorsal column stimulation have all been used as therapy for CRPS but their efficacy is undetermined.

Pharmacological therapy: a variety of medications have been reported to provide relief in CRPS and there is considerable overlap with agents used to treat neuropathic pain. The tricyclic antidepressants (amytriptyline) and anticonvulsants (carbamazepine, gabapentin, phenytoin) are effective. Intra-venous and topical lidocaine (lignocaine) and oral mexilitene are beneficial as is topical capsaicin. Most trials did not involve long-term follow-up. Corticosteroids were the only treatment with prolonged effectiveness, which is consistent with an inflammatory aetiology.

Abdominal cancer pain

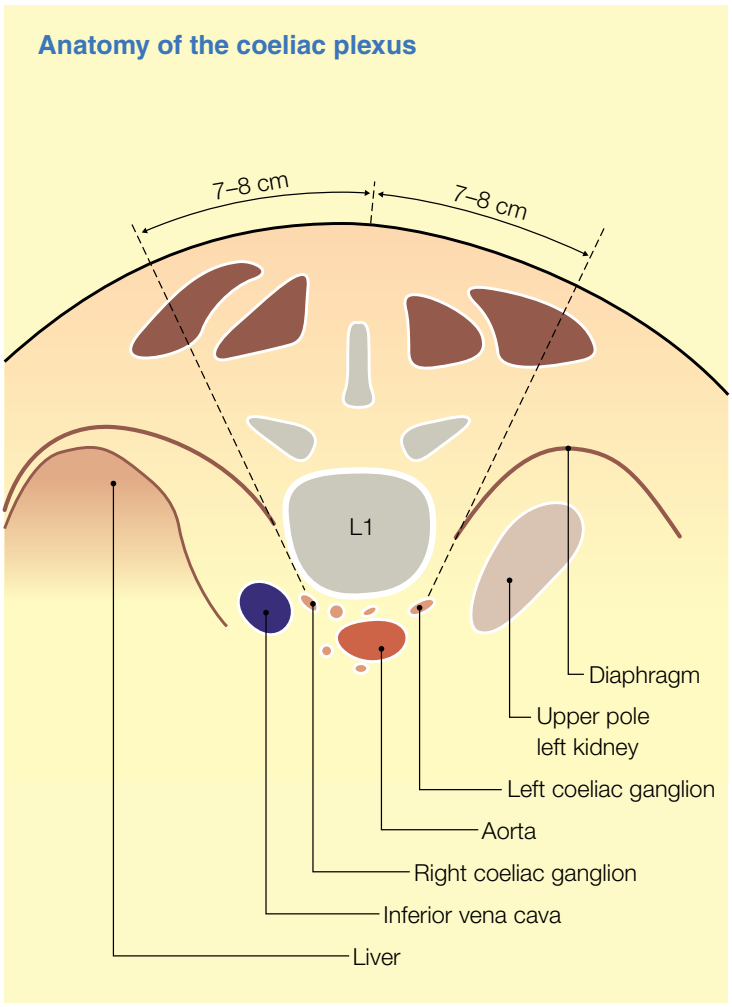
Over 50 trials have studied the benefits of coeliac plexus blockade (Figure 3) in abdominal cancer pain but only two are randomized controlled trials. Two meta-analyses have shown 70–90% relief for this treatment of pain in pancreatic cancer. It is widely used for the treatment of intractable pain in pancreatitis though the rare complication of paraplegia should be considered. More common complications include hypotension, diarrhoea, impotence (caused by decreased sympathetic function), pneumothorax and renal damage. Laparoscopic techniques have been proposed as a safer way to provide blockade without damaging the spinal arteries.

Pelvic cancer pain

Autonomic blockade in the form of a superior hypogastric block has been proposed as a form of analgesia for pelvic pain. This requires local anaesthesia or a neurolytic agent to be placed at the L5/S1 interspace. The lateral approach is similar to the technique for coeliac axis blockade, though the needle is directed 45° from a point 5–7 cm from the midline until the body of L5 is encountered. A medial approach has been described, which requires a needle to pass under the transverse process of L5, which can be impossible if sacralization of the lumbar vertebrae has occurred. Studies on this technique consist of case series used in the treatment of pelvic cancer pain.

Peripheral vascular disease

Lumbar sympathetic blockade and neurolysis has been shown to decrease pain in peripheral vascular disease. This is thought to result from a vasodilatory effect, though venous shunting has been shown to occur. It is useful in rest pain rather than for claudication. Technically the approach to blockade is similar to a coeliac plexus block, though at two levels lower. Some authorities propose a diagnostic block with local anaesthesia (10–15 ml of 2% lidocaine (lignocaine) or 0.5% bupivacaine) before embarking on a neurolytic procedure using 6% phenol, 3–5 ml. A common complication of this block is inner thigh pain, which is thought to be related to genitofemoral neuralgia.



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Other conditions

Herpes zoster

There is limited evidence that when sympathetic block is performed within 2 months of the onset of acute herpes zoster, there is a decrease in the incidence of post-herpetic neuralgia. It is postulated that this is due to an increased blood flow to the drug root ganglion, which prevents further neural damage.

Intractable cardiac pain

There is renewed incidence in the value of sympathectomy in the management of intractable angina. Most protocols propose a left thoracic sympathectomy initially. If no improvement occurs there is still benefit in attempting a left stellate ganglion block. There are case reports of the use of stellate ganglion block in the treatment of long QT syndrome and the possibility of post-block arrhythmias should be considered.

Erythromelalgia

Erythromelalgia is a rare syndrome of unknown cause, characterized by burning pain, redness, oedema and increased skin temperature in the legs or arms, or both. Sympathetic blockade reduces these symptoms. ◆

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Soft Tissue Pain and Physical Therapy

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Soft tissue pain is defined here as pain originating or appearing to originate from muscle, ligament or tendon. The phrase 'appearing to' is used because the pain may be referred from another tissue, usually in a proximal to distal direction.

Pathophysiology
Pain is a natural response to soft tissue injury and is one of the cardinal signs of inflammation. Acute pain is useful because it encourages protection of the damaged tissue, which gives it the best chance to heal. Prolonged pain can result in an established sensitization of the CNS from which pain will persist, independent of influences from the original soft tissue, resulting in chronic pain. The development of chronic pain is associated with psychosocial problems mediated at least partially by cortisol-based mechanisms. There will probably be some degree of neuroplastic changes towards chronicity related to central sensitization even in the sub-acute stage.

History
Acute soft tissue pain: the history invariably involves the application of a force to the tissue, excessive to its loading capacity, leading to structural damage. The force can be external (e.g. a physical blow) or it can come from within (e.g. by over-stretching). The patient can generally describe a specific incident with consequent pain.

A common form of soft tissue pain is exercise-induced muscle soreness that occurs gradually within 24 hours of unaccustomed, usually eccentric, exercise. It typically resolves after 72 hours with no associated damage.

Chronic pain, related, or perceived to be related to soft tissue, has a less obvious clinical history. There may or may not be a history of injury. It is obvious, however, that the pain has outlasted any useful process. The patient may have a psychosocial history of frequent healthcare use and many chronic pain sufferers have multiple somatic symptoms.

Differential diagnosis: structures giving rise to acute pain can be isolated by a history of injury, pain on palpation and pain on selective stretching or contraction of the tissue. Eliciting pain in the area of complaint by stressing distant tissues tests for referred pain. The determination of early neuroplastic changes which result in chronicity is a major diagnostic challenge and quantitative sensory testing methods are showing promise. Patients in the advanced stages of chronic pain typically have a long history of unsuccessful healthcare use from a variety of agencies. They often have signs of negative psychosocial traits such as depression and poor self-esteem. At this stage, attempts at differential diagnosis of a primary structure are meaningless, because the problem will have become dissociated from it.

Management
In an acute soft tissue injury, management of the underlying healing process ensures that pain at rest disappears with resolution of inflammation – usually within a week. There will be pain on movement and palpation for 3–6 weeks following injury. Pain after this time may be an early manifestation of neuroplastic changes towards chronicity. Inactivity because of pain rapidly leads to general and localized musculoskeletal and cardiovascular deconditioning. Therefore, a goal in acute pain management is prevention of chronicity. The cost of acute pain management is dwarfed by the severe human and socio-economic costs of chronic pain.

Acute pain
The aim of physical therapy for acute soft tissue pain is to restore the person to optimum function through early rehabilitation. There are long-standing anecdotal claims of its effectiveness. Heat, massage and exercise are the traditional methods of physical therapy for acute soft tissue pain.

- Cold is applied using sprays, contact packs and water baths to reduce bleeding, decrease inflammatory exudate and affect nerves to reduce pain. It is used as an immediate first-aid measure and a general pain-relieving modality, though it is less well tolerated than heat.
- Heat is applied to superficial tissues using contact heat packs, water baths or radiant infra-red lamps. Deeper structures can be heated using short-wave diathermy and ultrasound. Heating aims to improve tissue extensibility, increase blood flow and affect nerves to relieve pain. Heat should not be applied in the inflammatory or early healing stages of repair because it promotes bleeding and disrupts the newly forming circulatory system.
- Athermal electromagnetic energy is used to avoid the problems associated with heating tissue. It is applied with pulsed short waves, pulsed ultrasound and low-level light/laser to enhance the healing process and relieve pain.
- Electricity is used to stimulate nerves to reduce pain and there are also claims of optimizing the healing rate of tissue. Transcutaneous electrical nerve stimulation (TENS) devices are the most useful methods, though interferential current is also used.
- Acupuncture, sometimes combined with electricity, is now commonly used by physical therapists.
- Physical manipulation and mobilization of joints and soft tissue (e.g. massage, spinal manipulation) relieves pain by activation of nerves and/or by improved tissue extensibility.
- Exercise regimes are promoted and prescribed to improve the strength or extensibility of specific structures or to improve overall fitness and well-being.

Increased knowledge about the biological and biophysical effects of these methods and how they relate to mechanisms of pain has added weight to their claimed clinical effects. However, systematic reviews of clinical trials are almost unanimous in stating that there is insufficient scientific evidence of clinical effectiveness, with the low quality of trials proving a major barrier to such rigorous evaluation. (This criticism is not unique to physical therapies and harsh judgements should be reserved until the scientific evidence has matured.) Another barrier towards their evaluation is that the techniques tend to be used together in a wide number of permutations rather than on their own. There is further controversy in determining the optimum choice of dose and method of delivery of treatment.

Chronic pain
In chronic pain, a strictly biomedical approach aiming for cure is too limited to address the disabling effects of the pain. It is also potentially damaging because its lack of success can add to the patient's feelings of hopelessness, exacerbating the effects of chronic pain. Current thinking advocates a wider biopsychosocial approach to management, with clinicians and patients working together to maximize physical, functional and social activity while living with pain.

Biopsychosocial pain management is supported by scientific evidence and one of its cornerstones is physical therapy. A direct effect of chronic pain is that sufferers fear movement because they believe it will lead to tissue damage and more pain. Thus, they are inclined to do little for long periods, interspersed with relatively intensive bursts of activity when they feel more able. These intensive bursts of activity are liable to lead to flare-ups of pain, which promote further fear-mediated avoidance of activity and consequently further deconditioning.

Physical therapies such as ultrasound are likely to be counterproductive if used as putative agents of cure in a biomedical model of chronic pain. They may have a palliative role, but in biopsychosocial management of chronic pain the defining features of physical therapy are working with the patient to set activity-related goals and instilling habits of pacing of activity.

Physical therapy begins with educating the patient about living with chronic pain. The therapist explains the harmful effects of inactivity such as cardiovascular deconditioning and muscle wasting, which can have a marked effect. The therapist also helps patients to overcome their fear of movement, identifying the reasons for such fear and addressing misconceptions that lead to the belief that chronic pain is a sign of tissue damage. Gradual exposure to activity is a commonly used technique. Physical therapy encourages the patient to adopt an activity pattern of even pacing to smooth out the peaks and troughs of the activity–rest cycle. Education, goal setting and pacing are used to help the patient to cope with any flare-ups that occur. Physical therapy works best within a multidisciplinary team, and close liaison with the occupational therapy department, for example, benefits the rehabilitation of the chronic pain sufferer.

When acute injury occurs in someone with chronic pain, the difference between it and the concurrent chronic pain must be explained. The management of the acute pain should not compromise the continuing self-management of the chronic pain. Maintenance of general activity needs to be encouraged and successful resolution of the acute pain should not be allowed to raise false hopes of a similar reduction of the chronic pain.

Prognosis
The prognosis for acute soft tissue pain is good. Pain at rest should resolve of its own accord or under appropriate management within 1 week, and pain on movement and palpation should be gone within 3–6 weeks. A poor blood supply, however, will impair healing and leave the structure open to re-injury with recurrent pain. Another complicating factor is a history of excessive psychosocial stress, which has been shown to predispose an individual to chronic pain.

The prognosis of chronic pain is less certain. The pain is less likely to resolve and the associated negative effects of the pain on mood and psychological coping are likely to worsen without managed care. With managed care and continuing support, however, the chronic pain sufferer can be expected to attain a substantially high level of function and social participation. ◆

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Stimulation-produced Analgesia: Acupuncture, TENS and Alternative Techniques

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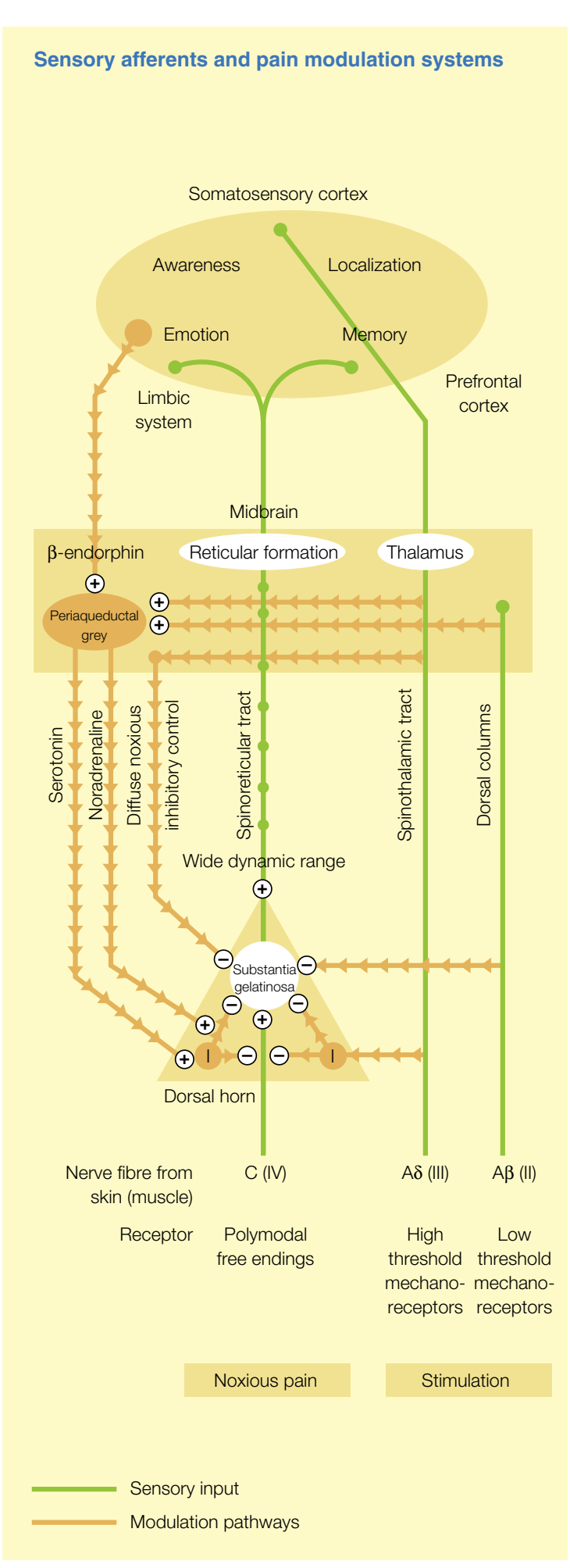
Stimulation techniques activate the body's intrinsic pain- modulation systems by the application of various forms of physical energy. Counter-irritation methods are not new. Acupuncture is described in *The Yellow Emperor's Book of Internal Medicine* in the 3rd century BC; the Egyptians used electric fish in 2500 BC and Hippocrates used them in 400 BC to treat headache and arthritis; the Romans understood the benefits of physical activity, hot baths and massage. We are now developing an understanding of the neurophysiological mechanisms underlying these techniques. Advances in basic science subsequent to the gate control theory of pain by Melzack and Wall in 1965 have provided a sound model around which research into this complex subject will revolve.

Noxious pain
Those suffering pain after tissue damage commonly describe it as aching, upsetting and poorly localized. Such sensory information originates in nonspecific peripheral polymodal nociceptors and travels via small, unmyelinated, slow C fibres to the first great relay centre in the substantia gelatinosa (between laminae 1 and 5) of the dorsal horn (Figure 1). Convergent wide dynamic range neurons act as gatekeepers to the slow, primitive, polysynaptic pathway to the reticular formation and onwards to complex integration in the great supraspinal centres. It is important to distinguish acute from chronic pain; the latter is associated with permanent excitability of the wide dynamic range cells (wind up) and formation of abnormal central neural connections (plasticity).



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Modulation of noxious pain
Dorsal horn (laminae 1 to 5): incoming noxious pain activity is reduced by inhibitory interneurons, presynaptic and postsynaptic inhibition, and specific receptors controlling ionic flux through nerve membrane channels. Modulatory input arrives via descending pathways and lateral branches from myelinated afferent A fibres. Aβ fibres arise in low-threshold mechanoreceptors (e.g. activated by conventional 'tingly' transcutaneous electrical nerve stimulation (TENS)) and Aδ in high-threshold (e.g. responsive to low-frequency needle manipulation). Pain-inhibiting neurotransmitters include metenkephalin, dynorphins A and B, and γ-aminobutyric acid. Cholecystokinin (CCK-8), substance P and other peptides antagonize the effects of spinal opioids and promote wide dynamic range excitability.

Supraspinal centres: the most important pain inhibitory neurotransmitter is β-endorphin, which is present in fibres connecting the hypothalamus to the periaqueductal grey. MRI scans and positron emission tomography have illustrated the many brain structures above the midbrain and thalamus that are activated by painful stimuli. Interconnections between the prefrontal cortex, limbic system (hypothalamus, hippo-campus, amygdala, cingulate gyrus) and reticular formation are responsible for the cognitive and emotional influences on the behavioural response to pain. There is widespread somatotopic projection in pain pathways and relay centres, in similar fashion to the well-known homunculus (with expanded face, hands and feet) in the somatosensory cortex.

Descending pathways: serotonin (5-HT) as a transmitter starts in the periaqueductal grey and descends to the dorsal horns in the spinal cord via the dorsolateral funiculus. Noradrenaline as a transmitter originates in the pons and descends in the same pathway. Diffuse noxious inhibitory control is a powerful pain-suppressing system triggered by painful stimulation anywhere in the body. All three pathways project to all segments of the spinal cord and inhibit dorsal horn activity.

Heterosegmental analgesia
Pain originating in one part of the body can be reduced by strong counter-irritation in another area. The noxious counter-irritant (localized to one segment) excites a loop, via the Aδ fibres, midbrain and descending tracts, to all segments not concerned with the noxious stimulus. Many techniques such as cupping, cautery, skin irritants, painful massage or joint manipulation, resemble acupuncture and TENS with respect to this powerful generalized effect.

Traditional Chinese acupuncture
Traditional Chinese acupuncture is a holistic system that was developed by meticulous observation over millennia. It incorporates elaborate concepts and theories to explain disturbed body functioning: Qi (the vital life energy flowing along meridians); bodily imbalance in the cosmic regulators Yin and Yang; re-establishment of normal equilibrium by insertion of needles at special points to disperse 'evil air'. Careful examination of the radial pulse and the tongue are essential aids to diagnosis. Europeans had been aware of these ideas for several hundred years but it took the reopening of China to the West after President Nixon's visit in 1972 to create a significant upsurge in medical interest. Many doctors undertook basic training in China and absorbed the classical theories to the extent that they could treat many common problems. Some developed their knowledge to an advanced degree. Others, convinced that acupuncture was effective, tried to rationalize it within the framework of known physiology and anatomy, and the Western scientific approach to acupuncture was born. Many modern practitioners no longer believe that meridians or discrete acupuncture points exist, yet they respect the observational skills of the ancient Chinese physicians. They have retained the ancient nomenclature and terminology and continue to use many of the powerful needling areas. Chinese 'Ah Shi' tender points correspond well with common musculoskeletal trigger points. Many other traditional Chinese points lie over nerve tracts or areas where nerves penetrate the superficial fascia.

Acupuncture treatment of tender areas
Trigger point therapy: common causes of trigger points are trauma, repetitive overstrain, emotional upset and excessive cold or heat. They are found in muscles, tendons, ligaments, joint capsules, periosteum and subcutaneous tissues. They may be active (producing unpleasant symptoms) or latent (found in symptomless people). They are usually localized to one body region and produce muscle weakness, shortening, palpable taut bands and fibrositic nodules. Often there is referred pain to an area distant from the trigger point, with a pattern specific to each disordered muscle. Pain is vague, poorly localized and unpleasant; for example trigger points in the sternomastoid in the neck may cause pain over the eye with no supraorbital tenderness. Deactivation may be by dry needling (acupuncture) or by wet needling (injecting dilute local anaesthetic or saline). Superficial needling into overlying subcutaneous tissues may also be effective.

Periosteal acupuncture may have a more powerful effect than subcutaneous or muscle stimulation. Selected known bony tender
areas may be 'pecked' by needles and radiation of pain noted. For example, needling the cervical articular pillar may produce pain radiation in the back, head or arms, and may be used to treat problems in the upper half of the body. The sacroiliac joint area may be used for problems in the lower back or legs.

Segmental acupuncture
Segmental acupuncture has been developed in The Netherlands over the past 15 years and draws together strands of known neuroanatomy and physiology. It is typical of the Western analytical approach. The body is divided into segments that comprise a dermatome, myotome, sclerotome and viscerotome, all having the same level of innervation and sensory input into the dorsal horn. The autonomic nerve supply within these segments is important because referred pain from internal organs is localized to the segmental dermatomes and myotomes (Figure 2).

Formulation of a segmental diagnosis

Disordered structure
Surface scars, old fractures, pathology of internal organs

Disordered function
Muscle hypertonicity, trigger points, palpitations

Segmental symptoms
Referred pain (visceral and musculoskeletal), hyperalgesia, autonomic upset (poor circulation, disordered sweating, pilomotor dysfunction, swellings, oedema, bone resorption)

2

Treatment of pain and muscle dysfunction is by stimulating segmental Aβ and Aδ fibres. This can be done by pressure, massage, muscle stretching, TENS or acupuncture. Dry or wet needling may be used near tender areas and in segmental skin, muscle and periosteal points. Depth of insertion is important. For example, the bladder 23 point lateral to lumbar 2 spine is on the thoracic 11 dermatome, but overlies the cervical 6/7/8 myotomes (latissimus dorsi) and the lumbar 2 sclerotome.

Electroacupuncture analgesia and TENS
Electroacupuncture analgesia via needles is usually restricted to the clinical environment. Low-cost TENS machines with reusable electrodes are commonly used in the domestic environment. Electrical stimulation has superseded repetitive manual twirling because it allows stimulation intensity and frequency to be controlled precisely (Figure 3). The distinction between conventional TENS and electroacupuncture analgesia has become blurred by the efficiency of modern skin electrodes and the variety of stimulation modes on modern stimulators.

Frequency dependent analgesia

Via Aβ fibres
- Recruited at 50–200 Hz
- Low intensity stimulation
- Occurs immediately
- Lasts only as long as stimulation
- Increased dynorphins in dorsal horn
- κ receptor activated in dorsal horn

Via Aδ fibres
- Recruited at 2–4 Hz
- High intensity stimulation
- Occurs after 20–30 minutes
- Lasts hours to days after cessation
- Increased metenkephalin in dorsal horn
- μ receptor activated in dorsal horn

Low frequency stimulation should be restricted to 20 minutes, because periods in excess of this produce increased levels of the pain facilitatory, opioid antagonist, CCK-8, in the dorsal horn. When electroacupuncture analgesia is used as pre-emptive analgesia for minor operations, or as the analgesic component for balanced general anaesthesia, the benefits may be maximized and prolonged by stimulating at varying frequencies between 2 and 100 Hz. This will produce dynorphins and enkephalins in the dorsal horn, β-endorphin in the hypothalamus and periaqueductal grey, and will prevent production of CCK-8.

Both electroacupuncture analgesia and TENS have been used successfully for a variety of chronic pain conditions. At low frequencies, care must be taken that painful muscle contractions do not occur. Patients may become tolerant to conventional TENS after weeks to months of good relief. Efforts to avoid this include using complex waveforms, randomly distributed pulses, multiple electrodes, and ramped pulses of rising intensity. An interesting new device (transcutaneous spinal electroanalgesia) uses ultrashort bursts of high voltage stimulation via skin electrodes along the central dorsal spine, with effects similar to dorsal column stimulation.

Microsystems

Auriculotherapy was popularized by Nogier in France in the 1970s. He mapped correspondence points in the ear for the entire body. The body is represented in an upside down position with the head in the lobe facing forwards. The spine runs up along the cartilaginous ridge on the outer ear with the lower limbs near the apex. The face, hands and feet have a relatively large projection just as in the somatosensory cerebral cortex. Nogier noted that physical pathology may be diagnosed by pressure sensitivity and skin resistance changes at the appropriate ear point. Treatment via needles, press studs, adhesive metal beads or electrical stimulation at this point produces analgesia in the distant muscle or joint. Other microsystems have been described in the scalp, face, hands and feet. Reflexology involves massaging relevant parts of the body map on the soles of the feet to treat systemic conditions.

Related complementary methods

Many complementary methods have a segmental approach and produce selective stimulation of Aβ and Aδ fibres. Physiotherapists use many techniques that stimulate receptors in joint capsules, muscles and skin (manipulation, muscle stretching, massage, vibration, ultrasonics, and hot or cold applications). Patients may be trained to apply acupressure themselves (e.g. pressing directly over trigger points). German neuraltherapy (therapeutic local anaesthesia) uses segmental diagnosis and involves injections around nerves, muscle tender points and selected periosteal areas. Chiropractic techniques use sudden thrusts to correct disorders of spine and joints. Osteopathy has a more holistic approach to restore function and posture via gentle massage and joint manipulation. There are numerous massage styles (e.g. Shiatsu, Rolfing). Some are fairly painful and recruit heterosegmental mechanisms. The Finnish sauna with hot baths, beating with birch leaves, and sudden cold immersion, is another example. Laser devices are available (particularly for needle phobics and children) but there is no Aδ stimulation and benefits may be related to tissue-healing properties rather than to pain modulation.

Unanswered questions

Prolonged pain relief – it is common for patients with chronic musculoskeletal problems to achieve relief and functional improvement lasting weeks or months after a single 10 minute acupuncture session. Professor Han of Beijing has proposed that there may be a reverberating mesolimbic loop of analgesia involving midbrain structures and periaqueductal grey to maintain descending modulatory activity.

Convergence – somatotopic convergence within central CNS structures is assumed to be the anatomical explanation for the various microsystems; the exact mechanisms are unknown.

Facilitation – little is known about the central and descending pain facilitatory systems and their role in maintaining chronic pain. The effects of counter-irritation methods are unknown. ◆

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Adverse Sequelae of Spinal Anaesthesia and Management of Postspinal Headache

E Anne Thornberry

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Adverse sequelae from spinal anaesthesia can occur early or late and be minor or major (Figure 1). An early complication occurs at the time the spinal anaesthetic is performed or during the course of the anaesthetic. Late complications present after the spinal anaesthesia has resolved. Minor adverse sequelae cause temporary discomfort or inconvenience to the patient while major sequelae are potentially life-threatening or result in prolonged or permanent signs or symptoms. There is some overlap between the groups. Early complications may be the origin of late sequelae and minor complications can become major if they are not managed appropriately. Late, major sequelae are uncommon. Serious complications, excluding postspinal headache, occur in about 1/22,000 spinal anaesthetics.

Adverse sequelae of spinal anaesthesia

Minor
Early complications
- Localized trauma
  - Localized pain
  - Root pain
- Bloody tap
- Failure of block
  - Dry tap
  - Inadequate spread
- Nausea and vomiting
- Pruritus

Late complications
- Neurapraxia
- Urinary retention
- Backache
  - Localized haematoma
  - Muscle spasm
  - Ligament strain

Major
Early complications
- Hypotension
- Bradycardia
- Respiratory depression
  - High block
  - Opiates
- Total spinal
- Local anaesthetic toxicity
  - Intravenous injection
  - Excessive dose
- Allergic reactions to local anaesthetic

Late complications
- Low CSF pressure symptoms
  - Headache
  - Neck stiffness
  - Tinnitus
  - Photophobia
  - Cranial nerve lesions
  - Subdural haematoma
- Meningitis
- Nerve root damage
  - Axonotmesis
  - Neurotmesis
- Spinal cord injuries
  - Trauma (e.g. needle damage, injection of local anaesthetic, injection of air)
  - Spinal cord ischaemia (e.g. compression, epidural abscess, epidural haematoma, anterior spinal artery syndrome)
  - Neurotoxic damage (e.g. arachnoiditis)
  - Cauda equina syndrome

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Minor sequelae

Early complications
Pain: localized pain on insertion of spinal anaesthesia can be minimized by good technique. Root pain is more difficult to avoid. Both of these complications are generally of short duration, but if multiple attempts are made to perform the dural puncture, localized bruising can occur, prolonging the discomfort.

Bloody tap describes the puncture of an epidural vein. It makes identification of the subarachnoid space difficult because blood can occlude the spinal needle. A dry tap describes the failure to find the dural sac. Both of these complications cause discomfort as a result of repeated attempts to achieve spinal anaesthesia.

Emesis: hypotension is a common accompaniment of spinal anaesthesia and is the most common cause of nausea and vomiting. Intrathecal opiates can also trigger emesis and may cause significant pruritus. The use of vasopressors, anti-emetics and small doses of an opiate antagonist can minimize these adverse sequelae.

Late complications
Nerve damage: neurapraxia describes an injury in which the nerve and axonal sheath remain intact. Recovery is complete and can be rapid or take several weeks. Generally neurapraxia is caused by stretching or compression of a nerve rather than direct trauma.

Urinary dysfunction: the urge to micturate is blocked during spinal anaesthesia and may lead to urinary retention in the immediate postoperative period. Care must be taken to prevent over-distension of the bladder, which can cause ischaemia of the submucosal stretch receptors in the bladder wall, resulting in prolonged bladder dysfunction.

Backache is commonly the result of local bruising of the soft tissues or periosteum. Ligament strain can occur if joints are stretched beyond their normal range of movement and is more likely if this position is held for some time (e.g. in lithotomy). Muscle spasm can be triggered by localized trauma and can be severe. It generally responds to bed rest and anti-inflammatory analgesics.

Major sequelae

Early complications
Cardiovascular disturbances: hypotension and bradycardia are the result of the normal physiological response to blocking the autonomic nervous system. Hypotension is exacerbated by hypovolaemia and under these circumstances can be severe and life-threatening. Obstetric patients are also at increased risk because of aorto-caval compression in the supine position.

If the spinal blockade extends beyond the level of T1, the sympathetic output to the heart is disrupted, resulting in profound bradycardia requiring rapid administration of an anticholinergic agent (e.g. atropine). Sudden-onset hypotension and bradycardia associated with nausea and vomiting and sweating is likely to be caused by a vasovagal faint.

Respiratory depression may be the result of extensive spread of the spinal anaesthesia blocking all the intercostal muscles. Above C6 all the muscles of respiration are paralysed and artificial ventilation is required. If opiates have been given intrathecally their direct action on the respiratory centre can cause respiratory depression; this can be delayed and present as a late complication.

Total spinal block is a spinal anaesthetic that spreads to include all spinal segments and the brain. It occurs if an excessive dose of local anaesthetic is administered. The patient experiences loss of consciousness, profound hypotension, bradycardia and respiratory arrest and requires urgent resuscitation to prevent cardiac arrest.

Local anaesthetic toxicity is extremely unlikely with spinal anaesthesia alone because the normal therapeutic dose is well within the margins of safety. Allergic reactions to local anaesthetics are extremely uncommon but some have been reported.

Late complications
Low CSF pressure: postspinal headache is the headache associated with low CSF pressure after a spinal anaesthetic and is also known as a postdural puncture headache. It is a severe, fronto-occipital headache and is classically postural, becoming more severe in the upright position. Associated symptoms include neck stiffness, tinnitus and photophobia. The headache is caused by loss of support of the brain tissue owing to a leak of CSF from the dural puncture site. This results in traction on innervated tissues such as the venous sinuses. Compensatory cerebral vasodilatation may contribute to the symptoms. Traction on the VIth cranial nerve can cause diplopia. Prolonged low CSF pressure can cause subdural bleeding as a result of tearing of the dural blood vessels.

Meningitis: a postspinal headache must be differentiated from meningitis. Meningitis may also present with headache and neck stiffness, but it is unlikely to be postural. It is associated with a fever and a raised WBC count. Meningitis may be septic, secondary to bacterial infection, or aseptic, secondary to chemicals, blood, pyrogens or viral infection.

Traumatic damage to nerve roots and spinal cord: direct injury to the spinal nerve roots or the spinal cord by needle damage or injection of local anaesthetic or air into the tissues can cause axonotmesis and neurotmesis. Axonotmesis is a degeneration of the axon with the axon sheath remaining intact; recovery is complete but slow. Neurotmesis describes disruption of both the axon and sheath with little chance of complete recovery. Both these injuries are extremely painful when they occur, but this early warning sign is lost if the procedure is performed under general anaesthesia.

Other spinal cord injuries
Infarction of the spinal cord can occur if the capillary blood flow to the cord is reduced for a significant length of time. This can result from severe arterial hypotension, direct compression of the capillary bed, venous hypertension or a combination. The blood supply to the spinal cord is from one anterior artery and two posterior spinal arteries. There are no anastomoses between the anterior and posterior arteries. Anterior spinal artery syndrome is a description of the neurological deficit that occurs if the anterior blood supply is interrupted but the posterior supply remains intact.

Haematoma and abscess formation are two recognized causes of cord compression leading to ischaemic damage. Puncture of an epidural vein with a spinal needle is unlikely to induce a significant haematoma in a normal individual but could do so in the presence of a coagulopathy or anticoagulation. An epidural abscess can develop as a result of introducing organisms from the skin or haematogenous spread. Initially, both present with backache and marked localized tenderness over the spine. An abscess may also present with malaise, fever and headache. Severe backache, weakness or bladder and bowel symptoms are late signs and indicate that urgent spinal decompression is required within 6–12 hours.

Arachnoiditis is inflammation of the arachnoid and pial meninges. Lignocaine can be neurotoxic in high doses and has been implicated in cases associated with the use of spinal catheters. Preservatives have also been blamed, in particular sodium bisulphite in the original chloroprocaine formulation. A feature of arachnoiditis is that the onset of neurological symptoms can be delayed and progressive.

Cauda equina syndrome describes a combination of leg weakness, perineal sensory loss, and urinary and faecal incontinence. This may be the result of trauma, ischaemia or chemical toxicity.

Management of postspinal headache

The reported incidence of postspinal headache is variable; with 25–27 G atraumatic needles the incidence is less than 1%. Younger patients are more vulnerable than older patients, women more than men, and pregnant women are at the greatest risk. Pencil-point, atraumatic spinal needles (e.g. Whitacre, Sprott) are thought to cause fewer headaches because they part the fibres of the meninges. Bevelled needles (e.g. Quincke) are more likely to cut the fibres.

The severity of symptoms range from a mild, postural headache to a severe, debilitating headache. It is usually self-limiting, resolving within 6–8 days, but can persist for months. The differential diagnosis includes a nonspecific headache, migraine, meningitis, intradural, extradural and subdural haematoma, pneumoencephalus, sinusitis or a headache associated with hypertension.

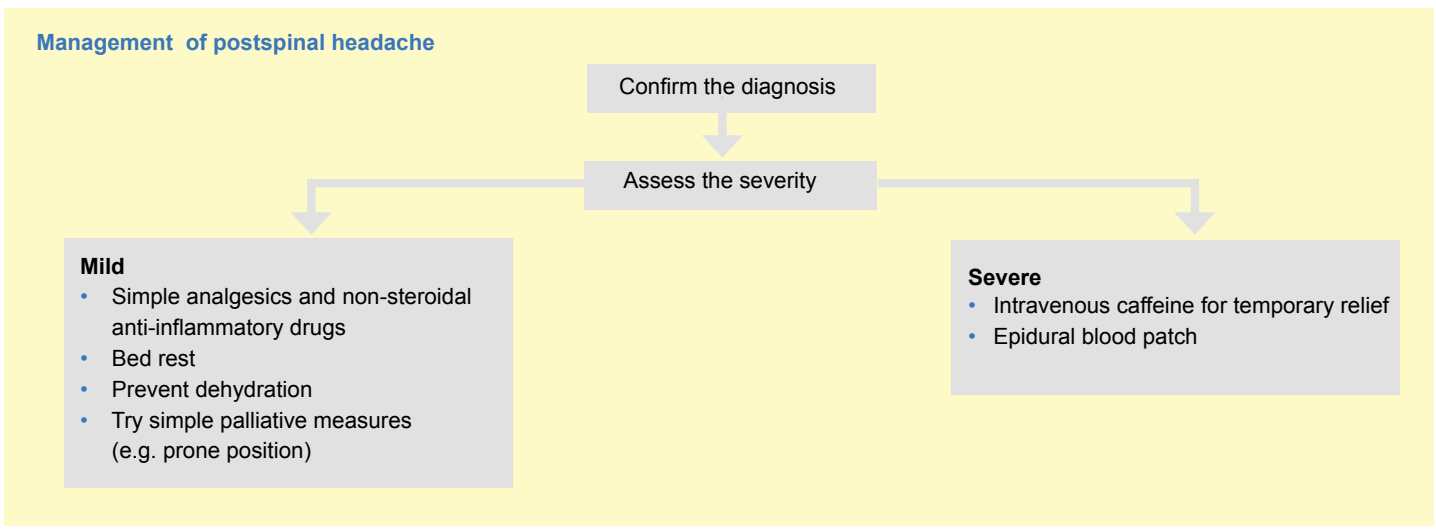
Mild symptoms

Mild symptoms can be managed with conservative treatment (Figure 2). Simple analgesics should be prescribed regularly, for example paracetamol, 1 g 4-hourly with a maximum dose of 4 g in 24 hours, or non-steroidal anti-inflammatory drugs (e.g. diclofenac, 50 mg 8-hourly). The patient should be encouraged to drink sufficient fluids to prevent dehydration. There is no proven benefit to overhydrating the patient with intravenous therapy but if the patient is unable to take adequate oral fluids this may be necessary. Bed rest helps to relieve symptoms. Raising the intra-abdominal pressure using abdominal binders or by asking the patient to lie prone can also provide relief. This rise in pressure is transmitted to the epidural veins and indirectly raises CSF pressure.

Attempts to use drugs to increase the rate of production of CSF have not proved beneficial. The use of intravenous sodium caffeine benzoate, 500 mg diluted in 1 litre of normal saline, infused over 1 hour, can reverse the cerebral vasodilatation and produce temporary relief. It is used as a palliative measure to support a patient until more definitive treatment can be instigated.

Severe symptoms

Severe or persistent symptoms are treated using an epidural blood patch (Figure 2). The principle of this procedure is to inject the patient's own blood into the epidural space. This has two actions – it indirectly increases CSF pressure, providing instant relief, and it clots over the hole, preventing further CSF leak until the hole closes spontaneously. The efficacy of this procedure is high, though it is not uncommon to require a second blood patch. The technique has a good safety record but backache after the procedure is common and may last for 2–3 days. The success of the epidural blood patch is improved if at least 15 ml of autologous blood can be injected. The injection should be slow, over at least 2 minutes, but if pain or paraesthesia develop, the procedure should be discontinued. Strict asepsis must be used to avoid meningitis. After the procedure, the patient should lie supine for a minimum of 30 minutes followed by gentle mobilization.



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Care of the Postoperative Unconscious Patient

Jenny Tuckey

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In the period immediately after surgery, the patient should be closely monitored in the recovery room or postanaesthesia care unit. The anaesthetist will delegate further care of the patient to a specially trained nurse. A comprehensive handover should be given that includes the patient's age and premorbid state, details regarding surgery, vascular access, invasive monitoring, peroperative analgesia and blood loss where indicated. Provision should have been made for postoperative analgesia and fluids.

The most important areas for close attention are:

- **a**irway
- **b**reathing and gas exchange
- **c**irculation
- unconscious state
- pain management
- temperature
- wound.

Airway of the unconscious patient

All airway emergencies can lead to hypoxaemia, hypercapnia and ultimately death if not promptly recognized and treated. Airway emergencies include:

- soft tissue obstruction
- laryngeal spasm
- laryngeal oedema
- haemorrhage
- tracheomalacia after thyroid surgery
- tumour.

The most common emergencies are discussed below.

Soft tissue obstruction occurs when the pharynx is blocked and the passage of respiratory gases is prevented. The most common cause is the tongue. Clinical signs of airway obstruction include snoring or crowing, flaring of the nares, and tracheal tug. With total obstruction, there is asynchronous movement of the chest and abdomen, and an absence of breath sounds and air movement at the mouth.

Treatment − the presence of foreign bodies in the mouth must be excluded. Manoeuvres such as chin lift and jaw thrust usually displace the tongue and improve the airway. A well-lubricated oral or nasal airway may help. Oral airways may provoke gagging, coughing, vomiting or laryngeal spasm in a semiconscious patient. A nasopharyngeal airway is tolerated better in an awakening patient but may provoke epistaxis.

Laryngeal spasm is a common cause of airway obstruction in the immediate postoperative period. This reflex contraction of the vocal cords may cause partial or complete obstruction. It is more common in children, smokers, asthmatics and following upper airway surgery. It may be provoked by secretions, extubation of the trachea or insertion of an artificial airway in a semiconscious patient. Optimal positioning or the use of an artificial airway does not relieve the obstruction.

Treatment − the patient's airway should be suctioned gently; 100% oxygen should be administered. Continuous positive airway pressure (CPAP) or gentle intermittent positive pressure ventilation should be applied by face mask. Care should be taken to avoid over-vigorous ventilation because oxygen will enter the stomach and encourage reflux and splinting of the diaphragm. If hypoxaemia ensues, prophylactic atropine, 600 µg i.v., will prevent bradycardia. Suxamethonium, 0.1−0.2 mg/kg, relaxes the cords and enables oxygenation. If the patient is at risk of aspiration, they should be re-intubated.

Laryngeal oedema: problematic swelling of laryngeal tissues occurs most often in children because of the small calibre of their airways. It results in stridor, inspiratory retraction of soft tissues, and a croup-like cough. It may be caused by laryngeal mucosal ischaemia following the use of an excessively large tracheal tube, trauma during intubation, or allergy.

Treatment − humidified oxygen should be administered; nebulized adrenaline, 5 mg in saline, and dexamethasone may also be required. In awake patients, the erect posture is beneficial. Anaphylaxis requires treatment with incremental intravenous adrenaline. Re-intubation may be necessary.

Breathing and gas exchange in the immediate postoperative period

Respiratory complications are the primary cause of life-threatening morbidity in the recovery room.

Postoperative hypoxaemia: arterial hypoxaemia is defined as an arterial oxygen tension less than that predicted for the patient's age and the prevailing barometric pressure. The causes of postoperative hypoxaemia are discussed below.

Decreased inspired oxygen − in practice, this occurs as a result of diffusion hypoxia. Nitrous oxide is about 35 times more soluble in blood than nitrogen. Following nitrous oxide anaesthesia, nitrous oxide diffuses out of the blood and into the alveoli in larger volumes than nitrogen diffuses in the opposite direction. As a result, the alveolar concentration of oxygen falls and arterial hypoxaemia may occur if the patient breathes room air. Diffusion hypoxia may be avoided by administering supplemental oxygen for 10 minutes after nitrous oxide anaesthesia.

Alveolar hypoventilation results from either abnormal control of breathing or abnormal mechanics of breathing (Figure 1). The elderly or debilitated are at greater risk of respiratory depression.

• Abnormal control of breathing – treatment is with oxygen, with awareness of the risk of normal haemoblobin oxygen saturation with hypercarbia. Use of naloxone, doxapram and flumazenil should be considered. The patient may require postoperative ventilation.

• Abnormal mechanics of respiration – the underlying cause should be treated. Oxygen should be given and drug treatment reversed. Bronchodilators and ventilation with or without a tracheal tube should be considered.

Increased ventilation/perfusion mismatch − anaesthesia induces a gas exchange abnormality as a result of atelectasis in the dependent parts of the lung. This is caused by a reduction in the functional residual capacity (FRC). FRC is reduced because of diminished inspiratory muscle tone at the induction of anaesthesia, resulting in loss of outward elastic recoil of the chest wall.

Cranial displacement of the diaphragm is due to a reduction in its muscle tone, so that it is no longer able fully to oppose the hydrostatic pressure of the abdominal contents. Reduction in FRC occurs whether the patient is paralysed or breathing spontaneously.

Airway closure becomes important when FRC is less than the closing capacity. The resulting airway closure and gas trapping causes an increase in venous admixture and shunt. Airway closure increases with advanced age and obesity. Abdominal incisional pain causes reflex diaphragmatic dysfunction. Shunt occurs with pulmonary oedema of any aetiology, consolidation and pulmonary aspiration.

Initial treatment includes oxygen therapy and management of the underlying cause (e.g. analgesia for pain). Effective epidural analgesia and aggressive chest physiotherapy optimize postoperative lung function after major trunk surgery.

Causes of alveolar hypoventilation

Abnormal control of respiration

- Drugs – volatile agents, induction agents (except ketamine), opioids (parenteral, 'spinal')
- Recent hyperventilation
- Preoperative CNS – trauma, haemorrhage, tumour
- Peroperative CNS – haemorrhage, thrombosis, emboli
- Hypothyroidism
- Hypothermia
- Obstructive sleep apnoea

Abnormal mechanics of respiration

- Upper airway obstruction
- Muscle weakness – residual neuromuscular blockade, muscle disease, aminoglycosides, electrolyte disturbance
- Abdominal 'splinting' – obesity, abdominal distension, pain, tight dressings
- Bronchospasm – known asthmatic, presence of tracheal tube, anaphylaxis
- Chest wall abnormality – congenital, trauma
- Phrenic nerve dysfunction – idiopathic, brachial plexus block, 'total' spinal

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Cardiovascular system

The cardiovascular system may be deranged immediately postoperatively. Commonly encountered problems are discussed below.

Postoperative hypotension can be caused by a reduction in preload, contractility or afterload.

Reduced preload is caused by loss of intravascular volume or diminished venous return. The most common causes of reduced preload are blood loss (e.g. on-going or inadequately replaced, exacerbated by coagulopathy), 'third space' losses and capillary leak. Reduced venous return can result from:

- postural changes (e.g. head-up tilt especially with regional block)
- supine hypotension syndrome (in late pregnancy)
- raised intrathoracic pressure (e.g. positive end-expiratory pressure, tension pneumothorax)
- massive pulmonary embolism (reduced return to the left atrium).
- residual effect of venodilating drugs (e.g. induction agents, volatile agents and glyceryl trinitrate).

Treatment involves enhancing venous return (e.g. by optimizing patient posture) and administering fluids. In difficult cases, a central venous line is a useful guide to fluid requirements.

Reduced myocardial contractility may be caused by the residual effect of anaesthetic drugs, pre-existing ventricular dysfunction or new myocardial ischaemia. It may be compounded by hypoxia, ischaemia, arrhythmias, hypothermia and acid–base or electrolyte disturbance.

Treatment aims to correct hypoxia, acid–base and electrolyte disturbance, and to optimize preload. Inotropes should be used if there is evidence of myocardial dysfunction. Ischaemia should be documented with an ECG and glyceryl trinitrate therapy considered.

Decreased afterload − postoperative causes of decreased afterload (reduced systemic vascular resistance) include diminished sympathetic tone secondary to regional block, vasodilators, septic shock and rewarming. Treatment involves optimizing preload, and use of vasopressors if there is clear evidence of reduced systemic vascular resistance.

Postoperative hypertension: the most common causes of postoperative hypertension are:

- pain (from wound, full bladder)
- pre-existing hypertension
- administered vasopressors
- hypoxia/hypercarbia.

The underlying cause should be treated (e.g. morphine for pain, catheterize bladder) and oxygen administered. Specific antihypertensive therapy may be required (e.g. hydralazine, β-blockers, nifedipine).

Myocardial ischaemia/infarction occurs most often in patients with a history of recent myocardial infarction, cardiac failure, arrhythmias, advanced age, aortic stenosis, or hypertension, or in those undergoing vascular or major trunk surgery. It occurs as a result of adverse myocardial oxygen supply/demand ratios (e.g. with hypoxia, hypotension, tachycardia or hypertension).

Extrinsic causes should be treated, and both oxygen and glyceryl trinitrate (sublingual or by infusion) administered. If there are no contraindications, low-dose aspirin should be given in case of infarction. Thrombolysis is contraindicated because of the recent surgery and the risk of haemorrhage.

Left ventricular failure implies reduced myocardial contractility and increased pulmonary capillary hydrostatic pressure resulting in pulmonary oedema. Reduced cardiac output results in impaired cognition, cool moist skin, oliguria and metabolic acidosis. Pulmonary oedema causes tachypnoea, hypoxia, cyanosis, fine-end inspiratory crepitations, and pink frothy sputum.

Treatment includes combinations of therapies to reduce preload and afterload, and increase cardiac contractility (e.g. oxygen, frusemide, inotropes, nitrates, incremental intravenous diamorphine and adoption of the sitting position).

Arrhythmias are usually benign but their effect on cardiac output should be ascertained. If new, a cause should be sought and treatment begun where possible.

The causes of arrhythmias include:

- residual anaesthetic drugs and gases; some inhalational agents (e.g. halothane) sensitize the myocardium to catecholamines
- pre-existing heart disease
- myocardial ischaemia
- hypoxaemia, hypercarbia, electrolyte and acid–base imbalance; hypokalaemia predisposes to arrhythmias and exacerbates digoxin toxicity
- increased sympathetic drive from pain
- increased vagal tone
- hypothermia.

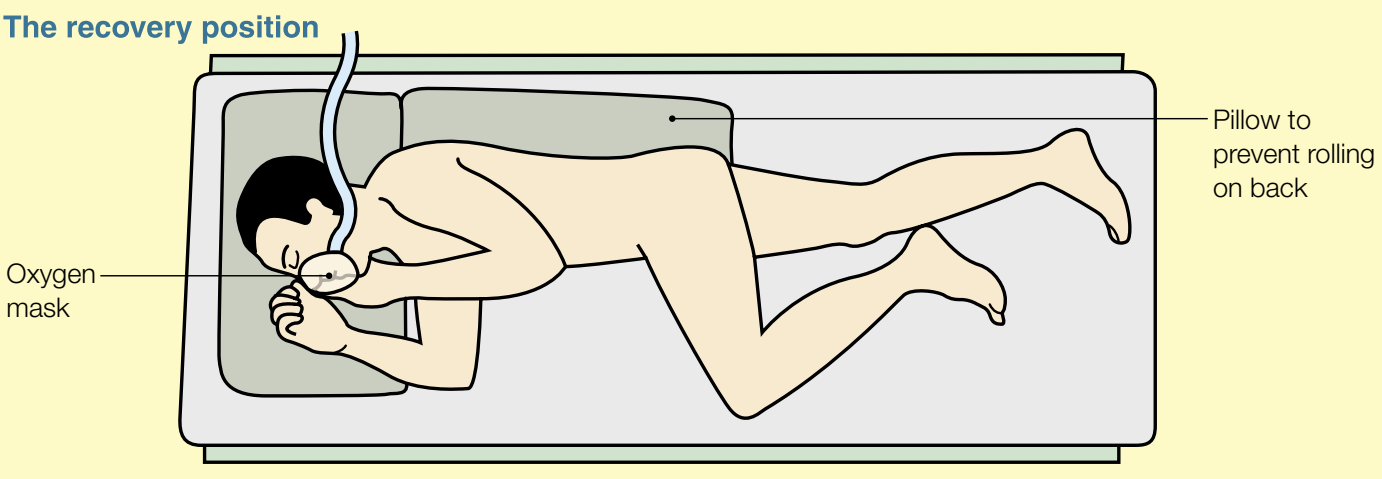
The common arrhythmias include sinus tachycardia, bradycardia, supraventricular tachycardias (SVT), ventricular tachycardias (VT) and conduction defects including complete heart block. Treatment should be individually tailored (e.g. analgesia for pain-induced sinus tachycardia, cardioversion for SVT and VT, and electrical pacing for complete heart block).

‘Neurological’ care of the unconscious postoperative patient

Patient posture: the position of choice for any unconscious patient is the ‘recovery’ position (Figure 2). This position displaces the tongue anteriorly, encouraging anterior displacement of secretions or vomitus. However, there are situations when the immediate postoperative position is determined by other factors (e.g. supine position if there is spinal instability or head-up tilt following neurosurgery).

When ‘recovering’ an unconscious patient, care must be taken to reduce skin damage in ‘pressure areas’. Padded cot-sides may be useful if the patient is restless. If recovery of consciousness is prolonged, the eyelids should be kept closed to prevent corneal drying and care should be taken to avoid corneal abrasions. Venous access ports must be accessible and secure, and catheters and drains should be positioned so as to be visible and facilitate drainage.

The recovery position



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Prolonged loss of consciousness: the duration of the unconscious state depends on:

- drugs used − long-acting drugs or drugs with active metabolites may cause delayed awakening
- duration of surgery − there is a greater potential for accumulation of drugs with repeated doses
- patient’s age − drug metabolism may be impaired with increasing age
- any intercurrent disease − renal, hepatic and thyroid pathology and hypothermia may result in delayed metabolism and clearance of sedative drugs
- adverse intraoperative events − hypoglycaemia, hyperglycaemia, cerebral ischaemia/hypoxia, thrombosis, haemorrhage, hypercarbia, a total spinal and the transurethral resection of the prostate syndrome.

Care of the postoperative unconscious patient

Care should be directed towards managing pain, temperature and the surgical wound.

Pain: in order to minimize sympathetic activation and ensure a comfortable return to consciousness, adequate analgesia must be administered and prescribed (e.g. intravenous morphine, epidural topped up).

Temperature: postoperatively, the patient’s temperature may be normal, increased or decreased.

Pyrexia may be caused by pre-existing fever, secondary to febrile transfusion reaction or, rarely, by malignant hyperthermia.

The patient should be cooled by fanning, tepid sponging and paracetamol suppositories. The source or cause of the pyrexia should be treated (e.g. transfusion should be stopped). In the case of malignant hyperthermia, administration of the causative agent should cease, and 100% oxygen, fluids, dantrolene, 1−10 mg/kg, and mannitol should be given. Any acid–base and electrolyte imbalance must be treated urgently.

Hypothermia is common perioperatively and may be defined as a core temperature of less than 36°C. Hypothermia can occasionally be advantageous (e.g. cerebral preservation before cerebral insult such as hypoxia or ischaemia); generally, however, hypothermia has adverse physiological effects on the postoperative patient. These include increased incidence of myocardial ischaemia, coagulopathy and delayed wound healing.

General anaesthesia resets the thermal inter-threshold range so that heat generating/conserving mechanisms are not activated until the core temperature has fallen by about 2.5°C. General anaesthesia causes a reduction in the basal metabolic rate, inhibits shivering and reduces the patient’s ability to conserve heat by vasoconstriction. Unaided rewarming postoperatively may cause adverse physiological alterations. The muscular activity of shivering causes a significant increase in metabolic rate, and oxygen consumption may increase as much as fivefold. This coincides with the period of recovery when the patient is most likely to become hypoxaemic for other reasons.

The incidence of postoperative shivering is 5−65%. It is more common after longer procedures, in young men, during anaesthesia employing spontaneous ventilation and following volatile rather than total intravenous anaesthesia. Surprisingly, there is a poor correlation between body temperature and the incidence of shivering postoperatively.

Hypothermia may be compounded by the sympathetic block associated with regional blockade. This ablates the core–shell divide and increases heat loss.

Methods of rewarming postoperative patients include use of a forced-air warming device, warmed fluids and minimizing skin exposure. Irrigation of body cavities (bladder) with warmed fluids may be used in severe cases. A number of drug remedies have been shown to reduce shivering (e.g. intravenous pethidine, 0.3 mg/kg, via κ receptors, and doxapram, 1.5 mg/kg).

Surgical wound: the wound should be inspected for bleeding, swelling, cyanosis or ischaemia. The circulation distal to rigid orthopaedic plasters and devices should be monitored for signs of ischaemia.

When wound haemorrhage occurs, pressure should be applied to bleeding points. If limbs are at risk of swelling they should be elevated. The surgeon should always be informed in cases causing concern to the anaesthetist or recovery room staff.

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Causes and Treatment of Postoperative Nausea and Vomiting

Shakil Abbas

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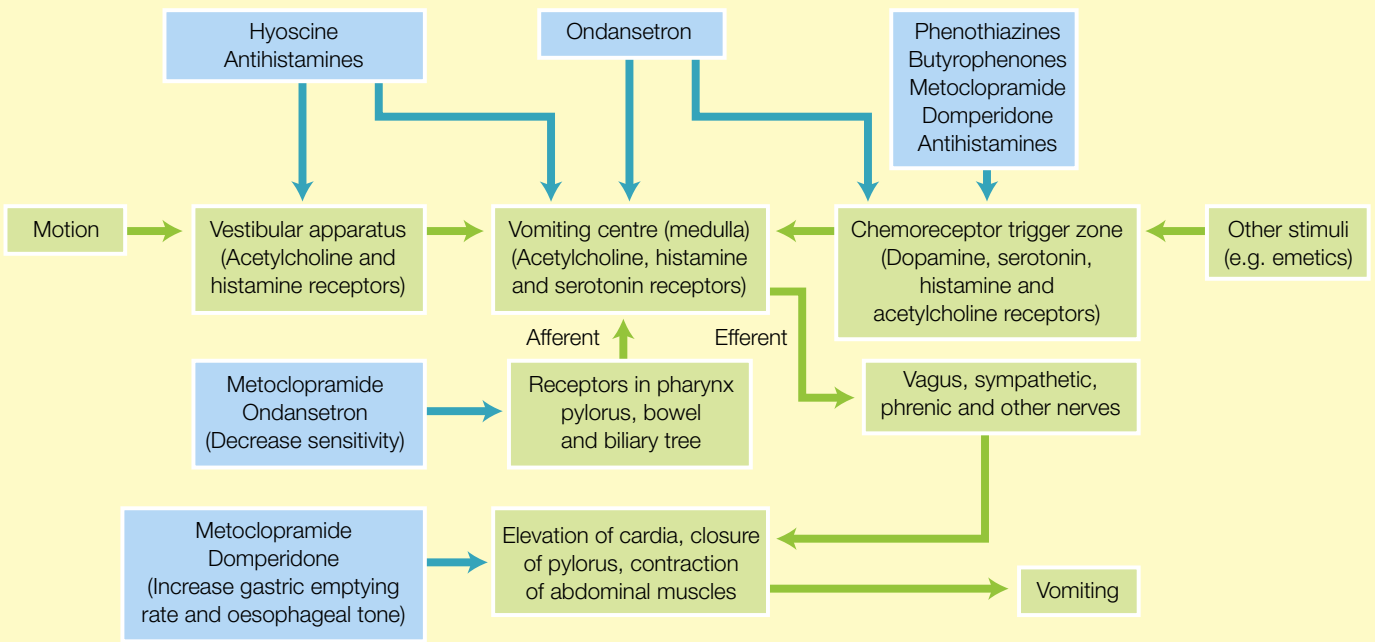
Postoperative nausea and vomiting are the most common and distressing manifestations of anaesthesia-related morbidity and the most common indication for the unplanned overnight admission of a patient scheduled for day-case surgery. The incidence is 20−30% and has remained fairly constant for decades, though it is higher in some surgical populations.

Nausea and vomiting following surgery may result in dehydration, electrolyte imbalance, delayed discharge, tension on suture lines, venous hypertension, increased bleeding under skin flaps, increased intracranial and intra-ocular pressure, and increased blood pressure and heart rate. The risk of pulmonary aspiration of vomitus is increased if the airway reflexes are depressed by the residual effects of anaesthetic agents.

Pathophysiology: the vomiting centre is located in the reticular formation in the medulla. It coordinates, but does not initiate, vomiting (Figure 1). It receives input from the cerebral cortex (e.g. visual, emotional, olfactory), gastrointestinal tract (autonomic afferent fibres), chemoreceptor trigger zone and the vestibular system. The chemoreceptor trigger zone is located on the floor of the fourth ventricle in or above the area postrema, outside the blood−brain barrier. It contains histamine, dopamine, acetylcholine (muscarinic), serotonin (5-HT_3) and opioid receptors. The presence of these receptors may explain the mechanisms behind the anti-emetic actions of antagonists at the histamine, dopamine, acetylcholine and serotonin receptors, along with the emetic effects of opioids.

Pathophysiology of vomiting and the sites and mechanisms of actions of anti-emetic drugs



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Causes

Causes of postoperative vomiting may be categorized into non-anaesthetic, anaesthetic-related and postoperative factors.

Non-anaesthetic factors

Patient-related factors

Age − incidence is higher in children. The peak incidence is at 11−14 years of age. Emesis decreases in old age.

Gender − women are more likely to vomit. This difference is not noted in pre-adolescents or in patients over 70 years old.

Obesity − increased body weight is associated with a greater incidence of postoperative vomiting. It may be related to increased residual anaesthetic agents in the adipose tissue, larger residual gastric volume and increased incidence of oesophageal reflux.

Anxiety − patients with high preoperative anxiety have a higher incidence of emesis. The possible reasons include an increased level of catecholamine release or an increase in gastric volume secondary to excessive air swallowing.

Previous postoperative nausea and vomiting − some individuals are susceptible to sickness. Those prone to motion sickness are more likely to vomit postoperatively.

Gastroparesis − patients with delayed gastric emptying may be at increased risk of vomiting after surgery. The condition may include gastrointestinal obstruction, cholecystitis, neuromuscular disorders and intrinsic neuropathies.

Surgical factors: patients undergoing long surgical procedures are more likely to vomit. Emesis is more likely after abdominal procedures, laparoscopy, dental extraction, dilatation of the cervix and ear operations. In children, there is a high incidence of emesis after strabismus surgery, orchidopexy, middle-ear surgery and adenotonsillectomy.

Anaesthetic-related factors

All the opioids possess marked emetic properties. Ether, cyclopropane and trichloroethylene are associated with a high incidence of postoperative vomiting, but there is little difference between the volatile anaesthetics currently used. Ketamine and etomidate have emetic effects; propofol has anti-emetic properties.

Vigorous positive pressure ventilation via a face mask may cause gastric distension with anaesthetic gases, leading to emesis postoperatively. Hypoxaemia at any stage and hypotension during regional anaesthesia induce vomiting.

Postoperative factors

Visceral or pelvic pain is a common cause of postoperative vomiting. Premature resumption of oral fluids, sudden changes in position and the sight and smell of offensive substances (e.g. vomitus, blood, faeces) can lead to vomiting.

Management

In patients with persistent nausea and vomiting, fluid and electrolyte replacement using intravenous infusions should be considered. Pain control should be optimized using non-opioid analgesics and/or local anaesthetic blocks. Patients with obtunded protective airway reflexes should be nursed in a lateral position.

Gentle handling of the patient is necessary. A nausea and vomiting scoring scale is used for monitoring.

Pharmacological management

No drug currently available will antagonize all the receptor sites involved in vomiting and therefore if one agent is ineffective, a second anti-emetic that acts on a different receptor should be administered. However, routine prophylactic use of an anti-emetic with every anaesthetic is not recommended.

Antidopaminergic agents

Prochlorperazine is one of the more commonly used anti-emetics in the phenothiazine group. It acts on the dopaminergic receptors in the chemoreceptor trigger zone, along with an α-adrenergic receptor-blocking property. Side-effects include sedation, hypotension, dysphoria and extrapyramidal effects (e.g. acute dystonia, akathesia, Parkinson-like rigidity).

Metoclopramide acts centrally by antagonizing the effects of dopamine. It also has a peripheral action on the gastrointestinal tract, which appears to be blockade of dopaminergic neurons that modulate acetylcholine release. It is structurally related to procainamide but has no local anaesthetic or anti-arrhythmic actions. It is a prokinetic, which increases lower oesophageal sphincter tone, speeds gastric emptying and increases the propulsive activity of gastrointestinal smooth muscle. The terminal half-life of metoclopramide is 4 hours. Side-effects include mild sedation, extrapyramidal reactions, restlessness, hunger, dizziness, anxiety and hyperprolactinaemia.

Droperidol is a potent neuroleptic with an anti-emetic effect, mediated via dopamine receptor antagonism. Anti-emetic effects may be achieved with doses that cause minimal sedation. The terminal elimination half-life is 2 hours, but the anti-emetic effect lasts longer. Droperidol may cause hypotension, secondary to an α-adrenergic receptor-blocking effect. Extrapyramidal reactions and sedation are other recognized problems.

Antihistamines: cyclizine antagonizes central histamine (H_1) receptors. It has a short duration of action of 4 hours. It can cause sedation and a dry mouth, but is not associated with extrapyramidal reactions. Other drugs in this group include promethazine, diphenhydramine and dimenhydrinate; they also possess anticholinergic properties.

Anticholinergics: hyoscine antagonizes muscarinic cholinergic receptors and thus has a central anti-emetic action. It is used to prevent motion sickness. The duration of action is short; elimination half-life is 1 hour. A transdermal preparation is available for a more sustained effect and fewer side-effects. Hyoscine can cause sedation, hallucination, dry mouth, tachycardia, mydriasis and cycloplegia. It is contraindicated in patients with narrow-angle glaucoma or urinary obstruction.

Serotonin antagonists: ondansetron was the first serotonin receptor antagonist used extensively in postoperative nausea and vomiting. Other drugs in this group include granisetron, tropisetron, itasetronan and dolasetron. Ondansetron binds at the serotonin receptor in the chemoreceptor trigger zone and at vagal afferents in the gastrointestinal tract. Clearance occurs primarily (95%) by hepatic metabolism, with an elimination half-life of about 4 hours. It is well tolerated and its other advantages are absence of sedation, extrapyramidal effects, adverse cardiovascular actions, dysphoria and dry mouth. It has minimal side-effects, which include dizziness, headache and impairment of liver function tests. The dose of ondansetron should be reduced in patients with hepatic insufficiency.

Corticosteroids: dexamethasone may be used as an adjunct to standard anti-emetic therapy in cases of persistent vomiting. Its proposed mechanism of action is decreased release of arachidonic acid, reduced turnover of serotonin and decreased permeability of the blood−brain barrier.

Non-pharmacological management

Stimulation of the acupuncture point PC6 (Nieguan) has been used for centuries in China to treat nausea and vomiting. Its use to prevent postoperative nausea and vomiting has met with varying degrees of success. However, there is the possibility of trauma to nerves and blood vessels or sepsis.

Diagnosis and Treatment in the Recovery Room

Anthony Beaumont

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The recovery room provides the facility to monitor and treat potentially life-threatening disturbances caused by anaesthesia, surgery or both. Complications occurring during the recovery from anaesthesia can be categorized as:

- cardiovascular (e.g. hypotension, hypertension, dysrhythmias, myocardial infarction, cardiac failure)
- respiratory (e.g. hypoxaemia, ventilatory failure, airway obstruction)
- others (e.g. nausea and vomiting, hypothermia, CNS disturbances, pain).

Hypertension

The incidence of hypertension increases with age. With the increasing number of older patients presenting for surgery, postoperative hypertension is a major problem for the anaesthetist. The incidence of postoperative hypertension may be as high as 60% depending on the patient and the surgical procedure; vascular surgery has the highest incidence.

Causes: the normal physiological responses to surgery include activation of the sympathetic nervous system and, therefore, an increase in blood pressure. Identification and treatment of the underlying cause (Figure 1) usually allows the blood pressure to return to normal in a short time. If hypertension develops in the postoperative period, it usually begins within 30 minutes of the end of the operation and is resolved within 4 hours of surgery. For this reason, if treatment is required, short-acting drugs can be used.

Causes of postoperative hypertension

Common causes

- Known hypertensive patient
- Pain
- Hypothermia
- Anxiety
- Blood gas disturbances (hypoxaemia, hypercarbia)
- Acute withdrawal of antihypertensive medication
- Distended bladder or bowel
- Fluid overload

Uncommon causes

- Undiagnosed phaeochromocytoma
- Acute drug withdrawal (e.g. sedatives)

1

Decision to treat: the accepted American Heart Association definition of hypertension is a blood pressure greater than 140/90 mm Hg. However, most would not regard this as high enough to warrant treatment in the post-anaesthetic period. In this situation, the accepted treatment threshold is a systolic pressure over 180 mm Hg or a diastolic pressure over 100 mm Hg, though there are instances when more aggressive treatment is warranted. These may include the type of surgery or the patient's cardiac status. On the other hand, if the patient is known to be hypertensive normally, higher levels of blood pressure may be accepted before perioperative treatment is begun.

If treatment is required, first-line therapy is as follows.

- Treat the underlying cause and check that ventilation and oxygenation are adequate. Measuring an arterial blood gas may assist in the assessment.
- Treat pain with opiates to the point of drowsiness. This should also relieve anxiety. (The combination of opiates and sedatives is not recommended.)
- Check for bladder and bowel distension and relieve them if appropriate.
- Warm the patient. If the patient is cold, re-warming may cause vasodilatation and hypotension.
- If the patient does not respond to first-line therapy, consider giving an antihypertensive agent (Figure 2).

Antihypertensive medication

Drug	Action
• Esmolol	Short-acting β-blocker. May need to be given by infusion of 25–300 μg/kg/minute
• Labetalol	α- and β-blocker. Increments of 5 mg may be given at 5-minute intervals to control blood pressure. May cause bradycardia
• Glyceryl trinitrate	Cutaneous patches, intravenous or sublingual routes. Causes dilatation of the venous system initially, then the arterial system
• Nifedipine	Calcium channel blocker. May be given sublingually. Relaxes arteriolar smooth muscle. Is a negative inotrope
• Clonidine	α_2-blocker. Has a sedative and analgesic action in addition to its blood pressure-lowering effect. Dose 50–100 μg i.v.
• Hydralazine	Arteriolar smooth muscle relaxant. May be given as a bolus, 25–50 mg i.v. Is not a negative inotrope
• Sodium nitroprusside	Arteriolar smooth muscle relaxant. Needs to be given by infusion in a light-protected system. Invasive blood pressure measurement is recommended

2

Hypotension

Hypotension may be defined as a reduction in blood pressure of more than 20–30% below the preoperative baseline. However, patient anxiety may have altered the preoperative values and they may not reflect the patient's true resting blood pressure.

The potential end-result of hypotension is hypoperfusion. In general, clinical signs of hypoperfusion are more important than numerical values of blood pressure. These signs include pale, cool skin, slow capillary refill time (> 2 seconds), sweating, tachycardia, reduced conscious level, tachypnoea, nausea and vomiting. Plasma lactate may be elevated as a result of anaerobic metabolism. The classic signs of hypotension and tachycardia may not always be seen in hypovolaemic shock if β-blockade is present.

Clinical examination of the central venous pressure may not be easy, but should be attempted. Ultrasound examination of the size of the internal jugular vein helps to assess the intravascular volume. If in doubt, a central venous catheter should be inserted to permit direct measurement of the central venous pressure.

Oxygen should be administered to all patients who are hypotensive until its aetiology has been elucidated and treatment has been given.

Causes (Figure 3): fluid loss is the most common cause of hypoperfusion either as a result of underestimated blood loss in the operating theatre or continued blood loss in the recovery room. Surgical drains are unreliable in assessing postoperative blood loss. Blood may clot before coming out through a drain or the drain may be positioned in a site distant from the source of bleeding. The response to a bolus of colloid, 10 ml/kg, is usually sufficient to diagnose hypovolaemia. If further fluid replacement is necessary it is guided by response to treatment.

Causes of hypotension

Fluid loss

- Unrecognized intraoperative blood loss
- Continuing haemorrhage

Myocardial dysfunction

- Myocardial ischaemia or infarction
- Rhythm problems
- Negative inotropic agents (anaesthetic drugs)
- Uncommon problems (e.g. tamponade, pulmonary embolism)

Vascular dysfunction

- Spinal anaesthesia
- Sepsis
- Anaphylaxis
- Rewarming
- Drugs (e.g. intraoperative hypotensive agents)

3

Vascular dysfunction – a reduction in vascular resistance may be suspected in patients who have a spinal or epidural as part of their anaesthetic, or in patients with sepsis (e.g. peritonitis). Residual anaesthetic drugs may also be a cause of hypotension. Drugs that increase arteriolar tone (Figure 4) may be required to increase the blood pressure above a minimum mean value of 70 mm Hg.

Myocardial dysfunction should be considered as a possible cause of hypotension if the central venous pressure is normal or high and there is no response to simple fluid administration. These patients require careful evaluation. ECG monitoring and a formal 12-lead ECG should be obtained and compared with the preoperative ECG for signs of ischaemia or infarction. Cardiac enzyme analysis (e.g. troponin) also helps in diagnosis. Treatment should centre on the restoration of myocardial blood flow and contractility using nitrates and inotropes. Dysrhythmias may also cause hypotension; treatment depends on their nature.

Drugs that increase arteriolar vascular tone

Drug	Effects
• Ephedrine	Predominantly β in effect with some α effects. Causes an increase in blood pressure and cardiac output. Preferred in pregnant women
• Metaraminol	Predominantly α in effect, causes a marked increase in systemic vascular resistance and blood pressure
• Methoxamine	Predominantly α in effect, causes a marked increase in systemic vascular resistance and blood pressure
• Adrenaline	α and β effects; increases blood pressure and cardiac output
• Noradrenaline	Predominantly a in effect, causes a marked increase in systemic vascular resistance and blood pressure

4

Shivering

Postoperative shivering may develop in up to 60% of patients recovering from general anaesthesia. It is a potentially serious complication because it increases oxygen consumption by up to 100% from baseline. Postoperative pain usually increases because the muscle activity 'stretches' the wound. Other complications of hypothermia following surgery include coagulation abnormalities, increased risk of infection, delayed wound healing and increased time spent in the recovery room. Two distinct patterns of shivering are observed in the postoperative period.

- The tonic pattern resembles normal shivering with a 4–8 cycle/minute waxing and waning pattern. This pattern is seen in thermoregulatory-induced shivering.
- The clonic phasic is characterized by a 5–7 Hz bursting pattern resembling clonus. This is the pattern seen in non-thermoregulatory-induced shivering.

Causes: there are a number of aetiological factors. The thermoregulation causes are:
- cold induced (normal thermoregulatory response to a reduction in core and skin temperature)
- cytokine release (fever and shivering in response to pyrogenic mediators released following surgery).

The non-thermoregulation causes are:
- pain
- response to volatile anaesthetic agents.

Treatment is aimed at returning the core and peripheral temperature to the normal range. Skin surface warming reduces shivering, because the regulatory system tolerates greater core hypothermia when cutaneous temperature is raised. A variety of drugs reduce shivering, including pethidine, clonidine, ketanserin, and magnesium sulphate.

Cyanosis

Postoperative hypoxaemia is common and may be caused by many factors. Hypoxaemia is usually detected using a pulse oximeter, because clinical evaluation often fails to recognize saturations below 80%. The causes of postoperative hypoxaemia include:
- atelectasis
- second gas effect (diffusion hypoxia)
- hypoventilation
- bronchospasm
- aspiration
- pneumothorax
- pulmonary embolism
- pulmonary oedema.

Atelectasis is the most common cause of a right to left shunt. It may occur as a result of collapse of a whole lung or diffuse segments within the lungs. Secretions or blood in the airways are common causes. Reduction in functional residual capacity is an almost inevitable consequence of anaesthesia because tone in the chest wall and diaphragm is reduced. If the functional residual capacity falls below the closing capacity, intrapulmonary shunting occurs. Patients at particular risk include the elderly, the very young, and patients with previous lung disease, pulmonary oedema, infection or obesity. These patients are all at increased risk of segmental collapse and secondary infection. Treatment should include sitting the patient up, physiotherapy, deep breathing exercises, incentive spirometry, intermittent continuous positive airway pressure (CPAP) or, in extreme cases, ventilation in an ICU.

The second gas effect is a transient cause of hypoxia that is easily prevented by the administration of oxygen. As nitrous oxide diffuses out of the blood into the alveolus it dilutes the alveolar gas. If the patient is breathing room air, a low alveolar concentration of oxygen results. For this reason, all patients who have received an anaesthetic containing nitrous oxide should receive supplemental oxygen for 10 minutes following cessation of the anaesthetic.

Hypoventilation is defined as a raised partial pressure of carbon dioxide in arterial blood (Pa_{CO_2}) as a consequence of alveolar hypoventilation. There are a number of causes:
- reduced respiratory drive
- reduced respiratory muscle function
- chronic or acute lung disease
- obesity.

A reduction in respiratory drive may be the result of anaesthetic drugs, especially opiates, which flatten the carbon dioxide response curve and shift it to the right. Respiratory muscle function is also reduced following surgery; upper abdominal surgery can result in a reduction in vital capacity of up to 60%.

Failure of reversal of neuromuscular blocking drugs can result in inadequate muscle function. This may be the result of hypothermia, hypermagnesaemia, acidosis, or the potentiation of neuromuscular blockade by other drugs (e.g. gentamicin) or by renal failure. Monitoring of these patients should include train-of-four monitoring of neuromuscular blockade, sequential blood gas estimations and clinical examination.

Treatment should follow the steps given below.
- Ensure adequate reversal of neuromuscular blockade.
- Titrate opiates to the patient's pain without causing excessive rises in Pa_{CO_2}. Where opiate overdose is suspected, small doses of intravenous narcotic antagonists may be needed and may have to be repeated, because the half-life of naloxone is shorter than that of most opiates.
- Epidural analgesia can reduce the hypoventilation usually seen after abdominal surgery.
- Intravenous doxapram, 1 mg/kg, may be beneficial in patients who are suspected of having a reduced respiratory drive. Doxapram may be given by infusion, if the initial intravenous bolus is effective.
- CPAP may assist in reducing the work of breathing; occasionally bilevel positive airway pressure is beneficial in patients with chronic lung disease.

Bronchospasm may occur following anaesthesia as a result of aspiration, intubation, a previous history of asthma, chronic obstructive pulmonary disease or drug reactions. Smokers are at particular risk, especially if they have not smoked in the 2 weeks before surgery. This group has increased airway sensitivity and an increased volume of bronchial secretions compared with non-smokers and patients who smoke up to the day of operation.

Bronchospasm may occur with cardiac failure, therefore the cardiovascular system should be examined for a raised jugular venous pressure and a gallop rhythm; ECG changes may also be present. A chest radiograph also assists in the differential diagnosis and helps to tailor therapy. CPAP is of considerable benefit in acute pulmonary oedema, but may be of little help in acute bronchospasm.

Treatment – first-line drug treatment is to administer nebulized β_2-stimulants. Occasionally, cholinergics or corticosteroid therapy may be indicated. If aspiration is suspected, antibiotics need not be begun immediately. Stomach contents are usually sterile and do not cause infection, but the resulting inflammation may make the patient more susceptible to infection. Routine treatment of the patient who has aspirated should include oxygen therapy, β_2-stimulants and careful monitoring for infection (e.g. fever, raised WBC count, sputum cultures, chest radiography).

Pneumothorax is usually the result of direct lung injury during surgery or the result of central vein cannulation. Pneumothorax as a result of ventilation is uncommon, unless very high ventilatory pressures have been used. Treatment depends on the size of the pneumothorax and whether ventilation is to continue into the postoperative period (Figure 5).

Pulmonary embolism is an uncommon, but important, cause of arterial hypoxaemia in the immediate postoperative period. Patients at risk include the obese, the elderly, patients with malignancy, patients with a history of embolic problems and those who have been relatively immobile before surgery.

The typical EGC changes ($S_1Q_3T_3$) are seldom seen; however, signs of right heart strain with sudden hypoxaemia, hypotension and pleuritic chest pain should raise the index of suspicion of a pulmonary embolism. The definitive test is pulmonary angiography or a ventilation–perfusion scan. The latter may not be reliable, however, in patients with atelectasis or pre-existing lung disease.

Treatment involves anticoagulation with intravenous heparin. For the patient who has a high risk of bleeding, treatment with tinzaparin, 175 µg/kg, is a useful (though unlicensed) alternative. Subsequently, patients are converted to oral warfarin therapy. An accurate diagnosis is therefore essential, to ensure that the post-surgical patient is not needlessly exposed to anticoagulation therapy.

Treatment of pneumothorax

Pneumothorax type	Treatment
• Less than 20% and unsymptomatic	Do not treat, monitor with frequent chest radiographs
• Greater than 20% or symptomatic	Insert narrow-bore catheter to drain the air (large-bore catheters are unnecessary)
• Tension pneumothorax	14 G canula inserted into the second intercostal space followed by catheter insertion
• Any pneumothorax in a ventilated patient	Insert narrow-bore chest drain

Pulmonary oedema: most patients who develop pulmonary oedema do so within 60 minutes following the end of surgery. Of these patients, 50% have a history of heart disease; others may have associated postoperative hypertension. The diagnosis may be suspected in patients with wheezing, and a previous cardiac history, and confirmed by a chest radiograph. Patients who have prolonged laryngeal obstruction may develop pulmonary oedema as a result of the sustained high negative intrathoracic pressures. The diagnosis is usually evident in such patients. Pulmonary oedema may also occur as a result of increased permeability in conditions such as disseminated intravascular coagulation, trauma, shock and sepsis. This type of oedema is often called acute lung injury and requires treatment in a critical care setting.

Treatment is aimed at the cause of the oedema. Relief of obstruction and oxygen therapy (Figure 6) is often sufficient to correct post-obstruction oedema. Traditional treatment with oxygen, diuretics, vasodilators and fluid restriction is often sufficient for most other causes. Occasionally CPAP, bilevel positive airway pressure or intubation and ventilation may be required for a few hours.

Stridor

Stridor is the result of extrathoracic obstruction of the airway. It may be caused by laryngeal oedema or 'laryngeal spasm'.

Laryngeal oedema may occur at the level of the vocal cords, the subglottic area, or in other areas of the larynx and upper airway. A precise diagnosis, made by fibre-optic laryngoscopy, is generally unnecessary for treatment. Inspiratory wheezing is characteristic and may lead to hypoxia, hypercapnia and respiratory failure, if pronounced. Reduction in stridor may indicate total obstruction of the trachea and, therefore, observation of air movement must be repeatedly confirmed. Causes include a large tracheal tube, tube movement, recent upper airway infection, or excessive coughing or bucking.

Treatment includes administering warmed, humidified oxygen. In severe cases, intravenous dexamethasone and nebulized racemic adrenaline (or 5 ml of 1:1000 adrenaline) are useful; ECG monitoring must be used while the latter is in progress. Adrenaline can be repeated, though reactive hyperaemia is possible with return of the symptoms. Reintubation is occasionally required.

Oxygen therapy devices

Oxygen delivery device	Advantages and disadvantages
• Nasal cannula	Simple, easy to use and well tolerated. 2 litres/minute equates to about 28% oxygen but is dependent on the patient's respiratory pattern. May dry out the nasal membrane if used with higher flow rates
• Simple face mask	Simple and easy to use. Delivered oxygen percentage (35–50%) depends on the patient's respiratory pattern and oxygen flow rate. Carbon dioxide accumulation may occur if the flow rate is less than 5 litres/minute
• Venturi mask	Delivers precise concentrations of oxygen (24%, 28%, 31%, 35% and 60%). Simple, reliable, effective and independent of the patient's respiratory pattern
• Non-rebreathing masks	May be used to deliver 60–90% oxygen. The mask must be tight fitting and the flow rate should be adjusted to prevent collapse of the reservoir bag during inspiration

'Laryngeal spasm': stridor caused by laryngeal spasm is often the result of mistimed extubation, debris on the vocal cords, the presence of an airway or irritation of the vocal cords. It is more common in patients who have a history of airway irritability and in smokers.

Treatment should include simple measures to ensure a patent airway such as head tilt and chin lift. Oxygen will be needed. CPAP via a face mask is often valuable. If these measures are ineffective, a small dose of suxamethonium may be necessary. Assisted ventilation is then required.

Prophylaxis has been recommended. Lignocaine (either intravenously or topically on the vocal cords) and intravenous corticosteroids have been used, but the most effective method is meticulous airway management, suctioning before extubation and correct timing of extubation.

Managing Postoperative Pain Relief

Mansukh Popat

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Pain following surgery is acute and self-limiting, but failure to relieve it is morally and ethically unacceptable. Good postoperative pain control alleviates the patient's distress and may also prevent or modify the physiological and psychological responses to surgery. There is no evidence that relieving postoperative pain speeds recovery and results in early discharge from hospital, but adequate pain relief results in fewer pulmonary complications and may reduce the transition to chronic postoperative pain.

The need for analgesia is generally straightforward, and provided the equipment and staff are available, the appropriate methods should be offered. To provide a rational approach to adequate postoperative pain relief, it is important to assess the factors described below.

Anaesthetic technique: the analgesia used during surgery influences the choice of postoperative technique.

Surgery

Site of surgery – generally, upper abdominal operations are more painful than those of the lower abdomen, which are more painful than peripheral operations. Operations on the thorax cause severe pain; those in the head and neck are usually only moderately painful.

Extent of operation – if only the superficial layers are cut, surgery is less painful than if muscles have been split. A muscle-cutting incision results in more pain than a muscle-separating incision.

Ambulation after surgery – pain relief in a patient who needs to be ambulant following surgery should be directed at ensuring that the patient is fit to go home on the day of surgery.

Age of the patient

Babies and infants – pain is a subjective phenomenon and its treatment depends on subjective assessment, which is difficult to determine in babies and infants. Drug handling by their immature systems is also a problem.

Elderly patients may not be able to cope with normal drug doses and a reduction in dose may be required. Frail patients may not be able to use technology such as patient-controlled analgesia (PCA) machines. Elderly patients also have a high incidence of co-existing disease.

Co-existing disease

Respiratory disease – care should be taken to avoid respiratory depression with opioids and possibly exacerbating asthma with non-steroidal anti-inflammatory drugs (NSAIDs).

Renal failure – patients with renal failure require a reduced dose of opioid and care should be taken with NSAIDs.

Head injury and impaired consciousness – problems include pain assessment, risk of respiratory depression and dose requirements.

Psychological state of the patient: patients differ in how they perceive pain, as shown by the variations in opioid requirement for different patients using PCA. Patient anxiety is increased by many factors (e.g. hospitalization, surgical diagnosis, and ability to cope with pain and an unfamiliar environment). Patients who are most anxious before surgery are more likely to be distressed following surgery. However, anxiety specifically related to the surgical experience is more important in pain control, because postoperative pain intensity is related to context-based (state) anxiety rather than to personality-based (trait) anxiety.

Staff and equipment: techniques such as epidural analgesia and PCA require adequately trained ward staff, appropriate equipment and experienced anaesthetists.

Methods of pain relief

Methods of providing postoperative pain relief are listed in Figure 1. Adequate pain relief can be provided easily with simple, safe and effective methods when the response of the patient to these treatments is measured, treatment is tailored to their individual needs and they are allowed to control pain relief. It is important to choose the appropriate drug, route and mode of delivery. Although single techniques are effective, a multimodal approach may provide effective analgesia while reducing the side-effects of any one method used alone.

Methods of providing postoperative pain relief

Drug treatment
- Opioids
- Non-steroidal anti-inflammatory drugs
- Paracetamol and combinations (e.g. paracetamol, 500 mg, plus codeine, 8 mg)

Regional anaesthetic techniques
- Central neuraxial blocks: epidural and spinal
- Peripheral nerve blocks
- Local infiltration

Psychological methods
- Relaxation
- Hypnosis
- Psychoprophylaxis

1

Opioids

Opioids are the mainstay of treatment for severe postoperative pain. Many opioids are available, but it may be better for an institution or ward to use one opioid so that all staff are familiar with its dose, side-effects and methods of administration. Morphine is the best known and most studied opioid and can be administered in a variety of ways (Figure 2).

Routes of administration of analgesics

Parenteral administration
- Intramuscular bolus on demand[1]
- Intravenous bolus[1]
- Continuous infusion[1]
- Patient-controlled analgesia[1]

Non-parenteral administration
- Oral[1]
- Buccal/sublingual[1]
- Rectal[1]
- Spinal and epidural[1]
- Intra-articular
- Transdermal[1]
- Inhalation

[1]Opiates may be given by these routes

2

Intramuscular administration of a bolus injection of morphine as required is still popular in many hospitals. Unfortunately the doses administered are often inadequate because of traditions, misconceptions and fear. Doctors and nurses have a misconception that opioids cause addiction, but this is not the case if they are used for acute pain. Staff shortage, distractions on the ward and controlled drug regulations result in a delay between the onset of the need for pain relief and its eventual administration, leading to low plasma levels of the drug and inadequate pain relief. Surveys suggest that up to 60% of patients treated in this way may be dissatisfied. The situation is improved by optimizing intramuscular opioid administration with the help of algorithms. A predetermined dose of morphine or pethidine is given every hour if the patient has moderate to severe pain. The nurses monitor pain and sedation scores, blood pressure and respiratory rate to decide if the drug should be withheld.

Intravenous administration: a small dose of opioid is administered and the dose is titrated to relieve pain. This method is effective but requires trained staff and monitoring and is therefore appropriate for patients in recovery and high-dependency areas rather than those on the general ward.

Continuous intravenous infusion is effective, but the dose is determined by trial and error. It is suitable when respiratory depression is desired (e.g. in ICU to sedate and ventilate patients).

PCA is commonly associated with the use of a patient-controlled device for administration of opioids by the intravenous route.

PCA is a goal-directed therapy. The goal is patient satisfaction. The patient is in charge and provides feedback control to the machine. The machine is programmed to deliver a small intravenous dose of opioid (bolus dose) when the patient presses a button. A safety feature (lockout time) is the time interval during which the machine will not deliver the drug despite the patient pressing the button. Although possible, a continuous background infusion is generally not used. For morphine, a bolus dose of 0.5–3 mg with a lockout time of 5–15 minutes is commonly used.

Advantages and disadvantages – PCA has advantages over other routes because it provides rapid, prompt drug administration via easy-to-use pumps. There is little difference in outcome between efficient intermittent intravenous injection and PCA. However, with PCA the patient determines the rate of intravenous administration of the drug thereby providing feedback control. PCA has been shown to provide greater patient satisfaction and to improve ventilation when compared with conventional routes. There is no significant difference between PCA and conventional analgesia regarding length of hospital stay. PCA should be safe and efficacious because plasma levels fall within the therapeutic window, but this is not always the case. Side-effects are similar to opioid use by other routes. Attempts at adding anti-emetics to opioids in PCA have not produced any benefits.

Monitoring is required for the safe administration of PCA. It should include pulse, blood pressure and respiratory rate. The level of sedation and pain should be assessed using sedation and pain scales. Other information that should be recorded routinely includes nausea and vomiting, itching, amount of drug used and amount of drug left and how many tries were successful. There should be clear nursing guidelines regarding the actions to be taken in cases of inadequate analgesia and when side-effects occur. Good risk management with PCA should emphasize the same drug, protocols and equipment throughout the hospital.

Non-opioid drugs

NSAIDs, paracetamol and paracetamol combinations are appropriate when patients can take drugs orally and are able to go home on the day of surgery. Alone, they do not reduce severe pain, but their efficacy as a component of multimodal analgesia is confirmed by enhancement of opioid-based analgesia. If patients can swallow it is best to give these drugs orally. NSAIDs given rectally or by injection do not perform better or faster than the same drug given at the same dose by mouth.

The side-effects of NSAIDs are serious and contraindications must be respected. The risks and benefits must be assessed in patients with gastrointestinal disease, renal impairment, asthma, bleeding diathesis and previous hypersensitivity.

Regional anaesthetic techniques

Epidural analgesia forms a major part of pain relief after major surgery to the abdomen, thorax or lower limbs. It requires trained staff to operate it and to monitor pain, nausea and vomiting, sedation scores, blood pressure, respiratory rate and sensory levels every hour. The pump and catheter site are checked regularly. Guidelines should be in place to treat complications. Debate continues on whether patients with epidural infusions should be nursed on wards or in high-dependency areas. Epidural anaesthesia alone may be used for surgery and extended for postoperative use or it may be used as a combined technique of general and regional anaesthesia. Local anaesthetics, opioids or a combination of both are commonly used.

Epidural local anaesthetics – the first major application of thoracic segmental epidural anaesthesia used lignocaine 1.5% as bolus or continuous infusion. Lignocaine causes acute tachyphylaxis and is therefore considered unsatisfactory; bupivacaine is now the most common drug used. Intermittent doses of bupivacaine, 0.25–0.5%, can be used, but the duration is limited to 3–4 hours. Instead, an infusion of bupivacaine 0.25% at a rate of 3–7 ml started immediately following the peak effect of a single dose of bupivacaine, 0.5%, maintains satisfactory analgesia. It is important that the epidural catheter tip is placed at the spinal level representing the centre of the segmental distribution of desired analgesia; for lower abdominal (T10–L2) operations the catheter tip should be at T12, for upper abdominal operations (T6–T11) at T8 and for thoracic operations (T4–T8) at T6.

Ropivacaine is less toxic than bupivacaine after intravenous administration in human volunteers. It is less lipophilic and has a higher clearance rate than bupivacaine. The sensory block produced by ropivacaine is similar to that produced by equipotent doses of bupivacaine, though the motor block is less pronounced and shorter in duration. This, plus a more favourable toxicity profile, may allow ropivacaine to be used in higher concentrations than bupivacaine.

Epidural opioids – following the discovery of opioid receptors in the spinal cord, opioids have been used extensively for epidural administration. Morphine was the first to be utilized but almost all the available opioids have been used. The analgesic action of an epidural opioid is best explained by its lipophilicity. A drug with a low partition coefficient between water and fat (i.e. morphine) is hydrophilic; fentanyl is considered lipophilic.

- A hydrophilic opioid, injected in the epidural space, is not absorbed by fat or by blood vessels near the site of the injection but slowly penetrates the dura. A slow vascular uptake maintains high CSF concentrations with actions on opioid receptors at various levels of the spinal cord and the CSF. This explains analgesia in the spinal dermatomes distant to the site of the injection and the possibility of late-onset side-effects.
- A lipophilic opioid injected epidurally is avidly absorbed by fat and blood vessels and leaves only a small amount of drug to cross the dura. Once in the CSF, it is rapidly absorbed in the blood; leaving small amounts of the drug in the CSF to act on the receptors; hence, the lack of side-effects and the short duration of action.

For these reasons, lipophilic opioids are best administered at dermatomes near the site of the surgery, whereas hydrophilic opioids can be used where the injection site is large or distant from the surgical site.

Combination of local anaesthetics and opioids – local anaesthetics and opioids have a synergistic effect at spinal cord level. Subthreshold doses combine synergistically and result in spinal analgesia with few side-effects. Combinations of opioids and local anaesthetics are useful in relieving pain, both at rest and on movement. Opioids are good for visceral pain and local anaesthetic for segmental analgesia. Currently the most favoured technique uses drugs such as fentanyl and diamorphine combined with bupivacaine.

Side-effects of epidural analgesia include complications of the technique (e.g. accidental dural puncture and headache, infection, haematoma, nerve damage). Epidural local anaesthetic may cause hypotension, motor block, immobility or toxicity as a result of accidental intravascular and intrathecal injection. Opioids may cause respiratory depression, nausea and vomiting, itching, urinary retention and somnolence

Other drugs – clonidine is a selective α_2-adrenergic receptor agonist. There is good evidence of synergism between opioids and clonidine at the spinal cord level. Clonidine, 3–5 μg/kg, has demonstrated an opioid-sparing effect.

Spinal analgesia: many operations in the lower abdomen or the lower limbs can be performed with intrathecal blocks using bupivacaine; analgesia lasts for a few minutes to several hours. It has been shown that addition of intrathecal opioids reduces the incidence of visceral pain intraoperatively and, when longer-acting drugs such as morphine and diamorphine are used, provides a few hours of postoperative analgesia. This approach has been used following analgesia for caesarean section when it is common to inject diamorphine, 0.25 mg, or preservative-free morphine, 0.1–0.2 mg, intrathecally.

Peripheral nerve blocks include plexus blocks (brachial plexus) or nerve blocks (sciatic, femoral). They may be administered as the sole anaesthetic, providing postoperative pain relief of varying duration depending on the drug used. They may also be used as part of a combined regional and general anaesthetic technique. Single-shot or catheter techniques are used. Bupivacaine is the most common local anaesthetic used in concentrations of 0.1–0.25% at 8–10 ml/hour. There is a theoretical suggestion that these techniques reduce the amount of opioids and other analgesics used postoperatively, but studies are inconclusive. These blocks require expertise to administer and are associated with several complications, especially when performed with the patient anaesthetized.

Local anaesthetic can also be injected in the intrapleural space with a Touhy epidural needle as a single-bolus or catheter technique. Indications include unilateral surgery where thoracic dermatomes are involved (e.g. mastectomy, cholecystectomy). Analgesia for thoracotomy is unsatisfactory and toxic doses are required for bilateral surgery or midline incisions. The mechanism of this block is probably by spread to the intercostal nerves. The technique can result in serious complications (e.g. pneumothorax) and should be practised by experienced anaesthetists only.

Local infiltration of the wound by the surgeon is commonly used after body cavity and surface operations. Conclusive evidence of its usefulness has been shown in hernia operations only.

Psychological techniques

The value of psychological preparation for surgery in reducing pain and thus analgesics is being increasingly recognized. Techniques include relaxation training, procedural information, cognitive coping methods and behavioural instructions.

Acute pain service

It is now a condition for accreditation for training by the Royal College of Anaesthetists that an acute hospital has an acute pain team. The functions of this team include patient management, staff and patient education, drawing up guidelines and risk management.

Postoperative Fluid Therapy

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Postoperative fluid therapy should be a continuation of the intraoperative fluid replacement planned by the anaesthetist and continued on the hospital ward. The fluids prescribed must take into account normal maintenance requirements and losses, and be adjusted for the nature of the surgical operation and coexisting medical problems. A working knowledge of the body fluid compartments and the redistribution of intravenous fluids within them, as well as daily requirements for water and electrolytes are essential.

Body fluid compartments

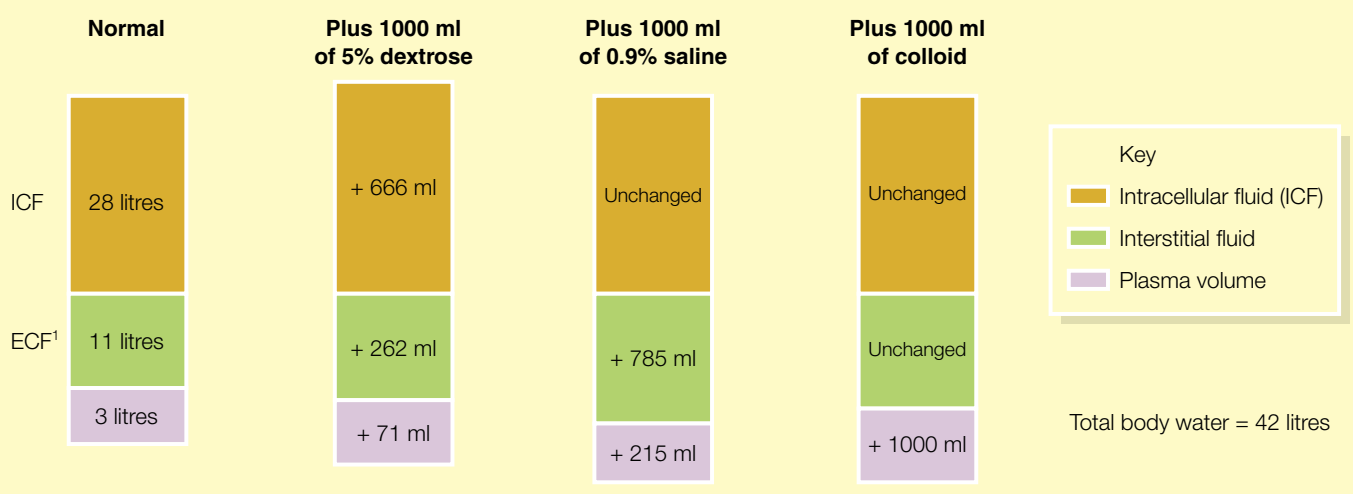
The body consists of two fluid compartments: the extracellular fluid (ECF) and the intracellular fluid (ICF). The ICF accounts for about two-thirds of the total body water. The ECF includes the blood plasma volume and the interstitial fluid volume (Figure 1).

Sodium is in diffusional equilibrium throughout the ECF but not the ICF, where potassium is the principal cation. The net result is that sodium-containing solutions are distributed throughout the body fluid compartments according to their sodium concentration relative to ECF. Therefore with infusions of 1000 ml the following occurs.

- Water (e.g. as 5% dextrose) is distributed throughout both body fluid compartments (ECF and ICF). Only a small proportion (about 3/42 or 71 ml) remains in the blood plasma volume after redistribution.
- Sodium is distributed throughout the ECF in proportion, but not in the ICF. Isotonic (0.9%) saline solutions remain in the ECF. A larger proportion (3/14 or 215 ml) remain in the blood plasma volume after redistribution.
- Solutions of large molecules, such as albumin and colloids, are distributed only within the plasma volume, assuming there is an intact capillary barrier.

True dehydration represents loss of water from all body compartments and ultimately requires water replacement. More commonly in the postoperative setting, there is predominant loss of ECF as both plasma and interstitial fluid, which requires replacement with sodium-containing solutions.

Body fluid compartments and their relative proportions in a 70 kg man



[1]Extracellular fluid (ECF) is composed of interstitial fluid and plasma volume.

1

Maintenance requirements

Simple and widely used formulae give an estimate of the basal requirements for water and electrolytes that must be provided in a postoperative fluid regimen. The return to enteral provision of fluid and nutrition should be achieved as soon as possible, and is often unnecessarily delayed.

The maintenance fluid requirements are about 35 ml/kg/ 24 hours of water or 4 ml/kg/hour for the first 10 kg body weight, plus 2 ml/kg/hour for each kg from 10 to 20 kg, plus 1 ml/kg/hour for each kg above 20 kg.

To maintain sodium balance, about 1–2 mmol/kg/day sodium is required and about 0.5–1 mmol/kg/day of potassium. These figures assume normal fluid losses (i.e. sweat, urine), and may need supplementing before or after surgery, depending on the patient's condition. For example, high-volume nasogastric aspirates result in large losses of potassium and hydrogen ions. The composition and volumes of some additional fluid losses are shown in Figure 2.

Suitable postoperative fluid regimens include maintenance requirements and additional supplementation of losses such as those described. There may also be the need for transfusion of blood products, which is not covered in this contribution.

Composition and daily fluid losses for a 70 kg man

Fluid	Volume (ml)	Na (mmol/litre)	K (mmol/litre)	Cl (mmol/litre)
Gastric	1500	10–140	5–40	50–150
Sweat	500	30–50	5	40–55
Ileal fluid[1]	3000	40–140	5–30	20–90
Diarrhoea	200–2000	20–160	10–40	30–120
Pulmonary losses	300			

[1]Including bile and pancreatic juice

2

Assessing the adequacy of fluid therapy

Maintenance requirements give a starting point for fluid prescription. Simple clinical findings such as skin turgor, dry tongue and thirst indicate more fluid is required. Examination of the cardiovascular system may reveal intravascular depletion. Persistent oliguria is a sign of inadequate fluid replacement, which precedes renal compromise; it is commonly untreated. If there is difficulty in assessing fluid losses and in high-risk cases, the use of indwelling urinary catheters with hourly urine output recordings and the use of central venous pressure monitoring are invaluable. Laboratory results such as low urine sodium (< 20 mmol/litre), high urine osmolarity (> 400 mOsm/kg) and increasing serum urea, serum lactate or a worsening metabolic acidosis may help to identify patients in whom postoperative oliguria is the result of inadequate fluid.

Specific problems

Third space fluid losses

In addition to blood loss and unavoidable losses of other fluids (e.g. gut fluids) there may be significant internal redistribution of body fluids, particularly within the ECF. These so-called 'third space' losses are caused by the sequestration of sodium-rich (isotonic with plasma) fluid from the interstitial space as a result of tissue trauma, inflammation or infection. The fluid lost in this way effectively represents an expansion of the ECF and may account for large fluid losses from the plasma, leading to circulatory hypovolaemia. Fluid sequestration may be extensive, but is difficult to quantify other than by its effect on depletion of the plasma volume.

Third space losses cannot be prevented by fluid restriction and require replacement if adequate circulating volume is to be maintained. In procedures where large losses of such fluid are anticipated (e.g. major bowel surgery, extensive pelvic dissection), the key to replacing such losses adequately lies in careful assessment of the circulating volume, clinically and using invasive monitoring such as central venous pressure measurement. Replacement of fluid sequestered in this way must be with isotonic fluids or colloids. The use of hypotonic solutions may promote hyponatraemia (see below).

The sequestered fluid usually returns to the circulation 2 or 3 days following surgery, often inducing a diuresis. Its return into the functioning ECF represents a reversal of the inflammatory response that promotes fluid sequestration.

Children

The postoperative fluid requirements for children may be calculated using the same formula described above for adults. Dextrose-containing solutions are often used because of concerns regarding possible hypoglycaemia in fasted children. In practice, this is a problem only in small infants and neonates, in whom the use of 10% dextrose is occasionally required. Neonates also have a limited ability to excrete a sodium load and weaker saline solutions may be more appropriate. In older children, dextrose/saline (e.g. 4% dextrose plus 0.18% normal saline) solutions are commonly used as maintenance fluids postoperatively. In most cases this is acceptable, but it must be remembered that such fluids are hypotonic and may lead to hyponatraemia in certain circumstances (see below).

Additional losses of fluids, such as high-volume nasogastric aspirates, must be replaced in addition to maintenance requirements. Third space losses, which can be significant in children, should be replaced with isotonic saline or colloid solutions directed at restoring and maintaining circulating plasma volume and preventing dilutional hyponatraemia.

The use of volumetric infusion pumps to control the delivery of fluid therapy in children is advisable both for safety and reliability.

Postoperative hyponatraemia

Several factors contribute to the development of postoperative hyponatraemia, but it is an avoidable iatrogenic complication with potentially disastrous consequences. Surgery, trauma, stress or infection may all cause the non-osmotic release of antidiuretic hormone, which tends to decrease renal free water clearance. This, combined with loss of sodium-rich fluids (e.g. to the third space or from an ileostomy), tends to generate an imbalance of sodium and water retention that may promote hyponatraemia. If this is unrecognized and fluid therapy is given as hypotonic saline (e.g. 4% dextrose plus 0.18% saline) or dextrose alone then hyponatraemia develops, sometimes rapidly, causing cerebral oedema and seizures. Hypotonic fluids should not be used to replace the loss of isotonic fluids.

FURTHER READING

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Postoperative Pulmonary Atelectasis

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Atelectasis is an absence of gas in part of or in the entire lung. Common causes include hypoventilation, bronchial obstruction (e.g. by sputum, foreign body or vomit), endobronchial intubation, or air space compression (e.g. by oedematous lung tissue, pleural effusion or haemothorax). All involve airway obstruction with distal gas trapping. Since the partial pressure of trapped gas is higher than that of mixed venous blood, uptake of alveolar gas occurs and the lung becomes less aerated. Usually this takes several hours or days, because poorly soluble nitrogen in alveolar gas slows absorption. However, uptake is accelerated if the inspired gas contains high concentrations of oxygen. Atelectasis is common postoperatively; depending on the definition used, its incidence is 20–69%. It causes pulmonary shunt and hypoxaemia, reduces lung compliance, increases the work of breathing and predisposes to pneumonia.

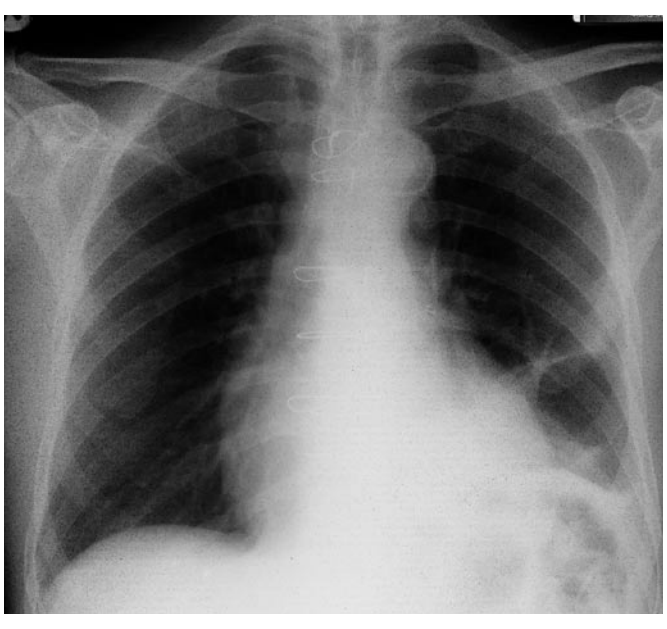
Diagnosis

The diagnosis of atelectasis can be made clinically, but is more often made radiologically.

Clinical diagnosis – atelectasis is suggested by reduced chest wall movement on the affected side, possibly with tracheal or mediastinal shift towards the lesion. Percussion note over the lesion is dull and breath sounds are usually reduced or absent over the affected area. Tachypnoea, tachycardia and hypoxaemia are common accompaniments.

Radiographic diagnosis (Figure 1) – depending on the degree of atelectasis, the chest radiograph may be normal or show signs of lung volume loss. Typical radiological signs include:

- pulmonary opacification distal to the occluded airway
- compensatory hyperexpansion of surrounding normal lung
- elevation of the diaphragm or ipsilateral hemidiaphragm
- shift of intrathoracic structures towards the collapsed segment of lung (e.g. interlobar fissure, trachea, heart, mediastinum or hilus)
- approximation of the ribs – unilateral atelectasis may cause the ipsilateral ribs to lie closer together.



1 Postoperative atelectasis. There is loss of left lung volume, elevation of the left hemidiaphragm with loss of definition of the medial aspect, and linear atelectasis of the left lower lobe (arrow).

Prevention

High-risk patients – physiotherapy reduces postoperative pulmonary complications only in high-risk patients; patients with the following high-risk factors should be identified:

- upper abdominal and thoracic incisions
- body mass index greater than 27
- history of smoking
- chronic obstructive pulmonary disease
- age over 60 years
- impaired preoperative cognitive function (reduced compliance with therapy).

Preoperative breathing exercises – physiotherapy is of most benefit when started preoperatively. Postoperative breathing techniques are easier to learn and practise in the preoperative period when there is no pain. Patients should be taught both deep and diaphragmatic breathing techniques. Effective deep breathing requires a maximal inspiration followed by a 3-second breath hold at full inspiration, before breathing out passively. As the chest expands, lung compliance increases, resistance to airflow decreases and lung re-expansion becomes easier. Diaphragmatic breathing may be facilitated if the patient places a hand over the upper abdomen while making a conscious effort to push outward on to the hand during inspiration.

Intraoperative management – postoperative atelectasis begins intraoperatively. Anaesthetic agents reduce respiratory muscle tone, causing a fall in functional residual capacity and collapse of small airways. The following interventions reduce the risk of atelectasis:

- ensuring adequate patient tidal volumes
- maintaining lung volumes, for example with continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP)
- avoiding accidental endobronchial intubation
- avoiding unnecessarily high F_iO_2
- humidifying inspired gases (e.g. use of a circle system) – without humidification, mucociliary transport becomes less efficient at clearing secretions; this predisposes to airway blockage and gas resorption
- use of a vital capacity manoeuvre – intraoperative lung inflation to an airway pressure of 40 cm H_2O for 7–8 seconds may expand all previously collapsed lung tissue.

Many of these prophylactic interventions are useful in managing postoperative, ventilated patients in the ICU.

Postoperative analgesia – thoracic epidural analgesia is preferable, but whatever the technique, patients are less likely to develop atelectasis if they are pain-free, can breathe deeply, cough well and cooperate with physiotherapy.

Treatment

If the cause of atelectasis is air space compression, the causal pathology (see above) should be treated. Otherwise, treatment of postoperative atelectasis depends on whether the patient is breathing spontaneously or receiving mechanical ventilation.

Spontaneously breathing patients

Humidified oxygen therapy prevents airway blockage and gas resorption.

Mobilization – in the standing position, the downward movement of the diaphragm is unimpeded by the weight of the abdominal contents. Walking increases cardiorespiratory effort, thus increasing diaphragmatic movement.

Positioning – in the awake patient, the dependent lung lies on the steep part of the compliance curve, whereas the non-dependent lung is on the flatter portion (Figure 2). The movement of the dependent hemidiaphragm is about twice as much as that of the non-dependent hemidiaphragm. Thus, a greater portion of the tidal volume goes to the lower lung. In spontaneously breathing patients, physiotherapy should be performed with the atelectatic side in the dependent position.

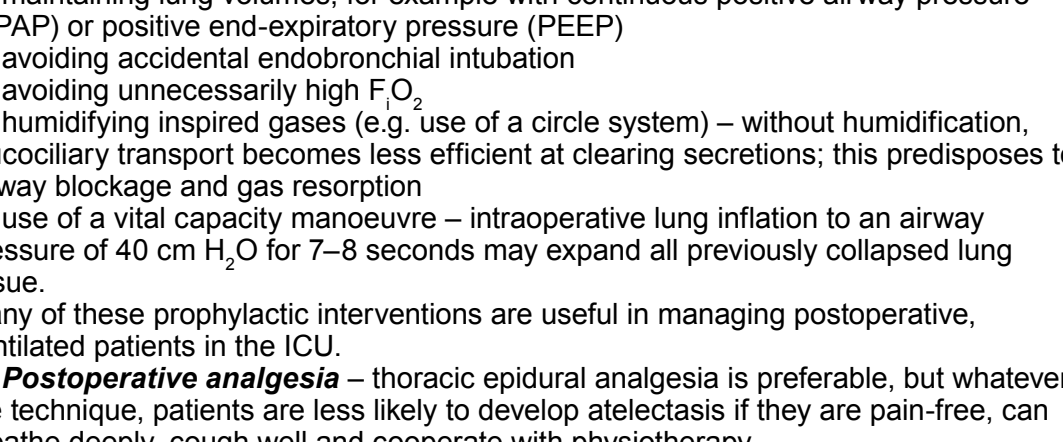
Breathing exercises – sequential diaphragmatic and deep breathing exercises (see page 11), with the addition of a forced expiration technique to help clear secretions, may re-expand a collapsed lung. To motivate patients, incentive spirometry may be used. This provides a visual clue (e.g. keeping ping-pong balls afloat within the device) or actual volume measurement that indicates how deeply the patient is breathing.

Intermittent positive pressure breathing (IPPB) is useful when atelectasis is persistent or the oxygen saturation in arterial blood is low. Following patient triggering, the IPPB device augments patient effort by applying a positive pressure throughout inspiration.

CPAP may reopen collapsed lung tissue.

Tracheal suction – the removal of tenacious sputum requires regular bronchial toilet; when regular orotracheal or nasotracheal suction is poorly tolerated, use of a minitracheostomy assists sputum removal.

Distribution of ventilation in the patient in the lateral decubitus position



Distribution of ventilation **a** when awake and **b** when anaesthetized. Induction of anaesthesia has caused a loss of lung volume in both lungs, with the non-dependent lung moving from a flat, non-compliant portion to a steep, compliant part of the pressure–volume curve. Thus, the anaesthetized patient in a lateral decubitus position has more of the tidal ventilation in the non-dependent lung (where there is the least perfusion) and less of the tidal ventilation in the dependent lung (where there is the most perfusion). V, alveolar volume; P, transpulmonary pressure. Reproduced with permission from Benumof J L, Alfrey D D. Anesthesia for Thoracic Surgery. In: Miller R D, ed. *Anesthesia.* 4th ed. Edinburgh: Churchill Livingstone, 1994: 1663.

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Ventilated patients

Humidified oxygen therapy should be administered. Occasional instillation of saline into the tracheal tube also moistens secretions.

Positioning – in anaesthetized and ventilated patients, lung volume is reduced, moving the non-dependent lung down the pressure–volume (P–V) curve to the steep, compliant part (Figure 2). Consequently, keeping the atelectatic lung uppermost improves ventilation.

Manual hyperinflation – 'bagging' with a Waters' circuit is often used in intensive care. The generation of high inspiratory pressures overcomes the critical opening pressures of surfactant-deficient alveoli, thereby expanding collapsed lung. Caution is advised because hyperinflation may risk pulmonary barotrauma.

CPAP or PEEP reopen some, but not all, collapsed lung tissue; discontinuation results in the rapid return of atelectasis.

Open-lung concept – this ventilator strategy can be used to minimize the effects of over-distending relatively normal lung, while optimizing recruitment in atelectatic alveoli. A static P–V curve is constructed by inflating the lungs with a series of increasing tidal volumes and measuring the corresponding airway pressures. PEEP is then set at about 2 cm H_2O above the point at which the slope of the P–V curve increases (lower inflection point) and the upper limit of the inspiratory plateau pressure is set below the point at which the slope of the P–V curve begins to flatten (upper inflection point).

Kinetic therapy beds may prevent the development of compression atelectasis by providing mechanical percussion and continual rotation along the patient's longitudinal axis.

Bronchoscopy is useful when obstruction of a large bronchus is responsible for atelectasis.

Prevention of Deep Vein Thrombosis and Pulmonary Embolism

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Thrombosis within the deep veins of the leg and/or pelvis can be classified into distal and proximal forms:
- distal deep vein thrombi occur in the deep veins of the calf
- proximal thrombi exist when the thrombus extends above the knee to the thigh or pelvis.

Deep vein thrombosis (DVT) carries a high incidence of pulmonary embolism (PE) – mechanical obstruction of a pulmonary artery or arteriole. The incidence of PE is much greater with proximal DVTs, occurring in up to 40% of cases. DVT and PE are collectively termed thomboembolic disease.

Incidence

The true incidence of DVT is not known. However, postoperative DVT is confirmed by venographic evidence in about 33% of patients if no prophylactic anticoagulant measures are taken. The incidence is higher with certain operations (e.g. total hip or knee arthroplasty; 40–70%).

Aetiology

The main risk factors for thromboembolic disease are:
- prolonged or major surgery
- malignancy
- pelvic, hip or leg fracture
- previous thromboembolic disease
- immobility (pre-existing or postoperative)
- age over 40 years
- hypercoagulable state
- obesity
- pregnancy
- oestrogen therapy (increased if ethinyl oestradiol dose > 50 µg/day)
- co-existing illness – heart failure, myocardial infarction, sepsis.

Pathophysiology

Three factors influence thrombus formation:
- abnormalities of blood flow (e.g. reduced lower limb flow occurs during postoperative immobility, dehydration, cardiac failure)
- injury to the vessel intima (e.g. following pelvic or lower limb trauma, local inflammation)
- changes to blood causing hypercoagulability (Figure 1).

Causes of blood hypercoagulability

Inherited
- Antithrombin III deficiency
- Protein S deficiency
- Protein C deficiency
- Mutation in factor V gene (causes resistance to activated protein C found in 60% of cases of idiopathic deep vein thrombosis)

Acquired

Physiological
- Pregnancy
- Obesity

Disease related
- Malignancy
- Congestive heart failure
- Nephrotic syndrome
- Lupus anticoagulant
- Thrombotic thrombocytopenic purpura

Drug induced
- Oestrogen therapy
- *Heparin-induced thrombocytopenia*

Perioperative management

Although it is often forgotten, the use of prophylaxis reduces the incidence of postoperative DVT from 30% to less than 5%. There are several techniques for the prevention of DVTs.

Preoperative – techniques include:
- heel cushions to prevent pressure on the calf veins
- elevation of the legs to promote venous drainage
- pharmacological methods – unfractionated heparin (UFH), low molecular weight heparin (LMWH), warfarin, dextrans, antiplatelet drugs (e.g. aspirin), hirulog (a direct-acting thrombin inhibitor given subcutaneously)
- caval filters.

Intraoperative prevention of DVTs involves the use of extradural and spinal anaesthesia.

Intraoperative and postoperative – techniques include:
- heel cushions to prevent pressure on the calf veins
- elevation of the legs to promote venous drainage
- graduated compression stockings
- intermittent pneumatic sequential compression devices
- electrical stimulation of the leg muscles
- pharmacological methods – UFH, LMWH, warfarin, dextrans, antiplatelet drugs, hirulog
- early postoperative mobilization.

Compression of the lower limbs increases blood flow through the deep veins and decreases stasis. Correctly sized and appropriately worn graduated compression stockings reduce the incidence of DVT by more than 50%. They are available in calf-length and thigh-length sizes. Thigh-length stockings can form constrictive bands if not worn correctly and are more likely to cause complications such as skin necrosis and arterial thrombosis. Importantly, no benefit has been demonstrated over calf-length stockings. Graduated compression stockings should be worn until the patient is fully mobilized.

The sequential inflation of bladders placed around the calf or foot assist in pumping blood through the deep veins. Sequential compression devices are most commonly applied in the operating theatre and removed at the end of a procedure. Calf devices appear to be more effective than foot devices. Prolonged postoperative use of sequential compression devices often fails because of poor patient compliance.

Pharmacological methods: UFH causes a confirmational change in antithrombin III (AT III), making it a rapid inhibitor of clotting co-enzymes IIa, IXa, Xa, XIa and XIIa. UFH inhibits thrombin by linking thrombin and AT III, thereby prolonging the activated partial thromboplastin time (APTT). It provides highly effective prophylaxis at a dose of 5000 IU s.c. 2–3 times a day. It is most effective when started at least 2 hours preoperatively and improved results have been obtained by titrating the dose to keep the APTT at the upper limit of the normal range. The requirement for blood tests makes this second method unpopular. The main side-effects are:
- bleeding
- thrombocytopenia
- osteoporosis
- paradoxical hypercoagulable state
- local bruising.

Thrombocytopenia and osteoporosis appear to be related to the large molecular size (molecular weight 12,000–15,000) of UFH; they are less common if LMWH (molecular weight 4000–6500) is used. LMWH is as effective as UFH in preventing the thromboembolic complications of surgery. It is also just as likely to produce unwanted bleeding, despite its smaller molecular size, making it less able to cross-link AT III and thrombin. However, less frequent injections are required with LMWH and it has fewer side-effects. After surgery, UFH and LMWH should be continued until full mobilization is achieved.

Intravenous low molecular weight dextrans are expensive, require intravenous administration and carry a significant risk of cardiac and anaphylactic complications. They are not as effective as heparin for thromboembolic disease prophylaxis. Hirulog is under investigation and is proving effective.

It is preferable for patient and clinician to avoid the need for injections. Oral heparin has low bioavailability, but the use of an adjunct to improve this is being studied. Warfarin, titrated to keep the international normalized ratio at 2.0, is as effective as subcutaneous UFH or LMWH at moderate-risk doses. Although bleeding problems appear to be no greater, there are concerns over warfarin's reversibility and the need for blood tests to monitor therapy. Aspirin prophylaxis has received new interest but has yet to prove as effective as UFH or LMWH.

Caval filters: in cases of recurrent PE secondary to DVT, a filter can be placed in the inferior vena cava to prevent onward passage of mobile clots. Although these devices reduce the incidence of PE, they may increase the incidence of recurrent DVT.

Anaesthetic management: spinal and epidural anaesthesia have the theoretical advantage of causing vasodilatation and increasing lower limb blood flow and may be associated with a decreased incidence of thromboembolic disease compared with general anaesthesia. It is most important to recognize 'at-risk' patients early and to provide appropriate thromboembolic disease prophylaxis. Perioperative prophylactic regimens vary between hospitals, but a suitable approach is described in Figure 2. Early mobilization can be encouraged by limiting the use of regional neuromuscular blockade (if possible), providing a rapid recovery from anaesthesia, ensuring good analgesia and facilitating the use of modern ambulatory devices if drug infusions are required. The oral contraceptive pill usually has a low oestrogen content and, though a risk factor for thromboembolic disease, a policy of withdrawing it before surgery is no longer justified.

Concerns exist regarding the use of regional anaesthesia in patients already receiving prophylactic anticoagulation, particularly in terms of the risk of epidural haematoma formation. Epidural or spinal techniques should not be performed within 6 hours of the injection of UFH or LMWH. Alternatively, the start of prophylaxis may be delayed until the regional block has been performed, but this may decrease its effectiveness.

Sample regimen for perioperative prophylaxis of thromboembolic disease

Low-risk patients (e.g. age < 40 years, minimal immobility – DVT risk < 2%)
- Early mobilization

Moderate-risk patients (e.g. age > 40 years, general surgery or leg fracture – DVT risk 10–20%)

Preoperative
- Calf-length graduated compression stockings (GCS)
- Enoxaparin, 20 mg o.d., or heparin, 5000 IU s.c. b.d. – if there is a high risk associated with bleeding (e.g. neurosurgery), a postoperative calf sequential compression device (SCD) can replace enoxaparin/heparin

Perioperative
- Calf SCD

Postoperative
- As preoperative until mobilized

High-risk patients (e.g. major hip/knee surgery or previous thromboembolism – DVT risk > 40%)

Preoperative
- Calf-length GCS
- Enoxaparin, 40 mg o.d., or heparin, 5000 IU s.c. t.d.s.

Perioperative
- Calf SCD

Postoperative
- As preoperative until mobilized

Effective prophylaxis: DVT and PE are significant causes of perioperative morbidity and mortality. Prophylaxis using a combination of compression techniques and anticoagulation is effective in reducing their incidence. Prophylaxis should begin preoperatively, compression devices must be applied properly and both continued until the patient is fully mobilized.

The Recovery Room

Andrew Yates

Andrew Yates qualified from St Thomas's Hospital, London, before joining the Royal Navy. As an Anaesthetist, he saw active service in the Falklands and in the Adriatic on HMS Ark Royal and was Principal Medical Officer to Royal Yacht Britannia. He is now a Consultant Anaesthetist in Portsmouth and Clinical Director of Theatres.

As the complexity of anaesthesia and surgery has increased, so has the ability to operate on a wider range of patients. Although the availability of an intensive care unit (ICU) is essential for some operations and a high dependency unit (HDU) is desirable for many others, most hospitals in the UK depend on the facilities available in the recovery room for early postoperative care. In many hospitals without an HDU, recovery facilities are available for the first 24 hours after surgery.

Design

Over the last 30 years, the recovery room in hospitals has evolved from a single holding area outside the theatre suite, to an environment where patients are stabilized and monitored, some for considerable periods of time, before return to the ward. This contribution does not directly address the design of the day case unit, but the same principles apply.

The design of a recovery area should benefit the patients and staff and should take account of the regulations and other factors described below.

Clinical considerations

The recovery room should be designed to suit the individual needs of each theatre suite. In some hospitals, this area may include an HDU or it may lead to an adjoining HDU and ICU. Other recovery rooms segregate children or those undergoing sedation or local anaesthetic procedures. The recovery room must be configured into the general layout of the theatre suite and should maximize the effective use of varying staff skill mixes. Ideally, recovery facilities should be centralized in the theatre suite.

Throughput: the main factor in designing an adequate recovery area is to know the throughput. A number of methods are used to predict the average occupancy of recovery areas. They all depend on a number of variables:

- number of theatres
- case mix
- number of patients per list
- envisaged change in workload over lifespan of theatre suite
- average length of patient recovery.

Patients should enter and exit through different doors. Anaesthetists, surgeons and theatre staff must have access to the recovery room from the theatre suites, but ward staff, porters and parents require access from outside. The increase of methicillin-resistant *Staphylococcus aureus* and other hospital-acquired infections impacts on these arrangements.

Size and shape: the correct size of the recovery room is crucial; if it is too small it will be the theatre bottleneck on which all activity throughout the theatres will depend. This may lead to pressure on staff to discharge patients sooner than they might otherwise. If the recovery room is too large, it will be wasteful of resources. It is recommended that there are a minimum of 1.5 beds per theatre with each bed space requiring a minimum of 9.3 m^2. It is important that the area is unobstructed. All patients should be observed easily with adequate space between each recovery bay and across the area for the passage of beds, radiographic equipment, staff and crash trolleys.

Building regulations and fire safety

From the start of planning, attention must be paid to regulations and guidance notices and the recovery planning team should be fully conversant with them. NHS Estates, an executive agency of the Department of Health, publishes a series of Health Bulletin Notices and other related guides, prepared in consultation with representatives and experts in their fields, which give information on all aspects of hospital design. Fire safety is a vital consideration and the design of the recovery room must allow the swift and safe removal of patients.

Health and safety

The Health and Safety at Work Act (1974) places a duty of care on every employer '… to ensure, so far as is reasonably practicable, the health, safety and welfare at work of all his employees…' (Section 2 (I)). A host of regulations and directives have been passed from the original Act, and all theatre staff should be aware of those applicable to their workplace. Likewise, the guidance of the 1989 Control of Substances Harmful to Health regulations must be adhered to and the Health and Safety Commission's Advisory Committee on Toxic Substances (ACTS) recommended in 1996 occupational exposure standards (OESs) for anaesthetic agents. Thought must be given, from an early stage in recovery room design, to all aspects of these Acts.

Environment

In the past, scant attention was paid to the working conditions of recovery staff even though they may be required to work for long hours. Regulations have improved the environment, but many existing recovery rooms fall below standard. When designing a recovery room, consideration must be given to the following factors:

- light (natural, artificial, direct, indirect)
- decor (floor, walls and ceiling)
- ventilation and climate (temperature, humidity, pollutant elimination and scavenging)
- preventing infection
- noise levels
- radiation screening
- communication.

Ideally, access to natural light improves the working environment, but the design of centralized recovery rooms often makes this impossible. It is important to have effective lighting for patient observation and for staff. The decor should be designed to make the surroundings pleasant. The creation of the correct environment is vital to the well-being of staff and patients. Department of Health requirements recommend 15 air changes per hour without recirculation. Particular attention must also be paid to the room temperature, which should be maintained at 19−22°C. The area should be free of draughts, the humidity should be maintained at 38–45%. There must be effective scavenging of exhaled anaesthetic gases. Noise levels should be minimized at all times and doors should be self-closing. Radiographs are often performed in the recovery room, therefore screening should be available. The recovery room should be considered as a clean site to minimize nosocomial infection.

Good communication systems are important. They should include intercom facilities to each theatre and rest area, emergency alarms and telephones. A rest area for staff should not be designed into the recovery room because it is essential that staff are able to leave the workplace and relax, if only for brief periods.

Equipment

Although recovery rooms vary, the basic items of equipment are universal.

General facilities

Clinical equipment

- There should be a fully equipped anaesthetic machine and ventilator; more than one in larger units.
- A full range of anaesthetic equipment and drugs should be to hand at all times, to deal with intubation, cardiac arrest, tracheotomy, anaphylactic reaction and malignant hyperpyrexia.
- There should be a defibrillator, ideally in the recovery room, or if not, close at hand.

Portable suction, oxygen supplies and battery-powered lighting should be available in case of electrical failure or if the room has to be evacuated.

- Patient-warming devices should be available.
- Large stocks of intravenous fluids should be present.

Cleanliness and tidiness: the following facilities are required to maintain cleanliness and tidiness in the recovery room:

- storage areas for linen, unused equipment and monitoring
- cupboards for drugs and separate secure unit for controlled drugs
- fridge-freezer for drugs and ice
- hand-washing facilities at suitable positions within the area
- separate clean and dirty areas, with enclosed sluice
- space for a desk with IT support and monitoring console
- individual suitable chair at each patient bay
- storage for bed oxygen cylinders
- portable screens.

Individual bay

The following items of equipment are essential in individual bays:

- bed or trolley that can tilt both ways, with protective sides available
- piped dedicated split oxygen supply and flowmeters with tubing to either an appropriate face mask, self-inflating resuscitation bag with anaesthetic mask or T-piece for laryngeal mask airway
- selection of oral and nasal airways
- piped vacuum suction
- sufficient electrical points (six 13 A sockets per bay)
- lighting (dependent on general levels in room)
- emergency alarm
- monitoring sufficient for individual requirement.

Monitoring differs depending on the patient, but, in the UK, it should follow the guidelines of the Association of Anaesthetists of Great Britain and Ireland. Monitors can be linked to a central console at the nursing station, but future developments may lead to 'cordless' continual monitoring of the patient from anaesthetic room to ward, for 24 hours or more after surgery.

Staffing

The recovery period is potentially dangerous, and it is estimated that 20% of patients develop one or more complications during this time; upper airway obstruction is the most common. Therefore, it is imperative that the recovery room has sufficient staff of the appropriate skill mix for the operative workload in the theatres. Each patient should be individually cared for until fully conscious, stable and maintaining their own airway.

With the decline in the number of nurses in theatre, there has been a steady change in the pattern of staffing in the recovery room. Currently, there is a mix of nurses and operating department assistants/practitioners. The recovery room is the only area in the theatre complex where basic and advanced nursing skills are needed side by side − and this responsible and rewarding role should be emphasized to the student nurse. All recovery staff must undergo structured training under close supervision before they are allowed to recover patients (ENB 182 and 183 or NVQ Level 3 in operating theatre practice). There is no other area in a hospital where non-medical staff routinely look after all aspects of patients emerging from the effects of all forms of anaesthesia after every type of surgery.

Notwithstanding the staffing constraints of hospitals in the UK, ward nurses would benefit from exposure to the recovery environment and recovery staff should have experience of the HDU and ICU. The trainee anaesthetist would also benefit from working in the recovery room and learning about the routine management of the postoperative patient. In some hospitals, a designated anaesthetist is available immediately to assist and advise the recovery staff. It is generally impractical to have a paediatric recovery nurse available at all times, but the team should be able to liaise with a member of the paediatric ward staff. All recovery staff must keep up to date with adult and paediatric resuscitation techniques.

Instructions to recovery staff

Whether a patient has been anaesthetized for 5 minutes or 5 hours, it is important that the anaesthetist hands over their care to the recovery staff in a correct and informed manner, giving all relevant information (Figure 1).

The anaesthetist should also provide instructions about the patient's recovery, with reference to analgesia, anti-emetics, fluid requirements, supplementary oxygen and rewarming. The anaesthetic record should be available together with the operation notes. The theatre practitioner who scrubbed for the surgeon should give a brief verbal résumé of the procedure. The anaesthetist should always remain until the recovery staff are confident the patient is stable. Patients are the responsibility of the anaesthetist until they are discharged to the ward.

Patient information required by recovery staff

- Name, age, American Society of Anesthesiologists (ASA) grade
- Operation and surgeon
- Type of anaesthetic (local or general)
- Any pre-existing condition of relevance (e.g. hypertension, diabetes, allergies)
- Method of airway maintenance during surgery
- Spontaneous or intermittent positive-pressure ventilation
- Opiate loading and other methods of pain control
- Whether reversal agents used
- If regional technique, method employed
- General condition during procedure (especially pulse and blood pressure)
- Fluid balance and blood loss during surgery
- Positioning of patient during surgery
- Any untoward events that occurred during surgery
- Dentition (crowns, bridges, loose teeth)

Discharge to the ward

Most patients are discharged to the general ward for continuing postoperative care. Each patient should fulfil the same criteria before discharge from the recovery room:

- patient conscious with a patent airway
- cardiovascular parameters stable
- respiratory pattern and depth adequate, with maintained oxygen saturation
- no excess bleeding from surgery
- patient comfortable (i.e. has adequate pain relief)
- patient adequately rewarmed
- urine output maintained (if monitored)
- prescription and epidural/patient-controlled analgesia charts written and legible
- fluid regimen and instructions to ward clearly stated
- surgical notes and instructions documented.

FURTHER READING

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Clark P, Jones J. *Brigden's Operating Department Practice.* Edinburgh: Churchill Livingstone, 1996.

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Immediate Postanaesthetic Recovery. Association of Anaesthetists of Great Britain and Ireland,1993.

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Adverse Drug Reactions

Norman Calvey

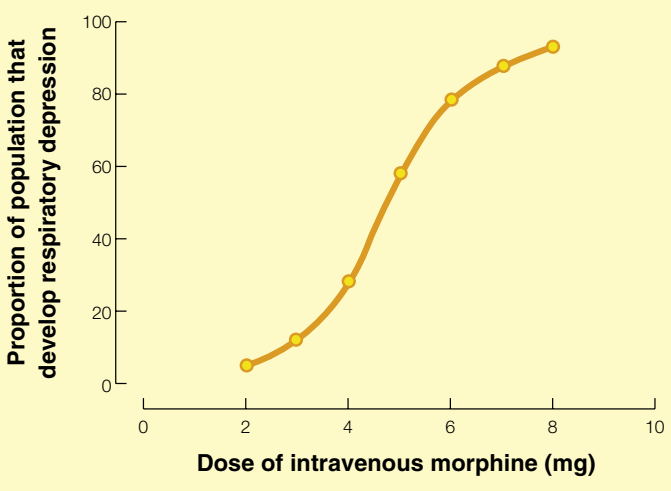
Norman Calvey is Honorary Senior Research Fellow in the University Department of Anaesthesia, Liverpool, UK. He qualified in science and medicine from Liverpool University and has worked in Departments of Pharmacology and Anaesthesia. His research interests include pharmacokinetics and drug isomerism.

Adverse reactions to drugs are relatively common and often cause iatrogenic disease. They present in different ways and vary in severity from mild skin rashes to the production of gross malignant and teratogenic changes. In the UK, adverse drug reactions are responsible for 3–5% of all hospital admissions, and occasionally cause death. In clinical practice, they are usually divided into Type A and Type B reactions.

Type A reactions are relatively common and are often related to the main pharmacological effects of drugs. They are usually well known and predictable and are sometimes referred to as 'mechanism-based reactions' or 'side-effects'. They are often dose related, and are usually more common when the drug dose is high. Many of the toxic effects of drugs on target organs are classified as Type A reactions (e.g. hepatic cirrhosis induced by paracetamol or isoniazid, or nephrotoxicity caused by angiotensin-converting-enzyme inhibitors). Most have a prevalence of more than 1/1000 (0.1%), and they are readily identified in preclinical and clinical trials. Patients vary in their susceptibility to Type A reactions, and they may be produced by a range of doses in different individuals. They are particularly likely to occur in the elderly or in patients with renal or hepatic impairment.

Many of the unwanted effects of morphine (e.g. sedation, respiratory depression, emesis, constipation, hypothermia) are typical Type A reactions; in some instances, individual variation in patient response corresponds to a characteristic S-shaped (sigmoid) curve (Figure 1). Consequently, they can be expected to occur in all patients who are given the drug at a sufficiently high dose. Similarly, the anticholinergic (antimuscarinic) effects produced by many agents (e.g. some H_1-histamine antagonists, β-adrenoceptor antagonists, antiarrhythmic drugs, anticonvulsants, phenothiazines) are classified as Type A reactions.

Inter-individual variation in response to morphine



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Type B reactions are usually unrelated to the main pharmacological effects of the drug and are often dose independent, relatively uncommon and unpredictable. In general, their prevalence is less than 1/1000 (0.1%), and they may not be identified in preclinical or clinical trials. Although they are less common than Type A reactions, they are a significant cause of serious adverse responses to drugs. In some patients their aetiology is obscure, but in others they are related to genetic predisposition or drug hypersensitivity.

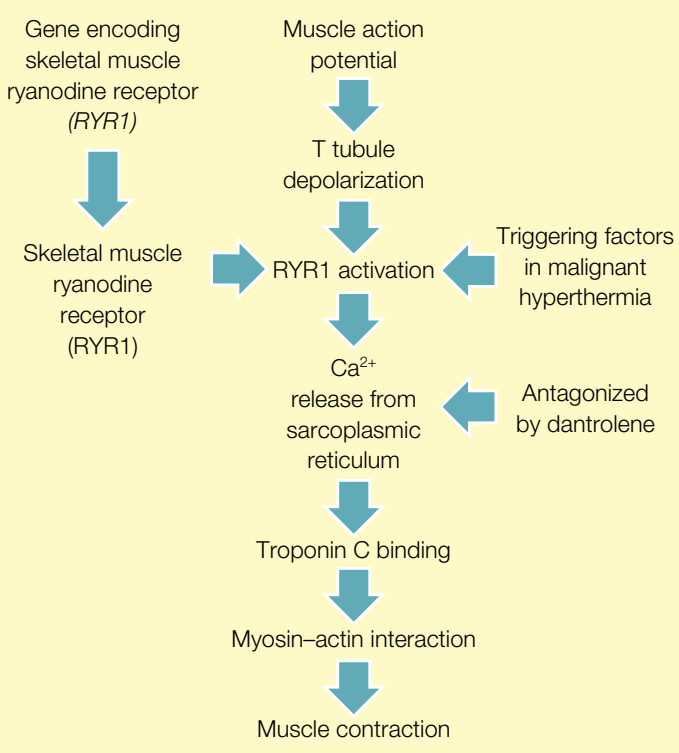
Reactions resulting from genetic predisposition (idiosyncratic reactions)

In anaesthesia, the three important drug reactions resulting from genetic predisposition are malignant hyperthermia, hepatic porphyria and prolonged apnoea induced by suxamethonium.

Malignant hyperthermia

Malignant hyperthermia (malignant hyperpyrexia) is an abnormality of skeletal muscle generally inherited by autosomal dominant transmission (see also page 222). In about 50% of patients, the condition is linked to an abnormality in the ryanodine gene (*RYR1*) on chromosome 19q (the long arm of chromosome 19). *RYR1* normally encodes the ryanodine receptor in the sarcoplasmic reticulum, which is activated in response to depolarization of the transverse tubules (T tubules) in the triads of skeletal muscle. Receptor activation results in Ca^{2+} release from the sarcoplasmic reticulum and initiates myosin–actin interaction and muscle contraction (Figure 2). In malignant hyperthermia, exposure to 'triggering agents' (i.e. suxamethonium or fluorinated anaesthetics) results in excessive Ca^{2+} release from the sarcoplasmic reticulum, producing muscle rigidity, metabolic and respiratory acidosis, tachycardia, hyperkalaemia and pyrexia. The mortality of malignant hyperthermia reactions used to be high (about 65%) but recently it has been reduced to 5–10%, mainly owing to greater aware-ness of the condition, the rapid instigation of methods to ensure cooling, and the use of dantrolene sodium (which uncouples T tubule depolarization from Ca^{2+} release).

Excitation–contraction coupling in skeletal muscle



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Susceptibility to malignant hyperthermia is confirmed by muscle biopsy and exposure to halothane and caffeine in *in vitro* conditions; in these circumstances there is a greater increase in tension than in normal muscle. Similar effects are produced by ryanodine and chlorocresol. If the diagnosis is confirmed, genetic counselling of patients and their families is essential.

Hepatic porphyria

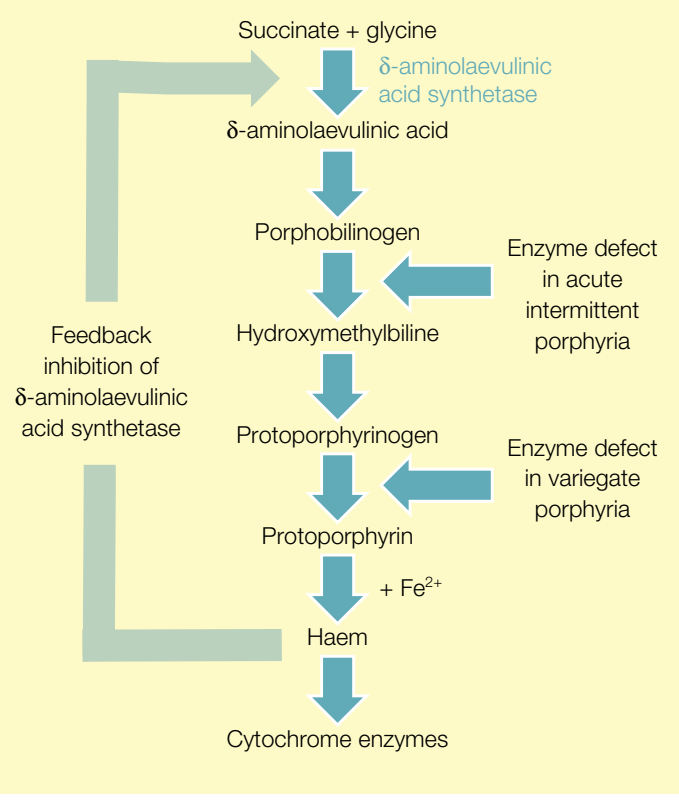
In certain hepatic porphyrias (particularly acute intermittent porphyria and variegate porphyria), attacks of the disease can be precipitated or exacerbated by certain drugs (particularly drugs that increase the synthesis of cytochrome P450).

In humans, haem has an essential role as the prosthetic group of various haemoproteins (e.g. haemoglobin, myoglobin, cytochrome oxidase, cytochrome P450). The synthesis of haem depends on the enzyme δ-aminolaevulinic acid synthetase (ALA synthetase) which catalyses the synthesis of δ-aminolaevulinic acid from succinate and glycine. Two molecules of δ-aminolaevulinic acid subsequently combine to form porphobilinogen, which is sequentially converted to hydroxymethylbiline, protoporphyrinogen and protoporphyrin. Finally, combination with divalent iron results in the formation of haem (Figure 3). In normal conditions, free haem exerts close feedback inhibitory control on the activity of ALA-synthetase; this is the main physiological factor controlling haem synthesis.

In the acute porphyrias (notably acute intermittent porphyria and variegate porphyria), there is a deficiency or reduced activity of one or more enzymes in this pathway (Figure 3); consequently, haem synthesis is decreased, causing activation of ALA-synthetase, and the accumulation of precursor porphyrins in tissues. Acute porphyrias are usually autosomal dominant conditions with a variable degree of penetrance and enzyme activity is typically about 50% of normal. Consequently, many patients remain asymptomatic for prolonged periods.

Exacerbations of acute intermittent porphyria are most commonly associated with neuromuscular weakness, neurological lesions, neuropsychiatric disturbances and abdominal pain; similar phenomena (as well as cutaneous manifestations) usually occur in variegate porphyria. Although attacks can be precipitated by physiological factors (e.g. menstruation, pregnancy), drugs that affect or induce cytochrome P450 (e.g. all barbiturates, phenytoin, carbamazepine, rifampicin) are more commonly involved, and should be avoided in patients with acute porphyria. These enzyme-inducing agents increase the incorporation of haem into cytochrome P450, decrease intracellular haem levels, and thus activate ('derepress') ALA synthetase (Figure 3). Consequently, porphyrin synthesis is increased and the disease may be exacerbated. Haem derivatives (e.g. haematin and haem arginate) suppress the enhanced activity of ALA synthetase and have an important role in the treatment of acute attacks of porphyria.

Hepatic synthesis of haem and cytochrome enzymes



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Prolonged apnoea induced by suxamethonium

Suxamethonium is an ester of choline and succinic acid, and conventional doses of the drug (1 mg/kg) have a duration of action of 3–5 minutes, owing to their rapid hydrolysis by plasma cholinesterase. Inheritance of genetic variants of cholinesterase may reduce the rate of ester hydrolysis, increase the duration of action and cause prolonged apnoea. Delayed hydrolysis may also predispose to tachyphylaxis and dual block.

Genetic variants in plasma cholinesterase are determined by four allelomorphic genes that have been identified at a single locus on chromosome 3. These genes encode the normal or usual enzyme (E_1^u), the atypical enzyme (E_1^a), the fluoride-resistant enzyme (E_1^f) and the absent or silent enzyme (E_1^s). The atypical enzyme is the most common genetic variant. In homozygous individuals, the atypical enzyme can be distinguished from the normal (usual) enzyme by its resistance to inhibition by the local anaesthetic cinchocaine (dibucaine). The 'dibucaine number' is defined as the enzyme inhibition (%) produced by dibucaine (10^{-5} mol/litre), using benzoylcholine as the substrate. Normal homozygotes (E_1^u E_1^u) have dibucaine numbers of 80; hetero-zygotes for the atypical enzyme (E_1^u E_1^a) have dibucaine numbers of 60, while homozygotes for the atypical enzyme (E_1^a E_1^a) have dibucaine numbers of 20 (Figure 4). Since four allelomorphic genes are present, ten genotypes have been identified, three of which show a greatly prolonged response to a conventional dose of suxamethonium. Their prevalence in Caucasian populations is just over 1/1000 (0.1%).

Recently, at least six additional allelomorphic genes have been identified by DNA-cloning techniques. In addition, a second distinct chromosomal locus has been identified, which is associated with two further genetic variants ($E_{Cynthiana}$ and C_5); these are thought to be responsible for increased cholinesterase activity.

In theory, the duration of action of other anaesthetic drugs that are esters (e.g. atracurium, mivacurium, procaine, esmolol, remifentanil) may be prolonged by genetic variants in plasma cholinesterase. Although this may occur with mivacurium, particularly when homozygotes (E_1^a E_1^a) or heterozygotes (E_1^u E_1^a) for the atypical enzyme are involved, it does not appear to be of clinical significance with other drugs.

Genetic variants in plasma cholinesterase that commonly prolong the effects of suxamethonium

	Genotype	Approximate prevalence	Dibucaine number
Normal cholinesterase	$E_1^u E_1^u$	950/1000	80
Significant genetic variants	$E_1^a E_1^a$	1/1000	20
	$E_1^a E_1^s$	1/10,000	20
	$E_1^s E_1^s$	1/100,000	None

Other genetic variants are of minimal clinical significance

Other drug reactions
Other drug reactions related to genetic predisposition include:
- haemolytic anaemia (antimalarial drugs)
- resistance to oral anticoagulants (warfarin)
- toxic effects of drugs (isoniazid, hydralazine, phenelzine)
- hypotensive responses (debrisoquine)
- increased intraocular pressure (corticosteroids)
- increased alcohol-induced facial flushing (chlorpropamide)

Reactions resulting from drug hypersensitivity (allergic reactions)

Hypersensitivity or allergic responses to drugs are abnormal reactions to drugs that are dependent on immunological factors; they are usually divided into four main types, depending on the mechanism involved.

Type I hypersensitivity (immediate type hypersensitivity)
In Type I hypersensitivity, drugs or their metabolites combine covalently with plasma or tissue proteins. The resultant antigenic complex induces the formation of IgE antibodies, which become attached to mast cells in various tissues of the body (e.g. skin, bronchial and intestinal mucosa, blood vessels, basophil leucocytes). On subsequent exposure to the antigen, adjacent IgE molecules on the mast cell membrane are cross-linked, resulting in Ca^{2+} entry, mast cell degranulation, and the release of various pharmacological mediators (e.g. histamine, heparin, 5-HT, leukotrienes, platelet-activating factor).

Type I hypersensitivity responses are most commonly seen in atopic patients given penicillins or cephalosporins; these groups of antibiotics are structurally related, and may show cross-sensitivity reactions. In the case of penicillins, degradation products (e.g. penicillinoyl derivatives) are believed to be the main antigenic determinants. Hypersensitivity responses may also be produced by insect stings and the oral ingestion of certain foods (e.g. eggs, fish, cows' milk, peanuts) or the medical use of foreign proteins (e.g. streptokinase, asparaginase, heparin, vaccines, blood products). They are occasionally implicated in adverse reactions to anaesthetic agents, including thiopental (thiopentone), suxamethonium and non-depolarizing relaxants. Clinical manifestations of Type I hypersensitivity include anaphylactic shock, hypotension, bronchospasm, laryngeal oedema and urticaria.

Anaphylactic shock is rare; it is an acute medical emergency. Circulatory support, oxygen administration and intramuscular or intravenous adrenaline (epinephrine) are essential, and may be life-saving. Other drugs (e.g. parenteral corticosteroids, H_1-histamine antagonists) may also be used, but are of less immediate value. Anaphylactic shock is usually considered to result from the generalized release of all the pharmacological mediators referred to above.

Bronchospasm is a serious complication of Type I hypersensitivity, and is mainly a result of the local formation and release of leukotrienes C_4, D_4 and E_4 ('cysteinyl-leukotrienes') from mast cells in the bronchial mucosa. Tracheal intubation and positive-pressure ventilation with 100% oxygen may be required, and in severe cases adrenaline (epinephrine) is necessary. In other instances, administration of β_2-agonists (e.g. intravenous or nebulized salbutamol or terbutaline) or aminophylline should be considered. In bronchospasm, β_2-agonists and aminophylline can be used concurrently because they act on different receptor systems.

Laryngeal oedema (angio-oedema) may present as glottic or subglottic oedema, and require urgent intubation or tracheostomy. Adrenaline (epinephrine) and oxygen therapy are often required. Intravenous H_1-receptor antagonists (e.g. chlorphenamine) and corticosteroids are sometimes useful, though their onset of action may be delayed.

Anaphylactoid reactions – histamine and other factors may be directly released from mast cells and basophils by non-immunological mechanisms. These phenomena are often referred to as anaphylactoid reactions, because they may be difficult to distinguish clinically from the anaphylactic responses associated with Type I hypersensitivity. Many therapeutic agents can produce local or generalized histamine release from mast cells, including:
- basic drugs (morphine, pethidine, tubocurarine, atracurium, suxamethonium, trimetaphan, vancomycin)
- solubilizing agents (polyethoxylated castor oil)
- radiocontrast media
- colloidal plasma expanders (modified gelatin and dextrans)
- polypeptides (polymyxin B, bradykinin, substance P, anaphylatoxins).

Anaphylactoid reactions are not uncommon in anaesthetic practice (particularly when high concentrations of drugs are rapidly injected into small blood vessels). They may occur more often when several different drugs are administered through small infusion needles; in these conditions, physicochemical combination may result in the production of colloid aggregates, resulting in histamine release. Anaphylactoid reactions present clinically as localized vasodilatation, hypotension or skin reactions; occasionally circulatory collapse or bronchospasm occur.

It may be difficult to detect patients who are susceptible to anaphylactoid responses, though individuals with a history of atopy (asthma, hay fever or eczema), or with a previous or family history of adverse reactions are particularly vulnerable. Some drugs appear to be relatively safe (e.g. etomidate, vecuronium, fentanyl, local anaesthetics). Preoperative prophylaxis with H_1- and H_2-receptor antagonists may confer some degree of protection in susceptible patients.

At least two intravenous anaesthetics (propanidid and althesin) have been withdrawn because of their association with severe anaphylactoid reactions.

Type II hypersensitivity (cytolytic reactions)
In Type II hypersensitivity, drugs combine with macromolecules or proteins in the cell membrane, forming an antigenic complex which induces the synthesis of IgG or IgM antibodies. These immunoglobulins then cross-react with the antigenic complex in the presence of complement, causing cell lysis or agglutination; alternatively, target cells are attacked by killer lymphocytes.

Type II hypersensitivity reactions usually involve the combination of drugs with proteins in erythrocyte, granulocyte or platelet membranes, resulting in haemolytic anaemia, leucopenia, agranulocytosis or thrombocytopenia.

Haemolytic anaemia is occasionally induced by methyldopa. Antibodies directed against rhesus antigens occur in 10–15% of patients, though clinically overt anaemia is less common.

Leucopenia is sometimes produced by phenothiazines, phenyl-butazone, carbimazole or clozapine. Although this complication is rare, antileucocyte antibodies or leucocyte lysis can often be detected in affected individuals. The condition may progress to agranulocytosis; its onset is usually delayed (3–12 weeks) but may occur with dramatic rapidity in susceptible patients.

Thrombocytopenia may be induced by heparin or thiazide diuretics; in some instances this is due to Type II hypersensitivity, and antiplatelet antibodies can be demonstrated.

Pancytopenia or aplastic anaemia is occasionally induced by drugs, though if it is caused by drug hypersensitivity is unclear.

Halothane hepatitis is also related to a Type II hypersensitivity reaction. One of the oxidative metabolites of halothane (trifluoroacetyl chloride) is thought to bind covalently with proteins in the hepatic cell membrane. In susceptible patients, antibodies to this complex are synthesized and cross-react with the antigenic protein adduct, causing cellular lysis and acute hepatic necrosis. In many patients with halothane hepatitis, the presence of cross-reacting antibodies can be demonstrated.

Type III hypersensitivity (immune-complex-mediated responses)
Type III reactions do not require previous exposure to drugs or toxins. They are usually caused by the formation of precipitin complexes (and complement fixation) by the reaction of circulating antibodies (IgG) with soluble antigens (e.g. bacterial toxins). Normally, precipitins are removed by the reticulo-endothelial system, but when excess antigen is present, immune complexes are deposited in the vascular endothelium. Type III hypersensitivity reactions are responsible for serum sickness, a systemic response to certain drugs (e.g. sulphonamides, penicillins, certain anticonvulsants) which usually occurs 7–14 days after exposure. Type III hypersensitivity may also be responsible for pathological changes in acute glomerulonephritis, polyarteritis nodosa and rheumatoid arthritis.

Type IV hypersensitivity (delayed, cell-mediated responses)
In delayed hypersensitivity, antibody formation is not involved, and the reaction results solely from the combination of antigen with T cell (killer) lymphocytes. The antigen or hapten is introduced by contact or injection and combines covalently with receptors on the lymphocyte membrane. This results in lymphocyte mitosis and the local release of lymphokines (e.g. lymph node permeability factor) that affect vascular permeability. A local inflammatory reaction usually occurs within 24–48 hours, resulting in erythema, induration, blistering and exfoliation, as a result of the accumulation of macrophages and lymphocytes at the site of injection.

Delayed hypersensitivity is responsible for the positive response to the Mantoux reaction and occurs in most forms of contact dermatitis, whether produced by metals or drugs. It is also a factor in many drug rashes, erythema multiforme (the Stevens–Johnson syndrome), and in the morbilliform rashes that are sometimes induced by ampicillin and amoxicillin (amoxycillin) in patients with glandular fever or chronic lymphatic leukaemia.

Adverse reactions to drugs during fetal life

Drugs administered during pregnancy may cross the placental barrier and adversely affect the fetus. The placenta consists of a vascular syncytial membrane, with the functional properties of a typical lipid barrier. Lipid-soluble, low molecular weight drugs are readily transferred across the placental membrane and their rate of removal from maternal blood is predominantly affected by:
- placental blood flow
- diffusional area
- concentration gradient.

In practice, all lipid-soluble drugs that cross the blood–brain barrier also cross the placenta and their elimination by fetal tissues may be prolonged. In contrast, polar (ionized) or large molecular weight compounds do not readily cross the placenta.

Inhalational anaesthetics, intravenous barbiturates and most opioid analgesics can diffuse from maternal plasma to the fetus, and when used in labour may produce respiratory depression in the newborn. Similar effects may be produced by some sedative and hypnotic drugs. Lipid-soluble β-adrenoceptor antagonists (e.g. propranolol, oxprenolol, metoprolol) can cross the placenta and may cause fetal bradycardia. In addition, fetal hypoglycaemia may be induced by insulin, oral hypoglycaemic agents or some β-adrenoceptor antagonists. When diazepam is used in late pregnancy (e.g. in the management of pre-eclampsia and eclampsia), it readily crosses the placenta, but is only slowly metabolized by the fetus. Its active metabolites (i.e. desmethyldiazepam, oxazepam) accumulate in fetal tissues, and can cause neonatal hypotonia and hypothermia.

Commonly used drugs with teratogenic effects

Drug	Effect on fetus
Methotrexate	Hydrocephalus, neural tube defects
Tretinoin	Hydrocephalus
Phenytoin	Cleft lip/palate, cardiac defects
Sodium valproate	Neural tube defects
Oestrogens	Vaginal adenosis, testicular atrophy
Aminoglycosides	Cochlear and vestibular damage
Tetracyclines	Dental pigmentation, enamel hypoplasia
Carbimazole	Goitre, hypothyroidism
Propylthiouracil	Goitre, hypothyroidism
Warfarin	Nasal hypoplasia, epiphysial calcification

More serious effects are produced by drugs taken during pregnancy that produce fetal damage or malformation (teratogenic changes). In early pregnancy (0–18 days) drugs that affect cell division (e.g. cytotoxic agents, folate antagonists) may affect formation of the blastocyst and cause fetal death. Nevertheless, fetal abnormalities are more commonly produced by drugs that are administered during organogenesis (2–8 weeks).

These drugs include methotrexate, tretinoin, phenytoin, sodium valproate, oestrogens, progestogens, aminoglycoside antibiotics, tetracyclines, antithyroid drugs and warfarin (Figure 5). In some instances, the effects of drugs may be delayed for many years. When stilboestrol was used in late pregnancy, alteration in the maternal hormonal environment produced vaginal dysplasia and malignancy in female offspring after a latent period of 10–20 years. ◆

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Anticoagulants and the Management of Coagulopathy

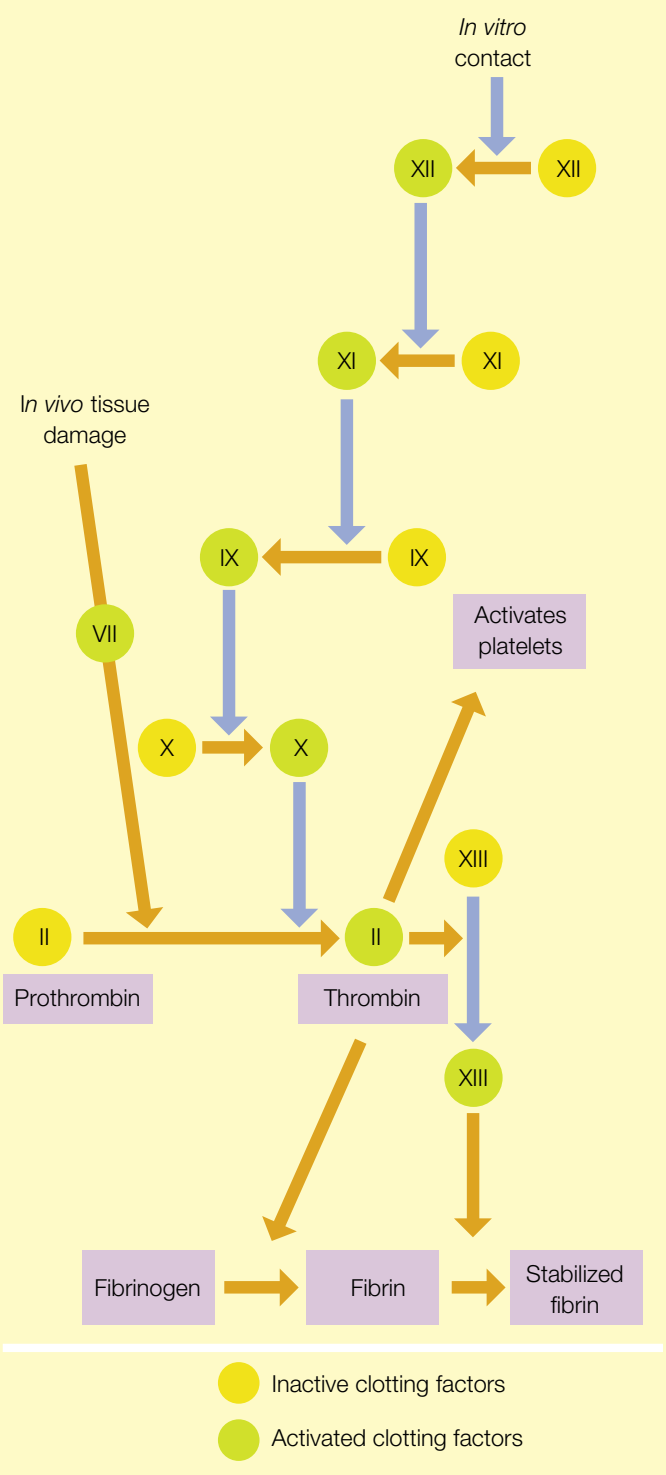
Barbara J Pleuvry

Barbara J Pleuvry is Senior Lecturer in Anaesthesia and Pharmacology at the University of Manchester, UK. She is a pharmacist by first degree but has been involved in teaching pharmacology to postgraduates and undergraduates for over 30 years. Her research interests include pain, analgesia and anticonvulsant drugs.

The prevention of blood loss from a damaged blood vessel is an essential feature of life. Injury to the skin and underlying structures leads to vasoconstriction, adhesion and activation of platelets to form a plug, or thrombus, that stops the bleeding, and fibrin formation, which reinforces the plug. A white thrombus forms initially in high-pressure arteries when platelets adhere to the damaged endothelium. The growing thrombus reduces arterial flow and the local stasis causes fibrin to be deposited, trapping erythrocytes so that a red thrombus is formed around the initial white thrombus. This may cause local ischaemia by blocking the artery. In low-pressure veins, red thrombi can develop without a central white thrombus and they often have a long tail of fibrin and trapped red cells, which can break free and form an embolus remote from the initial area of damage.

The blood coagulation cascade is shown in Figure 1. Modification of this cascade by drugs is clinically useful when there is a disorder of coagulation (coagulopathy).

Blood coagulation cascade



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Role of vitamin K

Vitamin K is a cofactor for the action of carboxylase enzymes that are important in the production of coagulation or clotting factors II, VII, IX and X. In addition, there are several other vitamin K-dependent proteins including osteocalcin in bone. Vitamin K is a fat-soluble vitamin derived from two sources. Vitamin K_1 (phytomenadione) occurs in plants. Bacteria in the gut synthesize vitamin K_2 (menaquinone), which is a series of compounds with side chains of different length. Both vitamins require bile salts for absorption, and deficiencies can arise due to obstructive jaundice when bile secretions are inadequate or absent. Such malabsorption syndromes may be treated with menadiol sodium phosphate, a water-soluble preparation. However, this is ineffective for haemorrhagic disease of the newborn or relative overdoses of coumarin-like anticoagulant drugs (see later) in which phytomenadione is the treatment of choice.

Anticoagulants affecting coagulation proteins

Warfarin and the coumarin anticoagulants

A haemorrhagic disease of cattle was found to be caused by a deficiency in plasma prothrombin caused by bishydroxycoumarin, a toxin found in spoiled sweet clover silage. This was synthesized as dicoumarol and subsequently its derivatives, particularly warfarin, have been widely used commercially as rodenticides and clinically as antithrombotic agents in humans. Warfarin is the most commonly used drug in the group and others, such as acenocoumarol and phenindione, are used only in patients who show idiosyncratic adverse reactions to warfarin. Vitamins K_1 and K_2 are activated in the body by reduction of the epoxide, generated by the carboxylation of prothrombin, to the hydroquinone form. This step is sensitive to the coumarins, which act effectively as vitamin K antagonists. The synthesis of all the vitamin K-dependent clotting factors is partially inhibited so the onset of the anticoagulant effect of coumarins is dependent on the degradation rate of the clotting factors in the plasma. The onset of action usually takes about 12 hours and maximum effects occur several days after the commencement of treatment. This long delay poses several problems in achieving a balance between giving enough to prevent excessive coagulation and giving too much, resulting in unwanted haemorrhage. Measuring the prothrombin time monitors treatment. Warfarin crosses the placenta readily. It is teratogenic in early pregnancy and may cause intracranial haemorrhage in the neonate during birth. It is thus avoided during pregnancy. Warfarin is also excreted in breast milk. This could pose a problem for suckling infants because they are inherently deficient in vitamin K owing to their lack of gut flora. However, phytomenadione treatment of the neonate is now routine and treatment of the mother with warfarin is not contraindicated. There are many drug interactions with coumarin anticoagulants of which the most important appears to be the risk of haemorrhage with the concurrent use of antibiotics such as co-trimoxazole and co-amoxiclav.

Heparin

Heparin is present in mast cells and is extracted from animal tissue such as beef lung or porcine intestinal mucosa. It is a family of sulphated glycosaminoglycans with a range of molecular weights and, because its constitution is variable, it is bioassayed against an international standard and is measured in units of activity rather than mass. Heparin is a rapidly acting anti-coagulant given intravenously or subcutaneously, with a short duration of action. It may be referred to as standard or unfractionated heparin to distinguish it from the low-molecular-weight heparins (e.g. dalteparin sodium, enoxaparin) which have a longer duration of action and are administered subcutaneously. Heparin is used in the treatment of deep vein thrombosis and pulmonary embolism and low doses may be used in anaesthesia to prevent the development of these two conditions in high-risk patients undergoing general surgery. The low-molecular-weight heparins are being increasingly used for this purpose. Heparin is used to maintain the extracorporeal circuits in cardiopulmonary bypass surgery and haemodialysis.

Heparin is an effective anticoagulant *in vivo* and *in vitro*. It activates a protease inhibitor, antithrombin III, which inhibits many of the active forms of the coagulation factors (Figure 1). Thrombin is particularly sensitive to standard heparin, which provides a catalytic template to which antithrombin III and thrombin bind. The low-molecular-weight heparins are not long enough to bind to both antithrombin and thrombin and have their main anticoagulant action via inhibition of activated factor X (Figure 1). They have minimal effects on clotting *in vitro*.

Heparin exhibits saturation kinetics with the apparent half-life increasing with dose. In contrast, the low-molecular-weight heparins have longer half-lives than standard heparin and because they follow first-order kinetics the half-life is not dependent on dose. This simplifies dose regimens.

The main unwanted effect of heparin is haemorrhage, which can be controlled by stopping drug administration or, if more active treatment is required, by administering the antagonist, protamine sulphate. It is a strongly basic protein that forms an inactive complex with the acidic heparin molecule. It is important that patients are not overdosed with this heparin antagonist because it can prolong bleeding time. Like most strong bases, protamine can release histamine and rapid intravenous injections can result in hypotension. It also activates the immune system and IgG- and IgE-mediated allergic responses have been described, particularly in patients with a history of fish allergy (protamine is derived from fish) or neutral protamine Hagedorn (NPH) insulin-dependent diabetes. Catastrophic pulmonary vasoconstriction is a rare, but often fatal, consequence of the use of protamine to neutralize heparin. A recent paper suggests that inhaled nitric oxide, a potent pulmonary vasodilator, is an effective treatment for this condition. Thrombocytopenia can occur with standard heparin, but is unlikely to be a serious problem in anaesthetic use unless therapy is prolonged.

Danaparoid sodium

Danaparoid sodium contains heparan sulphate (84%), dematan sulphate (12%) and chondroitin sulphate (4%). Its main effect is to inhibit factors Xa and IIa at a ratio greater than heparin with minimal effects on platelet function. In the USA, it is approved for the prophylaxis of deep vein thrombosis in patients undergoing elective hip replacement. It exhibits low cross reactivity with heparin antibodies and may be the treatment of choice for heparin-induced thrombocytopenia. It has recently been approved in the UK. Dematan sulphate is a glycosaminoglycan related to heparin and inhibits thrombin selectively. Its potential use as a sole agent in place of heparin is under investigation.

Antiplatelet drugs

Antiplatelet drugs are particularly effective in reducing thrombus formation in the arterial circulation where the anticoagulants mentioned above have little effect. Aspirin is the most important drug in this group because it alters the balance between thromboxane A_2, which promotes aggregation, and prostacyclin, which inhibits it (see *Anaesthesia and Intensive Care Medicine* **3:6:** 225). Prostacyclin can be used to prevent platelet aggregation but it is too short lived to have widespread application. It must be given by infusion and causes vasodilatation, resulting in flushing and headache.

Thrombin activates platelets (Figure 1) by inducing the expression of glycoprotein IIb and IIIa receptors which bind fibrinogen thus linking adjacent platelets. Inhibitors of this receptor have been recommended by the National Institute for Clinical Excellence (NICE) for high-risk patients with un-stable angina or non-Q-wave myocardial infarction and patients undergoing percutaneous coronary intervention. Abciximab is a monoclonal antibody that binds to the receptor, but should be used only once for the last group of patients. Eptifibatide and tirofiban are licensed for high-risk patients with unstable angina or non-Q-wave myocardial infarction.

Platelet activation is also induced by adenosine diphosphate (ADP) released from degranulating platelets. Clopidogrel and toclopidine inhibit the binding of ADP to its platelet receptor. They are licensed for the prevention of ischaemia, stroke or myocardial infarction in at-risk patients.

Fibrinolytic and antifibrinolytic drugs

Fibrin and fibrinogen are broken down by the protease plasmin, which is produced by the conversion of inactive plasminogen. Drugs that activate plasmin break up thrombi and are used in the treatment of life-threatening venous thrombosis and pulmonary embolism. Streptokinase, extracted from β-haemolytic streptococci, binds to the plasminogen exposing its active site and thus inducing plasmin-like activity. Antibodies to strepto-kinase appear after about 4 days and the drug should not be used again for at least 1 year. Alteplase, reteplase and tenecteplase are recombinant tissue plasminogen activators. Alteplase is unmodified human tissue plasminogen activator while the others have some amino acid sequences deleted to increase the elimination half-life to allow bolus administration. They are more selective for fibrin-bound plasminogen than for free plasminogen and are thus promoted as being clot selective.

Inhibition of plasminogen activation can be achieved with drugs such as tranexamic acid, which are used in conditions where there is a risk of haemorrhage such as prostatectomy and dental extraction for patients with haemophilia. Aprotinin inhibits proteolytic enzymes and is used for patients at risk of significant blood loss during surgery. ◆

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Antidepressants, Antipsychotics and Anticonvulsants

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Antidepressant drugs

Antidepressant drugs are used to treat clinical depression, the symptoms of which are shown in Figure 1. Characteristically, affective disorders are associated with changes in mood such as depression or mania. In some patients, the mood swings are always towards depression and this is known as unipolar depression. The remainder exhibit bipolar disease in which depression and mania alternate.

While the biochemical basis of depression is uncertain, many of the useful drugs acutely preserve noradrenaline (norepinephrine) and/or 5-HT (serotonin) at the synapse. However, in general, they require several weeks to take effect, which suggests that changes downstream from the acute effects are responsible for their beneficial effects in affective disorders. Downregulation of neurotransmitter receptors (e.g. a_2- and b-adrenoceptors) and 5-HT_2 receptors have been observed after long-term antidepressant therapy and may be relevant to their antidepressant activity. The mechanism of action of antidepressant drugs is summarized in Figure 2.

Symptoms of clinical depression and mania

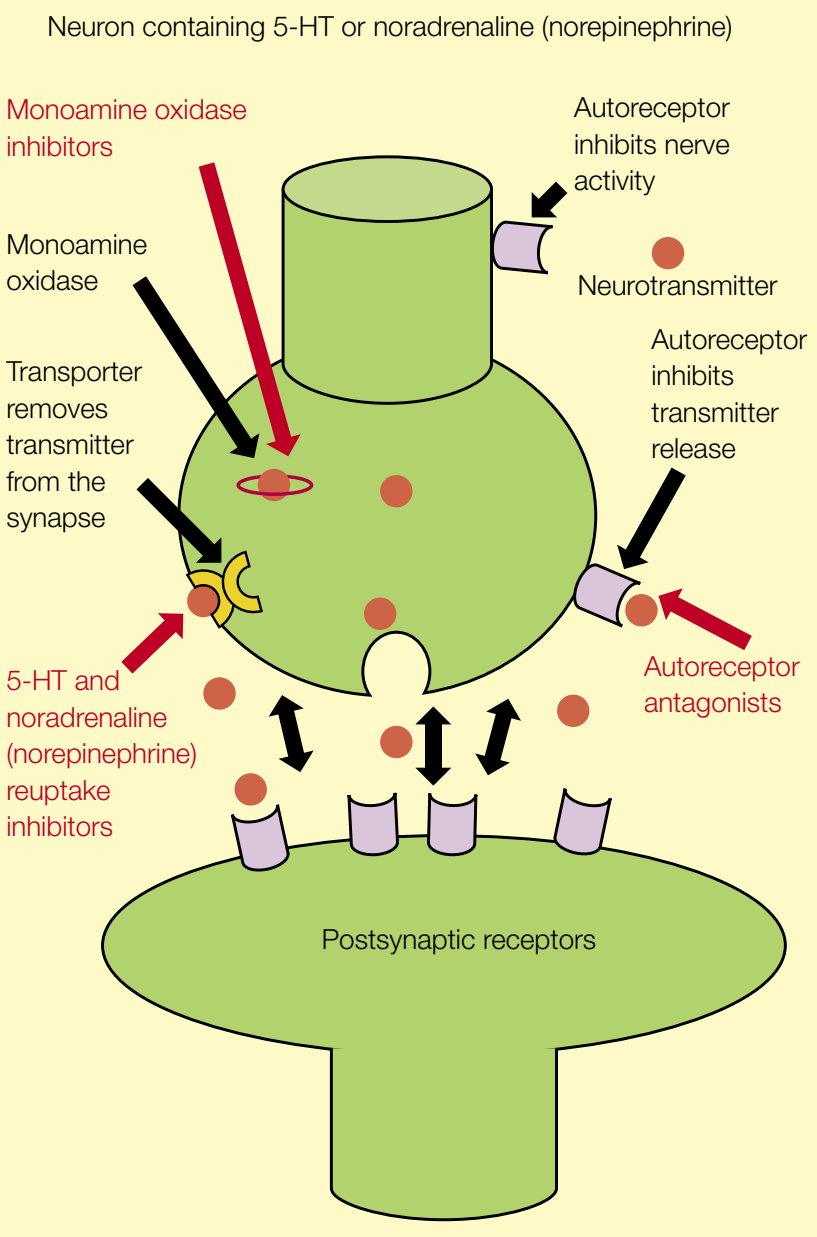
Clinical depression
- Depressed mood
- Loss of motivation
- Apathy
- Pessimism
- Low self-esteem
- Sleep disturbance
- Retardation of thought

Mania
- Excessive self-confidence
- Exuberance

Often combined with:
- Irritability
- Aggression
- Delusions

1

Sites of action of antidepressants



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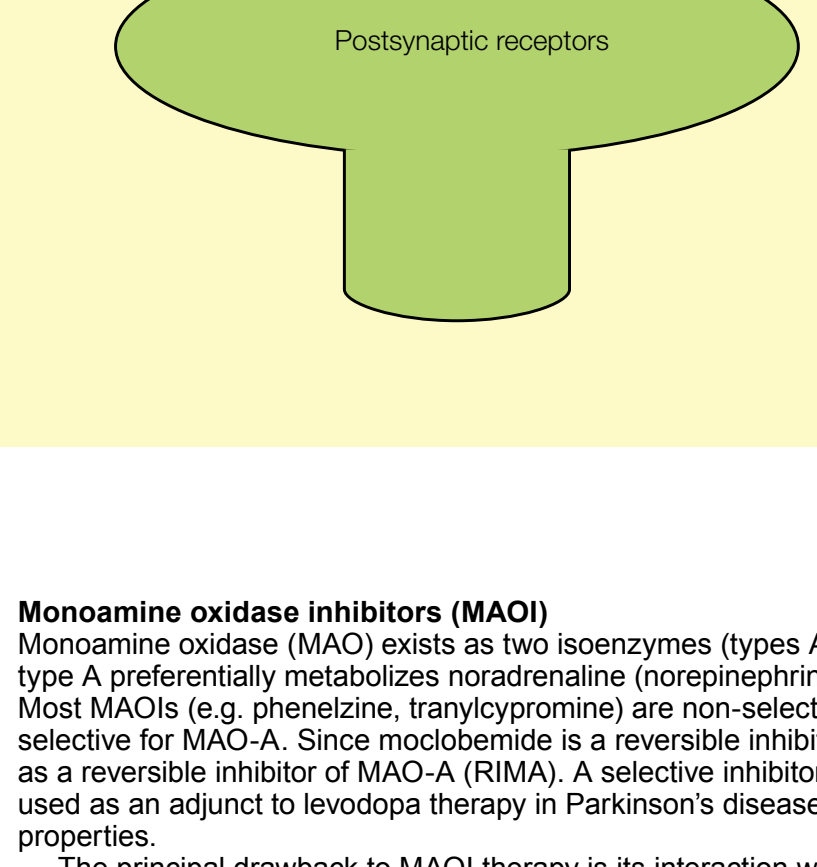
Monoamine oxidase inhibitors (MAOI)
Monoamine oxidase (MAO) exists as two isoenzymes (types A and B) of which type A preferentially metabolizes noradrenaline (norepinephrine) and 5-HT (Figure 3). Most MAOIs (e.g. phenelzine, tranylcypromine) are non-selective but moclobemide is selective for MAO-A. Since moclobemide is a reversible inhibitor it is sometimes listed as a reversible inhibitor of MAO-A (RIMA). A selective inhibitor of MAO-B, selegiline, is used as an adjunct to levodopa therapy in Parkinson's disease. It has no antidepressant properties.

The principal drawback to MAOI therapy is its interaction with drugs and certain types of food. Tyramine is an amine produced during fermentation and it is an indirectly acting sympathomimetic (i.e. it releases noradrenaline (norepinephrine) from vesicles within the nerve terminal cytoplasm). Once released into the cytoplasm it may leak out or be metabolized by MAO. Once ingested, tyramine is normally metabolized by MAO in the liver and gut wall so that little enters the systemic circulation. However, when MAO is inhibited, large quantities can reach the circulation and the noradrenaline (norepinephrine) released can cause a hypertensive crisis. Tyramine is found in ripe cheese (hence the 'cheese reaction'), concentrated yeast extracts (*Marmite*), vintage Chianti and broad bean pods.

MAOIs also interact with sympathomimetic agents found in cold cures, other antidepressants and the opioid analgesic pethidine.

Effects of monoamine oxidase inhibitors (Type A)



Abbreviation: MAO, monoamine oxidase

3

Inhibitors of noradrenaline (norepinephrine) and/or 5-HT transporters (reuptake inhibitors)
Once released from the presynaptic neuron, the activities of noradrenaline (norepinephrine) and 5-HT on the postsynaptic receptors are limited by an active reuptake process into the presynaptic terminal. Drugs that compete with the two amines for the carrier protein or transporter can inhibit this process. The tricyclic antidepressants (e.g. amitriptyline, imipramine) have similar activity on both the noradrenaline (norepinephrine) and 5-HT transporters while others have some selectivity for either noradrenaline (norepinephrine) or 5-HT (Figure 4).

Tricyclic antidepressants may cause hypotension, probably through an effect on the medullary vasomotor centre. They also have muscarinic acetylcholine receptor antagonist properties and thus cause dry mouth and blurred vision. Seizure threshold is reduced and, in overdose, convulsions may accompany excitement and delirium. Cardiac dysrhythmias are also common in overdose, and death can occur due to ventricular fibrillation. The serotonin selective reuptake inhibitors (SSRIs), such as fluoxetine, produce fewer side-effects, the most common being insomnia and nausea.

The uptake inhibitors do not precipitate the cheese reaction, but they are prone to other drug interactions. In particular, SSRIs in combination with MAOIs can cause hyperthermia and cardiovascular collapse, known as the 'serotonin syndrome'.

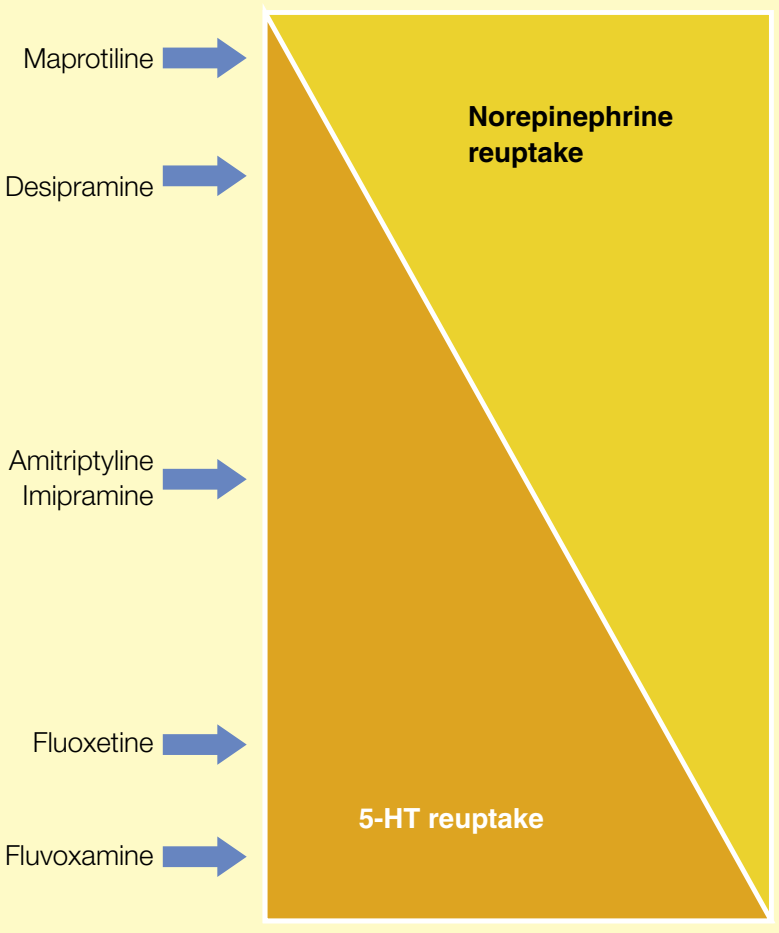
Atypical antidepressants
Some agents have no obvious action on either uptake or metab-olism of 5-HT or noradrenaline (norepinephrine). Mianserin may promote release of noradrenaline (norepinephrine) and 5-HT by acting as an antagonist on α_2- and 5-HT_2-autoreceptors.

Mood stabilizers
Lithium prevents the mood swings associated with unipolar depression and bipolar manic depression. However, during an acute attack, lithium is useful only in reversing the mania because it has no effect on depression. Lithium is limited to the prophylactic control of bipolar disease because of its toxicity. Antipsychotic drugs (see later) are equally effective in reversing mania and are less toxic than lithium.

The therapeutic actions of lithium are thought to involve the blockade of the phosphatidyl inositol pathways such that membrane phosphatidyl inositol is depleted and receptor-mediated effects linked to this second messenger system are inactivated. Toxicity appears to be related to the ability of Li^+ to replace Na^+ in excitable tissue. Although it enters the cell in place of sodium, it is not pumped out by Na^+/K^+-ATPase and its accumulation leads to partial depolarization of the cell. Toxicity is enhanced by Na^+ depletion and can be reduced with Na^+ replacement.

Some anticonvulsants such as carbamazepine and valproate (see later) have also been used to treat bipolar disorders.

Relative inhibition of noradrenaline (norepinephrine) or 5-HT transporters



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Antipsychotic drugs

Antipsychotic drugs may be used to treat schizophrenia, manic depression and psychosis caused by chemical or traumatic head injury. Typical symptoms of schizophrenia are shown in Figure 5. Schizophrenia occurs in about 1% of the population and has a tendency to run in families but other non-genetic influences are also important.

All antipsychotic drugs (also termed neuroleptic drugs or major tranquillizers) are dopamine antagonists. Neurolepsis is a state of altered consciousness characterized by quiescence, reduced motor activity and indifference to the surroundings. Anaesthetists have used these drugs in combination with potent opioid analgesics in techniques like neurolept analgesia and anaesthesia and as preanaesthetic medication.

Symptoms seen in schizophrenia

Positive symptoms
- Delusions
- Hallucinations
- Thought disorder

Negative symptoms
- Withdrawal from society
- Few emotional responses

5

The main neuronal pathways in the brain that use dopamine are shown in Figure 6. The mesolimbic and mesocortical pathways are important in the beneficial effects of dopamine antagonists in psychosis, but blockade of the nigrostriatal pathway leads to side-effects such as extrapyramidal disorders resembling Parkinson's disease. Blockade of the tubero-hypophyseal pathway increases prolactin release resulting in breast swelling, pain and lactation in men and women. Dopamine is also the neurotransmitter involved in vomiting induction at the chemoreceptor trigger zone thus many antipsychotics are used as anti-emetics.

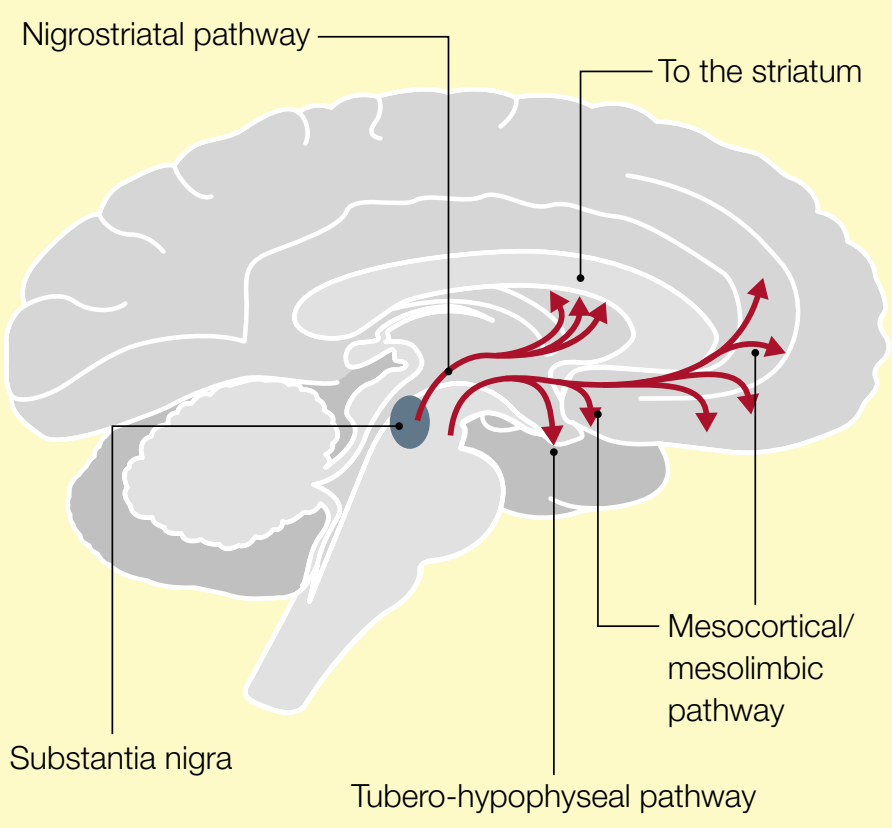
The two main groups of G-protein-linked dopamine receptors are D_1, the family that stimulate adenylyl cyclase and the D_2 family that inhibit or have no effect on adenylyl cyclase. Subgroups of these families are D_1 and D_5 in the D_1 family and D_2, D_3 and D_4 in the D_2 family. In general, the known actions of dopamine agonists and antagonists occur mainly via receptors of the D_2 family.

Since the distribution of these receptor subtypes differs in the CNS, there has been interest in developing selective compounds that might possess fewer side-effects. For example, the receptors in the basal ganglia, that mediate the extrapyramidal side-effects of dopamine antagonists are mainly of the D_2 subtype, thus drugs selective for D_3 or D_4 receptors may not possess this side-effect. Clozapine and other newer atypical antipsychotics have some selectivity for D_4 receptors and have a much better side-effect profile when used as antipsychotic agents than the traditional dopamine antagonists. However, they are also antagonists at several other non-dopaminergic receptors such as 5-HT_2, which may explain this phenomenon. The atypical antipsychotics are effective against positive and negative symptoms of schizophrenia, while the classical drugs are useful only for positive symptoms.

A rare complication of antipsychotic drug administration is the neuroleptic malignant syndrome characterized by rigidity, tremor, autonomic dysfunction and fever coupled with an increase in serum creatinine phosphokinase and white blood cell count. It is more likely to occur when high parenteral doses are used and there is appreciable mortality (over 10%). Treatment involves removal of the drug and supportive therapy. Unlike malignant hyperthermia induced by general anaesthetics, the use of drugs such as dantrolene does not appear to be helpful and a disorder of calcium metabolism in skeletal muscle is probably not the cause. However, there has been a report of both syndromes occurring in the same patient. Recovery occurs in about 14 days without any cognitive impairment unless high fever, hypoxia or other complications have induced these changes.

Individual antipsychotic drugs are compared in Figure 7.

Main dopaminergic pathways in the brain



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Comparison of individual antipsychotic drugs

Drug	Dopamine receptor selectivity	Other receptors antagonized	Comments
Classical			
• Chlorpromazine	D_2, D_3>>D_1, D_4, D_5	Many	Extrapyramidal effects Sedative Gynaecomastia Obstructive jaundice
• Haloperidol	D_2=D_3=D_4 >> D_1,D_5	Some effect on α-adrenergic and 5-HT_2	More extrapyramidal effects than above Little sedation
• Flupentixol (flupenthixol)	Little	Some effect on α-adrenergic and 5-HT_2	Available as a depot preparation Extrapyramidal effects Gynaecomastia
Atypical			
• Clozapine	Some selectivity for D_4	5-HT_2	No extrapyramidal effects Agranulocytosis May be effective in treatment-resistant patients Effective against negative symptoms
• Olanzapine	Some selectivity for D_4	5-HT_2	No extrapyramidal effects May be effective in treatment-resistant patients Effective against negative symptoms

7

Anticonvulsants

Anticonvulsant drugs are used to treat epilepsy, which affects about 1% of the population. Epilepsy is characterized by abnormal electrical activity over part or all of the brain detected as sharp waves and/or spikes on an electroencephalograph (EEG) recording. The EEG is obtained from electrodes distributed over the surface of the scalp. The clinical classification of epilepsy is shown in Figure 8.

In general, partial seizures are more difficult to treat than generalized seizures and 20–30% of patients do not have their seizures adequately controlled by current therapy.

Some of the currently available anticonvulsant drugs enhance inhibitory γ-aminobutyric acid (GABA) transmission either by inhibiting GABA metabolism (Figure 9) or by enhancing GABA transmission at the $GABA_A$ receptor via an action on a modulatory site such as the benzodiazepine receptor. Other drugs, such as phenytoin and carbamazepine, prevent excessive neuronal discharge by blocking voltage-dependent sodium channels. However, some (e.g. ethosuximide) block T-type calcium channels. Drugs that block excitatory neurotransmission are, in general, not clinically available, though some reports suggest that lamotrigine may have this effect. The commonly used anticonvulsants are compared in Figure 10.

Phenytoin is unusual in that it exhibits zero-order kinetics in the therapeutic dose range. The enzymes that metabolize phenytoin become saturated such that the rate of metabolism does not increase with increasing plasma concentration. Thus, small changes in dose can have a large effect on plasma concentration resulting in the need to control the plasma concentration carefully to maintain seizure control with minimal adverse effects.

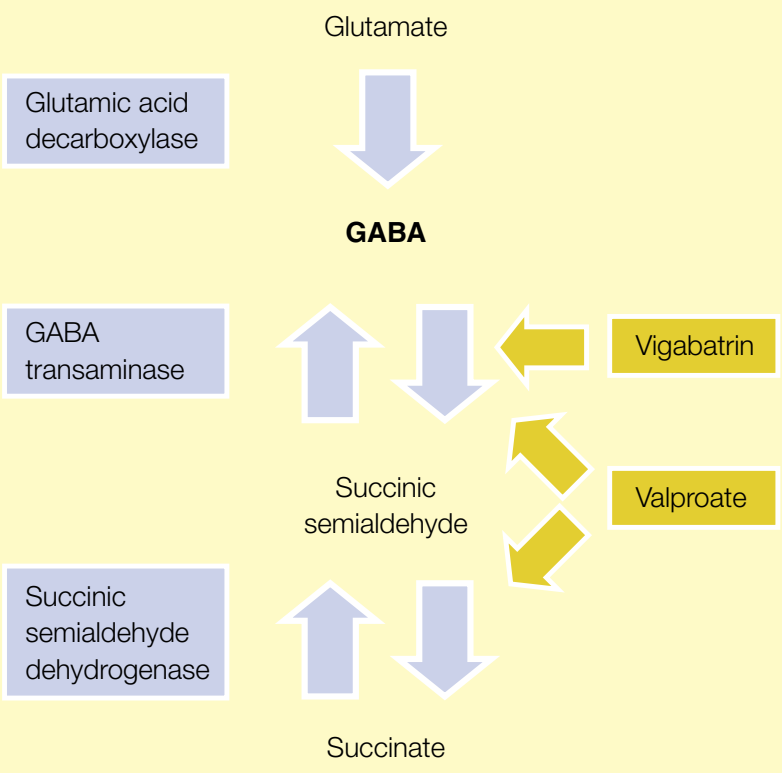
Classification of epilepsies

Generalized seizures
Abnormal electrical activity involving the whole brain
- Grand mal – tonic-clonic seizure involving synchronous muscle jerking and unconsciousness often including incontinence. Full recovery may take a few hours
- Petit mal – absence seizure when the patient, usually a child, ceases all activity but there is no excessive muscle jerking. The patient is unaware and recovers quickly

Partial (focal) seizures
Abnormal electrical activity occurs in a localized area of the brain and may be limited to that area or spread to a secondary generalized seizure
- Simple partial seizures – dependent on the site of the focus the seizure may be motor (jerking of a muscle group), sensory (e.g. unexplained smells) or autonomic (e.g. sudden pallor). There is no unconsciousness unless the seizure becomes generalized
- Complex partial seizures – apparently purposeful movements without conscious awareness. The movements may be stereotyped and can involve an emotional component

8

Anticonvulsants that inhibit γ-aminobutyric acid (GABA) metabolism



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Comparison of anticonvulsant drugs

Drug	Mechanism	Clinical use	Adverse effects	Other comments
• Benzodiazepines	Enhance γ-aminobutyric acid (GABA) transmission by modulation of the $GABA_A$ receptor	Mainly for emergency treatment of status epilepticus	Sedation and tolerance	Tolerance occurs too quickly for chronic use in most cases
• Carbamazepine	Use dependent on blocking sodium channels	Most seizure types but ineffective in petit mal	Ataxia, blurred or double vision	Induction of microsomal liver enzymes
• Ethosuximide	Inhibits T-type calcium channels	Useful only for petit mal and may make other types of seizure worse	Nausea, headache and anorexia	Use declining
• Lamotrigine	Use dependent on blocking sodium channels. May reduce glutamate release	Broad range of seizures including petit mal	Nausea, ataxia, hypersensitivity reactions	
• Phenobarbitone	Enhance GABA transmission by modulation of the $GABA_A$ receptor	Most seizure types but ineffective in petit mal	Sedation, low therapeutic index	Induction of liver microsomal enzymes Inexpensive – mainly used in the Third World
• Phenytoin	Use dependent on blocking sodium channels	Most seizure types but ineffective in petit mal	Ataxia, gingival hypertrophy, fetal abnormalities (cleft palate)	Induction of liver microsomal enzymes Metabolized by zero-order kinetics (see text)
• Valproate	Inhibits enzymes metabolizing GABA (see text). Also blocks sodium channels	Most seizure types including petit mal	Fewer than most others Gastrointestinal pain and nausea Fetal abnormalities (spina bifida) Rare hepatoxicity	
• Vigabatrin	Inhibits enzymes metabolizing GABA (see text)	All seizure types	Sedation and behavioural changes	Induction of liver microsomal enzymes

10

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Anxiolytics and Hypnotics

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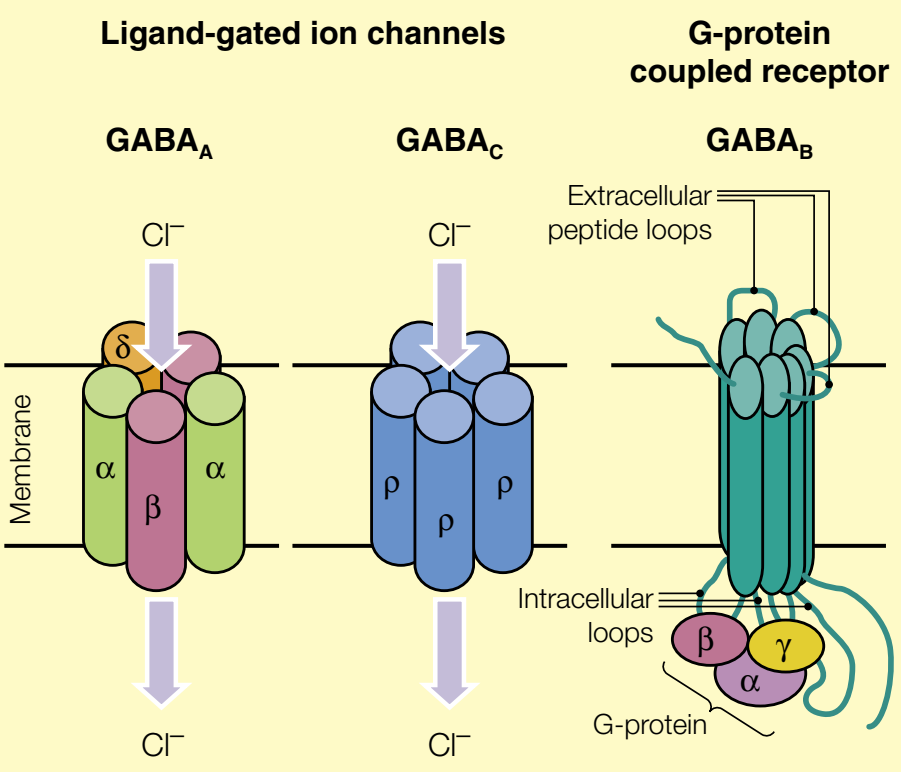
Until recently the pharmacology of drugs used to treat anxiety (anxiolytics) and insomnia (hypnotics) were identical because the same drugs were used for both purposes. While the anxiolytic action of hypnotics was probably an advantage, the hypnotic action of anxiolytics was a major drawback. Daytime drowsiness severely limited their usefulness in treating long-term anxiety states. More recently, drugs that lack marked hypnotic activity, acting on tryptaminergic receptors, have been introduced. These drugs (e.g. buspirone) have obvious advantages in psychiatry but they generally take several days or even weeks to produce their effects and are of limited use in anaesthesia.

γ-aminobutyric acid (GABA)

The traditional hypnotics and anxiolytic drugs, such as barbiturates and benzodiazepines, enhance GABA transmission via the $GABA_A$ receptor. GABA is the main inhibitory neurotransmitter in the brain and it is known to interact with three receptor types, $GABA_A$ and $GABA_C$, which are ligand-gated ion channels, and $GABA_B$, which is a G-protein-coupled receptor (Figure 1). The $GABA_C$ receptor is a simple form of the $GABA_A$ receptor in that all five subunits are of the same type, in this case the ρ subunit. The characteristics of these three receptors are listed in Figure 2.

The $GABA_A$ receptor is probably the most complicated. Five subunits are arranged in a rosette and the central area, where they meet, forms a channel through which chloride ions can pass. In normal circumstances, opening of the chloride channel causes the negative chloride ions to flow into the cell, causing hyperpolarization and thus inhibition of cellular activity. There are four types of subunit (α, β, γ and δ) which can make up the receptor, though the first three are the most common. The α and β subunits provide the binding site for the GABA molecule while α and γ subunits are necessary for benzodiazepine binding. Thus, benzodiazepines bind to a separate site from GABA and this 'benzodiazepine receptor' is just one of at least 11 modulatory sites on the $GABA_A$ ion channel. The barbiturates, neurosteroids and many general anaesthetic agents bind to other modulatory sites. (The neurosteroids are related to the steroid hormones but do not act on the conventional intracellular steroid receptors. Their function in the body is uncertain, but synthetic analogues include the steroidal anaesthetics such as alphaxalone, which was withdrawn from human use some years ago.)

Receptors for γ-aminobutyric acid (GABA)



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Characteristics of γ-aminobutyric acid (GABA) receptors

	$GABA_A$	$GABA_B$	$GABA_C$
Selective agonist	Muscimol	Baclofen	?
Selective antagonist	Bicuculline	Phaclofen or saclofen	?
Effector mechanism	Ligand-gated chloride channel	G-protein coupled	Ligand-gated chloride channel
Subunits	Pentamer with three different subunits	Not applicable	Pentamer with all identical subunits
Location	Widespread in CNS	Widespread in CNS	Retina of the eye

2

Benzodiazepines

Benzodiazepines enhance responses to GABA by increasing the affinity of the receptor to GABA. This is manifest as an increase in the frequency of the ion channel opening in response to GABA. Benzodiazepines have no effect on the gating mechanism of the channel and they are active only when there is continuing GABA transmission. Flumazenil is a benzodiazepine antagonist; it binds to benzodiazepine receptors but does not modulate the response to GABA. Thus, flumazenil will antagonize the actions of benzodiazepines but not the action of modulators binding to other sites or indeed GABA itself.

Benzodiazepines have five characteristic pharmacological actions (Figure 3) and thus it was surprising that the first candidate endogenous ligand to be found for the benzodiazepine receptor, ethyl-β-carboline, had diametrically opposite pharmacology. In animals (and the odd courageous human), β-carboline derivatives produced anxiety, even panic, convulsions and restlessness. Even more surprising was the observation that these effects, like those of the benzodiazepines, were antagonized by flumazenil, the benzodiazepine antagonist. A suggested explanation of this phenomenon (known as inverse agonism) is illustrated in Figure 4.

The $GABA_A$ receptor exists in two conformational states one of which binds GABA and opens the chloride channel and the other does not. In the absence of a modulator, these two states are in equilibrium and there is moderate, but not maximal, sensitivity to GABA. Benzodiazepines bind preferentially to the GABA-sensitive conformation and upset the equilibrium in favour of GABA responsiveness because the receptor cannot convert to the inactive form. In contrast, β-carboline derivatives prefer to bind to the inactive state and the equilibrium moves towards decreased GABA responsiveness. Flumazenil can bind to the receptor in either the active or inactive state, thus antagonizing the action of both the agonist and inverse agonist. Subsequent to the discovery of the β-carbolines, inverse agonists have been described at other non-benzodiazepine receptors.

Characteristic properties of benzodiazepines

Anxiolytic Anxiety is reduced but most drugs of this class are not antidepressant (exception alprazolam). Some short-acting drugs may produce aggression that has been described as a symptom of withdrawal

Hypnotic Slow wave sleep is reduced (useful for the treatment of night terrors that occur in this stage of sleep). All hypnotics reduce REM sleep and withdrawal is associated with a rebound increase in REM sleep and consequently excess dreaming which subjectively reduces the quality of sleep. Benzodiazepines cause less reduction in this part of the sleep cycle than other hypnotics

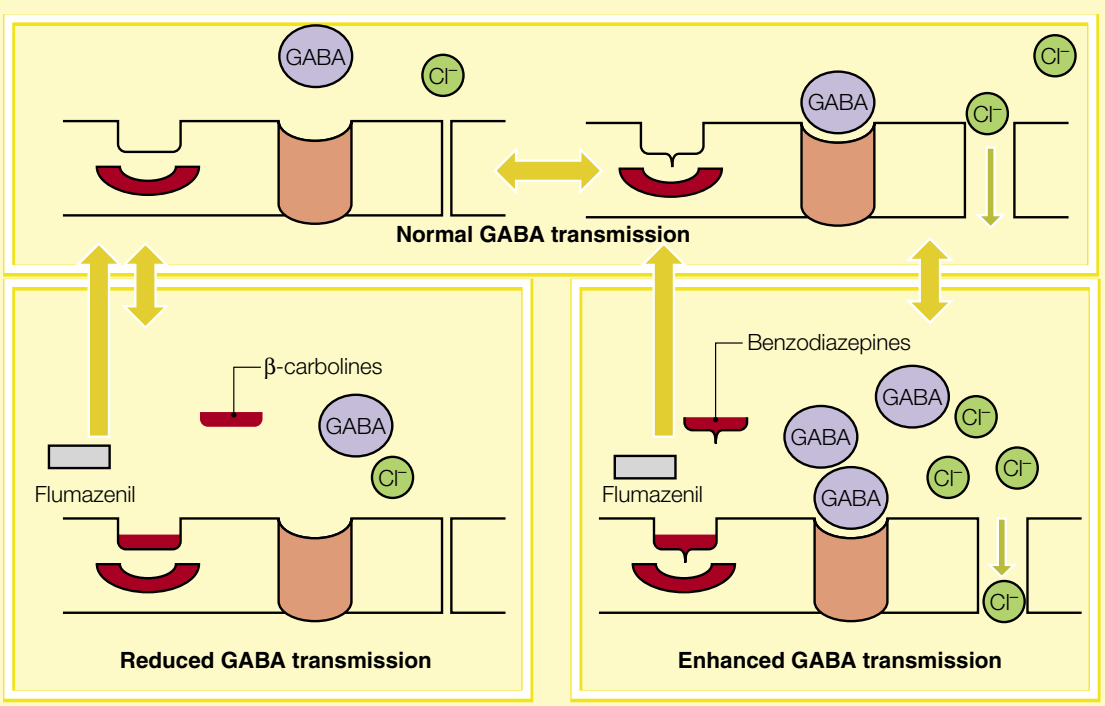
Muscle relaxant Muscle tone is reduced by a central action separate from sedation. Heightened muscle tone is seen in anxiety and is responsible for the headache and muscle pains associated with the condition. Benzodiazepines reduce this symptom

Anticonvulsant Tolerance to the anticonvulsant effects of benzodiazepines occurs rapidly so they are usually reserved for emergency use in status epilepticus rather than for chronic treatment of epilepsy. Clonazepam, a partial agonist at benzodiazepine receptors, has some selectivity for anticonvulsant actions

Amnesic Most produce some anterograde amnesia (lorazepam is particularly active in this respect). This property can be useful clinically when a patient has to undergo repetitive awake procedures that are undignified and embarrassing

3

Inverse agonism



4

Variety of benzodiazepine receptors: molecular biology indicates that each of the subunits making up the $GABA_A$ receptor has several variants to its amino acid make-up. These variations in structure can affect the binding characteristics of the subunits and thus the way that the receptor as a whole can be modulated. Some variants of the α and γ subunits do not bind benzodiazepines, thus making the $GABA_A$ receptors with this make-up insensitive to benzodiazepines. Tolerance to benzo-diazepines occurs owing to the induction of benzodiazepine insensitive subunits to make up the $GABA_A$ receptor. Other variants can bind benzodiazepine or similar molecules with slightly different structures, thus allowing selective modulation of a proportion of benzodiazepine receptors.

Selective benzodiazepine ligands: zolpidem has been classified as selective for type one of the two benzodiazepine receptors that have been described in association with the $GABA_A$ receptor. The nomenclature of these receptors is confused because some texts use BZ receptors, others BDZ receptors, and yet others BDZ receptors, since it was argued the receptors also bind molecules that are not strictly benzodiazepine structures. (Beware of advertisements for non-benzodiazepine anxiolytics: they may have different chemical structures but they still bind to benzodiazepine receptors; e.g. zopiclone.) The author uses the BDZ terminology. Zolpidem has selectivity for BDZ_1 receptors and has marked hypnotic activity with little anticonvulsant or muscle-relaxant activity. Some sources also question the presence of anxiolytic activity in this molecule. At present it is impossible to tie the main pharmacological actions of the benzodiazepines and related structure to activation of individual BDZ receptors. Some drugs selective for the various BDZ receptors are shown in Figure 5. Alpidem, which is also supposed to have some selectivity for BDZ_1 receptors, is anxiolytic but has negligible hypnotic activity.

The BDZ_3 receptors are sometimes called the peripheral benzodiazepine-binding site because they are not necessarily associated with $GABA_A$ receptors and are found in mitochondria within peripheral cells. They are probably involved in intra-cellular signalling. The natural ligands for BDZ_3 receptors are peptides, including the endozepines and Diazepam Binding Inhibitor (DBI). These peptides are inverse agonists at classical BDZ receptors. There are reports that BDZ_3 receptors may have a role in the CNS, which is activated by high doses of benzodiazepines and possibly carbamazepine.

Subtypes of benzodiazepine receptors

Receptor	Selective agonists	Selective antagonists
BDZ_1 (also ω or BZ)	Zolpidem Alpidem	Flumazenil Clonazepam
BDZ_2	Clonazepam	Flumazenil
BDZ_3	Alpidem	PK11195

5

Barbiturates

The barbiturates were once the mainstay of anxiolytic and hypnotic drug treatment, but only phenobarbital (phenobarbitone) used as an anticonvulsant, and thiopental (thiopentone) used as an intravenous anaesthetic, still have widespread clinical use. The clinical demise of these compounds resulted from their low therapeutic index. Increased dosage leads to respiratory and cardiovascular depression followed by death. Until the introduction of the benzodiazepines, when barbiturate use was widespread, they were the drugs of choice for suicides and poisoners. Indeed the amnesic action of the drugs meant that unintended overdoses were common in self-medicating patients.

Although barbiturates also enhance GABA transmission and, in low doses, have similar pharmacological properties to the benzodiazepines, they do so by altering the gating mechanisms of the chloride channel so that it stays open longer in response to GABA. This action occurs at a diversity of $GABA_A$ receptors, including those that are insensitive to benzodiazepines. In addition, at high doses of barbiturate, the chloride channel may be open for such long periods of time that the neuron becomes incapable of depolarization and thus inactive. Both these factors contribute to the increased toxicity of barbiturates over benzodiazepines.

5-hydroxytryptamine (serotonin)

A number of drugs active as either agonist or antagonist at 5-HT receptors have shown anxiolytic activity in animals. There are at least seven subtypes of 5-HT receptor with further subdivisions of some of them. Those with clinically useful agonists and or antagonists are listed in Figure 6. Some of them, such as ondansetron, a $5\text{-}HT_3$ receptor antagonist, failed to be effective anxiolytics in humans but others, such as buspirone, an agonist at $5\text{-}HT_{1A}$ receptors, has proved to be useful. Buspirone has some actions at dopamine receptors, but more selective agonists at $5\text{-}HT_{1A}$ receptors (e.g. gepirone, isapirone) also have anxiolytic activity in humans, suggesting that tryptaminergic actions are the important mechanism with respect to anxiolytic activity. Although the exact role of 5-HT in anxiety states is unknown, some recent evidence has suggested a link between the loss of $5\text{-}HT_{1A}$ receptors and loss of benzodiazepine sensitivity.

Therapeutically important 5-HT receptors

Receptor	Effector mechanism	Agonist	Clinical use	Antagonist	Clinical use
$5\text{-}HT_{1A}$	G-protein coupled	Buspirone	Anxiolytic		
$5\text{-}HT_{1D}$	G-protein coupled	Sumatriptan	Anti-migraine		
$5\text{-}HT_{2A}$	G-protein coupled			Ketanserin	Vasodilator
$5\text{-}HT_3$	Ligand-gated ion channel			Ondansetron	Anti-emetic
$5\text{-}HT_4$	G-protein coupled	Metoclopramide	Prokinetic		
		Cisapride (withdrawn)			

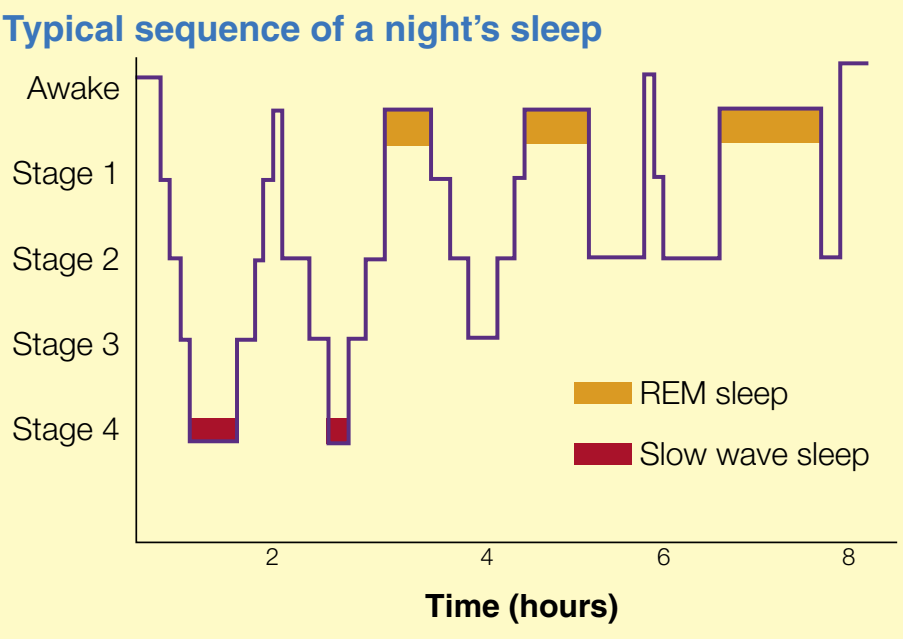
Histamine

Antagonists at histamine H_1-receptors produce mild hypnosis, but they are useful for this purpose only in sensitive individuals. Children are more likely to respond to antihistamines in this way and promethazine syrup is regularly used for sedation and hypnosis in children.

Hypnotic drugs

When a hypnotic drug is used to treat insomnia, the aim is to restore physiological sleep patterns to the patient. The stages of sleep may be recognized by characteristic electroencephalography (EEG) changes in brain activity. The deepest sleep (stage 4) is also known as slow wave sleep and is associated with a low metabolic rate and level of adrenal corticosteroid secretion. In contrast, the secretion of growth hormone is high. Another important stage of sleep is REM (rapid eye movement) sleep in which dreaming occurs. Diminution of this stage of sleep leads to irritability and anxiety. A typical sequence of a night's sleep is shown in Figure 7.

Typical sequence of a night's sleep



All hypnotic drugs reduce REM sleep though the barbiturates are worse than the benzodiazepines and there is some evidence that zolpidem (the BDZ_1 agonist) causes less disruption than the others. Withdrawal of hypnotics leads to a rebound increase in REM sleep with a consequent lack of deeper stages of sleep. This contributes to habituation because the patient does not feel rested. It follows that a drug that produces the closest to physiological sleep patterns is least likely to cause these withdrawal effects. Trials are under way to determine whether zolpidem may be closer to this ideal. Benzodiazepines also reduce stage 4 sleep but not the associated increase in growth hormone. This may be the base for their use in night terrors that occur during stage 4 sleep.

Some other agents (Figure 8) are still prescribed by some, usually elderly, practitioners, but in general they are not recommended. Most of these agents appear to potentiate GABA, but because of their antiquity this has not been studied rigorously. The exception is ethanol, which can potentiate GABA by several different mechanisms, dependent on the dose. The low-dose effects may occur only with a particular splice variant of the γ subunit. However, ethanol appears to have some actions at most ligand-gated ion channels. No hypnotic drug is recommended for long-term use.

Drugs used as hypnotics

Group	Examples	Comment
Barbiturates	• Pentobarbital (pentobarbitone)	Seldom used because of dangers of overdose and many drug interactions due to induction of liver enzymes
	• Amobarbital (amylobarbitone)	
	• Butobarbital (butobarbitone)	
Benzodiazepines	• Diazepam	Long-acting so more useful for patients with early wakening. Active metabolite.
	• Nitrazepam	
	• Temazepam	Short-acting so more useful for patients with long sleep latencies. Active metabolite but it is unimportant in overall activity of the drug
	• Zolpidem	Not a benzodiazepine structure. Selective hypnotic? Short duration of action. May produce more physiological sleep patterns
Antihistamines	• Promethazine	Also possess muscarinic antagonist properties so may cause dry mouth. Not effective in all patients. Used in children, but not recommended
	• Diphenhydramine	
Others	• Chloral hydrate	Irritant action may cause gastrointestinal tract disturbances
	• Meprobamate	Less effective than benzodiazepines and more toxic in overdose
	• Clomethiazole	Mainly used in the elderly because of reduced hang-over effects Dependence occurs
	• Ethanol	Self-medication

Anxiolytic drugs

While all of the drugs mentioned above as hypnotics can be used as anxiolytics, only benzodiazepines are used clinically for this purpose. The relative merits of drugs acting as agonists at $5\text{-}HT_{1A}$ receptors and those acting on benzodiazepine receptors are shown in Figure 9.

Drugs used as anxiolytics

Mechanism	Example	Comments
GABA enhancement	Diazepam	Sedation and dependence Fast onset of action Recommended only for short-term treatment
$5\text{-}HT_{1A}$ agonist	Buspirone	Delayed onset Little sedation and no dependence Not useful for panic attacks

FURTHER READING

Declerck A, Smits M. Zolpidem, a Valuable Alternative to Benzodiazepine Hypnotics for Chronic Insomnia? *Int Med Res* 1999; **27:** 253–63.
Rang H P, Dale M M, Ritter J M. Anxiolytic and Hypnotic Drugs. In: *Pharmacology.* 4th ed. Edinburgh: Churchill Livingstone, 1999; 528–38.

Body Compartments and Drug Distribution

Barbara J Pleuvry

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Once absorbed into the body a drug is distributed to various compartments that can be defined in a variety of ways.

Compartmental analyses

The compartments used in compartmental analyses to describe drug distribution and elimination bear no relationship to real body compartments. They are discussed in *Anaesthesia and Intensive Care Medicine* **2:6:** 237 and are based on mathematical modelling related to actual measurements of plasma concentration of drugs. In these models, the volume of distribution of the drug is the volume that would contain the administered dose assuming that the concentration was the same as that in the plasma. The practical use of compartmental and physiological pharmacokinetic models in anaesthetic practice is described elsewhere.

Body fluid compartments

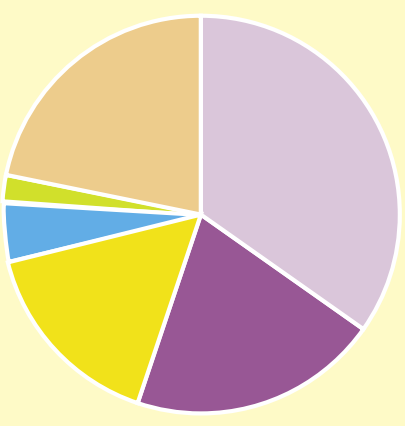
Most drugs are distributed in body fluids, therefore an alternative method of determining distribution is to consider body fluid compartments that have a finite volume. Figure 1 shows the percentage of water found in some types of tissue and it is interesting to note that the water content of blood is no greater than that of some solid tissues. Total body water is about 60% of body weight in a young adult man. In young women, the total body water averages about 50% of body weight because they have less muscle mass and more subcutaneous fat. Fat has a lower water content than most other tissues. Increasing age decreases the percentage of body weight that is water because water-rich muscle tends to be replaced with fat. The total body water can be divided into several parts (Figure 2).

Approximate water content of body tissues

	Percentage
Blood	80
Bone	30
Connective tissue	60
Fat	20
Kidney	80
Brain grey matter	85
Brain white matter	70
Skeletal muscle	75

1

Main body compartments as a percentage of body weight



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Extracellular fluid constitutes about 20% of body weight and includes blood plasma (4–5%), interstitial fluid (15–16%), lymph (about 1%) and a small amount of fluid in the pleural and abdominal cavities and in the pericardial sac. The latter small volumes together with CSF, digestive secretions and intraocular fluid are sometimes called transcellular water. These fluids are separated from the plasma by endothelium as well as an epithelial layer. The epithelial layer modifies the chemical composition of the transcellular fluid so that it is not a simple ultrafiltrate of plasma as is the interstitial fluid.

The remaining body water consists of intracellular fluid including fat (20%). Drugs may be bound or free in each of these fluid compartments but only free drug can pass between compartments.

Some small lipid-soluble drugs such as phenytoin, caffeine and ethanol are distributed in a volume that approximates to total body water. In women, total body water relative to weight is less than in men, therefore a given dose of alcohol per kg body weight produces a higher ethanol concentration. Some drugs are so large (e.g. heparin) that they cannot cross the capillary wall and are retained in the plasma compartment. In general, when drugs are confined to the plasma compartment it is because of their extensive binding to plasma proteins. The plasma volume is measured experimentally using Evans' blue dye, which binds strongly to plasma albumin. When drugs that are extensively plasma protein bound are given repeatedly their distribution gradually increases as unbound free drug escapes to other compartments and is no longer confined to a physiological fluid compartment. Very polar molecules cannot penetrate cells and their distribution is limited to extracellular fluids. Examples include quaternary ammonium compounds such as neostigmine and many neuromuscular blocking agents, the amino sugar antibiotics and mannitol.

With these exceptions, most drugs have volumes of distribution (i.e. the total quantity of drug in the body divided by the concentration in the plasma) that do not identify closely with any real anatomical compartment. If the drug is strongly protein bound outside the plasma then the volumes of distribution may be many times greater than body size. For example, the volume of distribution of some tricyclic antidepressants is more than 10 litre/kg body weight.

Interpretation of drug distribution in terms of organ or tissue spaces is complex and is discussed elsewhere.

Special compartments

Brain and CSF

The vascular endothelium enclosing the brain differs from most endothelial cells in that it lacks intracellular pores and pinocytotic vesicles, resulting in tight junctions between the cells, thus restricting the passage of aqueous bulk flow. The glial cells surrounding the capillaries also secrete chemicals that maintain the permeability characteristics of the endothelial cells. Transport across the blood–brain and blood–CSF barriers is selective and directional even for small ions such as potassium and chloride. Thus the composition of the blood and CSF is different (Figure 3).

Components of CSF and serum

Component	CSF	Serum
Protein	35 mg/dl (0.35 g/litre)	7000 mg/dl (70 g/litre)
Glucose	60 mg/dl (3.3 mmol/litre)	90 mg/dl (5 mmol/litre)
K^+	2.8 mEq/litre (2.8 mmol/litre)	4.5 mEq/litre (4.5 mmol/litre)
Ca^{2+}	2.1 mEq/litre (1.1 mmol/litre)	4.8 mEq/litre (2.4 mmol/litre)
Cl^-	119 mEq/litre (119 mmol/litre)	102 mEq/litre (102 mmol/litre)
pH	7.35	7.41

3

Circulating neurotransmitters, such as 5-HT, norepinephrine and dopamine pass across the blood–brain barrier only in trace amounts to avoid overstimulation of central neurons. Glucose is essential for neuronal function and is actively transported into the brain even when circulating concentrations are low.

Only drugs with high lipid solubility can penetrate the blood–brain barrier, which is found in most regions central to the arachnoid membrane. Exceptions include the area postrema on the floor of the fourth ventricle and the floor of the hypothalamus. The lack of a blood–brain barrier in these areas allows a number of blood-borne hormones (e.g. angiotensin II) to modulate the activity of the autonomic nervous system. The capillaries of the posterior pituitary and pineal gland are also permeable to allow the release of hormones into the systemic circulation.

Highly lipid-soluble drugs rapidly permeate the brain, the only limitation being cerebral blood flow, examples are anaesthetic drugs, the uptake and distribution of which are discussed in *Anaesthesia and Intensive Care Medicine* **2:6:** 241 and **2:7:** 277.

Strongly ionized drugs are excluded from the brain and organic ions are actively extruded from the CSF and brain. For example, the penicillins use the organic acid transport system, which is similar to the transport processes in the renal tubule.

Penetration of the brain by weak acids and bases is pH dependent and follows the rules described in *Anaesthesia and Intensive Care Medicine* **3:3:** 105.

Drugs administered into the epidural or subarachnoid space

When drugs are injected into the epidural space they reach spinal nerves by several different routes. The drugs diffuse rapidly into the CSF at the dural cuff and into the dural spinal nerve roots. Later the drug seeps through the intervertebral foramina where a local anaesthetic may produce paravertebral nerve block. The rate of penetration into the spinal cord depends on lipid solubility. Morphine, which is relatively poorly lipid soluble, penetrates the spinal cord slowly and thus the onset of analgesia is slow. However, the duration of analgesia is long because of slow egress from the cord. More lipid-soluble opioids (e.g. fentanyl, pethidine) have a faster onset of action but a shorter duration. The transfer of several local anaesthetic drugs from the epidural space to the systemic circulation exhibits biphasic absorption characteristics. The first, rapid phase is probably a result of the high concentration gradient between the drug in the epidural space and the blood. The slower phase results from distribution of the local anaesthetic into tissue and subsequent partitioning between the tissue and the blood. Much slower absorption into the systemic circulation occurs after subarachnoid administration of drugs due to the dilution into the CSF and the poor vascular perfusion of the subarachnoid space. Although the onset of action of most drugs acting on the spinal cord is faster with subarachnoid rather than with epidural administration, the characteristics related to lipid solubility still apply. However, the volume of the subarachnoid space is small and there is the potential for nerve damage. Distribution of drug within the CSF and into the brain can be slow and there is large inter-patient variability.

Fetus

The fetus acts as if it were a transcellular compartment because drugs need to cross cell membranes in order to penetrate the tissue. Like the blood–brain barrier the placental barrier consists of an epithelial layer with tight junctions between cells so that no molecular filter is present and penetration depends on lipid solubility rather than molecular size. However, the placental barrier does not protect the fetus from the unwanted effects of maternal drugs. Every drug given to the mother passes to the fetus to some degree.

Lipid-soluble drugs cross the placenta by simple diffusion. The rate of diffusion increases with increasing lipid solubility, decreasing molecular size and decreasing degree of ionization. Most drugs used in anaesthesia are highly lipid soluble and have low molecular weight and thus equilibrate with the fetal compartment in a single circuit. Transfer of drugs of this type is said to be flow-dependent.

Drugs such as the neuromuscular blocking agents are fully ionized in solution, they cross the placenta slowly and their transfer is said to be permeability dependent. The degree of ionization of a drug also affects its rate of passage across the placenta. The fetus has a pH about 0.1 lower than the mother therefore there is a tendency for basic drugs (e.g. some opioid analgesics) to be trapped on the fetal side of the placenta (see *Anaesthesia and Intensive Care Medicine* **2:5:** 171). Normally protein binding masks this effect, but it can cause problems if the fetus is acidotic.

The amount of drug transferred to the fetus also depends on the plasma concentration of free drug in the mother and the duration of exposure. The maternal plasma concentration of drug increases with dose and is greatest when the intravenous route is used. Protein binding is also important because there is equilibrium between bound and free drug and only the free drug can cross the placenta. High doses of drug may saturate the binding sites causing an increase in free drug and greater availability for placental transfer. Protein binding also provides a reservoir of drug in the maternal circulation that can prolong fetal transfer. In general, the fetal compartment equilibrates slowly with the maternal circulation and single therapeutic doses of a drug seldom cause significant problems in the fetus. For example, an induction dose of an intravenous anaesthetic to the mother is unlikely to anaesthetize the fetus because only a small fraction of the dose reaches the fetal brain. Prolonged exposure to maternal concentrations of a freely diffusible drug results in similar drug exposure to mother and fetus.

For flow-dependent drugs, significant falls in drug transfer can occur if blood flow to the placenta is reduced. This occurs during uterine contraction and techniques have been used to reduce fetal drug exposure by injecting a bolus of drug at the appropriate time.

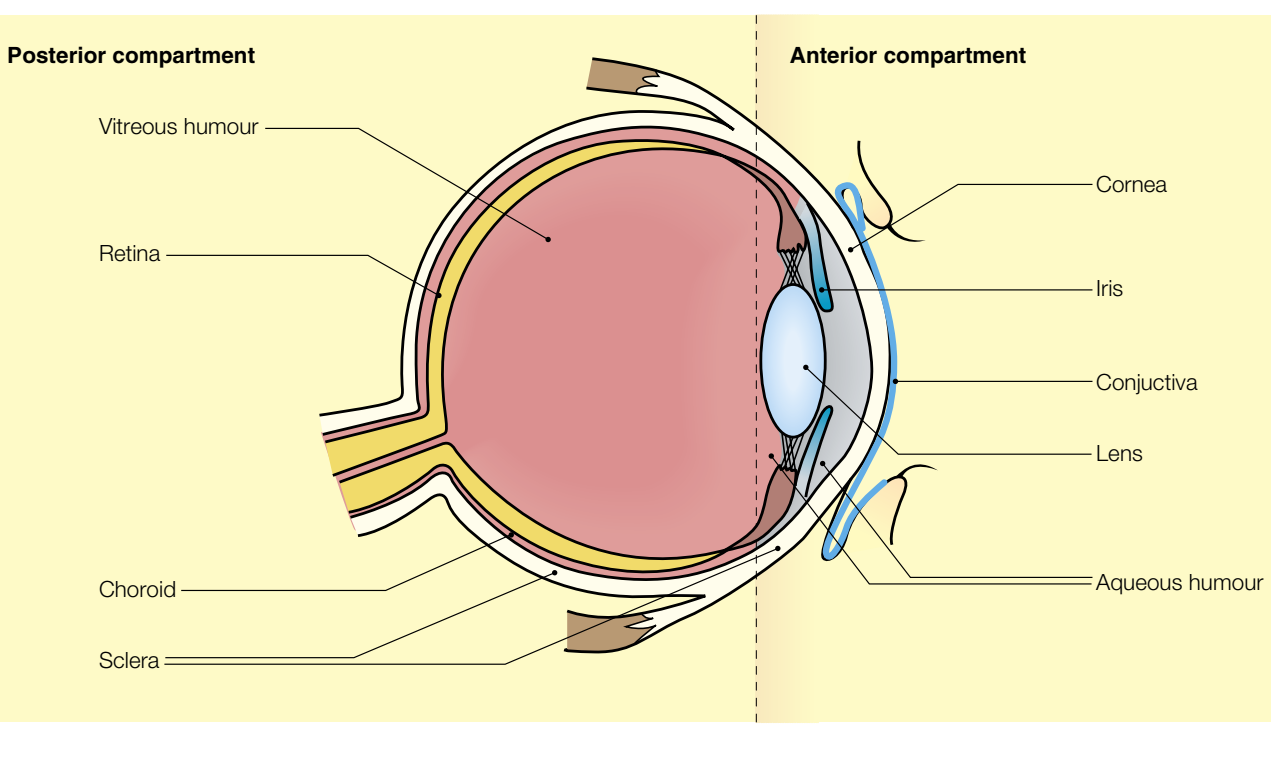
The placental transfer of some drugs used in anaesthesia is summarized in Figure 4.

Consequences of placental transfer of some drugs used in anaesthesia

Drug group	Effect on fetus	Comment
Opioids	Low Apgar scores at birth Respiratory depression in mother leading to fetal hypoxia	Cross placenta readily although different members of group differ in lipid solubility Morphine crosses the placenta least readily
General anaesthetic agents	Fetal depression Respiratory depression	More likely with prolonged induction to delivery time or high concentrations of drug
Neuromuscular blocking agents	Neonatal paralysis or slow commencement of respiration	Placenta crossed very slowly so seldom problems with normal doses
Local anaesthetic agents	Reduced motor tone	Probably does not occur Drugs are usually given via the epidural or intrathecal route and only small quantities reach the fetus

Although the fetus can metabolize many drugs, the enzyme systems are immature and the drug half-life may be increased. Examples include pethidine and lidocaine (lignocaine), which also have toxic metabolites with a long duration of action.

Eye
The sclera, conjunctiva, iris, retina, ciliary muscle and choroid have a moderately good blood supply but the cornea, lens and vitreous humour are avascular (Figure 5). Drugs can penetrate the structures and aqueous humour in the anterior compartment from the conjunctival sac. However, the volume of drug that can be administered by this route is limited. There is little perfusion each side of the conjunctival membrane, therefore the rate of drug movement from the tear film is proportional to lipid solubility and the degree of ionization of the drug. The cornea has a high water content and therefore water-soluble drugs (e.g. pilocarpine) can also penetrate into the aqueous humour. Many anti-infective agents can cross into the aqueous humour, but penicillins are actively extruded in the same way as they are from the CNS. Some drugs are bound to melanin which accounts for the slower onset of the mydriatic action of α-adrenergic agonists in patients with darkly pigmented irises. Drugs cannot reach the posterior compartment of the eye by diffusion from the conjunctival sac because the distance is too great. However, drugs can reach these structures through the systemic circulation. Melanin is also found in the retinal pigmental layer and chloroquine accumulates here causing retinal lesions that decrease visual acuity.



Skin and nails
Skin and nails are avascular, therefore penetration is relatively slow. Some drugs (e.g. the antifungal griseofulvin) have a high affinity for keratin and are concentrated in skin and nails. When treating microorganism infections of skin and hair it is important to consider the kinetics of turnover of these tissues. In the skin, microorganisms dwell in the stratum corneum, which is replaced every 2–3 weeks. Most drugs prevent the infection of new cells, therefore treatment for at least 4 weeks is required to eradicate the infection. Similar infection of the hair begins at the root, which is about 4 mm below the surface of the skin. Hair grows at 1 mm per week, therefore treatment must be continued for at least 6 weeks to be certain of cure.

Drug reservoirs

Protein binding: many drugs are bound to plasma proteins (see *Anaesthesia and Intensive Care Medicine* **2:8:** 314). Protein binding is usually reversible, though covalent binding of highly reactive drugs such as the alkylating agents can occur.

Fat is a large, non-polar compartment constituting on average 15–20% of body weight. Non-polar drugs can dissolve in fat where they exert no pharmacological action but form a large reservoir of drug in contact with the plasma. Blood supply to fat is relatively low, therefore partition occurs slowly and equilibrium between plasma and fat takes a long time to achieve. It is important to consider the amount of body fat when giving acute doses of highly lipid-soluble compounds such as the general anaesthetics and for chronic dosing with fairly fat-soluble drugs such as the benzodiazepines.

Fat also accumulates some food contaminants that are little metabolized, such as DDT, an insecticide widely used between 1940 and 1970. The content of DDT in human fat reached a peak in the 1970s. Since then its use has been banned and the concentrations in humans have gradually declined.

Bone: divalent metal ion chelating agents (e.g. tetracyclines) accumulate in bones and teeth where they may cause staining. This may be unsightly but is not dangerous. Toxic heavy metals (e.g. lead, radium) may also adsorb onto the bone surface and may become incorporated into the bone matrix. From there they may be released slowly into the blood causing toxic effects long after exposure has ceased. This accumulation of heavy metals by bone can be used therapeutically in the administration of strontium-89 in the treatment of bone metastases. Otherwise, drug access to bone is governed by the local blood flow.

Liver: prolonged treatment with the antimalarial quinacrine can result in liver concentration many thousand times that in the plasma. Amiodarone, a class III antidysrhythmic drug, accumulates in high concentration in the liver, lung and fat. It remains pharmacologically active for 6 weeks or more after administration has ceased.

Skin: when drugs are administered transdermally the skin may act as a reservoir continuing to supply the drug even after the skin patch has been removed. This has been reported for fentanyl patches (see *Anaesthesia and Intensive Care Medicine* **3:2:** 105). ◆

Bonding, Binding and Isomerism

Norman Calvey

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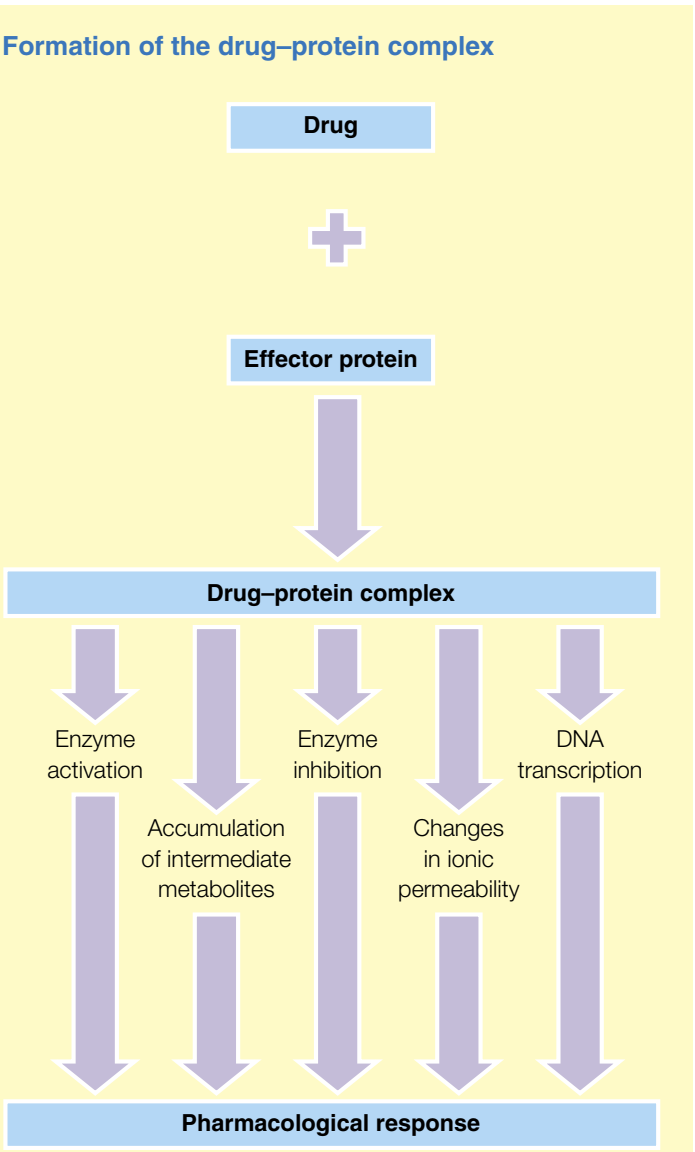
Some drugs are extremely potent agents, for example as little as several billion molecules of α-bungarotoxin, angiotensin II, or tetrodotoxin may produce effects on neuromuscular transmission, peripheral resistance, or nerve conduction. The body contains many trillions of molecules, therefore the effects of these drugs cannot depend on their random distribution, but must be governed by their selective binding to target cells or tissues. These principles were recognized by the German physician and scientist Paul Ehrlich more than 100 years ago, as summarized in his well-known dictum: *Corpora non agunt nisi fixata* (drugs will not act unless they are bound).

Although there are exceptions to this rule, it is applicable to almost all the drugs used in humans. The action of most drugs is dependent on their reversible binding to regulatory proteins in cells, which subsequently mediate their effects; binding to other cellular constituents is usually nonspecific and of lesser importance.

Binding of drugs to regulatory proteins

Regulatory proteins that mediate the actions of drugs are usually classified as enzymes, receptors, ion channels or other proteins (e.g. carrier proteins). A few drugs are bound by structural proteins (e.g. tubulin, immunophilin). Some drugs are bound by DNA (e.g. cytotoxic agents).

The combination of drug and effector protein usually results in the formation of a transient drug–protein complex, which produces secondary effects on protein function (Figure 1). The protein binding of drugs is also essential for their elimination from the body by metabolic enzymes or transport proteins.



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Drug binding and drug design

Recently, the molecular binding sites on many enzymes and receptors have been defined and characterized. In some instances, the effects of drugs have been related to their molecular structure, and paradigms of their binding sites on target proteins have been obtained. In other instances, it has been possible to determine the structure of receptors and drug–receptor complexes by X-ray crystallography or nuclear magnetic resonance spectroscopy. These techniques often allow the conformation of drugs at their binding sites to be established, as well as the structure and configuration of their target regulatory proteins.

As a consequence of these studies, three-dimensional models of drug–protein complexes may lead to the design and synthesis of chemical analogues that bind to target proteins with enhanced selectivity or affinity. Alternatively, large chemical libraries can be searched by computer programs for compounds with specific three-dimensional structures that will combine with the target receptor or enzyme protein.

Plasma protein binding

The binding of drugs by plasma proteins plays an important part in their distribution after oral or intravenous administration, and facilitates access to their site of action. Most drugs are relatively lipid soluble, with a low solubility in plasma water, therefore protein binding is essential for their transport and rapid distribution.

Drugs are usually reversibly bound to plasma proteins, according to the reaction:

unbound drug + protein ↔ drug–protein complex

During tissue perfusion, the concentration of unbound drug in plasma falls, and the protein-bound drug rapidly dissociates. Consequently, a continuous concentration gradient is present for the diffusion of drugs from plasma to tissues.

Quantitative aspects

Plasma protein binding of drugs may range from zero to almost 100% (Figure 2). There are considerable differences in the degree of protein binding, even among closely related drugs. Thus, the binding of local anaesthetics to α_1-acid glycoprotein ranges from 6% (procaine), 55% (prilocaine), 65% (lidocaine (lignocaine)) to 94–95% (ropivacaine and bupivacaine); these values are reflected by the binding of their bases to ion channels, which are responsible for differences in their duration of action and toxicity.

In general, only the unbound fraction of drugs in plasma is available for diffusion into tissues, and is therefore responsible for their pharmacological effects. For some drugs (e.g. diazepam, phenytoin, warfarin), unbound concentrations in plasma are only 1–2% of total plasma levels. They can be determined by *in vitro* techniques (such as equilibrium dialysis, ultracentrifugation or ultrafiltration). Salivary secretions and CSF samples may also reflect the concentration of the unbound drug in plasma.

Drugs and endogenous agents are bound by albumin, globulins or a combination of the two.

Plasma protein binding of some common drugs (at conventional plasma concentration)

Drug	Plasma protein binding (%)	Binding protein
Procaine	6	
Prilocaine	55	
Lidocaine (lignocaine)	65	
Tetracaine (amethocaine)	75	
Ropivacaine	94	
Bupivacaine	95	
Morphine	30	α_1-acid glycoprotein
Pethidine	64	
Fentanyl	80	
Alfentanil	90	
Pindolol	50	
Propranolol	80	
Atenolol	0	
Atracurium	< 20	
Vecuronium	< 20	
Pancuronium	30	α_1-acid glycoprotein
Tubocurarine	50	and albumin
Methohexital (methohexitone)	80	
Thiopental (thiopentone)	80	
Phenytoin	95	Albumin
Diazepam	97	
Warfarin	99	

2

Binding to albumin: albumin plays the predominant role in the binding of drugs by plasma proteins. Each albumin molecule has at least two binding sites with a variable affinity for drugs, and mainly binds acidic or neutral compounds (e.g. salicylates, non-steroidal anti-inflammatory drugs, tolbutamide, sulphonamides, oral anticoagulants). Some basic drugs and physiological substrates (e.g. bilirubin, tryptophan) are also bound by albumin.

Binding to globulins: plasma globulins mainly bind basic drugs (e.g. phenothiazines, local anaesthetics, opioid analgesics). Drugs are usually bound by β-globulins, or by an acute-phase protein (α_1-acid glycoprotein). Many vitamins and endogenous hormones are also bound by plasma globulins. Hydrocortisone (cortisol) is mainly bound with high affinity by a specific protein (transcortin). Similarly, thyroxine, oestrogens and progestogens are bound by specific globulins.

Binding to albumin and globulins: some muscle relaxants (e.g. tubocurarine, pancuronium) are bound to both albumin and globulins. The resistance to their action that is sometimes seen in liver disease may be related to increased plasma protein binding.

Plasma protein binding and pathological conditions

In pathological conditions associated with hypoalbuminaemia (e.g. hepatic cirrhosis, nephrosis, trauma, burns), drug binding to plasma proteins is modified. The plasma concentrations of unbound drugs may be increased, and can cause toxic effects, for example with prednisolone and phenytoin. These changes are most likely when drugs are given in large doses or intravenously. In these conditions, the binding of drugs by albumin may be saturated, causing an increase in their unbound concentrations. Well-perfused tissues and organs (e.g. heart, liver, kidneys, brain) may receive a higher proportion of the dose, resulting in toxic effects. A similar phenomenon may occur in those with renal impairment and in the elderly, possibly because of the altered affinity of drugs for albumin.

Plasma concentrations of the acute-phase globulin α_1-acid glycoprotein are often increased after surgery and in certain conditions (e.g. myocardial infarction, rheumatoid arthritis, ulcerative colitis, Crohn's disease, renal failure, malignant disease). In these conditions, the binding of basic drugs (e.g. propranolol, local anaesthetics, opioid analgesics) may be modified, resulting in a decrease in the concentration of unbound drug.

Plasma protein binding and drug elimination

Plasma protein binding may restrict the hepatic clearance of extensively bound drugs (> 70% bound) with a low intrinsic hepatic clearance (e.g. diazepam, phenytoin, warfarin). In these conditions, plasma protein binding may limit the access of drugs to hepatic enzyme systems, decreasing their clearance and prolonging their terminal half-lives. In other circumstances, plasma protein binding does not restrict the hepatic or renal elimination of drugs or drug metabolites. Some extensively protein-bound substances (e.g. para-amino-hippurate, diodrast and benzylpenicillin) are almost completely eliminated in a single passage through the renal circulation.

Plasma protein binding and drug interactions
Drugs that are extensively bound may be displaced from their binding sites on plasma proteins by other agents, thus producing drug interactions. In practice, most drugs are extremely potent, and their plasma concentrations after therapeutic doses are less than the millimolar levels required to saturate their binding sites. In these conditions, displacement reactions are unlikely; any displacement may transiently raise the unbound concentration, but this will usually be compensated for by increased renal and hepatic clearance.

For these reasons, it is now thought that plasma protein displacement reactions alone are not an important cause of drug interactions. When they occur, they are most likely to involve drugs or endogenous substances that are predominantly confined to plasma, and those that have a narrow therapeutic index.

Chemical nature of drug binding

The binding of drugs by regulatory or plasma proteins may involve at the least the four different types of chemical bonding described below.

Ionic (electrostatic) attraction: ionized compounds may be attracted to anionic or cationic sites on proteins, forming readily reversible bonds. Some tertiary and quaternary amines (e.g. acetylcholine, neostigmine, glycopyrrolate) are attracted by an anionic glutamate group (glutamate 202) in acetylcholinesterase, facilitating their reaction with the enzyme. Similarly, in the anticoagulant heparin an anionic pentasaccharide sequence is attracted to basic arginine residues in antithrombin III, forming a stable complex. This enhances inhibition of thrombin and other activated coagulation factors.

Dipole–dipole interactions: molecules with partially positive and partially negative charges can attract or repel each other in solution; opposite charges are attracted while similar charges are repelled. Nonpolar molecules can be attracted to each other by induced dipole–dipole interactions known as London forces. Both attractive and repulsive dipole–dipole interactions are usually collectively known as van der Waals forces, and are dependent on intermolecular distance. The critical distance at which intermolecular attraction is greatest is known as the van der Waals radius.

Hydrogen bonding is a powerful type of dipole–dipole interaction. It takes place between partially positive hydrogen atoms in secondary amine (-NH) or hydroxyl (-OH) groups and adjacent electronegative atoms with unshared electrons (e.g. oxygen, nitrogen or fluorine atoms). Hydrogen bonds are rapidly reversible bonds, the dissociation energy of which is higher than in other dipole–dipole interactions.

Covalent bonds are stable chemical bonds (owing to the sharing of a pair of electrons by two atoms). They have a relatively high dissociation energy (8–10 times that of hydrogen bonds) and typically occur between carbon and its compounds. Drugs that are bound to receptors and enzymes by covalent bonds (e.g. phenoxybenzamine, most monoamine oxidase inhibitors) usually have a long duration of action (days or weeks).

Isomerism

Isomers are chemical entities with identical numbers of different atoms. Although they have the same chemical composition and molecular formula, their physical and chemical properties may be different (depending on the type of isomerism involved). The two main types of isomerism are structural isomerism and stereoisomerism.

Structural isomerism
Structural isomers have an identical molecular formula but different chemical structures, because their individual atoms are not arranged in the same manner. Individual structural isomers are usually identified as entirely different drugs with distinctive names (e.g. isoflurane, enflurane).

Tautomerism (dynamic isomerism) is a type of structural isomerism. In tautomerism, two unstable structural isomers in equilibrium can be converted to each other (usually by pH changes). Tautomerism is partly responsible for the increased lipid solubility of thiopental (thiopentone) and methohexital (methohexitone) after intravenous use.

Stereoisomerism
Stereoisomers have the same molecular formula and chemical structure but a different configuration (i.e. the spatial arrangement of their substituent groups differs). They are usually classified as enantiomers or diastereomers.

Enantiomers are pairs of stereoisomers that are non-super-imposable mirror-images of each other. This type of stereoisomerism depends on the presence of a chiral centre in their molecular structure, which is usually a single carbon atom with four different substituents. Drugs with this type of structure (chiral drugs) have a mirror-image that cannot be superimposed on their original configuration, and therefore exist in two enantiomeric forms (R and S isomers). Both enantiomers are optically active; one of them rotates polarized light to the right (the (+) or (d) form), while the other rotates polarized light to the left (the (–) or (l) form). Consequently, individual stereoisomers are designated as R(+), R(–), S(+) or S(–). Equal mixtures of the two enantiomers (racemic mixtures) have no optical activity. In recent decades, progress in chemical technology has simplified the synthesis and preparation of individual R and S enantiomers (e.g. by asymmetric chemical syntheses, or by the chiral inversion of one enantiomer).

Diastereomers are pairs of stereoisomers that are not enantiomers (i.e. not mirror-images), and usually have different physical and chemical properties. Although some of the stereoisomers of methohexital (methohexitone), tramodol, atracurium and mivacurium are enantiomers, others are diastereomers.

Racemic mixtures: about 60% of commonly used anaesthetic agents are chiral drugs. Most of them are administered as racemic mixtures of R and S isomers, including most inhalational anaesthetics, some intravenous agents and local anaesthetics, and many autonomic drugs (Figure 3). Although both enantiomers have the same structure, they have a different configuration, and their substituent groups occupy different positions in space. Consequently, they may form different three-dimensional relationships in the asymmetric environment of receptors and enzymes, which mainly consist of L-amino acids with stereoselective properties. In these conditions, there may be differences between the pharmacodynamic activity and pharmacokinetic properties of individual enantiomers, since their relationship with specific receptor sites and hepatic enzyme systems may not be identical.

Some chiral drugs used in anaesthetic practice

Single isomers	Two isomers (racemic mixtures)	More than two isomers
• Etomidate	• Methohexital (methohexitone)	• Atracurium
• Levobupivacaine	• Thiopental (thiopentone)	• Mivacurium
• Ropivacaine	• Ketamine	
• Cisatracurium	• Halothane	
• Vecuronium	• Enflurane	
• Pancuronium	• Isoflurane	
• Rocuronium	• Desflurane	
• Hyoscine	• Prilocaine	
• Morphine	• Bupivacaine	
	• Adrenaline (epinephrine)	
	• Noradrenaline (norepinephrine)	
	• Dobutamine	
	• Atropine	
	• Glycopyrrolate	

Differences in pharmacodynamic activity: there are often differences in the potency of individual enantiomers (suggesting that drug action is related to interaction with proteins). Isoflurane is an example of this phenomenon; in most experimental conditions the S(+)-stereoisomer is about 20% more potent than its enantiomer. Greater differences in potency are not uncommon; thus, S(+)-ketamine is 3–4 times more potent than R(–)-ketamine, while l-atropine, l-noradrenaline, and l-adrenaline are 50–100 times more potent than their d-enantiomers. These differences in potency can be expressed by the eudismic ratio (stereospecific index), which represents the activity of the more active isomer (the eutomer) in relation to its antipode (the distomer). Eudismic ratios greater than unity may be due to differences in the affinity or intrinsic activity of the enantiomers.

In other instances, there are qualitative differences in pharmacological activity. Occasionally the enantiomers have complementary actions, and both contribute to the overall activity of drugs (e.g. tramadol, dobutamine). In other cases, one isomer is an agonist, while its enantiomer is a partial agonist or competitive antagonist.

Differences in pharmacokinetic properties: in some instances, one isomer is more rapidly metabolized than its enantiomer. Thus, R(+)-propranolol, R(–)-prilocaine and S(+)-ketamine are more rapidly metabolized than their enantiomers, and have a higher hepatic clearance. Alternatively, one enantiomer may inhibit the metabolism of its antipode (e.g. R(–)-ketamine). Similar metabolic interactions are known to occur with other chiral drugs (e.g. levomethorphan).

Some inactive enantiomers undergo unidirectional metabolic conversion (‘inversion’) to their antipodes. Both R(–)-ibuprofen and R(–)-fenoprofen are converted to their more active S(+)-enantiomers after oral absorption, thus enhancing the potency of the racemic mixture.

Differences in the metabolism and distribution of enantiomers can affect the pharmacokinetics of chiral mixtures, and the isomers may have different half-lives, clearances, and volumes of distribution.

Single enantiomers: a number of chiral anaesthetic agents (e.g. etomidate, ropivacaine, levobupivacaine) have been synthesized and used as single isomer preparations, which may have certain advantages. For example, levobupivacaine may be less cardiotoxic and have a longer duration of action than racemic bupivacaine; ropivacaine has similar properties. Cisatracurium is also a single isomer preparation, which is more potent and causes less histamine release than atracurium.

Some drugs derived from plants or organisms are also single stereoisomers (e.g. l-hyoscine), because naturally occurring enzymes are stereoselective and synthesize drugs in a distinct and specific configuration.

Complex stereoisomeric mixtures: some anaesthetic agents are administered as mixtures of more than two stereoisomers (Figure 3). Atracurium contains ten different stereoisomers, while mivacurium is a mixture of three isomers. Methohexital (methohexitone) was originally synthesized and used as two pairs of enantiomers (i.e. four isomers); the drug is now used as a chiral mixture of the two less excitatory forms.

Current perspective: in many countries, drug regulatory authorities have encouraged the development and use of new drugs as single stereoisomers. Since 1990, most new drugs have been used as specific enantiomers, and it seems likely that this trend will continue.

FURTHER READING

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CNS Stimulants

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CNS stimulants increase the activity of the brain and/or spinal cord. They have a long history beginning with the use of plants (e.g. *Camellia sinensis* contains caffeine, *Erythroxylum coca* cocaine) to produce psychostimulation, reduce appetite, fatigue and the tendency to sleep, and increase alertness and vigilance. CNS stimulants now include synthetic chemicals (e.g. amfetamines (amphetamines)) which are used widely for non-medical recreational or social purposes. Some have therapeutic uses in peripheral tissues, which may cause CNS stimulation as an adverse effect.

Classification of CNS stimulants as psychomotor stimulants acting on the cerebral cortex, analeptics stimulating medullary respiratory centres, or spinal cord stimulants enhancing reflexes can be misleading because stimulation is dose dependent and may spread to other CNS areas with high doses. Despite their long-established use, knowledge of the neurochemical effects of CNS stimulants in humans is incomplete. Nevertheless, their preferred grouping reflects the pharmacological mechanisms perceived to be responsible for their stimulant activity (i.e. sympathomimetics, methylxanthines or convulsants).

Sympathomimetics

Mechanism of action

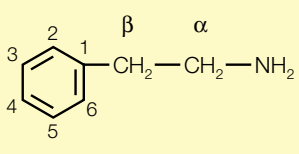
Numerous β-phenylethylamine derivatives structurally similar to the sympathetic nervous system neurotransmitter, noradren-aline (norepinephrine) exist as natural products, in foods (e.g. tyramine) or plants (e.g. ephedrine), and in synthetic drugs (e.g. amfetamine (amphetamine)) (Figure 1). They produce effects characteristic of increased sympathetic nervous system activity, hence the term sympathomimetics. Receptors for noradrenaline (norepinephrine) and two other important catecholamine messengers, adrenaline (epinephrine) and dopamine, are located in peripheral tissues and the CNS. Phenylethylamines, binding as agonists to postsynaptic receptors (e.g. phenylephrine (Figure 1f)) at α_1-adrenoceptors, elicit direct responses from postsynaptic neurons or effector cells. Some β-phenylethylamine derivatives lack the necessary molecular attributes to bind directly to catecholamine receptors (e.g. tyramine (Figure 1c)). This type of compound indirectly enhances the activity of endogenous monoamines (catecholamines and possibly the indolealkylamine, serotonin) by inhibiting monoamine:

- metabolism, by monoamine oxidases
- reuptake, into cells by transporters
- storage, in vesicles and extravesicular pools.

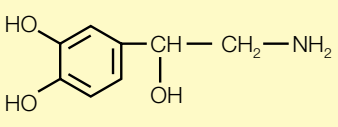
The extent to which a sympathomimetic acts directly and/or indirectly on receptors is not easily identified from its molecular structure, but can be determined experimentally. Most sympathomimetics have some affinity for catecholamine receptors. The type(s) of monoamine receptor (α-adrenoceptors, β-adrenoceptors, dopamine receptors, serotonin receptors) for which a sympathomimetic shows affinity is determined by its molecular structure, and may be different from the receptors acted on by endogenous biogenic amines. Thus, the pharmacological profile of a sympathomimetic may not be consistent with simple enhancement of physiological activity mediated by endogenous monoamine activity.

The biological effects of many catecholamines, including the major neurohumoral transmitters, are short lasting because of in-activation by enzymes, mainly monoamine oxidases (MAO), and/or reuptake into cells. Inhibition of MAO and/or uptake potentiates endogenous monoamines and directly acting sympathomimetics, therefore interactions between antidepressants working by these mechanisms and sympathomimetics cause, for example, hypertensive crisis. Substitution for H on the α-carbon in β-phenylethylamine blocks oxidation by MAO, consequently compounds such as amfetamine (amphetamine) and ephedrine with CH_3 on the α-carbon act for hours, not minutes (Figure 1). Cocaine and structurally related drugs potentiate endogenous monoamines and directly acting sympathomimetics, mainly by preventing transporters carrying monoamines into axon terminals or glial cells.

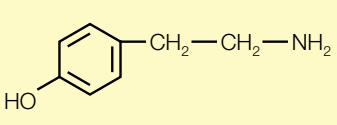
Some β-phenylethylamines with sympathomimetic, CNS stimulant and/or hallucinogenic activity



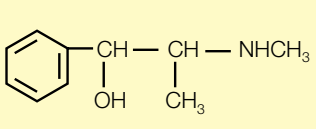
a β-phenylethylamine



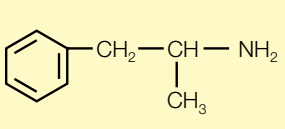
b Noradrenaline (norepinephrine)



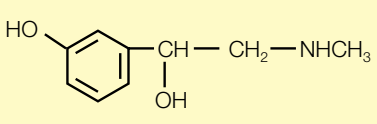
c Tyramine



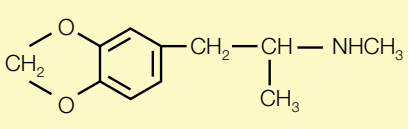
d Ephedrine



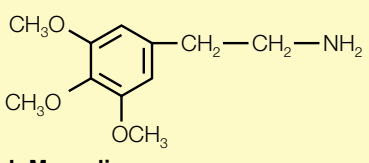
e Amfetamine (amphetamine)



f Phenylephrine



g 3,4-methylenedioxymethamfetamine (MDMA, Ecstasy)



h Mescaline

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The increased monoamine–receptor interactions produced directly or indirectly by sympathomimetics produce peripheral and central effects. Sympathomimetics are used clinically for their peripheral actions as mydriatics (phenylephrine) and nasal decongestants (ephedrine, phenylephrine). Although their decongestant effect is limited by rebound vasodilatation and congestion on withdrawal, sympathomimetics have widespread use in self-medication products on public sale. Even after local application to the eye or nose, systemic absorption of these agents can occur, producing adverse effects peripherally (e.g. arrhythmias, tachycardia, hypertension) and centrally (e.g. dizziness, insomnia).

Lipophilicity is one prerequisite for CNS drug activity, thus β-phenylethylamine derivatives with few polar groups tend to have greater CNS stimulant activity. This is illustrated by am-fetamine (amphetamine) (Figure 1e) and its active isomer, dexamfetamine (dexamphetamine), which lack OH on the β-carbon, as possessed by ephedrine, and are more potent CNS stimulants. Sympathomimetics producing CNS stimulation have limited, regulated therapeutic use: dexamfetamine sulphate and methyl-phenidate in the management of attention deficit/hyperactivity disorder and narcolepsy. CNS stimulants have no approved application in the treatment of depression, obesity, senility or the relief of fatigue, because of their toxicity and abuse potential.

Abuse

CNS stimulation – psychostimulation produced by amfet-amines (amphetamines) and cocaine appeals to some people for non-medical recreational purposes. Legislation controlling the manufacture, supply and possession of abused drugs has promoted the production and use of unregulated derivatives presumed, sometimes erroneously, to have a similar pharmacology to the parent compound. These so-called 'designer drugs' are not designed to improve the safety of established drugs, but to evade legal restrictions. In the case of CNS stimulants, the designer drugs in current use are structurally related to amfetamine (amphetamine). Many amfetamine (amphetamine) derivatives are manufactured for illegal recreational use, the most familiar being 3,4-methylenedioxymethamfetamine (Ecstasy; Figure 1g).

Hallucinogens – amfetamine-related compounds possess CNS activity, variously described as hallucinogenic or pyschoto-genic. Substitutions for OH on the β-phenylethylamine ring can produce compounds with marked hallucinogenic activity (e.g. methylenedioxy derivatives such as Ecstasy are more potent hallucinogenic agents than amfetamine). Dimethoxy derivatives of β-phenylethylamine (e.g. 2,5-dimethoxy-4-methamfetamine (street name, STP)) are structurally similar to the naturally occurring hallucinogen mescaline, extracted from *Lophophora williamsi* (Figure 1h). Although similar in structure to hallucinogenic β-phenylethylamines, mescaline does not have a significant effect on adrenergic mechanisms. Mescaline and other hallucinogenic β-phenylethylamines depress serotonergic neuron activity in the brain, a property shared with hallucinogens with an indolealkylamine structure (e.g. bufotenine, lysergide (lysergic acid diethylamide), psilocybin). Both chemical classes of hallucinogens produce qualitatively similar autonomic, sensory and perceptual effects. In addition, there is cross-tolerance between mescaline and lysergide. Indications are that these hallucinogens share a common site of action, possibly serotonin receptors.

Adverse effects – CNS stimulation and hallucinations appear to be separate actions of sympathomimetic amines. These parallel pharmacological effects of Ecstasy-like drugs attract abuse by numerous people seeking relief from fatigue and/or heightened sensory perception, particularly of audio and visual stimuli, with the further prospect of experiencing synaesthesia, elation and euphoria. These drugs can cause severe adverse effects consistent with their sympathomimetic, CNS stimulant and hallucinogenic properties, including agitation, convulsions, delirium, hyperreflexia, hyperthermia and ventricular arrhythmias. Adverse effects may occur with acute doses previously tolerated. Chronic use leads to tolerance, dependence and personality changes, including psychosis possibly secondary to organic brain damage. Failure by hospital staff in England to recognize and treat the adverse effects of Ecstasy has recently resulted in damages being awarded to a recreational drug abuser.

Anaesthesia

Patients with a history of acute or chronic amfetamine (amphet-amine) abuse or taking amfetamine-like drugs for medical reasons may present for surgery and general anaesthesia. Acutely these drugs release endogenous monoamines from neuronal stores, but chronic use may lead to depletion of these stores. This may result in a patient being unable to respond to stimuli normally modulating blood pressure, and possibly unexpected hypotension. Patients should therefore be withdrawn from amfetamine-like drugs before elective general anaesthesia. However, a recent paper reports successful anaesthesia in a patient with narcolepsy treated with a combination of amfetamine and dexamfetamine for more than 40 years (see Further Reading). Nevertheless, there are reports of severe hypotension in such patients if amfetamine-like substances are not withdrawn. Most authorities recommend intensive cardiovascular monitoring and the availability of a directly acting sympathomimetic (e.g. phenylephrine) if withdrawal is impossible before general anaesthesia.

Methylxanthines

Caffeine (1,3,7-trimethylxanthine) is the most potent CNS stimulant of the three major naturally occurring methylxanthines, the others being theophylline (1,3-dimethylxanthine) and theobromine (3,7-dimethylxanthine) (Figure 2). Although a weak CNS stimulant in comparison with sympathomimetics, caffeine occurs in coffee, tea, chocolate, cola and guarana drinks and has become established as the most widely consumed socially acceptable (i.e. legal) CNS stimulant in the world. In addition to its importance as an ingredient in beverages used for cultural and recreational purposes, caffeine can produce physical and psychic dependence, which contributes further to its frequent and sometimes excessive use. Caffeine is formulated into numerous compound analgesic preparations available to the public for the claimed purpose of enhancing the analgesic action, possibly by increasing gastrointestinal absorption of the analgesic. Solid dose forms of caffeine for CNS stimulation are also on public sale.

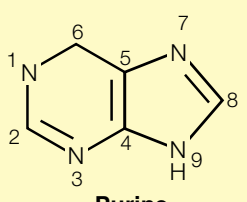
Mechanism of action – methylxanthines influence cell activity by three major mechanisms:

- antagonism at adenosine receptors
- inhibition of cyclic nucleotide phosphodiesterases
- translocation of intracellular Ca^{2+}.

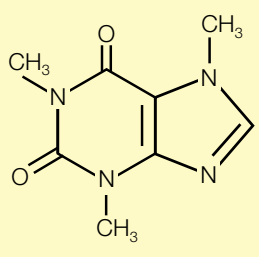
Endogenous adenosine (Figure 2) modulates the physiological activity of numerous cell types by binding to at least four types of specific G protein-linked receptors. Adenosine, interacting with receptors in the CNS, causes decreased release of excitatory neurotransmitters producing anticonvulsant, antipsychotic and sedative effects. Caffeine at concentrations producing CNS stimulation competitively antagonizes adenosine binding to its receptors; phosphodiesterase inhibition and Ca^{2+} mobilization occur at higher concentrations and contribute to its toxicity.

Clinical pharmacology – caffeine is used widely to relieve mental fatigue, produce wakefulness and shorten reaction times. Methylxanthines also have peripheral effects including bronchodilatation exploited clinically with theophylline and its more soluble derivative, aminophylline when CNS stimulation and insomnia can occur as adverse effects. Excessive amounts produce symptoms of anxiety, insomnia, restlessness, muscle tremor, tachycardia and extrasystoles. Large doses of caffeine may cause convulsive movements as stimulation spreads from higher centres to motor areas, medulla and spinal cord. The stimulant action of caffeine on the medullary vasomotor centre is usually offset by its peripheral vasodilator effect on arterioles; blood pressure is unchanged. The lethal dose of caffeine in humans is high, but death has been attributed to overdose with caffeine tablets.

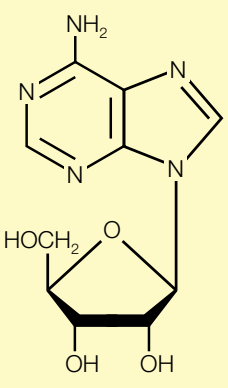
Methylxanthines: structural relationship to the purinergic neurotransmitter, adenosine



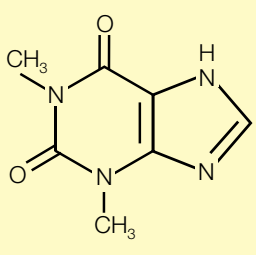
Purine



Caffeine
(1,3,7-trimethylxanthine)



Adenosine



Theophylline
(1,3-dimethylxanthine)

Theobromine
(3,7-dimethylxanthine)

2

Convulsants

Convulsions can be produced by agents acting in various ways at different sites. Many convulsants act by disinhibition (i.e. preventing the tone exerted by inhibitory neurotransmitters). This covers methylxanthines acting as adenosine receptor antagonists, but their social acceptance and low toxicity arbitrarily excludes them from this group, which includes convulsants such as the glycine receptor antagonist, strychnine. The group includes respiratory stimulants or analeptics, which were once widely used to treat ventilatory failure. In excessive dose, respiratory stimulants including nikethamide can cause convulsions, therefore physical methods of ventilatory support (e.g. nasal intermittent positive-pressure ventilation) are now first-line treatment.

Doxapram is the only drug in this group that is still generally available, owing to its wider margin of safety than other analeptics (e.g. nikethamide, ethamivan). In healthy individuals, doxapram increases tidal volume and respiratory rate and consequently produces a fall in the partial pressure of carbon dioxide in arter-ial blood ($PaCO_2$) and a rise in that of oxygen (PaO_2). The exact mechanism is unknown, but it is thought to involve stimulation of peripheral chemoreceptors in the carotid body. Single doses have a short duration of effect (less than 1 hour) owing to redistribution rather than metabolism; even so the drug has a short half-life (about 3 hours) and is usually administered intravenously as a continuous infusion. Doxapram is metabolized in the liver. The main metabolite, keto-doxapram, has some pharmacological activity and accumulates after prolonged infusions. The indication for doxapram treatment is limited to the management of patients with hypercapnic respiratory failure who are unsuitable for intubation and ventilation. It is contraindicated in respiratory failure secondary to asthma, pneumothorax, pulmonary embolism or oedema. Some recent studies investigated the usefulness of low doses of doxapram in the management of apnoea of prematurity (see Further Reading) and concluded doxapram may be a useful second-line drug when other therapies, including methylxanthines as first-line drug therapy, have failed. ◆

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Drug Targets

Barbara J Pleuvry

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Most drugs bind to a particular cellular component in order to produce their effects; exceptions are the osmotic diuretics and antacids. Some antitumour and antimicrobial drugs directly target DNA, but targeting proteins is the most common method of drug action.

General anaesthetics were thought to interact with membrane lipids (see page 329) but this has been questioned as more is revealed about how general anaesthetics modulate ligand-gated ion channels.

Typical protein drug targets

Carrier molecules

Ions and polar organic molecules require a carrier protein to transport them across the lipid cell membrane. Examples of therapeutic importance are the 5-hydroxytryptamine (5-HT) and noradrenaline transporters, which are inhibited by the tricyclic and related antidepressant drugs, the Na^+-K^+-$2Cl^-$ co-transporter, which is inhibited by loop diuretics and the proton pump, which is inhibited by omeprazole. Research in many pharmaceutical companies is targeting other carrier molecules such as glutamate and γ-aminobutyric acid (GABA) transporters, which may be the basis for new classes of drugs.

Enzymes

Most biochemical reactions occur through the actions of catalytic proteins called enzymes. They may be inhibited reversibly, such as the inhibition of cyclo-oxygenase by ibuprofen, or irreversibly, such as the inhibition of cyclo-oxygenase by aspirin. It is now known that many enzymes exist as multiple isoforms and some recently developed drugs have selectivity for one or more of these variants. Cyclo-oxygenase has two isoforms; COX-1 and COX-2. COX-2 is induced in activated inflammatory cells and produces the prostaglandin mediators of inflammation. COX-1 is expressed in most tissues and mediates many of the protective effects of prostaglandins. Drugs selective for the COX-2 enzyme (e.g. celecoxib, rofecoxib) are anti-inflammatory but do not cause the gastric irritation commonly seen with non-selective non-steroidal anti-inflammatory drugs in patients without gastrointestinal pathology.

Enzymes may also convert pro-drugs into an active form such as the conversion of heroin and codeine to morphine or zidovudine to zidovudine triphosphate. Toxic metabolites may also be produced by enzyme activity, for example trifluoroacetic acid from halothane and N-acetyl-p-benzoquinoneimine from paracetamol.

Drugs may also be a false substrate for an enzyme, thus blocking the normal function of the enzyme, for example the replacement of uracil by fluorouracil in DNA synthesis.

Voltage-gated ion channels

Some membrane-spanning proteins can change shape depending on the membrane potential. This allows ions access across the membrane through a central channel, which opens within the protein. The shape and size of the channel determines which ions pass through and the speed of passage depends on the transmembrane concentration gradient for that particular ion. Drugs can modulate the activity of voltage-gated ion channels by opening, closing or blocking them. In addition, a drug may act indirectly via G-protein modulation of channel opening.

An example of drug-induced channel blockade, which has been in routine clinical use for many years, is the action of local anaesthetics on sodium channels. Local anaesthetics simply block the sodium channel. In contrast, L-type calcium-channel blockers (e.g. verapamil, nifedipine) affect the gating process of the channel rather than blocking ion passage. Blockade of T-type calcium channels may be important in the anticonvulsant action of several drugs, such as ethosuximide and flunarizine.

Many biotoxins are selective for specific ion channels. For example, tetrodotoxin, from the Japanese puffer fish, blocks most sodium channels and scorpion α-toxin opens them. Ziconotide, a derivative of ω-conotoxin from sea snails, is an N-type calcium-channel-blocking drug and is being studied as a potential treatment for chronic pain. Potassium channel pharmacology is rapidly expanding and the basis of the vasodilator action of minoxidil and diazoxide has been revealed as the opening of ATP-sensitive potassium channels. In addition, the antidiabetic drug glibenclamide closes this channel. Non-selective voltage-sensitive potassium-channel-blocking agents include tetraethylammonium and 4-aminopyridine, but their clinical use is limited by convulsions and nausea. More selective drugs acting on the voltage-sensitive potassium channels are being sought.

Receptors

Receptors are defined pharmacologically as proteins that regulate a particular physiological role in response to recognition of a particular molecular shape. A typical example is noradrenaline (norepinephrine) activating the α-adrenoceptor and causing the contraction of vascular smooth muscle. Receptors are the targets of most drugs presently in use.

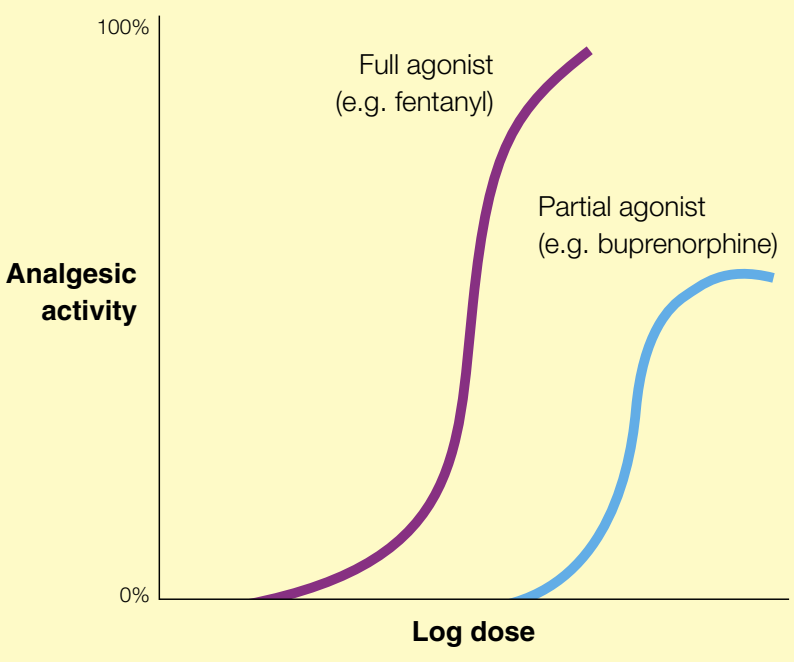
Agonists and antagonists

An agonist can be defined as a molecule that binds to a receptor, causing activation and a resultant cellular change. An antagonist may bind to the same receptor but cannot initiate a response, thus blocking that receptor to an agonist. Antagonists are sometimes defined as drugs that can prevent the action of an agonist, but this definition must apply equally to physiological or functional antagonism, where a drug exerts an opposite effect, thus antagonizing the action of an agonist. An example of such an interaction would be the antagonism of histamine-induced vasodilatation by adrenaline (epinephrine).

A full agonist can produce the largest response that the effector organ is capable of giving. The term efficacy has been used to describe the way that agonists can vary in the response that they produce even when occupying the same number of receptors. A high-efficacy agonist produces a maximum response even when occupying a small proportion of the available receptors.

A partial agonist cannot fully activate the receptor irrespective of the concentration available. In contrast to a full agonist, a partial agonist cannot exert a maximal response. Buprenorphine is a partial agonist at opioid μ receptors. Partial agonists have lower efficacy and cannot produce a maximal response even when occupying all the receptors (Figure 1).

Receptor agonists



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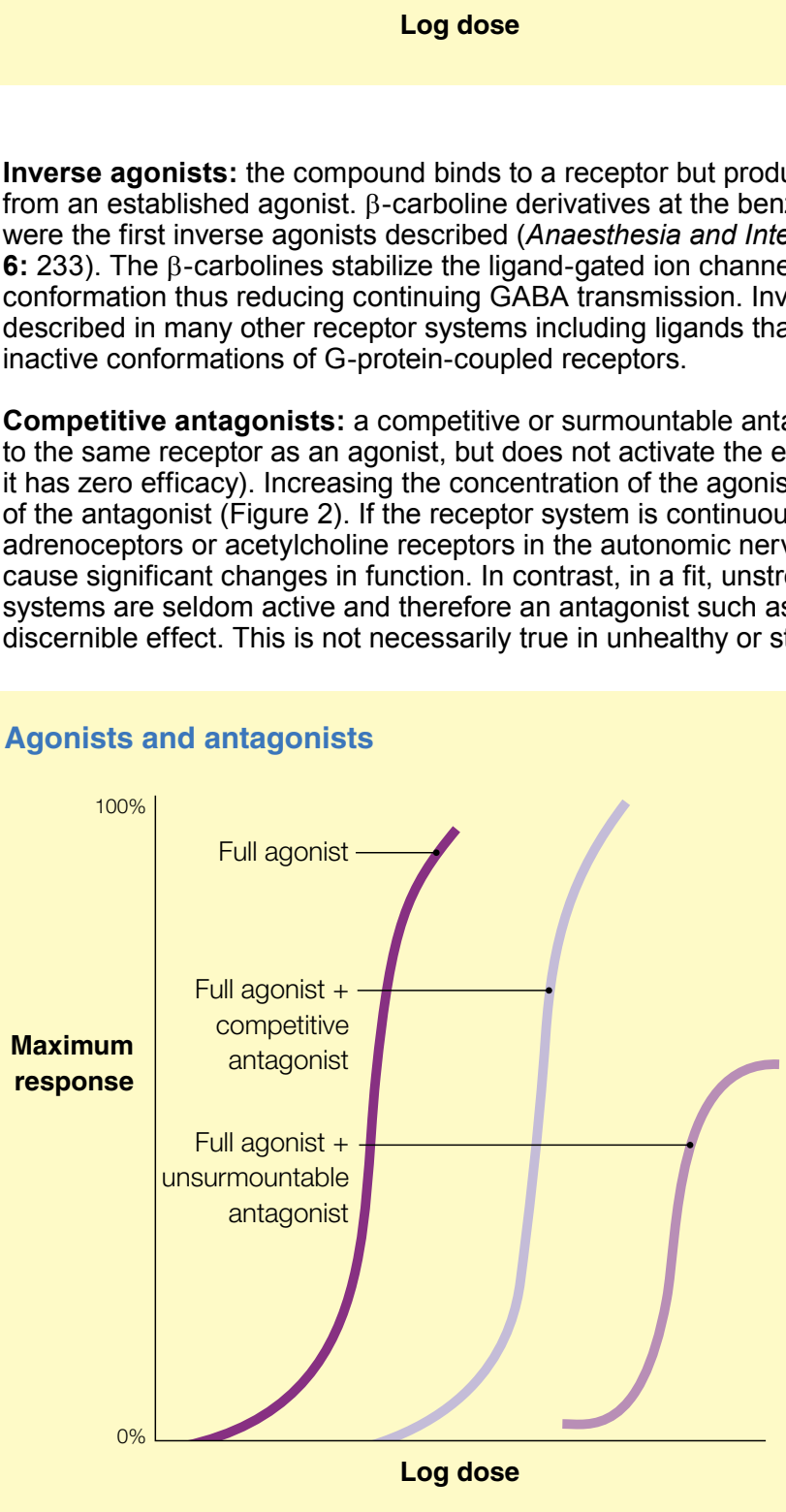
Inverse agonists: the compound binds to a receptor but produces the opposite effect from an established agonist. β-carboline derivatives at the benzodiazepine receptor were the first inverse agonists described (*Anaesthesia and Intensive Care Medicine* **2: 6:** 233). The β-carbolines stabilize the ligand-gated ion channel $GABA_A$ in its inactive conformation thus reducing continuing GABA transmission. Inverse agonists have been described in many other receptor systems including ligands that preferentially stabilize inactive conformations of G-protein-coupled receptors.

Competitive antagonists: a competitive or surmountable antagonist binds reversibly to the same receptor as an agonist, but does not activate the effector mechanism (i.e. it has zero efficacy). Increasing the concentration of the agonist can reverse binding of the antagonist (Figure 2). If the receptor system is continuously active, as are adrenoceptors or acetylcholine receptors in the autonomic nervous system, antagonists cause significant changes in function. In contrast, in a fit, unstressed person, opioid systems are seldom active and therefore an antagonist such as naloxone has no discernible effect. This is not necessarily true in unhealthy or stressed individuals.

Agonists and antagonists



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Non-surmountable antagonists: when receptor antagonism is established no amount of agonist will completely reverse it. Phenoxybenzamine is a non-surmountable antagonist and covalently binds to the norepinephrine-binding site on the α-adrenoceptors. Antagonists that bind to other sites on the receptor causing a change in the conformation of the agonist-binding site (allosteric antagonism) are also non-surmountable.

Receptor classification

Until recently, receptors were classified on the basis of their agonist and antagonist profiles. Molecular biology has demonstrated that receptors can also be classified according to their amino-acid sequences. Many of the receptors so detected have no known function.

Families of receptors

Four main families of receptors have been revealed by cloning and structural studies.

Ligand-gated ion channels: fast synaptic transmission is initiated by a neurotransmitter binding to a receptor that directly causes the opening of an ion channel. They are multi-subunit receptors in which all subunits traverse the membrane. Those most studied appear to be made up of five subunits, which may be of the same type, surrounding a channel. Some ligand-gated ion channels are compared in Figure 3. As with the voltage-gated ion channels, modulation of channel gating by the binding of ligands to a variety of sites on the receptor complex, can significantly affect function; the benzodiazepine modulation of the actions of the $GABA_A$ receptor is an important example.

Examples of ligand-gated ion channels

Name	Ion gated	Agonist	Antagonist	Modulator
• Nicotinic acetylcholine	Na^+	Suxamethonium	Vecuronium	
• $GABA_A$	Cl^-	Muscimol	Bicuculline	Benzodiazepines and general anaesthetics
• NMDA (glutamate)	Ca^{2+} Na^+	N-methyl-D-aspartate	Ketamine (channel blockade)	Glycine
• $5\text{-}HT_3$	Ca^{2+}		Ondansetron	

G-protein-coupled receptors: receptors linked to G-proteins or guanine nucleotide-binding regulatory proteins comprise most membrane-bound receptors. The receptor is composed of seven α-helices that traverse the membrane forming a bundle. Three extracellular and three intracellular loops connect the helices. The long third cytoplasmic loop provides the coupling with the G-proteins. The binding sites for agonists are often buried in pockets within the bundle of α-helices. The G-protein is a go-between connecting the receptor to a number of G-protein effectors including second messenger systems and ion channels. Some examples of G-protein linked receptors and their effectors or second messengers are shown in Figure 4.

Examples of G-protein-linked receptors

Receptor	Effector	Agonist	Antagonist
Muscarinic acetylcholine	Activation of phospholipase C (IP_3 and DAG)[1] Inhibition of adenylyl cyclase Activation of K^+ channels Inhibition of Ca^{2+} channels	Pilocarpine	Atropine
β_1-adrenoceptor	Activation of adenylyl cyclase	Dobutamine	Atenolol
μ opioid receptors	Inhibition of adenylyl cyclase Activation of K^+ channels Inhibition of Ca^{2+} channels	Morphine	Naloxone
D_2-dopamine receptors	Inhibition of adenylyl cyclase Activation of phospholipase C (IP_3 and DAG)	Bromocriptine	Spiperone

[1] IP_3, inositol triphosphate; DAG, diacylglycerol.

Direct enzyme-linked receptors possess large intracellular and extracellular domains joined by a single membrane-spanning helix. The extracellular domain provides the binding site for peptide agonists, usually growth hormones such as insulin. The intracellular domain is usually a protein kinase that phosphorylates amino-acid residues, often tyrosine, and the group has been called the tyrosine-kinase-linked receptor.

Intracellular receptors affecting gene transcription: these non-membrane-bound receptors may either be nuclear (e.g. thyroid hormone receptor) or cytosolic (e.g. glucocorticoid receptor). In the latter, the presence of a ligand leads to the movement of the receptor–ligand complex into the nucleus. Ligands for these receptors are lipid soluble and pass into the cell. The binding of the ligand to the receptor results in an uncurling of the receptor protein to reveal the DNA binding domain. An increase in RNA polymerase activity and the production of a specific mRNA occurs and protein production is enhanced. Alternatively, the receptor complex may switch off the synthesis of some proteins.

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Drugs and the Liver

Barbara J Pleuvry

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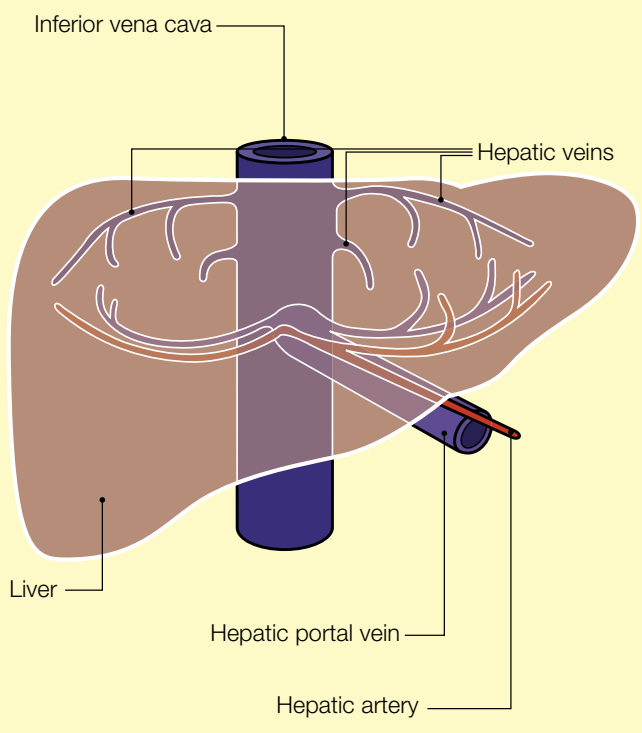
The multiple functions of the liver include the production of proteins (e.g. enzymes and clotting factors), storage of iron and glycogen, and the metabolism of fats, proteins, bile acids and bilirubin. Most important, from a pharmacological point of view, is that the liver controls much of the metabolism and excretion of drugs and toxins. These functions are carried out by the hepatocytes that make up 90% of the organ. Sinusoids, lined with Kupffer cells, lie between the hepatocytes and make up the biliary tree that comes together as the common bile duct before emptying into the duodenum. The blood supply of the liver is illustrated in Figure 1.

Blood supply of the liver



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Interactions between drugs and the liver can be divided into two main areas:

- how the liver and its diseases affect drug metabolism
- how drugs can affect the functions of the liver.

Drug metabolism in the liver and the effects of enzyme induction and inhibition on drug activity are discussed in *Anaesthesia and Intensive Care Medicine* **3:3** and **3:7**. Some of the drugs whose metabolism is severely affected in patients with liver failure are listed in Figure 2. They have high hepatic clearance. Any drugs used in anaesthesia (e.g. benzodiazepine, propofol) that are metabolized by the liver may show a prolongation of action is patients with liver disease. The remainder of this article concentrates on how drugs affect the biliary system and/or liver function.

Drugs to be used with caution in liver failure because of severely reduced metabolism

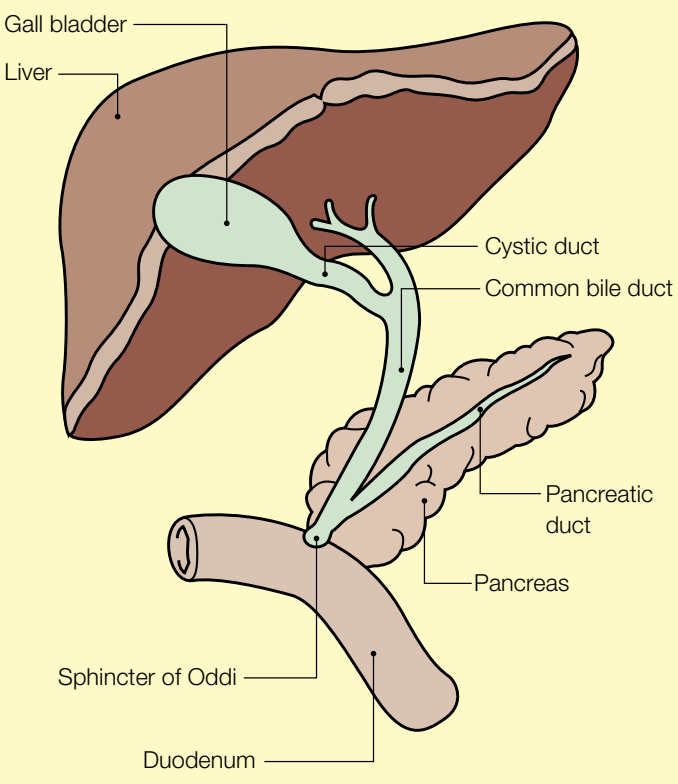
- Alprenolol
- Desipramine
- Isoprenaline
- Lidocaine (lignocaine)
- Morphine
- Nitroglycerine
- Pentazocine
- Pethidine
- Propoxyphene
- Propranolol

2

Drugs affecting the biliary system

The function of bile salts, which are present in bile, is to emulsify fats in the intestine so that pancreatic lipase, which is insoluble in lipids, can more readily attack the droplets. Bile salts are reabsorbed from the intestine via the hepatic portal vein and are recycled by the liver. Liver cells produce about 1 litre of bile per day, which is stored in the gall bladder (Figure 3) and released only through the hepatopancreatic sphincter (sphincter of Oddi) when chyme enters the duodenum. The formation of cholesterol gallstones (cholelithiasis) is the most common pathological condition of the biliary tract. Passage of gallstones down the bile duct can cause intense pain. Opioid drugs can reduce the pain, but some (e.g. morphine) can cause a spasm of the sphincter of Oddi and raise pressure in the bile duct. Co-administration of a muscarinic acetylcholine receptor antagonist or using a partial opioid agonist (e.g. buprenorphine) can reduce this. Pethidine has some intrinsic antimuscarinic activity and it may be less likely to produce sphincter of Oddi constriction. The smooth muscle relaxation produced by the release of nitric oxide from nitrates may also relieve biliary spasm.

Gall bladder



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If gallstones are non-calcified they can be dissolved by chenodeoxycholic acid and ursodeoxycholic acid. The former is identical to one of the natural bile acids in humans while the latter is found mainly in the bear. These two bile acids can be given orally and they decrease hepatic synthesis and secretion of cholesterol. They are treated like endogenous bile acids in the body. However, in most patients with gallstones, surgery or shattering the stone with lithotripsy is the treatment of choice.

Anaesthetic drugs and liver function

Many drugs, including those used in anaesthesia, are likely to affect liver function but in general these effects are transitory, small and without long-term consequences. However, in patients with existing hepatic dysfunction and multisystem organ failure even minor changes to hepatic function can be important.

Inhalational, intravenous and local anaesthetic agents can reduce liver blood flow. Because of its association with postoperative hepatic dysfunction (see later) halothane has received most attention in this regard. There is a dose-dependent decrease in portal liver blood flow that parallels the fall in cardiac output produced by halothane. There may be a compensatory, but limited, increase in hepatic artery blood flow. The overall reduction in liver blood flow caused by halothane decreases with time and is usually less than that induced by surgery alone. However, in patients whose liver function is severely compromised, the reduced blood flow and consequent hypoxia may be significant. Among the inhalational agents, isoflurane appears to have the least overall effect on hepatic oxygen supply and demand and may be the agent of choice for patients with liver disease. Intravenous anaesthetic agents appear to have little direct effect on liver blood flow but may have secondary effects owing to reduced cardiac output and sympathetic stimulation if ventilation is depressed. Ketamine has increased liver blood flow in some studies. The reduced liver blood flow induced by spinal or epidural administration of local anaesthetics mirrors the fall in mean arterial pressure.

Postoperative liver dysfunction

Almost all inhalational anaesthetic agents have been associated with postoperative liver dysfunction, but most attention has been focused on halothane. Halothane-associated hepatitis (see *Anaesthesia and Intensive Care Medicine* **2:1:** 7) has been attributed to a direct effect of halothane or a metabolite on liver cells, while fulminating hepatic failure has been attributed to an immune reaction following repeat halothane exposure. The classification of hypersensitivity reactions is shown in Figure 4. Some patients with the fulminating disease have highly reactive trifluoroacetyl proteins in their serum presumably derived from a halothane metabolite combined with a protein to form an immunogen. In animal studies an antigen to this protein can be expressed on the surface of liver cells and destruction of the cell occurs by type II hypersensitivity reactions involving killer T cells. The release of antibody-antigen complexes from the damaged cells can then cause type III reactions. Fulminating hepatic failure carries a high mortality but is rare (1/35,000 anaesthetics). Cross-sensitivity may occur with other halogenated anaesthetic agents that can produce trifluoroacetyl proteins (e.g. enflurane). However, because halothane is metabolized to a greater extent than most volatile anaesthetics it has the greatest propensity for the production of this protein.

Classification of hypersensitivity reactions

Type I	Immediate or anaphylactic (e.g. hay fever)
Type II	Antibody-dependent cytotoxic (e.g. autoimmune thyroiditis)
Type III	Complex-mediated via activated complement (e.g. farmer's lung)
Type IV	Cell-mediated (e.g. rheumatoid arthritis)

4

Halothane-associated hepatitis is characterized by an elevation of liver transaminase with transient jaundice but low morbidity. It may occur after a single administration of halothane and the incidence has been reported to be as high as 20%. However, there are many potential causes of postoperative liver dysfunction including hypoxia and hypotension and the diagnosis of halothane-associated hepatitis is by exclusion of other potential causes.

Other drugs and liver function

Ethanol causes dose-dependent liver damage and is the most common cause of cirrhosis. Many patients are asymptomatic but may present in hospital with gastrointestinal haemorrhage owing to portal hypertension secondary to the cirrhosis. The bleeding is most often from oesophageal varices. These may be treated by endoscopic injection of a sclerosant (an irritant that causes thrombus formation) such as sodium tetradecyl sulphate, ethanolamine oleate, sodium morrhuate, polidocanol. or even absolute alcohol. Other treatments involve surgical procedures.

Aspirin has been associated with Reye's syndrome in children, which involves fatty degeneration of the viscera and liver failure. The condition is associated with viral infections such as influenza, and in some countries is common when the fever has been treated with aspirin. Aspirin is no longer recommended for children under 12 years of age and the incidence of Reye's syndrome has reduced. However, not all reports have supported an association of aspirin with the syndrome. The hepatic toxicity of paracetamol is described in *Anaesthesia and Intensive Care Medicine* **2:11:** 457. Other compounds that can cause liver damage are listed in Figure 5. ◆

Additional drugs associated with hepatotoxicity

Androgens
Reversible obstructive jaundice

Chlorpromazine
Reversible obstructive jaundice

Isoniazid
Effects may be more profound in slow acetylators

Ketoconazole
Rare but often fatal liver toxicity can occur after cessation of drug Similar reports for fluconazole

Phenytoin
Effects may be more profound in slow acetylators

Solvents
Examples include toluene (glue sniffing), carbon tetrachloride and trichloroethylene (dry cleaning fluids)

Valproate
An increase in serum glutamic oxaloacetic transaminase is common, but hepatitis is rare

Drugs for Muscle and Joint Disease

Barbara J Pleuvry

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Joint disease

Drugs used to treat joint diseases such as osteoarthritis and rheumatoid arthritis are described elsewhere.

Osteoarthritis

Paracetamol is first-line pain therapy for osteoarthritis because only a minor inflammatory component is involved. Non-steroidal anti-inflammatory drugs (NSAIDs) can also be prescribed but gastrointestinal side-effects limit the usefulness of most agents that show little selectivity for the cyclo-oxygenase (COX)-2 enzyme. Recently introduced, selective COX-2 inhibiting drugs such as celecoxib and rofecoxib may be beneficial, but await detailed study. Neither paracetamol nor NSAIDs treat the disease, only the pain associated with it.

The main process involved in disease progression is cartilage destruction and some chondroprotective drugs (e.g. chondroitin, glucosamine, hyaluronic acid) have been used to try to halt or reverse the disease; long-term trials are awaited.

Rheumatoid arthritis

Rheumatoid arthritis is an inflammatory, autoimmune disease in which the immune system invades and destroys cartilage in the joint. NSAIDs and the anti-inflammatory glucocorticosteroids were formerly the mainstay of therapy, though gastrointestinal side-effects limited their use. Both groups of drugs inhibit the production of prostanoids. NSAIDs cause the inhibition of the COX enzyme responsible for converting arachidonic acid into the cyclic endoperoxides. Alternatively, glucocorticosteroids increase the cellular production of lipocortin, an inhibitor of phospholipase A_2 causing a decreased release of arachidonic acid and thus decreased prostanoid formation. In addition, glucocorticosteroids decrease COX-2 synthesis.

Disease-modifying anti-rheumatic drugs (DMARDs) have been recommended at an early stage in the development of the disease, despite their inherent toxicity. Used early in the disease process, DMARDs can maintain joint function at near normal, while later use causes only a mild improvement in an already disabled joint. Many DMARDs are classical immunosuppressants (e.g. methotrexate, ciclosporin (cyclosporin), azathioprine, cyclophosphamide). Gold and penicillamine are older treatments, the use of which is declining. In the UK, sulphasalazine is first-line therapy but its mechanism of action is unknown.

A decrease in the activity of tumour necrosis factor (TNF) in rheumatoid arthritis has a beneficial effect. Two approaches have been used to achieve this outcome. Infliximab is a preparation of anti-TNF-α antibodies and etanercept contains soluble TNF receptors fused to the Fc portion of human IgG.

Gout

Gout is a familial disease associated with an overproduction of purines. It is characterized by recurrent attacks of arthritis caused by the deposition of sodium urate in joints and cartilage; the base of the big toe is the joint most commonly affected. Acute attacks of gout result from the shedding of urate crystals from the slow build-up of urate on cartilaginous surfaces. The engulfing of crystals by phagocytosis causes the release of inflammatory mediators such as interleukin-1 (IL-1) and the lipoxygenase product LTB4. There is also activation of the kinin complement and plasmin systems.

Acute attacks of gout may be treated with NSAIDs (e.g. indomethacin, ketoprofen, naproxen, piroxicam, diclofenac). These drugs inhibit prostaglandin synthesis and urate crystal phagocytosis. Salicylates reduce urate excretion and therefore should not be used in gout. An alternative for the treatment of an acute attack is cholchicine, which inhibits leucocyte migration and phagocytosis. It prevents the polymerization of tubulin into microtubules thus reducing cell motility. The most common side-effect is gastrointestinal disturbances. The long-term treatment of gout involves inhibiting uric acid synthesis with allopurinol (a xanthine oxidase inhibitor), or increasing uric acid secretion using probenecid or sulphinpyrazone. Neither treatment is effective for acute attacks and may precipitate them (particularly allopurinol) or make them worse. Several diuretic agents are also uricosuric agents (e.g. probenecid) and may enhance the predisposition to urate renal stones.

Skeletal muscle relaxants

Skeletal muscle relaxants used to treat muscle spasticity or chronic spasm may act centrally (baclofen, benzodiazepines, tizanidine) or peripherally (dantrolene, botulinum toxin). Older centrally acting muscle relaxants include mephenesin, carisoprodol, methocarbamol and meprobamate. They are less effective than the drugs described below and are more toxic in overdose. Their use is not recommended as first-line treatment.

Baclofen is used to treat chronic spasticity resulting from conditions such as multiple sclerosis or traumatic partial section of the spinal cord. It is ineffective in cerebral spasticity caused by birth injury or stroke. Baclofen is an analogue of γ-aminobutyric acid (GABA) which penetrates the blood–brain barrier. It is not antagonized by bicuculline and is a selective agonist for the $GABA_B$ receptor. Unlike the $GABA_A$ receptor, which is a ligand-gated ion channel, the $GABA_B$ receptor is G-protein coupled and mediates inhibition of adenylyl cyclase. Baclofen inhibits monosynaptic and polysynaptic activation of motor neurons in the spinal cord. Baclofen is the only drug acting on the $GABA_B$ receptor that has significant clinical use, though antagonists appear to have anticonvulsant actions, which are being investigated. The most common side-effect is drowsiness and sedation, but nausea and muscle hypotonia may also occur. Some patients also report mood disturbances such as depression and anxiety.

Benzodiazepines reduce muscle tone by a central action and can be used for muscle spasm due to many causes including tetanus. Muscle relaxation probably contributes to their use as anxiolytics. Benzodiazepines enhance the response to GABA, acting at the $GABA_A$ receptor.

Tizanidine, like baclofen, is mainly used to treat spasticity caused by multiple sclerosis or spinal cord damage. It is an α_2-adrenoceptor agonist and acts by increasing presynaptic inhibition of motor neurons in the spinal cord. Its side-effects are similar to those of other α_2-adrenoceptor agonists (i.e. sed-ation, dry mouth).

Dantrolene has been used for severe chronic spasticity of skeletal muscle, neuroleptic malignant syndrome and malignant hyperpyrexia. Dantrolene blocks Ca^{2+} release from the sarcoplasmic reticulum by limiting the capacity of Ca^{2+} and calmodulin to activate the ryanodine (RYR-1) receptor, this reduces muscle contraction. This action is peripheral, therefore dantrolene lacks the CNS side-effects seen with other skeletal muscle relaxants and is probably the treatment of choice for muscle spasm. However, the dose should be increased slowly and liver toxicity has been reported. Dantrolene is used for the treatment of muscle spasm associated with amyotrophic lateral sclerosis. It may cause excessive muscle weakness.

Botulinum toxin injected directly into the affected muscle has been used to treat strabismus, blepharospasm and other spastic conditions such as spasmodic torticollis and foot deformities caused by spasticity in children with cerebral palsy. Careful placing of the injections is essential because a misplaced injection results in paralysis of a non-affected muscle. Botulinum toxin contains several components (A–G), of which A and B are used clinically. Each component is a peptidase that cleaves a protein, such as a synaptobrevin or a synaptotaxin, involved in transmitter release. Botulinum toxin is highly specific for acetylcholine release and inhibits skeletal muscle and parasympathetic function. Treatment lasts for 3–4 months and recovery is due to nerve sprouting. Immunoresistance may occur with repeated use. Under the trade names Botox® or Dysport®, botulinum A toxin-haemagglutinin complex has been used cosmetically to reduce facial lines.

Drugs for myasthenia gravis

Myasthenia gravis is a defect of neuromuscular transmission, which causes skeletal muscle weakness that fluctuates and can be exacerbated by exercise of the muscle. Thus, sustained contraction of muscle is impossible and typical symptoms are dropping of the eyelid. In over 90% of patients, antibodies are present to the nicotinic acetylcholine receptor on the motor end-plate. However, the severity of the disease does not correlate well with the antibody titre. The thymus may be responsible for the initial pathogenesis, but it is not required for perpetuation of the disease. At least 70% of patients also have thymic hyperplasia and thymectomy may be helpful in some cases, particularly in young women, and is mandatory if a thymoma is present (15% of cases). A few patients have a mutation of the acetylcholine receptor. These congenital cases do not respond to treatment with anticholinesterase agents.

Anticholinesterase agents prevent the breakdown of acetylcholine by acetylcholinesterase in the synaptic cleft and allow more time for the transmitter molecule to find a functioning receptor. The effect in most patients is dramatic and the use of a short-acting anticholinesterase agent, edrophonium, is used as a diagnostic test for the disease. However if the disease is severe, there are insufficient nicotinic receptors to initiate an action potential and anticholinesterase agents become ineffective. Anticholinesterase agents also potentiate acetylcholine at the parasympathetic effector junction but tolerance to this effect occurs and it is not necessary to add a muscarinic receptor antagonist routinely to the regimen. The anticholinesterase agents used to treat myasthenia gravis are listed in Figure 1; they are all reversible anticholinesterase agents. Irreversible anticholinesterase agents (e.g. ecothiopate iodide) are no longer on the market in the UK, but are still available on a named-patient basis for use under expert supervision.

Anticholinesterase agents used in myasthenia gravis

Drug	Duration of beneficial effect	Comments
Neostigmine	Up to 4 hours	A muscarinic acetylcholine receptor antagonist may be required in the early stages
Distigmine	Up to 24 hours (longest duration of action)	Danger of cholinergic crisis is greater than with the shorter acting drugs
Edrophonium	Up to 5 minutes	Used only for diagnosis and for assessing the need for dose adjustment
Pyridostigmine	More than 4 hours	Slower onset than neostigmine, but smoother action

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The antibodies in the plasma can be removed by plasma exchange, which is effective in the short term. Longer term reduction in antibody titre can be achieved with immunosuppressive compounds such as glucocorticosteroids, azathioprine and ciclosporin (cyclosporin). ◆

Enzyme Inducers and Inhibitors: Addition, Subtraction and Synergism

Norman Calvey

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Enzyme inducers and inhibitors

Enzymes are biological catalysts that play a crucial role in metabolism. Under normal conditions, their concentration and activity in individual subjects are mainly dependent on genetic and physiological regulation. Most enzyme systems are subject to inhibitory feedback control (i.e. their activity is inhibited by their metabolic products); similarly, increased utilization of their metabolites increases their activity. In certain enzyme systems, synthesis and activity can also be induced or inhibited by other agents. Enzyme induction and inhibition is particularly important in the hepatic mixed function oxidase system (cytochrome P450), which plays a central role in drug metabolism.

Cytochrome P450

Cytochrome P450 is present in the smooth endoplasmic reticulum (the microsomes), and consists of many different forms of a superfamily of haemoproteins. This enzyme system is responsible for most hepatic drug oxidation and reduction, as well as some hydrolytic reactions. More than 70% of hepatic cytochrome P450 is encoded by three gene families (*CYP 1*, *CYP 2* and *CYP 3*); drug metabolism in humans is mainly dependent on seven isoforms (CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 and CYP 3A4). The predominant and most important isoform in humans is CYP 3A4, which is often involved in drug interactions.

Induction of cytochrome P450: several drugs selectively increase the synthesis and activity of certain isoforms of cytochrome P450. Enzyme induction usually occurs within 3–5 days, and is associated with an increase in the endoplasmic reticulum, biliary secretion and liver weight. In humans, the main clinically significant enzyme-inducing agents are the barbiturates, phenytoin, carbamazepine, griseofulvin and rifampicin (Figure 1). Chronic alcohol consumption and some polycyclic aromatic hydrocarbons (e.g. 3-methylcholanthrene and benzpyrene) also induce certain isoforms; some of these compounds are present in tobacco smoke and grilled meats.

Inducers and inhibitors of cytochrome P450

Inducers
- Barbiturates
- Phenytoin
- Carbamazepine
- Rifampicin
- Griseofulvin
- Alcohol (chronic consumption) (tobacco smoke, grilled meat)
- Polycyclic hydrocarbons

Inhibitors
- Imidazoles (ketoconazole, itraconazole, omeprazole, cimetidine, etomidate)
- Macrolide antibiotics (erythromycin, clarithromycin)
- Antidepressants (most)
- Human immunodeficiency virus protease inhibitors (indinavir, nelfinavir, ritonavir)
- Cyclosporin
- Amiodarone
- Gestodene
- Grapefruit juice

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Enzyme-inducing agents commonly affect one or more specific enzyme isoforms. Thus, polycyclic hydrocarbons mainly induce CYP 1A1 and CYP 1A2, while barbiturates and phenytoin affect CYP 1A2 and CYP 3A4. Rifampicin is a potent inducer of CYP 2D6 and CYP 3A4, while ethyl alcohol affects CYP 2E1, which is responsible for the defluorination of many inhalational agents. Enzyme induction of cytochrome P450 often increases glucuronyl transferase activity, and thus enhances glucuronide conjugation; it commonly reduces effective plasma concentrations of other drugs, and may cause certain agents to increase their own metabolism (autoinduction).

Induction of cytochrome P450 may have secondary effects on other enzyme systems. Hepatic enzyme induction decreases intracellular haem, and thus reduces its negative inhibitory effects on amino-laevulinic acid and porphyrin synthesis; this may be important in patients with acute porphyria.

Inhibition of cytochrome P450: certain isoforms are competitively inhibited by other drugs (e.g. CYP 2D6 is inhibited by quinidine). Imidazole derivatives (e.g. ketoconazole, itraconazole, omeprazole, cimetidine, etomidate) combine with haem and non-competitively inhibit CYP 3A4 and certain other isoforms (e.g. CYP 1A2, CYP 2C8 and CYP 2D6). In addition, cyclosporin, amiodarone, many macrolide antibiotics, some antidepressant drugs, most anti-HIV protease inhibitors and grapefruit juice inhibit cytochrome P450 (particularly CYP 3A4) (Figure 1). Certain synthetic progestogens (e.g. gestodene) are oxidized by CYP 3A4 and combine with it covalently (suicide inhibition). Enzyme inhibition may increase the plasma concentrations of other concurrently used drugs, and interactions are not uncommon.

Induction and inhibition in other enzyme systems

Enzyme activity in other systems can also be modified by drugs. Certain bacterial enzymes (e.g. β-lactamases) are readily induced by many penicillins; similarly, enzyme induction may play an important part in acquired resistance to cytotoxic agents. In addition, many enzyme systems are inhibited by drugs, and enzyme inhibition may be the main mechanism of drug action (see *Anaesthesia and Intensive Care Medicine* **2:8:** 322).

Addition, subtraction and synergism

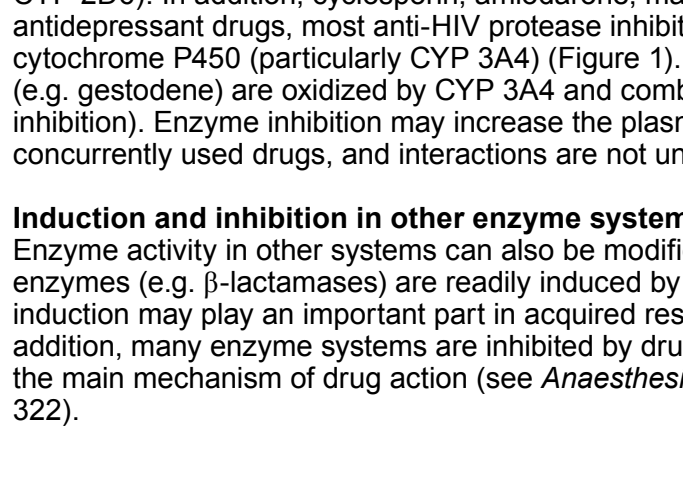
When two or more drugs are used concurrently, one drug may affect the action of the other. The terms addition, subtraction, and synergism are sometimes used to describe the effects observed when drugs are used in combination.

Addition

Addition or summation represents the additive effects of two or more similar drugs when used in combination; it is not a true interaction, and merely represents the sum of the effects of each agent when given alone. It is probably the most common effect observed when two drugs with similar actions are used simultaneously.

When two or more inhalational anaesthetics are used together, their potencies are additive. The potency of inhalational anaesthetics is expressed as the minimum alveolar concentration (MAC) value, which is defined as the minimum steady-state concentration that produces no reaction to a surgical stimulus (skin incision) in 50% of subjects at atmospheric pressure. When two different agents are administered simultaneously, their activities (when expressed as MAC values) are additive. Thus 0.5 MAC of nitrous oxide (52% v/v) and 0.5 MAC of halothane (0.37% v/v) have an equal effect to 1.0 MAC of either agent, or 1.0 MAC of any other inhalational anaesthetic. These relationships are traditionally expressed in the form of an isobole (a graph showing equi-effective combinations of drugs; Figure 2).

Isobole showing equi-effective concentrations of halothane and nitrous oxide



The two axes represent alveolar concentrations of halothane (abscissa) and nitrous oxide (ordinate). Points on the line correspond to equi-effective combinations of the two agents (with the same effect as the minimum alveolar concentration (MAC) of halothane; 0.75%, v/v). The linear relationship between the variables indicates that their potencies are additive. The line can be extrapolated to the ordinate, which it intercepts at the putative MAC of nitrous oxide

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The additive potencies of combinations of inhalational agents have been used to determine the MAC of nitrous oxide (104% v/v), and have been used to support the unitary concept of anaesthetic action. In practice, combinations of anaesthetics may show slight deviations from exact additivity (e.g. nitrous oxide and isoflurane), which are usually considered to reflect patient variability.

Subtraction

Subtraction is more commonly referred to as drug antagonism, and occurs when the effects of one drug are reduced or abolished in the presence of another. The following are the three main groups of drug antagonists.

Reversible competitive antagonists (e.g. atropine, atracurium, esmolol, naloxone, flumazenil) combine reversibly with receptors but do not produce biological responses. They progressively reduce the pharmacological effects produced by agonists. Reversible competitive antagonists cause the parallel displacement of the logarithmic dose–response curve to the right, but do not affect the slope or the maximum response.

Irreversible competitive antagonists (e.g. phenoxybenz-amine) form stable chemical bonds with receptors and dissociate slowly from receptor sites. They characteristically result in non-parallel displacement of the logarithmic dose–response curve to the right, decreasing the slope and the maximum response.

Non-competitive antagonists interfere with the action of other drugs by:
- chemical antagonism
- physiological (functional) antagonism
- pharmacokinetic antagonism.

Synergy

Synergy occurs when the combination of two drugs with similar properties produces supra-additive effects (i.e. greater than those expected by simple summation). When benzodiazepines and intravenous anaesthetics are used concurrently, synergic effects on hypnosis may be observed. Synergic reactions between drugs are sometimes described or interpreted by isoboles.

Potentiation

Potentiation refers to the enhancement of the effects of one drug by another, but is usually used when the two drugs have dissimilar actions (e.g. cocaine potentiates the effects of noradrenaline (norepinephrine) on blood pressure). ◆

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Enzymes

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Enzymes are catalytic proteins that mediate almost all biochem-ical reactions in humans. The term enzyme means 'in leaven', and enzymes in yeasts and moulds have been used in the preparation of bread and cheese and the fermentation of wine for several millennia.

Enzymes (E) combine with substrates (S) forming an enzyme–substrate complex. The binding of the substrate is often stereoselective, and its structure is strained by high-energy intermolecular forces. Consequently, its bonds are easily broken, resulting in the formation of an enzyme–product complex and reaction products (P):

$$E + S \leftrightarrow E - S \rightarrow E - P \rightarrow E + P$$

Enzyme activity may depend on non-protein factors (co-enzymes); these may be ions or simple organic compounds. Many water-soluble vitamins are co-enzymes in biochemical reactions.

Enzymes and drug action

Receptor activation
When drugs combine with receptors, they often indirectly affect the activity of intracellular enzymes, including:
- adenylyl cyclase
- guanylyl cyclase
- phospholipase C
- protein kinase A.

Many receptors that control cellular growth and differentiation are inherent protein kinases and phosphorylate membrane proteins.

Enzyme inhibition
Drugs may also directly affect enzymes and modify their activity; they are often chemical analogues of endogenous substrates. Enzyme inhibition may be the main mechanism of drug action (Figure 1). Drugs may inhibit enzymes by reversible inhibition, irreversible inhibition or lethal synthesis.

Reversible inhibition is usually competitive. Drugs compete with natural substrates for enzymes, resulting in the formation of a reversible enzyme–inhibitor complex (both *in vitro* and *in vivo*). Edrophonium is a reversible inhibitor of acetylcholinesterase; its quaternary group forms an ionic bond with the enzyme, which readily dissociates when the plasma concentration falls. Consequently, its effects are usually transient.

Drugs that act by enzyme inhibition

Drug	Inhibited enzyme
• Allopurinol	Xanthine oxidase
• Aminophylline	Phosphodiesterase
• Aspirin	Cyclo-oxygenase
• Captopril	Angiotensin-converting enzyme
• Disulfiram	Aldehyde dehydrogenase
• Methotrexate	Dihydrofolate reductase
• Neostigmine	Acetylcholinesterase
• Phenelzine	Monoamine oxidase
• Warfarin	Epoxide reductase

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Irreversible inhibition usually involves the formation of a stable chemical bond between an inhibitor and the enzyme. Regeneration of the inhibited enzyme is impossible; a latent period is required for enzyme resynthesis before normal function is restored. Irreversible enzyme inhibitors (e.g. methotrexate, most monoamine oxidase inhibitors) have a prolonged duration of action.

Inhibition by lethal synthesis: drugs are sometimes converted to metabolites that interfere with normal biochemical pathways. Fluorouracil is metabolized to a nucleotide that cannot be converted to thymidylate; consequently, DNA synthesis is inhibited.

Drug activation
Inactive drugs (pro-drugs) may have to be metabolized to active derivatives (e.g. enalapril). Some drugs (e.g. paracetamol) may be converted to toxic metabolites.

Enzymes and drug elimination

Most drugs are relatively lipid soluble, and are metabolized to less active, water-soluble derivatives before they are eliminated. Hepatic enzyme systems play the predominant role in drug metabolism, though some drugs are partly or completely degraded at other sites:
- plasma (e.g. suxamethonium, remifentanil)
- intestine (e.g. morphine, salbutamol)
- kidney (e.g. midazolam, dopamine)
- lung (e.g. angiotensin I).

Hepatic metabolism
The reactions mediated by hepatic enzymes are divided into:
- phase I reactions (functionalization reactions)
- phase II reactions (conjugation reactions).

Phase I reactions usually result in drug oxidation, reduction, or hydrolysis. Phase II reactions involve the conjugation of phase I metabolites or unchanged drugs with other chemical groups (e.g. glucuronides). Some drugs (e.g. oxazepam) are entirely metabolized by phase II reactions. Both phase I and phase II reactions generally increase the water solubility of drugs and facilitate their renal elimination.

Phase I reactions
Phase I reactions are carried out by the smooth endoplasmic reticulum or 'microsomes'. A non-specific enzyme system (cytochrome P450) is responsible for most drug oxidation and reduction and some hydrolytic reactions. Cytochrome P450 consists of many different forms of a superfamily of genetically related haemoproteins. During drug oxidation, the oxidized (Fe^{3+}) form of cytochrome P450 combines with the target drug. The resultant complex is then reduced by cytochrome P450 reductase and reacts with molecular oxygen. Finally, the oxidized drug is released and cytochrome P450 is regenerated. The enzyme system may also mediate reductive metabolism in hypoxic conditions (e.g. halothane), and the hydrolysis of some esters and amides (e.g. pethidine).

Cytochrome P450 isoforms: there are many genetically distinct forms of cytochrome P450 in human tissues. Three gene families (*CYP 1, CYP 2* and *CYP 3*) contain numerous enzyme isoforms and encode more than 70% of hepatic cytochrome P450. Seven distinct isoforms are mainly responsible for drug metabolism in humans (Figure 2). Individual hepatic isoforms have different but overlapping substrate specificities, and metabolize drugs at different rates; they are variably expressed in other tissues and differ in their susceptibility to enzyme induction and inhibition. Some enzyme isoforms (CYP 2C18 and CYP 2D6) are subject to genetic polymorphism. The different isoforms of cytochrome P450 are partly responsible for inter-individual differences in drug metabolism, and are an important cause of variability in drug response.

The main isoforms of cytochrome P450 involved in drug metabolism

Enzyme isoform	Typical substrate	Inducing agents
• CYP 1A1	Theophylline	Polycyclic hydrocarbons
• CYP 1A2	Erythromycin	Phenobarbital (phenobarbitone) Phenytoin
• CYP 2C9	Phenytoin	Rifampicin; carbamazepine
• CYP 2C19	Diazepam	Phenobarbital (phenobarbitone)
• CYP 2D6	Codeine	?
• CYP 2E1	Fluorinated anaesthetics	Phenobarbital (phenobarbitone) Ethanol
• CYP 3A4	Midazolam	Phenobarbital (phenobarbitone) Glucocorticoids

2

Induction of cytochrome P450: the synthesis and activity of some isoforms of cytochrome P450 can be selectively increased by other drugs (Figure 2); enzyme induction commonly occurs within several days. Activity of CYP 1A2 is induced by barbiturates, phenytoin, and polycyclic hydrocarbons in meat and tobacco smoke; enzyme induction may also increase liver weight and biliary secretion. CYP 2E1, responsible for the defluorination of many inhalational agents, is induced by ethanol and phenobarbital (phenobarbitone) as well as by fasting, obesity and diabetes. CYP 3A4 is induced by many agents, including glucocorticoids, some antibiotics and phenobarbital (phenobarbitone). Many drugs that induce cytochrome P450 also enhance glucuronyl transferase activity.

Induction and inhibition of cytochrome P450 in humans is often responsible for clinically significant drug interactions.

Inhibition of cytochrome P450: some isoforms of cytochrome P450 are competitively inhibited by other drugs (e.g. CYP 2D6 by quinidine). Certain imidazole derivatives (e.g. ketoconazole, omeprazole, cimetidine, etomidate) non-competitively inhibit certain isoforms (e.g. CYP 3A4) by combining with haem. In addition, some synthetic corticosteroids (e.g. gestodene) are oxidized by CYP 3A4 and combine with it covalently (suicide inhibition). Furafylline affects CYP 1A2 in a similar manner.

Other phase I reactions are independent of cytochrome P450. Dopamine and tyramine are metabolized by mitochondrial monoamine oxidase. Ethyl alcohol is oxidized and chloral hydrate is reduced by alcohol dehydrogenase in the cytoplasm.

Phase II reactions
Phase II reactions (conjugation reactions) usually involve the addition of glucuronide, sulphate, acetyl, or methyl groups to phase I metabolites or unchanged drugs.

Glucuronide conjugation is the most important of these reactions. Glucuronyl transferase catalyses the transfer of glucuronide groups (from uridine diphosphate-glucuronide) to unconjugated compounds. Several endogenous compounds (e.g. bilirubin, thyroxine) as well as many drugs (e.g. chloramphenicol, morphine) are conjugated to glucuronide metabolites, which have a low pK_a and are extremely water soluble.

Sulphate conjugation may occur in the gut wall or the cytoplasm of the liver cell. It is involved in the metabolism of chloramphenicol and isoprenaline.

Drug acetylation takes place in several tissues (e.g. spleen, lung, liver); its rate and extent is affected by genetic polymorphism. Isoniazid, hydralazine and phenelzine are acetylated by hepatic enzymes.

Methylation plays an important part in the metabolism of catecholamines by catechol-o-methyltransferase.

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Factors Affecting Drug Absorption and Distribution

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The bulk transfer of drugs in the blood stream is little influenced by the chemical nature of the drug. However, most drugs have to cross membranes to exert their pharmacological effect and this occurs by diffusional transfer, the nature of which differs widely depending on the chemical nature of the drug.

The membranes surrounding cells are lipid bilayers containing proteins (e.g. receptors and carrier molecules) and are intrinsically lipophilic. Drugs can cross the lipid membrane by passive diffusion or carrier-mediated transport, which often involves the expenditure of energy. However, there are aqueous channels through which small water-soluble molecules, such as ethanol, can pass. The ordered nature of the lipid bilayer makes it impossible for these aqueous channels to be wide enough to admit drug molecules larger than about 0.4 nm. A few large molecules, such as insulin, transfer across the membrane by a process known as pinocytosis in which the cell membrane invaginates to make a vesicle round the extracellular molecule and transports it into the cell or out of the other side.

In order for a drug to pass from the extracellular to the intracellular space it has to cross one cell membrane. However, for a drug to pass from the lumen of the gut into the systemic circulation it has to cross the epithelial barrier of the intestinal mucosa, a tightly connected layer of cells, which means that two cell membranes have to be crossed. Vascular epith-elium, which drugs have to cross to reach the internal organs of the body, is more complex and is discussed later in this article.

Diffusion through lipids

If the electronic charge is evenly distributed over the whole molecule the compound is non-polar and diffuses freely into lipids and crosses membranes easily. Thus, lipid solubility, or the partition coefficient between the aqueous environment and the lipid phase of the membrane, is one of the most important predictors of how well a drug is absorbed orally and how well it penetrates the various body tissues.

Anaesthetics are highly lipid soluble and are rapidly absorbed if given orally, though they are seldom given by this route. However, the author remembers a study in which she was given 10 times the anaesthetic dose orally of *Althesin*, a steroidal anaesthetic combination now withdrawn from human use. It tasted like paint stripper and luckily was metabolized rapidly by the liver before it entered the circulation. The point of the experiment was to study the extent of first-pass metabolism of the drug. The lipid solubility of intravenous anaesthetics ensures that their distribution from blood to brain is rapid and that they are extensively metabolized by the liver.

Large, very polar molecules such as the aminoglycoside antibiotics, which carry a basic charge, are effectively excluded from crossing membranes. They are not absorbed orally and, if injected, remain in the extracellular fluid.

Significant proportions of drugs are weak acids or bases and thus the ratio of the lipid-soluble non-ionized molecule to the ionized molecule depends on the pH of the environment. The pH of some body fluids is shown in Figure 1.

Normal pH range of some body fluids

Cerebrospinal fluid	7.3
Gastric juice	1.0–3.0
Large and small intestine (ileum)	8.0
Plasma	7.4
Small intestine (duodenum)	5.0–6.0
Urine	4.0–8.0

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The proportion of a drug that is non-ionized and thus easily passes through membranes, can be calculated from the Henderson–Hasselbalch equation:

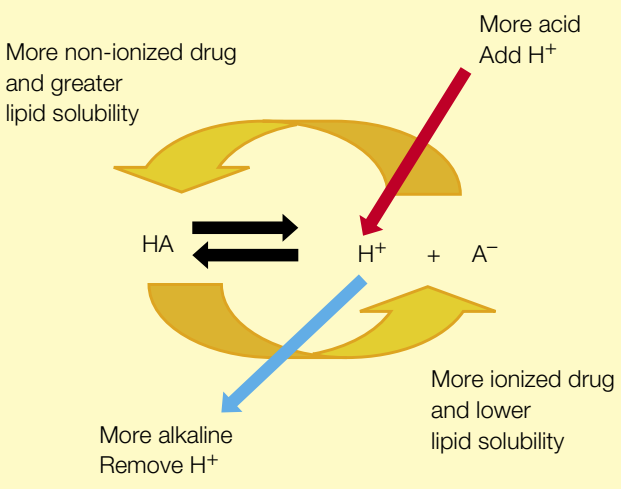
$pH = pKa + \log [A^-]/HA$ (acid form)

$pH = pKa + \log [B]/[BH^+]$ (base form)

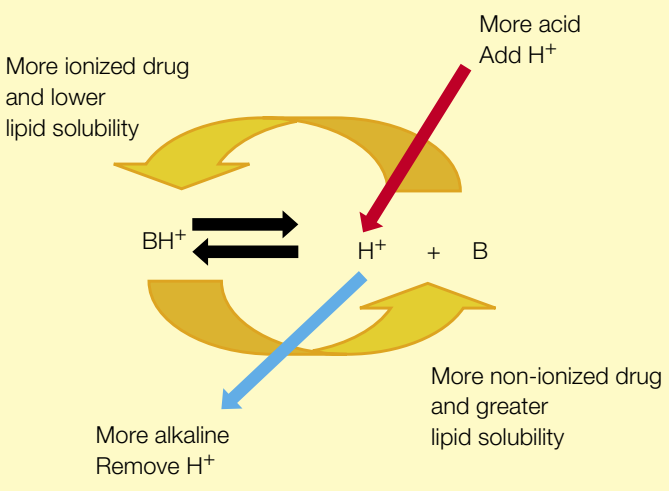
pKa is the negative logarithm of the dissociation constant in the same way that pH is the negative logarithm of the hydrogen ion concentration. From the above equation, pKa is equal to the pH where 50% of the drug is ionized. That is log $[A^-]/HA$ and log $[B]/[BH^+]$ are both log [50%]/[50%] which equals log 1 which antilogs to 0. A simple method of predicting whether a drug will be ionized is shown in Figure 2.

Method of predicting whether a drug will be ionized

Weak acid (e.g. aspirin)



Weak base (e.g. amphetamine)



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For a weak acid, an acid environment such as is found in the stomach or in acid urine, favours the passage of drug across membranes. Therefore a weak acid is absorbed more rapidly in the stomach than in the intestine. However, the increased absorptive area of the small intestine means that the largest total quantity of a weak acid is absorbed from the intestine rather than from the stomach. Similarly, a weak acid is more readily reabsorbed from acid urine than from alkaline urine. Thus, acid urine promotes the retention of a weak acid in the body and alkaline urine promotes its excretion in the urine. The opposite applies to a weak base, a fact known to amphetamine addicts who take sodium bicarbonate to alkalinize the urine in order to retain the drug for longer in the body.

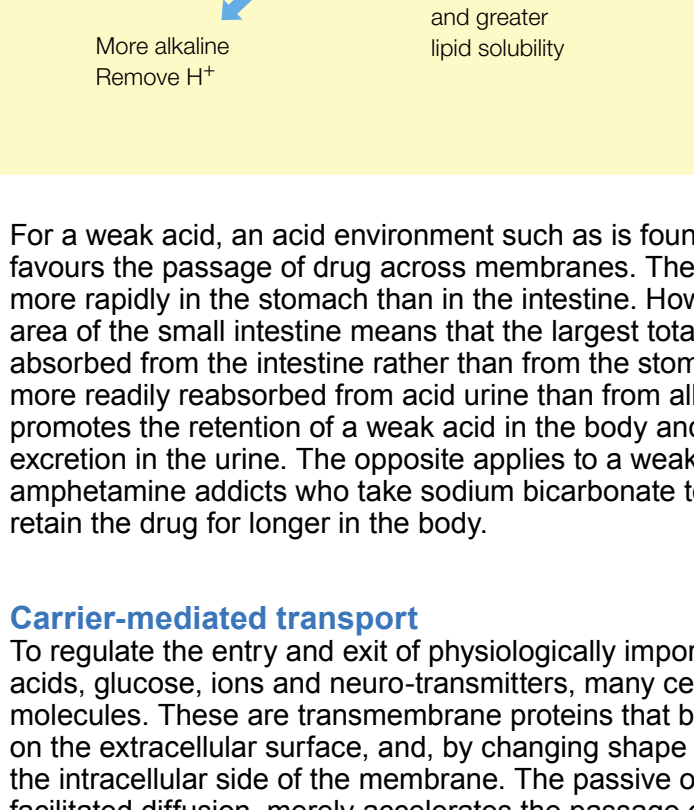
Carrier-mediated transport

To regulate the entry and exit of physiologically important molecules such as amino acids, glucose, ions and neuro-transmitters, many cell membranes contain carrier molecules. These are transmembrane proteins that bind to the desired molecule on the extracellular surface, and, by changing shape can deposit the molecule on the intracellular side of the membrane. The passive operation of such a system, facilitated diffusion, merely accelerates the passage of the molecule in the direction of its electrochemical gradient, and does not involve the expenditure of energy. Active transport using an energy source such as the hydrolysis of adenosine triphos-phate (ATP) can move a molecule against its electrochemical or concentration gradient. If a drug structurally resembles a substrate for a carrier protein it can cross a membrane using this mechanism; examples are methyldopa, levodopa and thyroxine.

Bioavailability

Bioavailability is the fraction of the ingested dose of a drug that reaches the systemic circulation. A drug injected into the blood stream is considered to have a bioavailability of 100% and the bioavailability of a drug by any other route is usually compared with this value. Practically, the area under the plasma concentration time curve for the drug is measured when the drug is given intravenously and via an alternative route such as orally (Figure 3). The two values are compared and the oral plasma concentration time curve is expressed as a percentage of the intravenous plasma concentration time curve. Reasons for low oral bioavailability are suggested in Figure 4. The concept of bioavailability does not consider the peak concentration of the drug or the time taken to reach that peak and is thus of limited value when comparing formulations of a single drug (see below). Thus the term bioequivalence, where there is evidence that similar pharmacological responses are obtained, is more useful.

Determining the percentage oral bioavailability



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Binding of drugs to plasma proteins

Many drugs bind to plasma proteins so that only a fraction of the drug is free in the plasma and capable of producing pharmacological effects. Most commonly, drugs bind to albumin but some, such as quinine, bind to β-globulin and acid glycoproteins. Acidic drugs such as warfarin and non-steroidal anti-inflammatory drugs (NSAIDs) have a high affinity for the binding sites of plasma albumin, but some basic drugs such as the antidepressants are also bound.

Most drugs are pharmacologically active at concentrations that do not saturate plasma protein binding sites and thus the fraction of drug bound is independent of the drug concentration. However, the binding sites of a few drugs, such as tolbutamide and some of the sulphonamides, are almost saturated at therapeutic concentrations and thus the addition of more drug increases the concentration of free drug by a much greater amount than might have been expected.

Possible reasons for low oral bioavailability

- Drug has low lipid solubility (highly ionized) (e.g. vecuronium, streptomycin)
- Drug is broken down by the acid medium of the stomach (e.g. benzylpenicillin)
- Drug is metabolized by enzymes in the gut wall (e.g. tyramine in food)
- Drug is metabolized in the liver before entering the systemic circulation (e.g. lidocaine (lignocaine), morphine)

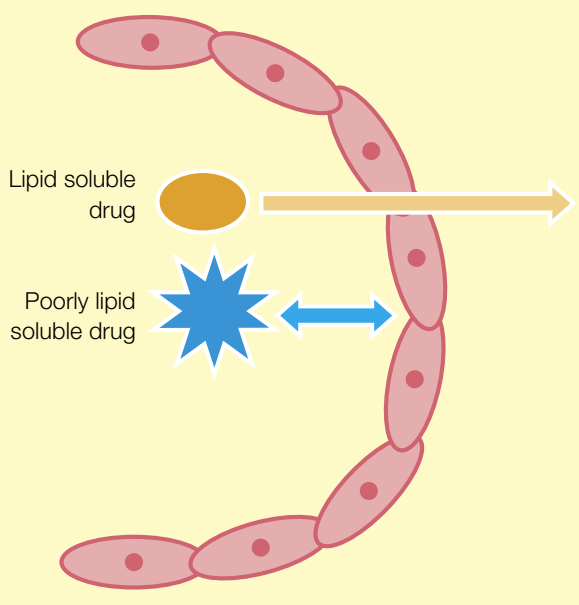
4

Because many drugs have affinity for albumin binding sites, competition between them was thought to be an important site of drug interaction. However, it is now considered to be a minor problem in most cases.

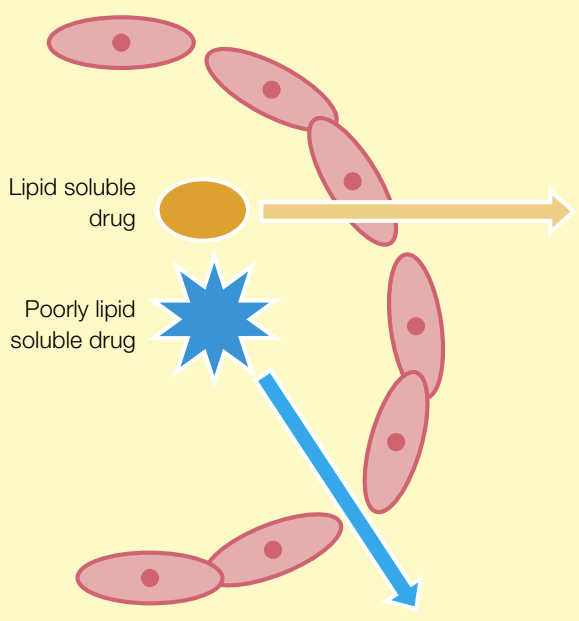
Blood–brain barrier
In most areas of the body, there are gaps or fenestrations between the cells of the vascular endothelium which are packed with a mass of proteins that act as a filter to the passage of molecules. Large molecules are retained while small molecules pass through readily. However, in the brain (and the placenta) there are tight junctions between the cells that allow the passage only of molecules that can pass through the cells. Thus, drugs with low lipid solubility are effectively excluded from the brain (Figure 5). This includes some antibiotics and anti-cancer drugs.

Passage of drugs through capillaries

Most brain capillaries



Non-brain capillaries and those near the chemosensitive trigger zone



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The blood–brain barrier can be used to exclude a drug action from the brain for therapeutic benefit. For example, levodopa is used to treat Parkinson's disease, a deficiency of dopamine in the basal ganglia, but it is metabolized to dopamine in the periphery as well as in the CNS where it exerts unwanted cardiovascular and emetic action. When it is combined with a dopa decarboxylase inhibitor that cannot cross the blood–brain barrier (e.g. benserazide or carbidopa) a lower dose of levodopa can be used and the incidence of adverse effects reduced. Emesis induced by dopamine occurs at the chemosensitive trigger zone (CTZ) which, although within the brain, is surrounded by a leaky area of the blood–brain barrier. This enables the CTZ to respond to blood-borne emetic substances. During inflammation the blood–brain barrier can be disrupted and this accounts for the successful use of systemic penicillin for the treatment of meningitis.

Volume of distribution
The volume of distribution is calculated from the total quantity of drug in the body, divided by the concentration in the plasma. Thus, it is the volume occupied by the drug if the concentration throughout the body was the same as in the plasma. It does not identify closely with any real anatomical compartment. Some drugs, such as heparin, are so large that they cannot cross the capillary wall and are retained in the plasma compartment (0.05 litre/kg). Others, such as the neuromuscular blocking agents are polar and cannot penetrate cells. Their distribution is limited to extracellular fluids and their volume of distribution is in the region of extracellular fluid volume (0.2 litre/kg). Similarly, they are unlikely to cross the blood–brain or the placental barriers. Drugs such as ethanol are distributed in the total body water (0.55 litre/kg) because they penetrate readily into cells. However, if a drug binds outside the plasma compartment (e.g. digoxin) or partitions into fat (e.g. the anaesthetics) then distribution volumes are much greater than total body water.

Drug delivery systems

Absorption and transport of a drug to its receptor site in the body is part of optimal drug therapy. While the ease of oral administration makes it the best route in many cases, some patients require alternative routes because of bowel obstruction or emesis. Traditional oral or even parenteral administration may not achieve the maintenance of adequate concentrations of drug at the receptor for as long as it is needed and rapid removal of the drug when its effect is no longer required. The oral route is complicated by metabolism of the drug in the gut or liver, resulting in low systemic bioavailability.

Modern biopharmaceutical technology has also produced some delivery systems that allow precise control of drug input into the body by more unorthodox routes.

Topical and transdermal systems
Transdermal drug delivery refers to the delivery of a drug into the systemic circulation across intact healthy skin and a number of novel systems have been described. These can be distinguished from classical topical application formulations in that the latter are generally applied to broken, diseased or damaged skin. Even morphine has been used topically as an infused gel dressing in the treatment of painful skin ulcers. However, the topical application requires an occlusive dressing to prevent the drug being lost by leakage or absorption on to clothes or dressings.

One drug group that is an exception to the rule that topical applications are useful only if the skin is damaged is the NSAIDs. These preparations are widely advertised for acute and chronic painful conditions. Although there has been some scepticism whether topical NSAIDs have any action other than as rubefacients, a detailed analysis of randomized controlled trials of topical NSAIDs found that the preparations were more effective than placebo and that in general the side-effects were less than when bioequivalent doses were given orally.

The advantages of transdermal delivery of drugs are that gastrointestinal absorption and first-pass metabolism in the liver are avoided, thus increasing bioavailability. It is convenient and painless and provides sustained serum concentrations without peaks and troughs. In healthy skin the outermost layer, stratum corneum, is thick, avascular, lipophilic and keratinized and serves as a barrier to the intrusion of most chemicals. Below this are the more aqueous epidermis and dermis, which are the main sites of uptake of drugs that have penetrated the skin into the systemic circulation. In view of this, in order to be suitable for transdermal delivery, the drug must possess high lipid solubility, a typical example is glyceryl trinitrate.

Blood flow through the skin varies with temperature and skin permeability varies at different sites. Thus, delivery systems contain a rate-controlling membrane that limits drug release to the skin surface. Transdermal fentanyl, for example, consists of a four-layer patch. The upper layer is impermeable, preventing loss of drug and the entry of foreign substance. The drug reservoir contains fentanyl and alcohol (to enhance absorption) in a gel. Below this is the rate-controlling ethylene vinyl-acetate copolymer and finally a silicone adhesive impregnated with fentanyl enabling rapid absorption of the opioid on patch application. The rate of fentanyl delivered is directly proportional to the size of the patch. However, even with the drug-saturated adhesive layer, the absorption of drug into the systemic circulation is slow during the first 4 hours and steady state is not reliably reached by 24 hours. After removal of the patch there is continuing absorption from a subcutaneous depot, resulting in a very slow fall off in biological activity. These observations, together with doubts concerning the incidence of respiratory depression in unmonitored patients, have curtailed the use of fentanyl for postoperative pain. However, transdermal fentanyl has some advantages when used to treat chronic pain.

Nicotine is also well absorbed through the intact skin and nicotine patches are widely used to treat withdrawal symptoms that accompany cessation of smoking tobacco. The limitations of passive transdermal delivery have prompted studies of other means of enhancing transdermal drug delivery. Iontophoresis, in which ions of soluble salts are introduced across the skin or a mucosal surface by an electric current, provides a rapid rise in the systemic concentration of drug. Although the cost and size of the iontophoretic device may limit its usefulness, an iontophoretic 'on-demand' pain management system for fentanyl (E-TRANS) is undergoing trials.

Oral transmucosal administration
A greater range of drugs can be administered using the transmucosal route while retaining many of the advantages of transdermal applications. Drugs are usually supplied as a tablet, lozenge or lollipop and allowed to dissolve in the saliva either under the tongue (sublingual) or in the cheek (buccal). Unlike skin application, depots of drug do not form by this route and the drug can be removed from the mouth to terminate activity.

Fentanyl and buprenorphine, being lipid soluble, are particularly well absorbed by the sublingual route, while morphine is poorly absorbed and this contributes to the inconsistent efficacy of morphine give sublingually or buccally. Fentanyl lollipops, a sweetened lozenge on a stick, are currently marketed for premedication in children and for breakthrough pain in patients with chronic pain. Sublingual glyceryl trinitrate is used to treat angina thus avoiding first-pass metabolism in the liver.

Inhalational administration
Gaseous and volatile agents such as the inhalational anaesthetics are administered and eliminated from the body through the lungs. The lungs have a large surface area and a high blood flow such that rapid changes in drug concentration can be achieved. The speed at which equilibrium is reached between alveolar air and the blood is fastest if the gas or vapour is relatively insoluble in blood or tissue. Thus, nitrous oxide has a fast onset and offset of effects while diethyl ether is relatively slow. Some drugs intended to act locally in the lungs are also given by inhalation: for example β_2-adrenoceptor agonists (e.g. salbutamol) for the treatment of asthma. This limits the adverse systemic effects of the drug. However, some systemic side-effects still occur because some drug is absorbed into the systemic circulation.

Extradural administration
Drugs, particularly local anaesthetics and opioids, may be administered into the area between the dura mater of the spinal cord and the periosteum lining the vertebral canal. This epidural space is filled with blood vessels, lymphatics and adipose tissue, and drugs can penetrate rapidly into the dural root sleeves close to the dorsal root ganglia. Arachnoid villi may penetrate through gaps in the dura into the extradural space aiding penetration of drugs into the nerve root across the thin arachnoid membrane. The extent and duration of the effects of drug administered by this route depend on the concentration of the drug and the volume injected. Some uptake of drug into the spinal cord also occurs.

Pregnant women may be more susceptible to extradural administered drugs because the peridural venous plexus is extended owing to compression of the vena cava by the uterus and baby. This can reduce the potential epidural space, requiring a reduction of dose. ◆

FURTHER READING
Nimmo W S. The Promise of Transdermal Drug Delivery. Br J Anaesth 1990; 64: 7–10.

Gastric Disorders

Barbara J Pleuvry

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Peptic ulceration (duodenal and gastric) affects 10% of the population at some time and most people have suffered from indigestion, dyspepsia or heartburn, many times. The causes include overindulgence, poor cooking, anxiety and the side-effects of non-steroidal anti-inflammatory drugs (NSAIDs). *Helicobacter pylori* also has an important role in ulcer formation.

Control of gastric acidity

The function of the stomach is to store ingested food and present it to the small intestine as a premixed, predigested chyme (juice). To achieve this, the stomach contains three layers of muscle for efficient mixing of food and secretes 2–3 litres/day of gastric juice from the gastric glands. The composition of gastric gland secretions is shown in Figure 1.

Secretions of the gastric glands

Secretion	Function	Originating cells	Site
Gastric lipase	Digests fat in infants	Chief cells	Near base of gastric glands
Gastrin	Stimulates HCl and enzyme secretion and stimulates gastric motility. Acts on a gastrin (cholecystokinin-B) receptor	Enteroendocrine cells	At the base of the pyloric glands Reaches site of action in the blood
Histamine	Stimulates HCl secretion Acts on histamine H_2-receptors	Enteroendocrine cells (mast cell like)	Close to parietal cells in gastric gland Diffuses to site of action
Hydrochloric (HCl)	Destroys pathogens, activates pepsin and lipase, reduces iron to useable Fe^{2+}	Parietal cells	Top half of acid gastric glands and some in the pyloric glands
Intrinsic factor	Enables absorption of vitamin B_{12}	Parietal cells	Top half of gastric glands and some in the pyloric glands
Mucus	Protects mucosa from HCl and enzymes	Mucosal cells	Surface of the mucosa and in the neck of the gastric glands
Pepsinogen	Converted to pepsin which digests proteins	Chief cells	Near base of gastric glands
Renin	Coagulates milk protein in the infant	Chief cells	Near base of gastric glands
Serotonin	Stimulates gastric motility	Enteroendocrine cells	At the base of the gastric gland
Somatostatin	Inhibits gastric, bile and pancreatic secretion and inhibits gastric motility	Enteroendocrine cells	At the base of the gastric gland

1

Peptic ulceration and gastro-oesophageal reflux disease are common pathological conditions associated with high gastric acid concentrations and reflux of stomach acid into the oesophagus, respectively. Drugs that reduce gastric acidity are effective treatment for these conditions. In women undergoing caesarean section, significant morbidity and mortality is associated with the aspiration of gastric contents and it is recommended that they receive antacid prophylaxis before surgery.

Antacids

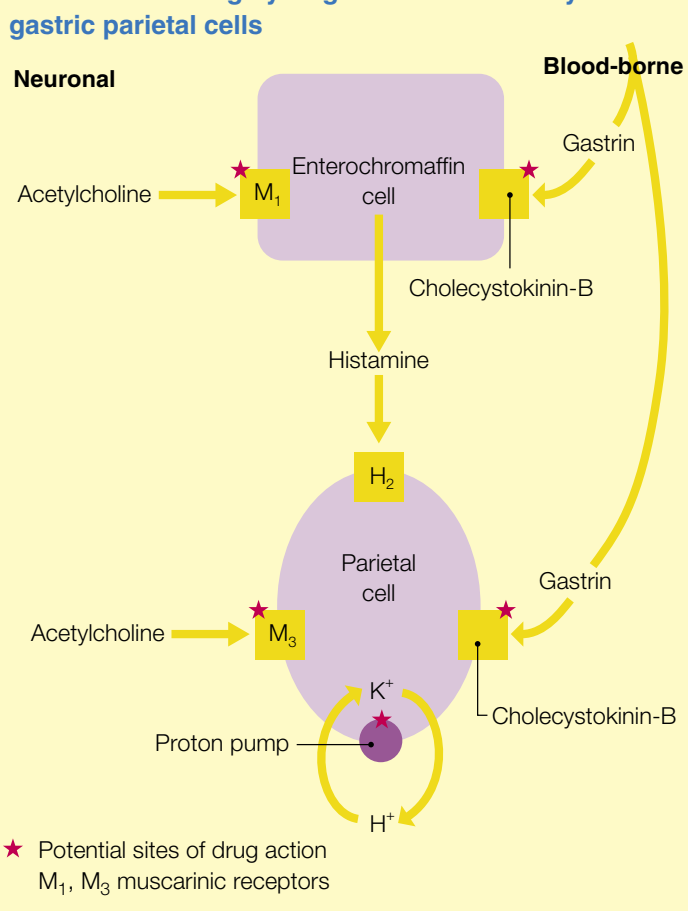
The easiest way of decreasing gastric acidity is to neutralize it with a weak base because most peptic activity ceases above a pH of 4–5. Many over-the-counter indigestion treatments contain aluminium hydroxide, magnesium hydroxide or magnesium trisilicate. In general, liquid preparations are more effective than tablets. Although magnesium- or aluminium-based preparations may enhance duodenal ulcer healing they are less effective than the other acid-reducing strategies described below. It has been suggested that antacids also increase the production of protective prostaglandins and combine with noxious substances in the stomach. The role of these additional properties is unclear. Aluminium-containing preparations are associated with constipation while magnesium-based preparations may induce diarrhoea. Both sodium bicarbonate and calcium salts may be effective for a short time, but both induce a rebound increase in acid secretion that has caused them both to fall out of favour. For antacid prophylaxis before caesarean section, a non-particulate antacid is desirable and sodium citrate is used routinely. Antacids may be combined with each other (to no obvious clinical benefit) or with an antifoaming agent (e.g. simethicone) which may be of particular use in the treatment of hiccup. Alginates may also be added, which produce a raft on top of the gastric contents and may help to protect the oesophagus in heartburn.

Drugs reducing the release of gastric acid

Factors facilitating proton release from the parietal cells are summarized in Figure 2. Vagal stimulation causes the release of acetylcholine which acts on muscarinic (M_1) receptors on the enterochromaffin-like cells to cause a release of histamine and directly on muscarinic (M_3) receptors on the parietal cell. Some textbooks suggest that M_2-receptors instead of M_3-receptors may be involved. Histamine may also be released from the entero-chromaffin-like cells by gastrin acting on the gastrin or cholecystokinin-B (CCK-B) receptor. It may also act directly on the parietal cell, presumably on another CCK-B receptor, because proglumide, a CCK-B receptor antagonist, prevents its action. Histamine, acting on H_2-receptors on the parietal cell, causes the release of hydrogen ions via H^+/K^+-ATPase (the proton pump). This is associated with the extrusion of chloride ions by a potassium/chloride symporter that is not shown in Figure 2.

Thus, drugs with inhibitory effects at four sites have the potential for reducing gastric acid secretion (Figure 2). Muscarinic antagonist drugs are seldom used to reduce gastric acid secretion mainly because of the extensive side-effects caused by blockade of other muscarinic receptors leading to blurred vision and dry mouth. Pirenzapine, a selective M_1-receptor antagonist, causes fewer side-effects than non-selective muscarinic antagonists, and can reduce gastric acid secretion by over 40%. The exact site of this action is uncertain but M_1-receptors are believed to be present in parasympathetic ganglia and their antagonism prevents post-synaptic vagal stimulation of the parietal cell. However, it is less effective than the other treatments mentioned below and is of only historical interest.

Factors facilitating hydrogen ion secretion by gastric parietal cells



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Histamine H_2-antagonists (e.g. cimetidine, ranitidine) are available over the counter and are used in the treatment of peptic ulcers and reflux oesophagitis. They are capable of reducing basal and food-stimulated gastric acid by 90%. They have also been used to reduce gastric acidity before caesarean section.

Proton-pump inhibitors (Figure 3) are prodrugs that are stable at neutral pH, lipid soluble and devoid of pharmacological activity. They are weak bases that accumulate in the acidic secretory canaliculi of the parietal cells, where they are activated by a proton-catalysed process to produce thiophilic silfenamide and sulfenic acid. They bind covalently with the sulfhydryl groups of the cysteines situated on the extracellular domain of H^+/K^+-ATPase. Binding to cysteine 813 is essential for irreversible inhibition of the proton pump. Proton-pump inhibitors are not acid stable therefore they have to be enteric coated so that they are dispersed and absorbed at alkaline pH. Although their plasma elimination half-life is relatively short (1–2 hours), the irreversible nature of their action means that once daily administration is adequate. Proton-pump inhibitors promote the healing of peptic ulcers to a greater extent than H_2-receptor antagonists and they are also suitable for reducing gastric acidity before caesarean section. Proton-pump inhibitors in combination with an antibiotic such as amoxicillin (amoxycillin), clarithromycin or metronid-azole are recommended for the eradication of *H. pylori*. The drugs used clinically to reduce gastric secretion are listed in Figure 3.

Drugs used clinically to reduce gastric acid secretion

Drug group	Comment
H_2-receptor antagonists	
Cimetidine	Inhibits drug metabolism and has some affinity for androgen receptors where it is an antagonist
Famotidine Nizatidine Ranitidine	These agents have less effect on drug-metabolizing enzymes and androgen receptors
Proton-pump inhibitors	
Omeprazole	Also used for Zollinger–Ellison syndrome
Esomeprazole Lansoprazole	Also used for Zollinger–Ellison syndrome
Pantoprazole	More acid stable than others
Rabeprazole	

3

Negative influences on the release of gastric acid include somatostatin acting on the ST_2-receptor and prostaglandin E_2 acting on the EP-receptor. There have been some preliminary trials of octreotide, a long-acting somatostatin analogue in Zollinger–Ellison syndrome, a pancreatic tumour that secretes gastrin. However, the drug must be given parenterally, so it is of limited use in its present form. Misoprostol is a stable analogue of prostaglandin E_1 that has been used to reduce the gastric damage caused by chronic NSAID administration. Side-effects include diarrhoea, abdominal cramps and uterine contraction.

Mucosal protective agents

Once acid-induced gastric damage has occurred, pepsin can cause the hydrolysis of mucosal proteins, which contributes to mucosal erosion and ulceration. This process can be inhibited by sulfated polysaccharides such as sucralfate, which is an octasulfate of sucrose complexed with aluminium hydroxide. In the presence of acid, sucralfate crosslinks and polymerizes to produce a viscous sticky gel that adheres to epithelial cells, particularly ulcer craters. This protects the surface from further damage by acid, pepsin or bile salts. Sucralfate also binds to bile salts and stimulates the production of prostaglandins and epidermal growth factor. Both of these properties may contribute to ulcer healing. Sucralfate is also used in the prophylaxis of stress ulcers in ICUs. The main side-effect of sucralfate is constipation and it may inhibit the absorption of other drugs such as cimetidine and phenytoin.

Other compounds thought to provide a protective coat over ulcer craters are the colloidal bismuth compounds, bismuth subcitrate and tripotassium dicitratobismuthate. Bismuth compounds are also thought to inhibit pepsin activity and increase prostaglandin and mucus production. There is some evidence that they have a toxic effect on *H. pylori*, but they are usually used in combination with antibiotics. Ranitidine bismuth citrate is a recommended alternative to proton-pump inhibitors for the eradication of *H. pyl*ori.

Carbenoxolone is mainly of historical interest. It is a derivative of glycyrrhizic acid (found in liquorice root) and is thought to increase the quantity and viscosity of mucus in the stomach, thus enhancing the mucosal barrier. However, it has significant mineralocorticoid activity, which limits its usefulness. In addition, its ulcer-healing properties are no better than those of the H_2-receptor antagonists discussed above.

Controlling gastrointestinal motility

Prokinetic drugs

Gastrointestinal motility is stimulated by activation of the parasympathetic nervous system that releases acetylcholine onto muscarinic receptors. Thus, muscarinic agonists (e.g. bethanicol) and anticholinesterase agents (e.g. pyridostigmine, neostigmine, distigmine) can increase intestinal activity and have been used to treat paralytic ileus. However, parasympathetic effects such as bradycardia and sweating limit their usefulness.

More selective pro-kinetic drugs include metoclopramide and cisapride, both of which are agonist at 5-HT_4-receptors. Cisapride is the more selective of the two and can be used for treating reflux oesophagitis, usually in combination with a H_2-receptor antagonist. The actions of cisapride are to increase the lower oesophageal sphincter pressure, increase gastric emptying and possibly improve oesophageal peristalsis. However, a recent report of serious cardiac arrhythmias occurring in patients given this drug have caused a re-evaluation. Metoclopramide has several mechanisms of action that contribute to its prokinetic effects. As a 5-HT_4-agonist it stimulates excitatory neurons, suppression of inhibitory neuron activity is brought about by 5-hydroxy-tryptamine (5-HT_3)-receptor antagonism (which occurs only at high doses) and peripheral dopamine (D_2)-receptor blockade reduces the inhibitory action of dopamine on cholinergic neur-ons in the gastrointestinal tract. Metoclopramide has additional anti-emetic activity owing to central D_2-receptor antagonism and 5-HT_3-antagonist activity. Both domperidone and ondansetron also possess some moderate prokinetic activity because of their peripheral D_2- and 5-HT_3-antagonist activity, respectively.

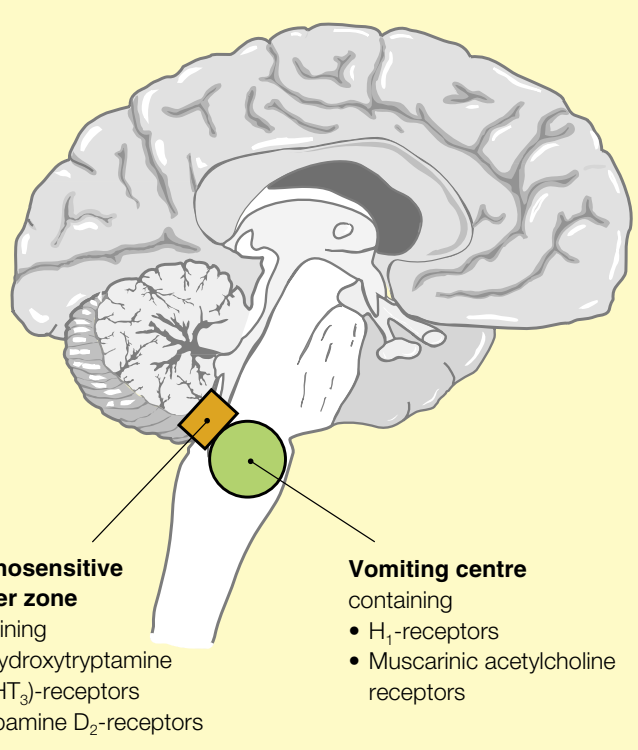
Erythromycin also has some prokinetic properties because it increases lower oesophageal sphincter pressure and increases gastric and small bowel, but not colonic, activity. It is thought to act on the motilin receptor. Motilin is a gastrointestinal tract hormone that participates in the initiation of motor responses that propel food through the stomach and the intestine.

Controlling vomiting

Emetic and anti-emetic drugs

The anatomy and physiology of vomiting and anti-emetic drugs is discussed elsewhere. Briefly, the two main parts of the brain involved in vomiting are the chemoreceptor trigger zone in the area postrema on the floor of the fourth ventricle and the vomiting centre in the medulla (Figure 4). Activation of D_2-receptors and/or 5-HT_3-receptors are responsible for activating vomiting at the chemoreceptor trigger zone and histamine H_1-receptors and muscarinic receptors for acetylcholine activate the vomiting centre. The principal anti-emetic drugs are antagonists at these receptors (Figure 5). Anti-emetic drugs may be used to treat postoperative nausea and vomiting (PONV), chemotherapy-induced vomiting, vomiting due to vestibular disturbance, including motion sickness and vomiting in pregnancy. However, therapy is not advised during the first trimester and subsequent use should be limited to severe vomiting.

Vomiting centre in the medulla



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Anti-emetic drugs

Pharmacological action	Comments
Dopamine antagonists	
Chlorpromazine Perphenazine Prochloperazine Trifluoperazine	All may cause dystonic reactions due to dopamine receptor antagonism in the nigrostriatal tract May also block H_1 and ACh M receptors. Chlorpromazine is more sedative than the rest
Metoclopramide	Similar profile to above, but it is also prokinetic and in high doses is a 5-HT_3 antagonist
Domperidone	Penetrates the CNS poorly so is less likely to produce dystonic reactions. Only useful for moderately emetogenic chemotherapy
5-HT_3 antagonists	
Granisetron Ondanseton Tropisetron	They have both peripheral and central actions. Used for chemotherapy induced emesis and postoperative nausea and vomiting
Antihistamines (Histamine H_1-receptor antagonists)	
Cinnarizine Cyclizine Meclozine Promethazine	Mainly used for vestibular disorders. They are effective in emesis from other causes but are not usually the drug of choice. Drowsiness is the most significant side-effect together with antimuscarinic actions like dry mouth
Muscarinic acetylcholine receptor antagonists (ACh M)	
Hyoscine	Typical antimuscarinic action (e.g. blurred vision, dry mouth)

5

Opioid receptors are also present on the chemoreceptor trigger zone and are responsible for the emetic actions of opioid analgesics. It has been suggested that endogenous opioid peptides have a role in vomiting via δ receptors at the chemoreceptor trigger zone and μ receptors at the vomiting centre. Nitrous oxide is believed to release endogenous opioids. Some recent studies have suggested that when nitrous oxide is used as part of an anaesthetic regimen there is a significantly higher incidence of PONV and a higher need for anti-emetic drugs than in nitrous oxide free regimens.

In addition, prevention of enkephalin breakdown may be a mechanism by which cytotoxic drugs cause emesis. Stimuli from the pharynx and stomach also induce vomiting, probably via activation of 5-HT_3-receptors on the visceral afferent nerves. Vomiting can be induced by ipecacuanha, which acts as an irritant in the stomach via the action of two constituent alkaloids, cephaeline and emetine. This may be used to stimulate vomiting after oral ingestion of a toxin, provided that it is not corrosive and the patient is fully conscious. Lower doses of ipecacuanha act as an expectorant. Thus, 5-HT_3 antagonists act peripherally and centrally as anti-emetics.

Non-pharmacological techniques used to prevent PONV include acupuncture, electroacupuncture, transcutaneous electric nerve stimulation and acupressure. They are more effective than placebo in adults but not in children. Electrical stimulation of the vestibular system, using a nuchal-positive electrode placed over both mastoid processes also reduces the need for anti-emetic drugs in PONV. ◆

FURTHER READING

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Histamine and Antihistamines

Roger Small

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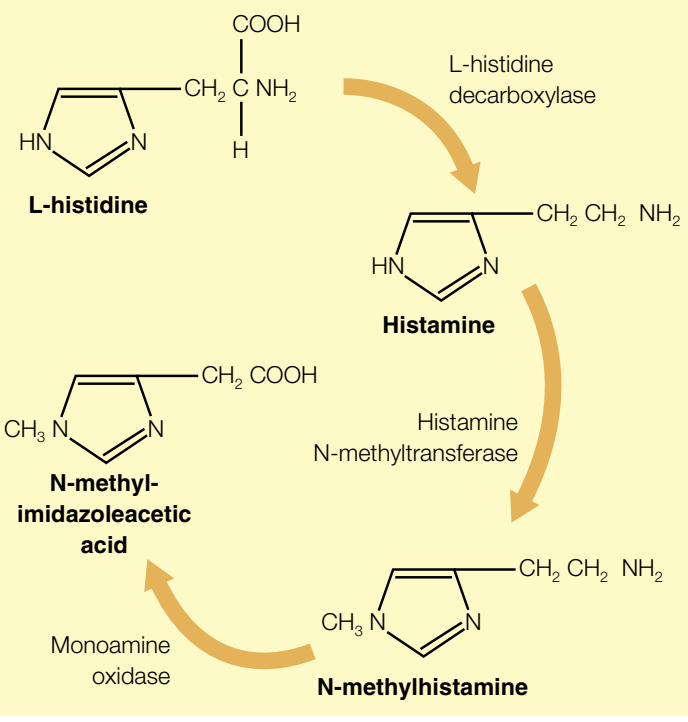
Histamine

Histamine is found in all mammalian tissues. It is formed from histidine by the action of L-histidine decarboxylase. Histamine is metabolized mainly by the actions of histamine-N-methyltransferase and monoamine oxidase (Figure 1).

Biosynthesis and major metabolic pathway for histamine



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Mast cells are the main storage site for histamine. There are high numbers of mast cells in the lung, skin and gastrointestinal mucosa and therefore these tissues contain the highest concentrations of histamine. In the blood, histamine is stored in basophils. Within the mast cells and basophils, histamine is stored as a granular complex with a heparin of high molecular weight and an acidic protein. Other histamine-containing cells include the histaminocytes of the stomach and the histaminergic neurons of the hypothalamus. The axons of the histaminergic neurons run in the medial forebrain bundle to supply large areas of the cortex and midbrain.

Histamine is released from mast cells and basophils during allergic or inflammatory reactions. The interaction of antigen with IgE antibodies anchored to the cell surface triggers a rise in the cytosolic concentration of free calcium ions. This causes exocytosis of the histamine storage granule followed by the release of histamine from the granule by the process of cation exchange. Many agents that are stronger organic bases than hist-amine (e.g. suxamethonium, morphine, radiocontrast media, carbohydrate plasma expanders) can enter mast cells and basophils and directly displace histamine from the storage granules. The actions of histamine are mediated by histamine receptors of the H_1, H_2 and H_3 subtypes. Figure 2 lists the properties of these receptor subtypes and the effects that they mediate.

Histamine receptors and the effects they mediate

Receptor subtype	Selective agonist	Selective antagonist	Location	Effect mediated	Signal transduction process
H_1		Mepyramine Chlorpheniramine Cetirizine Terfenadine	Smooth muscle of gastrointestinal tract and airways	Contraction	G_s modulation of phospholipase C with IP_3 production and Ca^{2+} release from endoplasmic reticulum
			Vascular endothelium Endothelial cells of postcapillary venules	Vasodilatation via NO release Contraction and increased vascular permeability	
H_2	Dimaprit	Cimetidine Ranitidine	Cardiac atria and ventricles	Increased rate and force of contraction	G_s modulation of adenylyl cyclase, with cAMP production, activation of PKA and increase (cardiac and parietal cell stimulation) or decrease (vasodilatation) in $[Ca^{2+}]$
			Vascular smooth muscle	Delayed vasodilatation	
			Gastric parietal cells	HCl secretion	
H_3	(R) α-methyl -histamine	Thioperamide	Histaminergic neurons in hypothalamus	Presynaptic inhibition of transmitter release	G protein mediated inhibition of Ca^{2+} influx

2

Antihistamines

Competitive antagonists at histamine H_1-receptors

Antagonists at H_1-receptors are stable, lipid-soluble amines that have the ethylamine side-chain of histamine. They reversibly inhibit the peripheral effects of histamine, such as contraction of gastrointestinal and airway smooth muscle, stimulation of sensory neuron terminals (itching) and oedema resulting from increased permeability of post-capillary venules. They also reversibly inhibit the more rapid of the two vasodilatory responses to histamine. Competitive antagonists at H_1-receptors are divided into sedating (first-generation) and non-sedating (second-generation) agents (Figure 3). First-generation anti-histamines have effects unrelated to their blockade of H_1-receptors (e.g. sedative, anti-emetic and anticholinergic).

Antagonists at H_1- and H_2-receptors

First-generation (sedating) H_1-antagonists

- Alimemazine (trimeprazine)
- Azatadine
- Brompheniramine
- Chlorphenamine (chlorpheniramine)
- Clemastine
- Cyproheptadine
- Diphenhydramine
- Hydroxyzine
- Triprolidine

- Cinnarizine
- Cyclizine
- Meclozine
- Promethazine

Have antagonist activity at muscarinic acetylcholine receptors. Useful in the control of nausea and vomiting associated with motion, Meniére's disease or gastric irritation

Second-generation (non-sedating) H_1-antagonists

- Acrivastine
- Cetirizine
- Fexofenadine
- Loratidine

- Mizolastine
- Terfenadine

Block cardiac delayed rectifier K^+-channels and may induce hazardous ventricular tachydysrhythmias

H_2-antagonists

- Famotidine
- Nizatidine
- Ranitidine

- Cimetidine

Binds to hepatic cytochrome P450. Beware interference with the metabolism of benzodiazepines, warfarin, phenytoin and theophylline

3

Most drugs from both groups are absorbed rapidly after oral administration. The sedative effects of the first-generation antihistamines depend on their ability to cross the blood–brain barrier. Second generation antihistamines do not cross the blood–brain barrier to any appreciable extent. Most of the sedating and non-sedating antihistamines are metabolized by hepatic mixed-function oxidase enzymes.

Sedating antagonists at H_1-receptors are useful in the treatment of allergic reactions such as seasonal allergic rhinitis and conjunctivitis (hay fever). Protection against the effects of allergen exposure is usually incomplete. In hay fever, antihistamines may reduce rhinorrhoea and sneezing, but are less effective against nasal congestion. Antihistamines have limited effectiveness in controlling allergic reactions because allergen exposure triggers the release of several other potent mediators as well as histamine. Several proprietary formulations of chlorpheniramine are sold to the public for the relief of hay fever.

Sedating antihistamines are also useful in controlling allergic reactions to drugs, the itching associated with urticarial skin rashes and insect bites and stings. Chlorpheniramine or promethazine may be administered by slow intravenous injection as an adjunct to adrenaline (epinephrine) in the emergency treatment of anaphylaxis.

All first-generation antihistamines have sedative activity, but promethazine may be prescribed for the short-term treatment of insomnia. Several proprietary formulations of promethazine and diphenhydramine may be sold to the public for the control of insomnia. Promethazine is commonly used as a sedative/hypnotic pre-anaesthetic in children. H_1-antagonists (cinnarizine, cyclizine, meclozine, promethazine) that also block muscarinic acetylcholine receptors are useful in the control of certain types of nausea and vomiting. These H_1-antagonists are ineffective against agents that induce vomiting by a direct action on the chemosensitive trigger zone. However, they can suppress the nausea and emesis associated with motion sickness or Meniére's disease. They can also suppress emesis induced by agents that act locally to irritate the stomach. The anti-emetic activity of these H_1-antagonists depends, at least in part, on their ability to block muscarinic acetylcholine receptors located at the level of the vestibular nuclei, the nucleus solitarius and the medullary vomiting centre. They are most effective if given before the onset of nausea. Meclozine may be sold to the public for the prophylaxis of motion sickness. The H_1-antagonists that also cause muscarinic blockade should be used with caution in prostatic hypertrophy, urinary retention, narrow angle glaucoma and pyloroduodenal obstruction.

Unwanted effects of first-generation antihistamines are common but tend to be mild. They all cause drowsiness. The sedative effects of H_1-antagonists may extend into the following day, may impair performance at skilled tasks and are enhanced by ethanol. Drugs with significant muscarinic blocking activity cause dry mouth, blurred vision, gastrointestinal disturbances and urinary retention. Other side-effects include hypotension, hypersensitivity reactions, tremor, convulsions, blood dyscrasias and hepatic dysfunction.

Non-sedating antagonists at histamine H_1-receptors are used for the symptomatic relief of allergic disorders such as hay fever and urticaria. They may also be used to alleviate the effects of insect bites and stings. Acrivastine, cetirizine and loratidine can be sold to the public for hay fever relief in adults and children over 12 years of age. Unwanted effects (e.g. headaches, dizziness) of second-generation antihistamines are usually mild and uncommon. However, mizolastine and terfenadine have the propensity to block myocardial potassium channels of the delayed rectifier type. For this reason they may prolong the QT interval of the ECG and carry a low risk (0.25 reactions per million doses) of precipitating hazardous ventricular arrhythmias such as torsade de pointes. It is therefore recommended that mizolastine and terfenadine are avoided if there is significant hepatic impairment, hypokalaemia or known or suspected prolonged QT interval. They should also be avoided if the patient is receiving other drugs known to prolong the QT interval or to delay their metabolism. Fexofenadine is an active metabolite of terfenadine that does not block cardiac potassium channels.

Competitive antagonists at histamine H_2-receptors
Antagonists at H_2-receptors inhibit the cardiac stimulation, gastric acid secretion and delayed vasodilatation induced by histamine (Figure 3). Inhibition of gastric acid secretion is the only effect of these drugs that is exploited therapeutically. They inhibit HCl secretion induced by histamine or gastrin and reduce the HCl secretion induced by acetylcholine released from postganglionic parasympathetic (vagal) nerve terminals. The antagonists at histamine H_2-receptors are used to promote the healing of gastric and duodenal ulcers. They are also beneficial in the treatment of ulcers induced by non-steroidal anti-inflammatory drugs and in the relief of gastro-oesophageal reflux disease. Cimetidine, famotidine, nizatidine and ranitidine can be sold to the public for the short-term relief of heartburn, dyspepsia and hyperacidity in those over 16 years of age.

Unwanted effects of antagonists at histamine H_2-receptors include diarrhoea and other gastrointestinal disturbances, headaches, rashes, tiredness and, occasionally, mental confusion. Most of the antagonists at histamine H_2-receptors also act as antagonists at androgen receptors and can cause gynaecomastia. They should be used with caution in patients with hepatic or renal impairment because their tendency to cause confusion may become more pronounced unless the dose is reduced. The antagonists at histamine H_2-receptors are, to a variable extent, excreted in milk and should be avoided in patients who are breast-feeding. Manufacturers advise avoiding these agents during pregnancy. Cimetidine binds to hepatic microsomal cytochrome P450 and therefore inhibits the metabolism of agents such as benzodiazepines, warfarin, phenytoin and theophylline and should be avoided in patients stabilized on them.

Antagonists at histamine H_3-receptors
No antagonists at H_3-receptors are in clinical use.◆

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Inhalational Anaesthetics

Nigel Harper

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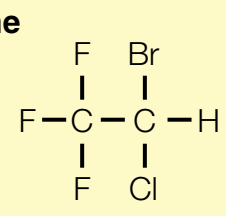
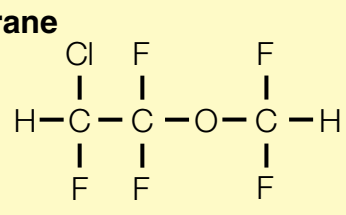
The volatile anaesthetic agents are halogenated hydrocarbons. They are more dense than water and when a vaporizer is used in a circuit, water vapour can condense on the surface of the volatile agent, reducing its vaporization. Isoflurane and enflurane are structural isomers (not stereoisomers because there is no chiral centre) (Figure 1). In general, increasing the halogenation of the molecule confers increasing potency. The addition of fluoride atoms confers greater stability and, in general, a lower boiling point and a higher saturated vapour pressure (SVP). Thus, the substitution of the choride atom in isoflurane (SVP 32 kPa) by a fluoride atom results in desflurane, which is hardly metabolized at all, boils at room temperature and has an SVP of 88.3 kPa (Figure 2). Greater solubility in blood or oil is associated with higher potency and a corresponding low minimum alveolar concentration (MAC). The molecular weights of the volatile anaesthetics in current use are similar (168–200 Da) and it follows that 1 ml of liquid produces a similar volume of saturated vapour (about 200 ml). This calculation becomes important when designing the new generation of administration devices that use direct injection of liquid agent into the circuit.

Chemical formulae of the commonly used volatile anaesthetic agents

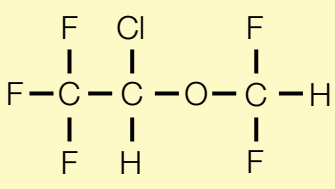
Halothane



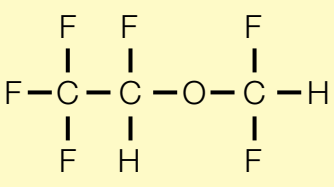
Enflurane



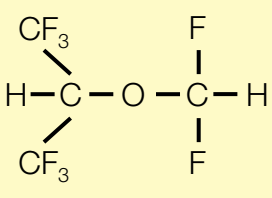
Isoflurane



Desflurane



Sevoflurane



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Physicochemical properties of the inhalational agents

	Formula	Boiling point (°C)	Saturated vapour pressure at 20°C	Blood gas partition coefficient	Oil gas partition coefficient (kPa)
Halothane	$C_2HBrClF_3$	50.2	32.4	2.3	224
Enflurane	$C_3H_2ClF_5O$	56.5	22.9	1.9	96
Isoflurane	$C_3H_2ClF_5O$	48.5	31.9	1.4	91
Sevoflurane	$C_4H_3F_7O$	58.5	21.3	0.6	53
Desflurane	$C_3H_2F_6O$	23.5	88.3	0.42	19

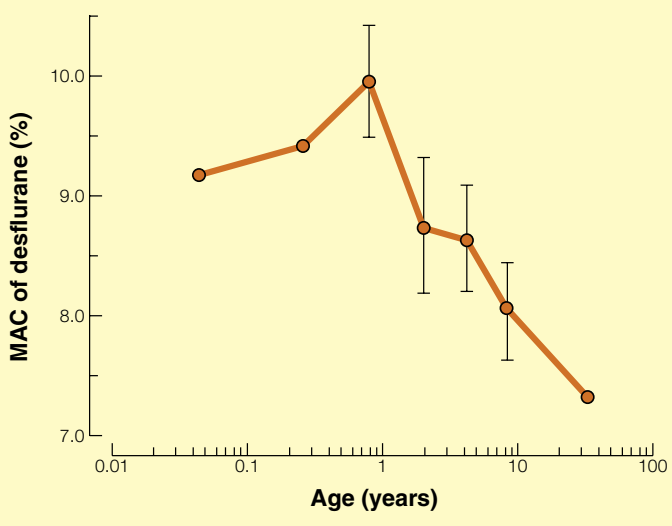
2

MAC

The MAC is the concentration (volumes %) of an agent in oxygen that prevents movement in response to a standard surgical incision in 50% of the population. MAC changes if anaesthetic adjuncts (e.g. nitrous oxide, opioids or benzodiazepines) are co-administered. Although it has been stated that an inspired concentration of 1.2–1.3 × MAC prevents awareness, it must be appreciated that MAC is calculated on the basis of movement and not on the basis of awareness. MAC varies with age; it is maximum at about 1 year and rapidly declines in adulthood (Figure 3). Compared with MAC at 20 years, the MAC is reduced by 20% at 40 years of age and by 40% at the age of 80 years.

The MAC of the volatile agents is reduced by the co-administration of nitrous oxide; 60% nitrous oxide reduces the MAC of isoflurane by about 40%, sevoflurane by 24% and desflurane by 20%. There is some evidence that the MAC of isoflurane decreases with duration of anaesthesia. MAC_{awake} refers to the concentration of agent at which consciousness is regained. There is less variation in MAC_{awake} than in MAC (Figure 4).

Variation of minimum alveolar concentration (MAC) with age



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Minimum alveolar concentration (MAC) for skin incision and regaining consciousness for the volatile agents

	$MAC_{skin\ incision}$	MAC_{awake}
Halothane	0.74	0.38
Enflurane	1.7	0.5
Isoflurane	1.2	0.36
Sevoflurane	2.0	0.36
Desflurane	6.0	2.6

4

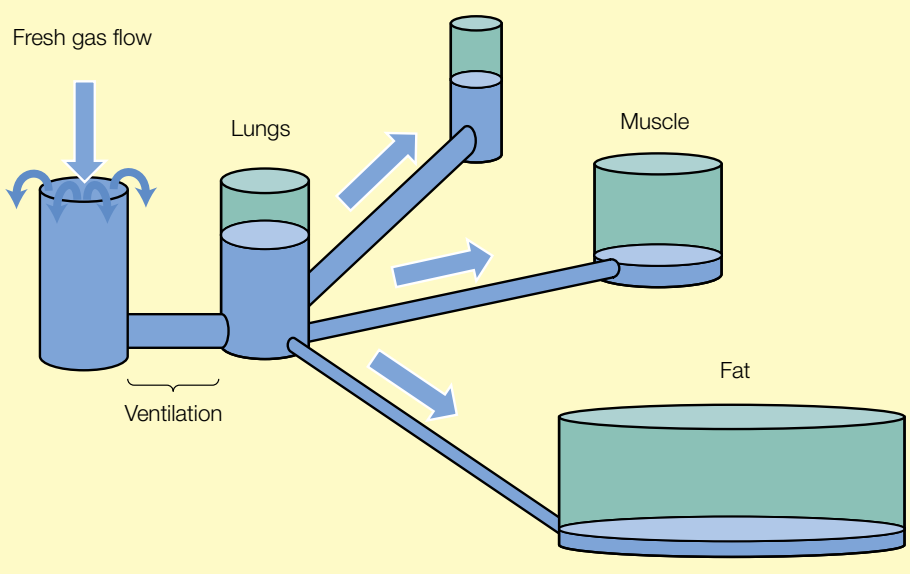
Uptake and distribution of volatile agents

There is increasing evidence that much of the action of volatile agents is at spinal level but, for the purposes of this discussion, the site of action will be assumed to be in the brain. The depth of anaesthesia depends on the partial pressure or tension of the agent at the site of action. Because volatile agents are present in their dissolved state in the body, their tension, or the avidness with which the molecules attempt to leave the dissolved state, is the important determinant of their effect in the CNS. An agent that has a low blood gas solubility coefficient (i.e. is poorly soluble in blood, such as sevoflurane) achieves a given tension faster than a more soluble agent (e.g. halothane) because fewer molecules need to be delivered to the pulmonary capillary blood from the alveoli per unit time. This phenomenon more than outweighs the higher MAC of the less soluble agents. Partial pressure is related to concentration in a gas mixture (partial pressure = concentration x barometric pressure) but the concentration (or number of molecules per unit volume) of a gas in a liquid depends on its partition or solubility coefficient. The inspired concentration of the agent is by far the most important determinant of how rapidly its tension builds up in blood and 'overpressure' is used in everyday practice to accelerate induction of anaesthesia. The end-tidal (alveolar) partial pressure of inhalational agent approximates to the brain tension only at near-equilibrium.

The partial pressure of volatile agent in any particular tissue depends on the delivery of agent via the blood, the partial pressure gradients between the tissue in question and the surrounding tissues, the affinity of tissues for the agent (tissue/gas partition coefficient) and the diffusibility of agent between one tissue and another. Changes in partial pressure with time are both perfusion and diffusion limited. At equilibrium, the partial pressure will be the same in all tissues, but this situation may take many hours to achieve. Diffusion between tissues probably becomes important only after the initial rapid uptake phase and is probably more important during recovery from anaesthesia. This may explain why the MAC_{awake} for different agents is less varied than the $MAC_{skin\ incision}$.

Uptake of an inhalational agent from the breathing system comprises the rapid 'wash-in' of agent into the functional residual capacity followed by distribution to the tissues. The rate of uptake into the tissues depends on blood flow, the solubility of the agent in the tissue and the total capacity of the tissue for the agent. The classical water analogue model was described by Mapleson (Figure 5). This model explains why a reduced cardiac output is associated with a shorter induction time. The reduced cardiac output is represented by a reduction in the diameter of the pipes to all the cylinders with the exception of that representing the brain. Cerebral blood flow is preserved as a result of autoregulation and, because the flow to the other cylinders is diminished and the inflow of agent into the lungs is unchanged, the transport of agent to the brain per unit time is increased and the desired brain partial pressure is attained more rapidly. The Mapleson model can also explain the effects of changes in ventilation.

Water analogue model



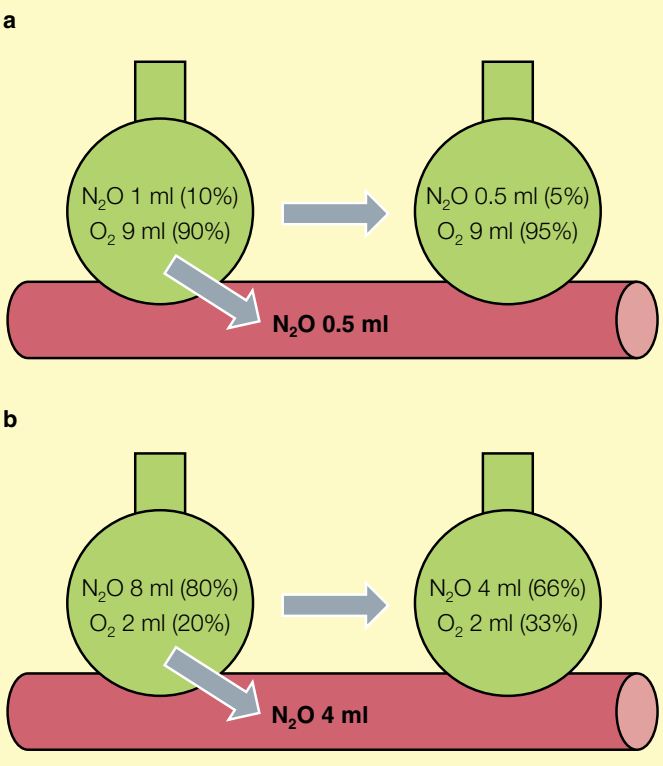
The tissues are represented by cylinders containing water; the volume representing the total storage capacity of that tissue. The head of water pressure represents the partial pressure of inhalational agent. The diameter of the interconnecting pipes represents transport of the inhalational agent in blood and is therefore proportional to the blood flow multiplied by the blood gas partition coefficient of the agent. The largest diameter pipe connects the lungs with the brain and viscera, the second largest to the muscle, and the smallest to the fat group consuming 75%, 23% and 2% of the cardiac output, respectively. The fat has the poorest perfusion but the largest capacity for inhalational agents. The partial pressure gradient between the alveoli and any particular tissue is represented by the difference in water level between the cylinder representing the lungs and the cylinder representing the various tissue compartments. Because the pipe leading to the cylinder representing the brain and viscera has the largest diameter, the partial pressure in the brain follows the alveolar partial pressure more closely than in other tissues.

5

The concentration effect

The concentration effect explains the observation that the higher the inspired concentration of inhalational agent, the faster the rise in alveolar concentration. During induction of anaesthesia the uptake of the inhalational agent from the alveoli per unit time is much greater than the uptake of the less soluble oxygen and nitrogen. Taking the latter part of inspiration and expiration together, the greater uptake of the inhalational agent in comparison with oxygen and nitrogen tends to reduce the concentration of the agent in the alveoli and, consequently, its partial pressure falls progressively until a new breath replenishes the supply of agent to the alveoli. This effect is more marked if the inspired concentration of agent is small because, although the absolute quantity of agent taken up is less, its partial pressure is reduced to a proportionally greater extent before the next inspiration begins (Figure 6).

The concentration effect



The uptake of nitrous oxide from the alveoli into the pulmonary capillaries. Each imaginary alveolus has an initial volume of 10 ml. **a** In the upper, left alveolus there is a low initial concentration of nitrous oxide. Of the 1 ml initially present at the end of inspiration, half is taken up into the pulmonary capillary before the alveoli are replenished during the next inspiration. As a result the volume of nitrous oxide in the alveolus has fallen to 0.5 ml. This represents a fall of 50% in the concentration, and therefore partial pressure, of nitrous oxide during one respiratory cycle. In **b** there is a higher initial concentration of nitrous oxide (80%, lower left). Again, half is taken up (4 ml) but the resulting fall in alveolar concentration is less: from 80% to 60% (lower right). This effect explains why a high inspired concentration of inhalational agent is associated with a rapid increase in alveolar concentration.

The second gas effect

Nitrous oxide (the first gas) is taken up from the alveoli in large quantities because its high concentration more than offsets its relative insolubility. The nitrous oxide that is taken up is replaced from the inspired gas, thus effectively increasing alveolar ventilation. The increase in alveolar ventilation also increases the supply of the second 'gas', for example isoflurane, to the alveoli. The alveolar concentration of isoflurane is thereby increased and its brain tension rises more rapidly than if nitrous oxide were not present. The second gas effect is more marked for more soluble second 'gases', such as halothane than for less soluble second 'gases', such as sevoflurane.

Metabolism and toxicity

Sevoflurane is less chemically stable than the other agents in current use. It undergoes significant biodegradation in the body and is also degraded by contact with carbon dioxide absorbents. About 3% of sevoflurane is biotransformed by the 2E1 isoform of cytochrome P450 to hexafluoroisopropanol and inorganic fluoride. Although 7 MAC hours of sevoflurane is associated with plasma fluoride concentrations of up to 40 μM, no convincing evidence of renal dysfunction in normal individuals has been published. The reaction with soda lime results in the formation of Compound A, a vinyl ether that results in renal tubular necrosis when administered in large concentrations to rats. It is thought that Compound A is conjugated with cysteine following which a toxic metabolite is released by the action of the enzyme β-lyase in the kidney. The concentration of β-lyase in the kidney in man is much less than in the rat. Compound A formation is favoured in the presence of dry soda lime at high temperatures.

Effects on the CNS

All the volatile agents impair the normal autoregulation of cerebral blood flow; it is increased four-fold by 1.6 MAC halothane and doubled by 1.6 MAC enflurane. The effect of isoflurane, sevoflurane and desflurane is less. The increase in cerebral blood flow can be attenuated by deliberate prior hyperventilation. All the agents, except halothane, cause a dose-related reduction in cerebral oxygen consumption. EEG activity is reduced in a dose-related fashion. Enflurane produces characteristic excitatory spikes at concentrations above 1.5 MAC, particularly in association with hypocapnia and it is prudent to avoid this agent in epileptic patients. Sevoflurane anaesthesia is associated with persistent EEG activity at 10–14 Hz at deeper planes of anaesthesia than the other agents, but is not epileptogenic.

Cardiovascular effects

All inhalational agents adversely affect the cardiovascular system to some extent (Figure 7). Several mechanisms are involved:

- direct depression of the vasomotor centre
- depression of baroreceptor reflexes
- depression of cardiac contractility
- dilatation of peripheral vessels causing a fall in systemic vascular resistance
- autonomic effects
- sensitization of the myocardium to catecholamines.

The combined effect is a dose-related fall in mean arterial pressure. Sevoflurane has the best cardiovascular profile and halothane the worst. Desflurane is associated with a sympathetically mediated sinus tachycardia when the concentration is increased rapidly above 1 MAC. This effect is attenuated by the addition of nitrous oxide.

In contrast, halothane may be associated with a dose-related bradycardia, slowing of atrioventricular conduction and ventricular arrhythmias. Halothane and enflurane decrease calcium ion release from the sarcoplasmic reticulum and marked hypotension may occur in patients taking calcium antagonists. Halothane has the greatest catecholamine-sensitizing effect and enflurane the least.

Coronary artery steal has been attributed to isoflurane, which dilates epicardial resistance vessels, but there is no evidence of an increase in perioperative cardiac events in clinical studies.

Sevoflurane appears to preserve the balance of epicardial to endocardial blood flow better than isoflurane and is associated with less reduction in mean arterial pressure.

Relative effects of the inhalational agents on the cardiovascular system

	Cardiac index	Heart rate	Systemic vascular resistance	Sensitization to catecholamines
Halothane	Large reduction	No change or small reduction	Reduction	++++
Enflurane	Reduction	No change	Reduction	–
Isoflurane	Reduction	No change or small increase	Reduction	+
Sevoflurane	No change	No change or small increase	No change or small reduction	+
Desflurane	No change	Large increase	No change or small reduction	–

Effects on respiration

All of the volatile agents depress the ventilatory response to hypercarbia and, to a greater extent, hypoxia in a dose-related fashion. Enflurane appears to have the greatest respiratory depressant effect and halothane the least. Isoflurane at 1 MAC depresses the ventilatory response to hypercarbia by 50% and the response to hypoxia is abolished. Airways irritation is most marked with desflurane and least with sevoflurane.

Renal effects

The fall in systemic arterial pressure induced by inhalational agents is associated with a fall in renal blood flow, glomerular filtration rate and urine output. Release of fluoride from these agents as a result of metabolism may impair renal function. A plasma concentration greater than 50 μM/litre has been considered to be renotoxic, but this threshold is probably spurious because the tissue concentration in the kidney is more important. Significant plasma concentrations of fluoride ions have been described after enflurane and sevoflurane anaesthesia, but the clinical significance is unclear. Nevertheless, it is prudent to avoid enflurane and sevoflurane in patients with pre-existing renal impairment.

Hepatic effects

The extremely rare fulminant hepatitis following halothane was originally thought to be the effect of a toxic metabolite produced by a reductive pathway. The current theory is that oxidative metabolism of halothane produces a trifluoroacetyl (TFA) halide. This compound changes the structure of cytochrome P450 and other proteins converting them into haptens, resulting in a dramatic inflammatory response in the liver in susceptible individuals. The presence in the plasma of anti-TFA antibodies is common in patients with halothane hepatitis but not other forms of hepatitis. Minor hepatic dysfunction associated with a transient rise in transaminases is more common and may be associated with a direct hepatotoxic effect of reductive metabolites.

Hepatic portal blood flow is reduced concomitantly with cardiac output and the portal venous oxygen saturation is reduced markedly. As a result, the liver depends on hepatic arterial flow to a greater extent. Autoregulation of the hepatic arterial bed is severely impaired by halothane, to a lesser extent by enflurane and sevoflurane, and least by isoflurane.

Neuromuscular effects

All inhalational agents potentiate the effects of neuromuscular blocking agents by reducing the release of acetylcholine at the neuromuscular junction and via a direct effect on contractility. Halothane has the least effect, enflurane, isoflurane and des-flurane are intermediate, and sevoflurane has the greatest effect.

Effects on the immune system

The volatile agents tend to produce an increase in the numbers of neutrophils but their function may be impaired. There is no evidence that the incidence of postoperative infection is influenced by the choice of anaesthetic agent.

Xenon

Xenon has an extremely low blood gas solubility (0.2) and a MAC of 63–71%. It is a dense gas with a high viscosity and its concentration is measured using a mass spectrometer or by its effect on the speed of sound. It is separated from air by fractional distillation. Xenon appears to produce anaesthesia by inhibiting NMDA channel opening. It has no smell, is not irritant, and produces rapid onset and offset of anaesthesia. Metabolism is almost nonexistent. Cardiovascular and respiratory stability is excellent though cerebral blood flow is increased. It may be associated with nausea. In common with nitrous oxide, it accumulates in air-filled body cavities. Although expensive, it has been used inclosed breathing systems; 60–70% can be scavenged and recycled.

The effects of barometric pressure on inhalational anaesthesia

Depth of anaesthesia is dependent on partial pressure and not concentration. Plenum vaporizers mix a definable ratio of carrier gas and gas that has been saturated with vapour. The vapour pressure of volatile agents depends on temperature only and not on atmospheric pressure. At high altitude it is unnecessary to alter the vaporizer setting to obtain the same clinical effect as at a lower altitude. The delivered concentration of volatile agent is reduced but the partial pressure remains unchanged. The desflurane vaporizer is an exception; it mixes pure desflurane vapour to the desired volume percent. The delivered partial pressure is reduced if the barometric pressure is reduced. At a barometric pressure of 80 kPa, a desflurane vaporizer set to 6% delivers the agent at a partial pressure of only 4.8 kPa. It is worth noting that infrared analysers measure the partial pressure of agent, not the concentration. The partial pressure of agent required to produce a clinical effect is unchanged at high altitude, but the concentration is increased. The concept of MAC is therefore unhelpful at high altitude.

Occupational exposure

There is continuing debate concerning the possible deleterious effects of occupational exposure of operating theatre personnel to inhalational agents. In the UK, the Health and Safety Commission's Advisory Committee on Toxic Substances has recommended the following Occupational Exposure Standards which came into force in 1996. Each is a maximum exposure over an 8-hour time-weighted, average, reference period: nitrous oxide 100 ppm; enflurane 50 ppm; isoflurane 50 ppm; halothane 10 ppm. This is a fifth of the exposure level at which no effects were seen in experimental animal studies.

Intravenous Induction Agents

J Max Fryer

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The first successful intravenous anaesthetic agents (IAAs) were produced in 1932 when sulphur was substituted for oxygen in the barbiturate ring to produce the thiobarbiturates. Waters and Lundy in the USA used thiopental (thiopentone) clinically in 1934. At that time, anaesthesia was usually induced by the inhalation of irritant anaesthetic vapours such as diethyl ether. Ether is irritant to the airways and induction slow, often with a prolonged excitement phase. IAAs produce a rapid smooth induction of general anaesthesia that is more pleasant for patient and anaesthetist. Thiopental (thiopentone), despite its imperfections, remains the gold standard for comparative purposes. Other IAAs in clinical use include methohexitone, etomidate, propofol and ketamine. The properties of the ideal IAA are given in Figure 1.

Properties of the ideal intravenous anaesthetic agent

Presentation and storage
- Water soluble
- Stable in solution at room temperature and on exposure to light
- Long shelf life

Rapid onset in one arm–brain circulation time
- Rapid penetration of the blood–brain barrier
- Highly lipid soluble (a large percentage non-ionized at body pH) and sufficient agent free to transfer (not highly protein bound)

Low side-effect profile
- No pain on injection
- Absence of excitatory effects on induction (coughing, hiccup or involuntary movement)
- Smooth emergence without confusion, restlessness or vivid dreams
- No emetic effects

Rapid recovery and lack of cumulation on repeat dosage
- Rapid redistribution to vessel-rich tissue
- Rapid clearance and metabolism to water-soluble non-active and non-toxic metabolites preferably in the liver, blood or other organs of the vessel-rich group
- Minimal disturbance of psychomotor skills and memory in the immediate recovery period

High degree of safety
- High therapeutic ratio
- Minimal cardiovascular and respiratory effects
- No release of histamine and no hypersensitivity reactions
- Safe if inadvertently injected into an artery, subcutaneously or into the nervous system (accidental epidural injection of thiopental (thiopentone) has been reported with no long-term sequelae)
- No venous sequelae (thrombophlebitis)

Little or no effect on other drugs and disease states
- No interaction with neuromuscular blocking drugs
- Can be used in patients with muscular dystrophy or porphyria

Other considerations
- Analgesic in subanaesthetic concentration

1

Mode of action

The site of action of IAAs is uncertain. There is no structural similarity between different agents and no reversing agent has been discovered. IAAs have effects on many other cells including phagocytes, the vascular endothelium and platelets, suggesting a number of modes of action. Isomerism is important in some cases suggesting a possible receptor-binding site. Meyer and Overton noted that volatile anaesthetic potency was related to lipid solubility and distortion of the lipid bilayer was considered a possible but nonspecific, site of anaesthetic action. Research has been directed towards the cell membrane proteins that regulate the functions of the neuron.

There is evidence that IAAs may act, in part, through the ligand-gated ion channels by enhancing the effects of inhibitory neurotransmitters especially γ-aminobutyric acid (GABA). Agonists at the postsynaptic $GABA_A$ receptor open the chloride ion channel. The influx of chloride ions into the neuron results in hyperpolarization. Thiopental (thiopentone) binds to the β subunits of the GABA receptor, increasing the time that the chloride channel is open. Benzodiazepines increase the frequency of opening of the chloride channel and bind to the α subunit. Thiopental (thiopentone) has an effect on the voltage-gated sodium and potassium channels. Propofol is thought to exert its main action by reducing the opening time of the sodium channels. In mice, the ED_{50} for propofol is decreased in the presence of the $GABA_A$ receptor agonist muscimol and increased in the presence of the antagonist bicuculline suggesting an action at the $GABA_A$ receptor. Propofol is known to reduce N-methyl-D-aspartate (NMDA)-activated currents. The main action of ketamine is inhibition at the NMDA receptor, but naloxone partially reverses ketamine analgesia suggesting additional action at the opiate receptors.

Pharmacokinetics

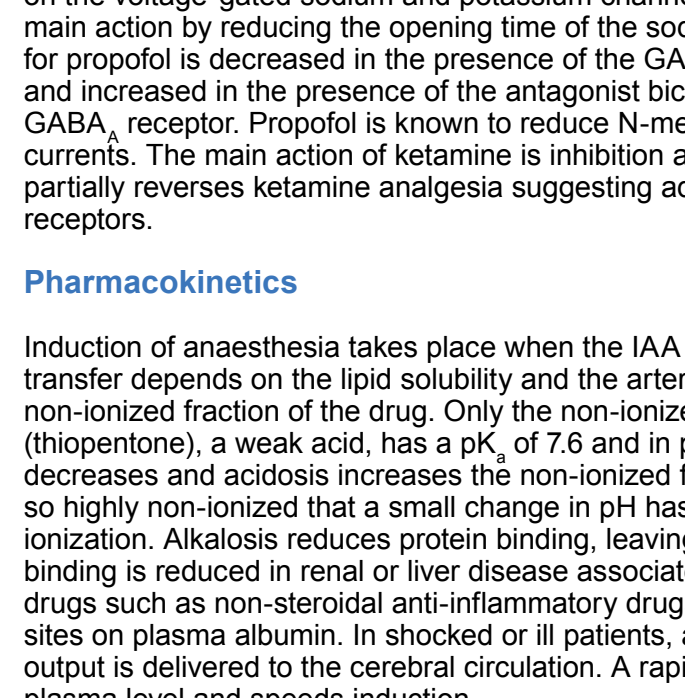
Induction of anaesthesia takes place when the IAA diffuses into the brain. The rate of transfer depends on the lipid solubility and the arterial concentration of the unbound, non-ionized fraction of the drug. Only the non-ionized fraction is lipid soluble. Thiopental (thiopentone), a weak acid, has a pK_a of 7.6 and in plasma 61% is non-ionized. Alkalosis decreases and acidosis increases the non-ionized fraction. Propofol and etomidate are so highly non-ionized that a small change in pH has little effect on the degree of ionization. Alkalosis reduces protein binding, leaving more IAA free for transfer. Protein binding is reduced in renal or liver disease associated with low plasma albumin and by drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) that bind to the same sites on plasma albumin. In shocked or ill patients, a greater proportion of the cardiac output is delivered to the cerebral circulation. A rapid injection gives a higher peak plasma level and speeds induction.

The distribution and elimination of an IAA follows a three-compartment model. After injection, there is a high plasma level of the drug followed by a redistribution phase and elimination.

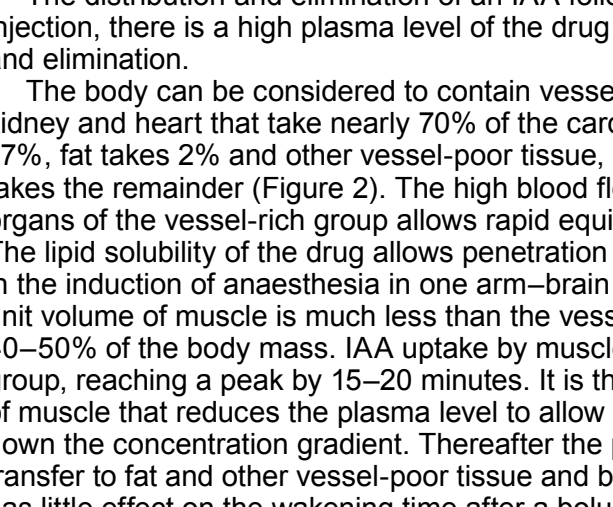
The body can be considered to contain vessel-rich organs such as the brain, liver, kidney and heart that take nearly 70% of the cardiac output at rest. Muscle takes 17%, fat takes 2% and other vessel-poor tissue, such as bone and connective tissue, takes the remainder (Figure 2). The high blood flow in proportion to the size of the organs of the vessel-rich group allows rapid equilibration of IAA within the tissues. The lipid solubility of the drug allows penetration of the blood–brain barrier resulting in the induction of anaesthesia in one arm–brain circulation time. The blood flow per unit volume of muscle is much less than the vessel-rich group, but muscle makes up 40–50% of the body mass. IAA uptake by muscle lags behind that of the vessel-rich group, reaching a peak by 15–20 minutes. It is the uptake of IAA by the large volume of muscle that reduces the plasma level to allow the IAA to leave the brain by diffusion down the concentration gradient. Thereafter the plasma level falls by the relatively slow transfer to fat and other vessel-poor tissue and by metabolic clearance. Blood flow to fat has little effect on the wakening time after a bolus of IAA, but fat may store significant quantities of IAA after repeat boluses or infusions especially in the obese. Agents with a higher rate of metabolism have increased clearance and a shorter terminal half-life, which improves the recovery profile and allows the use of infusions.

Distribution and elimination of intravenous anaesthetic agents

Perfusion and tissue mass



Redistribution of thiopental (thiopentone)



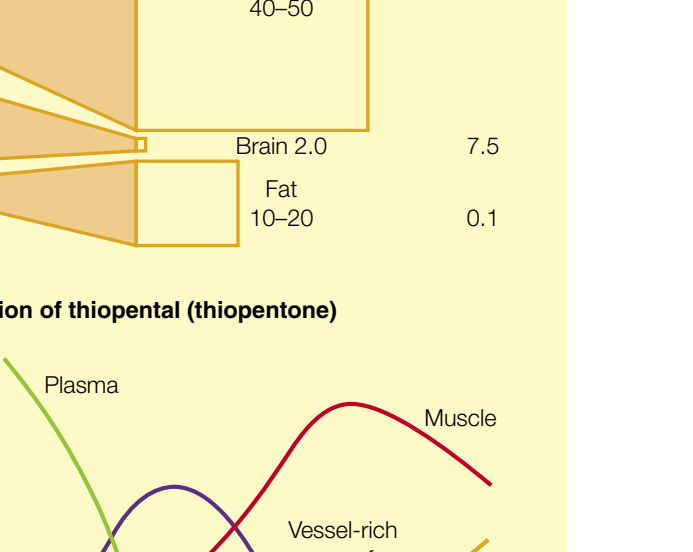
2

Barbiturates

The barbiturate ring is shown in Figure 3. There are four groups of barbiturates.
- The oxybarbiturates have hydrogen at position 1 and oxygen at position 2. They are of little clinical use because of delayed onset and prolonged action.
- The thiobarbiturates have hydrogen at position 1 and sulphur at position 2. Substitution of sulphur into pentobarbitone produces thiopental (thiopentone).
- Methyl barbiturates have a methyl group at position 1 and oxygen at position 2. Methohexitone is used commercially.
- Methyl-thio barbiturates have a methyl group at position 1 and sulphur substituted for oxygen. They are very potent but have marked excitatory effects and cannot be used clinically.

The potency of the barbiturate is increased as more carbon atoms are added to the side chains at position 5. An aromatic nucleus in the side chains at position 5 gives convulsant properties whereas a phenyl group produces an anticonvulsant. Some features of IAAs are compared in Figure 4.

The barbiturate ring



3

Comparison of some features of the intravenous anaesthetic agents

	Thiopental (thiopentone)	Methohexitone	Propofol	Etomidate	Ketamine
pH	10.5	11.1	7.4	8.1	3.5–5.5
pK_a	7.6	8.0	11.0	4.24	7.5
Protein bound (%)	80.0	80.0	98.0	75.0	12.0
Free non-ionized (%)	61.3	80	99.97	99.1	44.3
Terminal half-life (hours)	11.6	3.9	1.5–4.4	5.4	3
Hypersensitivity reaction	1:18,000	1:5,000	1:100,000	1:450,000	Very rare
Induction blood pressure change (%)	–8	–8	–17	–2	+28
Induction pulse change (%)	+14	+15	+7	+8	+33
Induction pain (%)	0	30–50	10–30	40–60	0
Induction movement (%)	0	5	5–10	30	Very little
Induction hiccups (%)	0	30	5	20	Very little
Induction apnoea (%)	6	20	40	20	Rare
Recovery restlessness (%)	10	5	5	35	Common
Recovery nausea (%)	7.5	7.5	5	20	Common
Recovery vomiting (%)	7.5	5	5	20	Common

Thiopental (thiopentone) (5-ethyl-5-(1-methylbutyl)-2-thio-barbiturate)
Thiopental (thiopentone) is presented as a pale yellow powder in an ampoule containing 6% anhydrous sodium carbonate in an inert atmosphere of nitrogen. It is poorly soluble in water but dissolves in the alkaline solution produced by the sodium carbonate. The 2.5% solution has a pH of 10.5. The inert nitrogen prevents degradation by oxygen and carbon dioxide. The aqueous solution is stable for 2 weeks. There is no added preservative but the alkaline solution is bacteriostatic and safe to keep for 48 hours. The induction dose is 4–5 mg/kg. Injection of thiopental (thiopentone) is painless even in small veins. Induction is smooth with unconsciousness in one arm–brain circulation time. The alkaline thiopental (thiopentone) is less soluble when injected into the blood at pH 7.4 allowing microcrystals to form. Injection into an artery is painful probably because of the microcrystals occluding small arterioles causing thrombosis. Extravasation to subcutaneous tissues may lead to necrosis. Thiopental (thiopentone) is antanalgesic in subanaesthetic concentrations. Rectal thiopental (thiopentone) has been used in children at a dose of 44 mg/kg, but absorption is unpredictable and careful nursing observation is required.

Initial recovery results from redistribution; it is smooth with a low incidence of restlessness or nausea and vomiting. Metabolism in the liver is slow and repeat or large doses lead to cumulation and delayed recovery. Only 10–15% of the remaining thiopental (thiopentone) is metabolized per hour. The sulphur is replaced with oxygen to produce pentobarbitone and the side chains at position 5 are oxidized. Renal excretion of thiopental (thiopentone) is 0.3%.

Methohexitone (α-dl-1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbiturate
Methohexitone was withdrawn in 1999 for an initial period of 12 months owing to production difficulties. The manufacturers hope to restart supply by mid-2001. Methohexitone is similar to thiopental (thiopentone) and is used as a 1% solution. There are four isomers of methohexitone but only the α d and l forms have anaesthetic properties. Induction of anaesthesia with 1–1.5 mg/kg is rapid, but pain on injection is common especially if the small veins on the hand are used. Excitatory movements, coughing and hiccups occur frequently. Methohexitone causes pain if injected into an artery, but thrombosis with the 1% solution is unusual. Epileptiform activity has been recorded by EEG but clinical fits are rare. Recovery from methohexitone is more rapid than from thiopental (thiopentone), because metabolism is significantly faster. Its use in day case anaesthesia had been superseded by propofol, but methohexitone is favoured for chair dental work and ECT.

Sterically hindered alkyl phenol

Propofol (2,6-di-isopropylphenol)
Propofol is a colourless to pale straw-coloured liquid that is slightly soluble in water. It was first released in 1977 in cremophor oil. Following reports of hypersensitivity reactions to the solvent, propofol was reformulated in a 1% aqueous emulsion containing soya-bean oil and egg phosphatide (*Intralipid*). Propofol has a neutral pH and a pK_a of 11.0 making it 99.97% non-ionized and highly fat soluble. It is 98% bound to protein.

Induction of anaesthesia with 2–2.5 mg/kg is smooth and pleasant with a low incidence of excitatory movements. Epileptiform fits during recovery have been recorded. Closing of the eyes is delayed compared with thiopental (thiopentone) and can lead to a relative overdose. A better endpoint is the loss of verbal contact.

Pain on injection through small veins is common and reduces the use of propofol in children. Injection of 1% lidocaine (ligno-caine) before the injection or mixing 20 mg of lidocaine (ligno-caine) with an ampoule of propofol reduces the incidence of pain. Lidocaine (lignocaine) can destabilize the soya-bean emulsion.

Propofol does not contain preservative and the aqueous emulsion is a good bacterial medium. Propofol should not be drawn up until immediately before injection. Propofol does not cause any ill effects if injected perivascularly or into an artery. Hypertriglyceridaemia can occur after prolonged infusions. Metabolism is mainly in the liver, but occurs during the anhepatic phase of liver transplant. Up to 10% may be metabolized in the gastrointestinal tract. The main metabolites are the glucuronide and quinol. The quinol metabolite explains the green-coloured urine that is sometimes seen after an infusion. Only 0.3% is excreted unchanged in the urine.

Carboxylated imidazole

Etomidate (D-ethyl-1-(α-methyl-benzyl)imidazole-5carboxylate)
Etomidate is presented as a clear solution of 20 mg in 10 ml of water and 35% propylene glycol. Etomidate is unstable dissolved in pure water. The pH is 8.1 and the pK_a 4.2. Etomidate is a base and 99% of the drug is non-ionized in the blood. Protein binding is 75%. The induction dose is 0.3 mg/kg.

Pain on injection is common and there is a high rate of thrombophlebitis in the postoperative period (30% by the third postoperative day) especially if the small veins on the hand are used. Recent work suggests that the solvent, propylene glycol, is the cause of thrombophlebitis.

Etomidate causes the least cardiovascular depression of the IAAs. Excitatory side-effects are common (involuntary movement 40% and cough or hiccups 10%) but are reduced by prior administration of an opiate. Recovery is less pleasant for the patient with increased restlessness, nausea and vomiting. Etomidate is a powerful antisteroid drug. Etomidate infusions were used in intensive care, but the mortality rate was higher than expected. Investigations showed that etomidate suppresses adrenocortical secretion by inhibiting mitochondrial, cytochrome P450-dependent, 11 β hydroxylase. This can be measured after an
induction dose, but the effect is not clinically significant unless an infusion is given. Metabolism is in the liver and plasma byesterase hydrolysis with 2% excreted unchanged in the urine.

Phencyclidine derivative

Ketamine (2-o-chlorophenyl-2-methylaminocyclohexanone hydrochloride)
Ketamine is a racemic mixture of two enantiomers; the S(+) enantiomer is 3.4 times more potent than the R(–) enantiomer. It is soluble in water and presented as a 1%, 5% and 10% solution. The pH is 3.5–5.5 and the pK_a 7.5. It is highly lipid soluble with 12% protein bound and 44% non-ionized. Ketamine produces dissociative anaesthesia. A dose of 2 mg/kg produces unconsciousness in 1–2 minutes. The endpoint can be difficult to judge with the patients often staring into the distance for a short while. Unlike most induction agents, ketamine increases the pulse rate, blood pressure and intracranial pressure. Salivation is increased and a muscarinic drug such as glycopyrrolate is usually given. The airway is well maintained but cannot be guaranteed. Induction is smooth but restlessness, dreams and hallucinations often complicate recovery. Benzodiazepine premedication reduces emergence delirium. Recovery is by redistribution, then metabolism, mainly in the liver by demethylation and hydroxylation by cytochrome P450. One metabolite, nor-ketamine, has one-third to one-fifth the activity of ketamine. Most of the ketamine is excreted in the urine as the glucuronide with 2.5% unchanged. Ketamine is analgesic. Up to 0.5 mg/kg produces intense analgesia without unconsciousness or delirium, allowing patients to undergo painful procedures such as physiotherapy for fractured ribs. An oral dose of 20–50 mg has been advocated for treatment of resistant chronic neuralgic pain.

Pharmacodynamics

CNS
Thiopental (thiopentone) and ketamine are anticonvulsant. Epileptiform activity has been recorded with methohexitone, etomidate and propofol, but all are anticonvulsant at higher doses. Propofol has been shown to reduce the degree of fits produced by ECT. All the IAAs, except ketamine, reduce the cerebral metabolic rate leading to a reduction in brain blood flow and a reduction in intracranial and intraocular pressure. Ketamine produces a dose-dependent increase in intracranial pressure.

Cardiovascular system
The barbiturates reduce myocardial contractility and promote venous pooling. The cardiac output and blood pressure fall with a small rise in the pulse rate. Methohexitone causes less myocardial depression than thiopental (thiopentone). In healthy patients, etomidate has little effect on contractility and there is only a small reduction in blood pressure. Etomidate is often used in the ill and elderly, but the cardiovascular stability in such patients is often poor and etomidate must be given with caution. Propofol produces the most marked fall in blood pressure. There is little reduction in contractility, considerable vasodilatation and a small increase in heart rate. In the elderly, the blood pressure and cardiac output can fall by more than 50% with delayed redistribution and recovery. The effect is dose dependent and minimized by a slow injection. In contrast, ketamine increases the heart rate and blood pressure by 20–40%. Noradrenaline production is increased. Ketamine can be used under difficult circumstances such as in the battlefield or for on-site procedures following major accidents.

Respiration
With the exception of ketamine, the IAAs depress respiratory drive. The barbiturates produce respiratory depression by a direct effect on the respiratory centre. The partial pressure of carbon dioxide in arterial blood increases and pH falls. Etomidate is the least respiratory depressant but the ventilatory response to carbon dioxide is reduced. Propofol has the most profound effect. Apnoea after induction is common and more prolonged than with other agents. The carotid body is sensitive to hypoxia and most anaesthetic agents increase that sensitivity during the induction of anaesthesia resulting in a sigh or deep breath. Propofol inhibits the response to hypoxia. Without the sigh or deep breath the oxygen saturation may fall during induction. Pre-oxygenation or asking the patient to take two big breaths of room air during induction reduces the incidence of desaturation at induction. Thiopental (thiopentone) increases laryngeal reflexes to the extent that coughing and laryngeal spasm can occur if there is stimulation from saliva, blood or the insertion of an airway or laryngeal mask. Propofol reduces the laryngeal reflexes and the short period of apnoea following induction aids the early insertion of a laryngeal mask airway. Ketamine has little effect on the respiratory centre and the ventilatory response to carbon dioxide is unaltered. The airway is usually well maintained but cannot be guaranteed, especially at higher doses when laryngeal reflexes may become obtunded.

Hepato-renal system
Any reduction in blood pressure following the induction of anaesthesia reduces both hepatic and renal blood flow, but there is little evidence that this is clinically significant. The barbiturates suppress the inhibitory pathways running from the hypothalamic nuclei to the posterior lobe of the pituitary, resulting in an increased production of antidiuretic hormone (ADH). Urine production is reduced to 10% of normal. Propofol, etomidate and ketamine have no effect on ADH secretion. The barbiturates induce liver enzymes.

Uterus and fetus
Thiopental (thiopentone) remains the induction agent of choice for caesarean section. It readily crosses the placenta, but fetal plasma levels are lower than maternal. Redistribution allows the plasma levels to fall by delivery so that the fetus is relatively unaffected. Propofol has been linked with reduced Apgar scores at 1 minute and is not recommended for obstetric anaesthesia, although recent work questions this view. There is limited information on the placental transfer of etomidate, but it has been used successfully in obstetrics. None of the IAAs have a significant effect on uterine muscle tone.

Muscles
Skeletal muscle tone is reduced only at a high dose. Muscle movement in response to pain is common with all IAAs unless anaesthesia is supplemented with opiates or with a volatile agent.

Concomitant disease
The barbiturates and etomidate may precipitate porphyria in susceptible patients. Propofol and ketamine are thought to be safe. The respiratory depressant effects of the IAAs are exaggerated in patients with muscular dystrophy. If general anaesthesia cannot be avoided, propofol with its high clearance allows more rapid recovery. Patients with myxoedema are very sensitive to IAAs especially the barbiturates. Myxoedema should be treated before induction of anaesthesia.

Safety
Hypersensitivity reactions to IAAs are uncommon but can be serious. Etomidate has the lowest incidence of reactions. The therapeutic ratio (ED_{50}:LD_{50}) in mice is low (3–4) for the barbiturates and propofol; etomidate is a little higher. The corticosteroid-based IAA *Althesin* (withdrawn in 1984) had a therapeutic ratio of 32, a property shared by other corticosteroid-based IAAs. Unfortunately the newer corticosteroid IAAs have produced marked excitatory movement in human volunteer studies and none have progressed to commercial use.

Contraindications to the use of IAAs include airway obstruction, known allergy, and for the barbiturates and etomidate, porphyria. IAAs should be used with caution in patients with ischaemic heart disease, constrictive pericarditis, asthma or epilepsy.

Ion Channels

Richard J Prince

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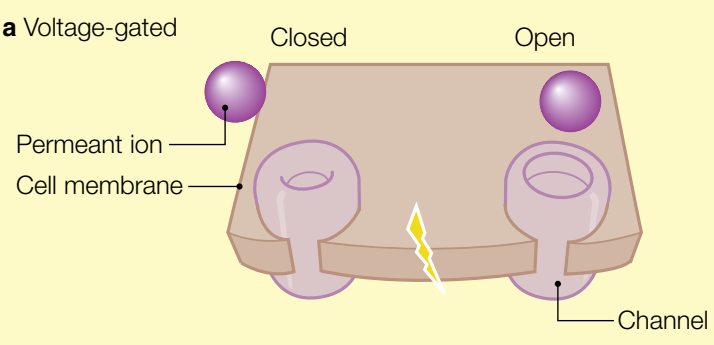
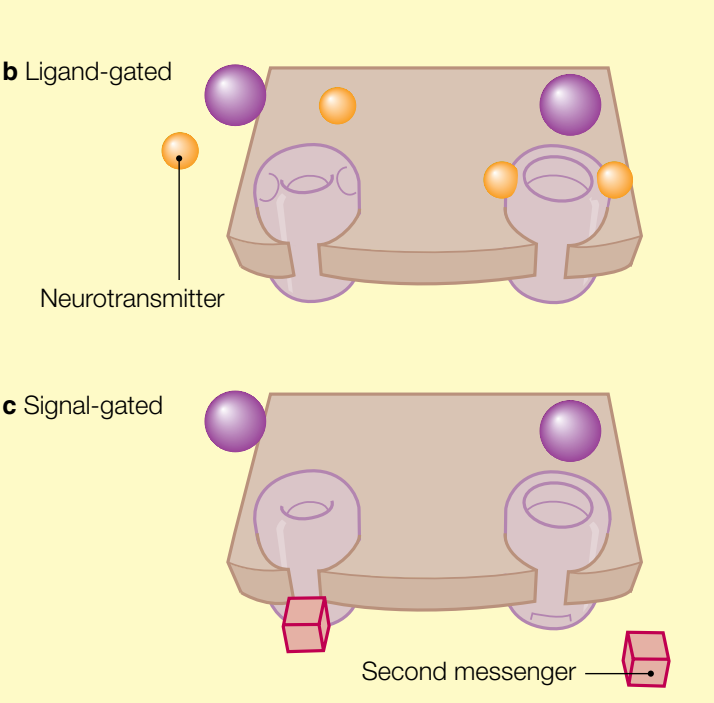
The rapid movement of ions across cell membranes depends on a group of proteins known collectively as ion channels. Although they are all water-filled transmembrane pores, ion channels are structurally and functionally extremely diverse.

Typically, cells contain many different channels but only a few (leak channels) are constantly open. The opening and closing, or 'gating', of the remaining channels is tightly controlled using a variety of mechanisms (Figure 1). For example, voltage-gated channels, respond to changes in membrane potential, and ligand-gated channels open when a neurotransmitter binds to their extracellular domains.

Mechanisms for controlling channel gating





a Voltage-gated channels open in response to changes in the membrane potential. **b** Ligand-gated channels open when neurotransmitters bind to sites in their extracellular domains. **c** Signal-gated channels respond to the binding of intracellular second messengers to their intracellular domains. Some signal-gated channels, such as the ATP-sensitive K^+ channel, close when the second messenger binds as illustrated here, others such as Ca^{2+} sensitive K^+ channels are activated by second messenger binding.

1

Ion selectivity

Ion channels are usually selective for particular ions. Most are selective for Na^+, K^+, Ca^{2+}, Na^+/K^+ or Cl^-. Selectivity arises because ions do not simply fall through the channel pore but interact with a series of mechanical and charge barriers. The ion must conform to charge (cation or anion) and size (maximum and minimum diameter) criteria dictated by the channel structure.

The precise effects of activating a particular class of channel depend on the ion selectivity of the channel and on the particular ionic and electrical gradients across the cell membrane. Despite this complexity, the generalizations shown in Figure 2 hold for many cell types.

Distribution of organic ions across the cell membrane

Intracellular environment	Cell membrane	Extracellular environment	Change in membrane potential
Na^+ 12 mM	←	Na^+ 145 mM	Depolarization
K^+ 140 mM	→	K^+ 4 mM	Hyperpolarization
Na^+/K^+ selective	↔	Na^+ in, K^+ out	Depolarization
Cl^- 4 mM	←	Cl^- 120 mM	Hyperpolarization
Ca^{2+} 0.1 mM (free)	←	Ca^{2+} 2.5 mM	Diverse

The major inorganic ions are asymmetrically distributed across the membrane of a typical excitable cell and move down their electrochemical gradient (arrows) when permeable channels are opened. The movement of Na^+, K^+ and Cl^- ions produces characteristic changes in membrane potential: either depolarization (becomes more positive) or hyperpolarization (becomes more negative), but influx of Ca^{2+} has complex effects because Ca^{2+} functions as an intracellular second messenger and can activate other types of ion channel

2

Voltage-gated channels

Three families of voltage-gated channels have been identified on the basis of ion selectivity: Ca^{2+}, K^+ and Na^+ channels. They are thought to have evolved from a common ancestor and share many structural features. Within each family there are several channel subtypes that differ in their voltage sensitivity, tissue distribution and pharmacology. Voltage-gated Ca^{2+} channels, for example are subdivided into L-, N-, P- and T-types.

With a few exceptions (e.g. inward rectifier K^+ channels) most voltage-gated channels respond to changes in membrane potential in the same way: they open when the membrane depolarizes. After opening, some channels spontaneously enter a closed or inactivated state. Inactivation occurs rapidly in many Na^+ and Ca^{2+} channels but is slow or absent in certain K^+ channels.

Voltage-gated Na^+ and K^+ channels: the generation of action potentials depends on the interplay of voltage-gated Na^+ and K^+ channels. Action potentials occur in excitable cells when the membrane is depolarized beyond about –50 mV (threshold potential). This produces a transient increase in Na^+ permeability and a depolarization to about +30 mV owing to the rapid activation and inactivation of voltage-gated Na^+ channels. Simultaneously, a slow, sustained increase in K^+ permeability develops as voltage-gated K^+ channels open. This repolarizes the membrane to the resting potential of about –65 mV.

Voltage-gated Ca^{2+} channels: compared with action potentials, voltage-gated Ca^{2+} channel activation generates only small currents. However, because Ca^{2+} functions as an intracellular messenger, voltage-gated Ca^{2+} channels link electrical activity to changes in cell function. Important examples include the stimulation of vesicle fusion and neurotransmitter release at presynaptic nerve terminals and stimulation of contraction in cardiac and smooth muscle.

Drugs acting at voltage-gated channels

Local anaesthetics (e.g. lidocaine (lignocaine)) block voltage-gated Na^+ channels in nociceptive neurons and prevent the generation and propagation of action potentials, thereby producing anaesthesia. Similarly, block of cardiac voltage-gated Na^+ channels mediates the actions of class I antiarrhythmic drugs (e.g. lidocaine (lignocaine), flecainide).

Calcium antagonists typified by verapamil, diltiazem and the dihydropyridines (e.g. nifedipine) are useful antihypertensive and anti-anginal drugs because they specifically block L-type Ca^{2+} channels present in vascular smooth muscle and so cause vasodilatation. Verapamil and diltiazem also have antiarrhythmic properties (class IV antiarrhythmic drugs) because they block L-type Ca^{2+} channels in the atrioventricular and sinoatrial nodes of the heart.

Ligand-gated channels

Ligand-gated channels are divided into two main families, the nicotinoid channels and the ionotropic glutamate receptors. These protein families are not evolutionarily related but have similar functional properties. In both cases the ion channel is opened by the binding of a neurotransmitter to a specific receptor site located in the extracellular portion of channel complex. Four subfamilies of nicotinoid channel have been identified, of which two are cation selective (nicotinic acetylcholine receptors and 5-HT_3 receptors), and two Cl^- selective (γ-aminobutyric acid type A ($GABA_A$) receptors and inhibitory glycine receptors). All nicotinoid channels are pentameric proteins composed of homologous subunits. Within each subfamily, a range of subunits has been identified, which cells can assemble in different combinations to yield functionally distinct channel subtypes. Ligand-gated channel subtypes differ in their tissue distribution and pharmacology.

The most important function of ligand-gated ion channels is fast synaptic transmission. Excitatory transmission at the neuromuscular junction, for example, is mediated by nicotinic acetylcholine receptors located on the postsynaptic muscle membrane, while in the CNS a similar function is performed by ionotropic glutamate receptors. Conversely, $GABA_A$ and glycine receptors are responsible for fast synaptic inhibition.

Drugs acting at ligand-gated channels

Hypnotics, anxiolytics and anaesthetics: $GABA_A$ receptors are the targets of a wide range of sedative drugs including the benzodiazepines (e.g. diazepam), the barbiturates (e.g. thiopental (thiopentone)) and the general anaesthetics etomidate and propofol. These drugs all bind to allosteric sites on $GABA_A$ receptors and enhance inhibitory neurotransmission by potentiating the actions of GABA. Other sedative/psychoactive drugs inhibit excitatory neurotransmission. Examples include the dissociative anaesthetic ketamine and the hallucinogen phencyclidine, which block CNS ionotropic glutamate receptors.

Neuromuscular blocking agents: at the motor endplate, two classes of drug block neuromuscular transmission by binding to muscle-type nicotinic acetylcholine receptors. Non-depolarizing blockers (e.g. atracurium) are competitive antagonists, which occupy the acetylcholine binding sites of the receptor but do not open the channel. By contrast, the depolarizing blockers (e.g. succinylcholine) are high-affinity agonists that produce prolonged activation of the receptor. This causes sustained depolarization of the muscle membrane and thus prevents further electrical activity.

FURTHER READING

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Local Anaesthetic Agents

Malachy O Columb

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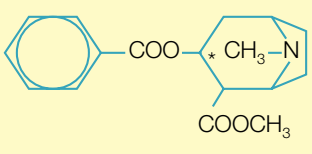
Since topical cocaine was first used for eye surgery by Koller in 1884, drugs that have 'membrane stabilizing activity' have been in widespread clinical use. In addition to local anaesthesia, related uses include the treatments of arrhythmias, epilepsy and neuropathic pain syndromes. Other significant milestones in the development of this class of drugs were procaine (1898), lidocaine (lignocaine) (1943) and bupivacaine (1957). Despite the numerous advances in the last 40 years in virtually all other aspects of anaesthetic pharmacology there has been no significant advance since bupivacaine. There have, however, been improvements in our understanding of dosing, particularly in combinations with other analgesics such as opioids and more recently with the appreciation of stereochemistry.

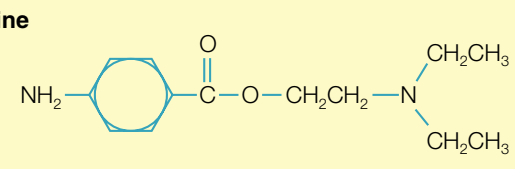
Chemistry

Local anaesthetics consist of three components: an aromatic ring, a link and an amine (Figure 1). Most anaesthetics are tertiary amines. They can be classified into two groups based on the nature of the link to amino amides [-NH-CO-] and amino esters [-O-CO-]. Being weak bases, they are solubilized for injection as strong, conjugate, acidic, hydrochloride salts (pH 3–6).

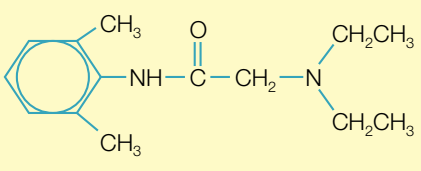
Cocaine



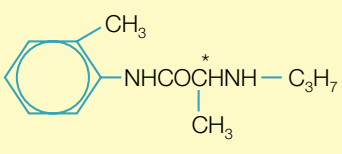
Procaine



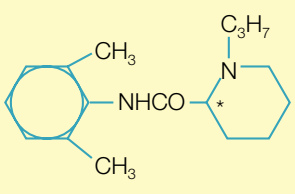
Lidocaine (lignocaine)



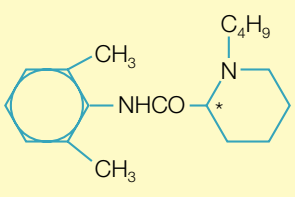
Prilocaine



Ropivacaine



Bupivacaine and levobupivacaine



* Denotes asymmetric carbon atom

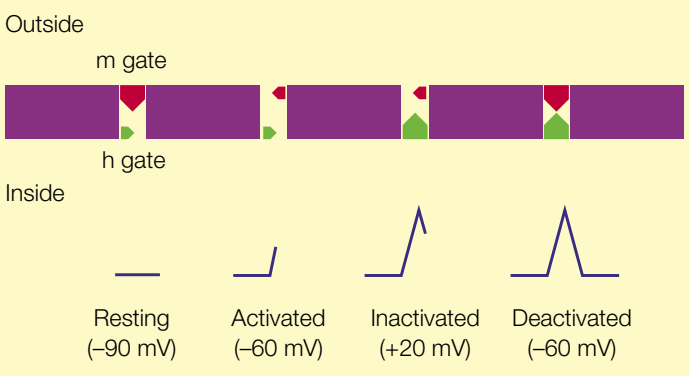
1

Mechanism of action

Local anaesthetics act by blocking the inward sodium current at the sodium ionophore during depolarization, thus preventing propagation of the axonal action potential. When delivered by injection, the local anaesthetic is predominantly in the acidic, ionized form (pH 3–6). This dissociates in the relatively alkaline perineural tissues (pH 7.4) to lipid-soluble, free base. This crosses the axolemma and re-ionizes in the acidic axoplasm to the active moiety, which blocks the sodium ionophore from within the cell or from the membrane lipid bilayer. It is therefore the non-ionized form that promotes delivery into the axon, and the ammonium or ionized state that provides activity. The ionophore exists in four states: resting, activated, inactivated and deactivated (Figure 2). Block is more readily achieved when the ionophore is activated than inactivated, and least readily achieved when deactivated and resting. During activation, the outer m gate opens at threshold potential (–60 mV) and ionized drug may gain direct access to the ionophore from outside. In the inactivated state, the inner h gate, which is voltage sensitive (+20 mV), closes after depolarization and prevents backward propagation of current. During the deactivated state (–60 mV), both m and h gates are closed so that the local anaesthetic can gain access only from within the membrane. During the resting phase (–90 mV), the inner h gate opens to prime the m gate for voltage-sensitive opening, so that ionized drug can gain access from the axoplasm.

The speed of onset of block is related to the concentration of molecules of local anaesthetic that are in the free base or non-ionized state. This depends on the initial dose, the dissociation constant (pK_a) and the pH of the tissues. By convention, dissociation constants are applied to the acidic forms and this sometimes causes confusion as inversions of the Henderson–Hasselbach equation (1) are often used depending on whether an acid or base is involved.

The four states of the sodium ionophore with axonal action potentials



2

$$pH = pK_a + \log([base] / [acid]) \quad (1)$$

$$\text{For an acid: } pH = pK_a + \log([ionized] / \{non\text{-}ionized\}) \quad (2)$$

$$\text{For a base: } pH = pK_a + \log([non\text{-}ionized] / [ionized]) \quad (3)$$

It is perhaps simpler to use equation 1 or a modification for all substances and consider only the acidic version:

$$pH = pK_a + \log([dissociated] / [associated]) \quad (4)$$

It is then helpful when looking at the pK_a for 'bases' to consider them in the acidic ionized form (Figure 3). Equations 1 and 4 can be further modified to:

$$pK_a - pH = \log([acid] / [base]) \quad (5)$$

$$pK_a - pH = \log([associated] / [dissociated]) \quad (6)$$

Using either equation and given that pH = 7.4, it can be seen that more molecules of bupivacaine (86%) will remain in the associated (ionized) form compared with lidocaine (lignocaine) (72%), and therefore the onset of action will be slower.

$$0.8 = \log([BH^+] / [B] \quad \text{versus} \quad 0.4 = \log([LH^+] / [L])$$

Typical pK_a, octanol partition coefficient and plasma protein binding values

Drug	pK_a	Partition coefficient	Protein binding (%)
Lidocaine-H^+ (LH^+)	7.8	43	64
Prilocaine-H^+	7.9	25	55
Bupivacaine-H^+ (BH^+)	8.2	346	93–95
Ropivacaine-H^+	8.2	115	94
Procaine-H^+	8.9		
Chloroprocaine-H^+	9.1		

3

The speed of onset of local anaesthesia can be accelerated by alkalinization or carbonation of the injectate. The addition of bicarbonate causes the strong conjugate acidic ammonium ions to dissociate and increase free base concentrations. The ingress of carbon dioxide into the axoplasm renders the interior even more acidic and this encourages re-ionization in a process referred to as diffusion trapping. Similarly, the acidic environment of an abscess will decrease the proportion in the free base state and this may explain the resistance to conduction block in such situations.

It is, however, useful to put the role of pK_a and pH into perspective. Chloroprocaine (used in the USA) has a very high pK_a (Figure 3) consistent with a very slow onset of block, but it is used when a fast onset is required for epidural anaesthesia (e.g. for emergency caesarean section). As a 3% w/v solution, larger doses can be given because of its low potential for systemic toxicity owing to ester hydrolysis. Thus, dosing is more important than pK_a.

The potencies of local anaesthetic agents are related to lipid solubility and are quantified as octanol partition coefficients (Figure 3). In addition, for agents that are enantiomers (enantiomorphs, optical isomers), it has been suggested that S-enantiomers are more potent than R-enantiomers. However, these apparent differences in potency are inconsistent and may be simply related to differences in vasoconstrictive and pharmacokinetic properties.

Local anaesthetic agents cross the membrane lipid bilayer as free base, however, the ionized form may enter from outside if the ionophore is repeatedly activated or opened. This gives rise to the phenomenon of frequency-dependent (or phasic) block. The onset of block with agents that have more ionized molecules outside the membrane can therefore be accelerated by stimulation. Thus, frequency-dependent block is better demonstrated for bupivacaine than for lidocaine (lignocaine).

Pharmacokinetics

Local anaesthetic agents are weak bases and, as such, become bound in the plasma to α_1-acid glycoproteins. Amino esters undergo rapid ester hydrolysis by plasma pseudocholinesterases and therefore have a lower potential for systemic toxicity. Amino amides undergo phase I and II hepatic cytochrome P450 metabolism. Phase I includes hydroxylation, N-dealkylation and methylation. Phase II includes conjugation with amino acids, such as glycine.

Toxicity

Since Albright reported six cases of cardiovascular collapse in 1979, following presumed accidental intravenous administration, attention has been focused on developing safer drugs, using lower doses and safer administration. Toxicity is usually manifested initially by subjective neurological disturbances, such as dizziness, circumoral tingling, metallic taste, diplopia and tinnitus. Objective signs include inappropriate agitation or sedation, tremor, myoclonic activity and epilepsy. The CNS signs usually precede the onset of hypotension with ventricular tachycardia or fibrillation. In animal studies, the ratio of CNS signs to cardiovascular collapse has been described for the various local anaesthetics to quantify a potential safety margin.

The likelihood of toxicity depends on the drug, dose, rate and site of injection, systemic absorption, acidaemia and clearance. Because of the multifactorial nature of toxicity, it has not been possible to establish absolute recommendations for maximum safe doses. Some information is, however, useful and the data in Figure 4 are provided for guidance only.

Cardiac arrest due to local anaesthetic toxicity with the pipecoloxylidine derivatives (e.g. bupivacaine), is more resistant to treatment. Ventricular tachycardia and fibrillation may induce a form of frequency-dependent entry of ionized drug into the myocardial cell, enhancing further toxicity. At the higher plasma concentrations associated with cardiovascular collapse it is likely that some cerebral protection may be provided due to direct anaesthetic effects. Therefore resuscitation attempts should be maintained as long as practical. Avoidance and treatment of acidaemia, hypercarbia and hypoxia will be useful. Atropine and adrenaline (epinephrine) may be required, the latter in addition to offset systemic vasodilatation. Bretylium may be useful as an antiarrhythmic agent in this setting for resistant ventricular arrhythmias.

Suggested maximum doses in a period of 4 hours

Local anaesthetic	Without adrenaline (epinephrine) (mg/kg)	With adrenaline (epinephrine) (mg/kg)
Cocaine	1.5	
Chloroprocaine	10	12
Lidocaine (lignocaine)	3	7
Prilocaine	4	8
Bupivacaine	2	4
Levobupivacaine	2	4
Ropivacaine	2.5	5

Specific local anaesthetic agents

Cocaine is a benzoic acid ester, which is used for topical anaesthesia of the mucosa of the upper airway because of its vasoconstrictor activity. Other local anaesthetics exhibit a biphasic effect on vasomotor tone – vasoconstriction at lower and vasodilatation at higher concentrations. The use of adrenaline (epinephrine) as a vasoconstrictor is unnecessary, particularly as cardiotoxicity may occur due to cocaine having indirect sympathomimetic activity. Cocaine blocks the presynaptic reuptake of noradrenaline (norepinephrine). Toxicity is enhanced because it is also resistant to metabolism by plasma pseudocholinesterases. Ester hydrolysis results in the release of ecgonine, a cerebral stimulant.

Lidocaine (lignocaine): the dimethylbenzene moiety is termed xylene. The amide link confers the term xylidine or xylidide. The major metabolite of N-dealkylation of one of the C_2H_5 groups is monoethylglycine xylidide (MEGX). Hepatic amidases result in various xylidine metabolites. Drugs that decrease hepatic blood flow, such as propranolol, will decrease metabolism and clearance. Lidocaine (lignocaine) is also used as a class 1_bantiarrhythmic agent.

Prilocaine is an exception in that it is a secondary amine. The monomethylbenzene moiety is termed toluene. The amide link confers the term toluidine. The o-toluidine metabolite of prilocaine can oxidize haemoglobin to methaemoglobin. Methylene blue can be used to reduce this ferric form back to the usual ferrous state. Prilocaine undergoes extensive pulmonary uptake, which results in lower systemic plasma levels and lower likelihood of toxicity. As a result, it remains the drug of choice for intravenous regional anaesthesia (Bier's block).

Bupivacaine is the butyl (C_4H_9) derivative of N-alkyl pipecoloxylidine and is therefore part of the same homologous series as mepivacaine (methyl: CH_3) and ropivacaine (propyl: C_3H_7). All pipecoloxylidine derivatives have an asymmetric carbon atom which confers chirality or enantiomerism. The usual preparation of bupivacaine is as a racemate. Following N-dealkylation, the pipecoloxylidine metabolite still has some activity.

Ropivacaine (or propivacaine) is the S-enantiomer of the propyl (C_3H_7) derivative of N-alkyl pipecoloxylidine. Metabolites include 3-hydroxyropivacaine (40%) and pipecoloxylidine (5%). The octanol partition coefficient for ropivacaine (115) suggests lower potency when compared with bupivacaine (346), but ropivacaine may exert more vasoconstrictor activity to offset this.

Levobupivacaine is the S-enantiomer of racemic bupivacaine. The plasma-bound fraction of levobupivacaine is greater at 95% compared with the racemate at 93%. *Chirocaine* is bound by Directive 91/507 of the European Economic Community (EEC), which states that the % w/v should be expressed in terms of the agent (free base) alone and not the hydrochloride salt. So levobupivacaine, by virtue of being expressed as free base, has 11% more molecules than the equivalent % w/v of the racemate bupivacaine (*Marcain*), which predates the directive. This difference in expressed formulation should be considered when comparing it with other local anaesthetics.

Stereochemistry

The pipecoloxylidines can exist as two enantiomers, R(+) and S(–). The prefixes R (rectus) and S (sinister) refer, respectively, to the clockwise or anticlockwise arrangement of atoms or molecules around the asymmetric carbon atom based on an arbitrary hierarchical series of sequence rules. They are not consistently related to rotations of planes of polarized light, and are therefore independent of other prefixes or terminologies, such as *d, l,* D, L, (+), (–), dextro or laevo.

Evidence from animal and human models has suggested that, among certain chiral local anaesthetics, the S-enantiomer was less toxic than the R-enantiomer and thus less toxic than the racemate. S-propivacaine (ropivacaine, *Naropin*) was developed for clinical use. Two clinical toxicology studies in human volunteers showed that 12–25% more ropivacaine could be tolerated before the onset of CNS toxicity. This perceived advantage for ropivacaine was based on the assumption of equipotency with bupivacaine. Two recently published studies using the minimum local analgesic concentration (MLAC) model found that ropivacaine was 40% less potent than bupivacaine. The human toxicology and MLAC efficacy studies have been formally compared to derive therapeutic indexes and the relative therapeutic ratio in humans for both local anaesthetics. The relative therapeutic ratio (ropivacaine:bupivacaine) for clinical CNS toxicity of 0.75 was found to be significantly in favour of bupivacaine. The perceived benefits for ropivacaine in relation to toxicity, motor-block sparing and differential sensory blockade may have to be re-evaluated, and may simply be explained by potency issues.

The most recent development has been that of S-bupivacaine (levobupivacaine). A human toxicology study has demonstrated that human subjects tolerated a median dose of levobupivacaine for the onset of CNS symptoms that was 5% greater than the racemate. In addition, levobupivacaine caused a significantly lower reduction in cardiovascular performance as assessed by stroke index, acceleration index and ejection fraction. Some of these effects may represent less vasodilatation and reductions in preload due to the significant augmentation of diastolic pressure with the racemate. An efficacy MLAC study showed that the potency of levobupivacaine was 98% that of the racemate on a % w/v basis (87% in molar terms). Again comparing therapeutic indexes, the relative therapeutic ratio (levobupivacaine:racemic bupivacaine) for CNS toxicity is 1.03 and therefore marginally in favour of levobupivacaine.

Emla

The development of *Emla* (eutectic mixture of local anaesthetics) for topical use has been welcomed, particularly in paediatric practice. This 50:50 solid solution of lidocaine (lignocaine) and prilocaine as lipid-soluble free bases has the lowest melting point of any combination. This defines the eutectic point and thus the eutectic mixture. Methaemoglobinaemia caused by extensive application and systemic absorption of prilocaine in infants has been reported. Amethocaine is now also available for topical application.

The future

Greater understanding of the role of chirality in local anaesthetic pharmacology is still required to justify clinical use further. Local anaesthetic-sparing combinations with other analgesics continue to be studied to develop synergistic regimens. Research is continuing into alternative approaches such as selective binding and inhibition of the sodium ionophore with dilutions of naturally occurring toxins, such as tetrodotoxin. It has become clear from errors in the development of enantiomers for clinical application that determining the relative potencies of drugs is of prime importance in evaluating claims for perceived advantages in toxicity and blocking characteristics.

FURTHER READING

Reynolds F. Does the Left Hand Know What the Right Hand is Doing? An Appraisal of Single Enantiomer Local Anaesthetics. *Int J Obstet Anesthesia* 1997; **6:** 257–69.

Major Trauma and Exsanguination

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Major trauma causes life-threatening injuries to single or multiple body systems and organs. Most patients with major trauma die at the incident site and only a small proportion with injuries and haemorrhage present for treatment. Their outcome depends on early corrective management and is influenced by their age, the mechanism of injury and any pre-existing disease process. Exsanguination is blood loss from the vascular compartment (loss at site of injury; e.g. fractured shaft of femur) and fluid shift to the extravascular space (obligatory oedema in tissues).

Blood loss

In an adult weighing 70 kg the normal blood volume is about 5 litres. Any significant loss can lead to hypovolaemia resulting in reduced preload and cardiac output. Blood loss is classified on the volume or the percentage loss in a healthy young adult (see Figure 2, page 289). Haemorrhagic shock following depletion of circulatory volume (exsanguination) leads to poor tissue perfusion, cell hypoxia or anoxia and finally cellular and tissue death. Haemorrhagic shock progresses through four stages if untreated and correlates to the volume of blood loss.

Initial stage (Class I)
Reduced cardiac output with lowered oxygen delivery leads to anaerobic metabolism at the cellular level.

Compensatory stage (Class II)
Neurological (sympathetic), endocrine and chemical responses ensure adequate tissue perfusion and delivery of oxygen to vital organs with progressive vasoconstriction in skin, viscera, muscle and kidneys. A fall in blood pressure is detected by baroreceptors, and this activates the sympathetic system via the vasomotor centre. Sympathetic stimulation triggers the fight, flight and fright response (e.g. cold and clammy skin, tachycardia, tachypnoea). The renin–angiotensin–aldosterone system is activated leading to fluid retention, reduced urinary output and vasoconstriction to help maintain blood pressure. Raised levels of cortisol and other stress hormones contribute to hyperglycaemia, shifting fluid into the vascular compartment, thus increasing circulatory volume. Antidiuretic hormone and aldosterone production is also stimulated leading to fluid and sodium retention and potassium excretion by the kidneys. The usual sign of this stage is tachycardia, but in severe and rapid blood loss, stimulation of ventricular distortion receptors can lead to vagally mediated bradycardia.

Progressive stage (Class III)
Reduced circulation and oxygen supply to the vital organs results in organ failure. Increased capillary permeability and loss of autoregulation reduces coronary blood flow leading to myocardial depression. Serum creatinine in the kidney is raised as are amylase and lipase in the pancreas, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the liver. Ischaemic cells in the gut allow entry of bacteria and endotoxins.

Refractory stage (Class IV)
This is the irreversible terminal stage in which multiple organ failure occurs.

Cell damage
Anaerobic respiration and metabolism in the cell produce lactic acid contributing to metabolic acidosis. If adequate perfusion is not restored, cells swell causing cellular damage and death. Leakage of potassium and lysosomal enzymes from ischaemic cells combined with other toxic metabolites leads to precapillary vasodilatation and increased capillary permeability. This accounts for increased capillary filling and transudation of fluid to the interstitial compartment and a further fall in the intravascular volume.

Resuscitation may also have adverse effects, known as reperfusion injury (e.g. restoring oxygen delivery to tissues may trigger further cell damage). Experimental studies show that allopurinol may have a protective effect at cellular level.

Management

The A (airway), B (breathing) and C (circulation) approach ensures appropriate prioritization and management of life-threatening states. It is important to correct the physiological status and detect the specific cause of haemorrhage. Treatment involves:

- adequate oxygen delivery and consumption
- rapid and adequate fluid replacement in the intravascular compartment and prevention of further loss
- use of pharmacological agents.

Oxygenation
Rapid correction of pulmonary gas exchange is essential. High flow oxygen is essential and should be given by simple or advanced airway techniques and assisted mechanical ventilation. The aim is to increase arterial blood oxygen by augmenting the fraction of oxygen in inspired air (FiO_2), improving oxygen delivery and reducing unnecessary oxygen consumption.

Oxygen delivery can be optimized by improving microvascular circulation, the pulmonary ventilation-to-perfusion ratio and individual organ perfusion. Oxygen consumption and demand can be reduced by relieving pain and stress using analgesics and sedatives, assisting the work of breathing by using mechanical ventilation and avoiding hyperthermia because it increases the metabolic rate.

In a severely shocked patient, mechanical ventilatory assistance is required if the partial pressure of oxygen in arterial blood (PaO_2) stays below 8.7 kPa despite high flow oxygen, and if the respiratory work required to maintain adequate ventilation is excessive.

Fluid
Rapid and adequate volume replacement is paramount. A bolus of fluid, 20 ml/kg, should be administered rapidly as a fluid challenge and repeated as required to maintain correction. Failure to respond to the fluid is an indication that the amount transfused is inadequate or that there are continuing or unrecognized fluid losses. Whether to use crystalloids or colloids is debated, however, either can be used initially because it is rapid replacement that is important. Crystalloid solutions help to replace the intravascular volume rapidly but the effect is short lived. Colloid solutions help to augment the intravascular volume and the effect lasts longer. A combination of the two can help to attain an optimum result, a 2:1 ratio of crystalloid:colloid works well, but must be closely monitored to ensure adequate volume replacement. A small volume of hypertonic saline or *Dextran* given over a short period may help to improve cardiovascular function and may protect against reperfusion injury.

Haemodilution is beneficial, a fall of haematocrit to 30% improves microcirculation and allows optimal oxygen delivery to tissues. A fall below 25% or blood loss over 1.5 litres requires replacement of erythrocytes. Cross-matched blood is ideal, but if there is severe and rapid blood loss, matched blood or if necessary O negative uncrossed blood should be given. Use of SAG-M blood (plasma-poor red cells in **S**aline, **A**denine maintains 2,3-DPG activity in stored blood, **G**lucose and **M**annitol) allows better uncoupling of oxygen in cells. Further blood loss can be prevented by splintage, elevation of limbs, direct pressure and operative intervention.

Pharmacological assistance
Pharmacological agents should be considered when adequate fluid replacement and corrective gas exchange have failed to achieve cardiovascular stability. They are needed to improve the microvascular circulation and in doing so improve tissue oxygen delivery, reduce afterload and improve cardiorespiratory function.

Inotropic agents increase myocardial contractility but risk being slightly arrhythmogenic. They are classified as β_1-sympatho-mimetics (dobutamine, dopamine) or phosphodiesterase inhibitors (amrinone). In addition to improving contractility, dobutamine causes mild vasodilatation and improves oxygen consumption. Dopamine at low dose (1–5 μg/kg/minute) vasodilates and improves renal perfusion and at high dose (> 10 μg/kg/minute) affects vasoconstriction. Amrinone has a mild vasodilatory effect.

Adrenaline (epinephrine) stimulates contractility at low dose (0.01–0.2 μg/kg/minute) and is a vasoconstrictor at high dose.

Vasodilators reduce the filling pressure (preload) and the resistance against which the heart pumps (afterload) with a reduction in pulmonary congestion. Coronary artery dilatation improves myocardial oxygenation. Nitroglycerin affects venous dilatation at low dose and arterial dilatation at high dose. Nitroprusside and morphine affect venous and arterial dilatation and morphine also acts as an analgesic. Furosemide (frusemide) is a venous dilator and a loop diuretic.

Vasopressors: adrenaline (epinephrine), noradrenaline (nor-epinephrine), and phenylephrine, cause peripheral vasocon-striction to maintain circulation to the vital organs.

Acid–base balance can be corrected by adequate ventilation and improved cardiac output. Sodium bicarbonate is occasionally used in patients with pre-existing hyperkalaemia (e.g. those taking spironolactone) and may be exacerbated by massive blood loss. Diuretics (e.g. furosemide (frusemide)) are used in the later stages to reduce pulmonary congestion.

Late stages of shock
'Supranormal' levels of cardiorespiratory function, micro-circulation and individual organ flow may need to be attained in severe or late stages of shock to ensure good recovery, correct the oxygen debt that may follow tissue hypoperfusion and prevent reperfusion injury.

In the late stages of shock, prostacyclin may help the microcirculation by selectively reducing postcapillary resistance and reducing capillary leak.

Organ susceptibility to microcirculation disturbance in shock may vary. Prostacyclin improves splanchnic blood flow, preventing gut mucosal ischaemia and may help renal perfusion. Mannitol improves osmotic diuresis and may reduce the risk of reperfusion injury. Furosemide (frusemide) helps to increase renal prostaglandin production and thus improve renal circulation. Prostacyclin and prostaglandin E may help pulmonary parenchymal blood flow. ◆

FURTHER READING

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Malignant Hyperthermia

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Malignant hyperthermia (MH) was first defined as a clinical entity in 1960, when Jim Collier, a consultant anaesthetist in Melbourne, Australia, reported a strange reaction a young man had developed with halothane anaesthesia. Collier identified the hyperthermic response to anaesthetic vapours and the familial nature of predisposition to MH (several ether anaesthetic-related deaths had occurred in the patient's family).

Clinical features

The clinical features of MH comprise two groups that are causally but not clinically related (Figure 1).

Clinical features of malignant hyperthermia

Metabolic
- Hypercapnia
- Tachycardia
- Hyperthermia
- Acidosis
- Cyanosis

Muscle
- Spasm, rigidity, contracture
- Hyperkalaemia
- Myoglobinaemia/uria
- Raised creatine kinase
- Renal failure
- Disseminated intravascular coagulopathy

The first sign may be muscle spasm after suxamethonium (succinylcholine), though in the absence of this drug, muscle spasm usually develops later in response to administration of anaesthetic vapours. Probably as a response to this muscle spasm, skeletal muscle fibres become damaged (probably as a result of ischaemia), and potassium, myoglobin and creatine kinase are released into the circulation. Serum potassium can rapidly reach high levels (up to 15 mmol) that can be lethally cardiotoxic. Myoglobin can be deposited in the renal tubules, which can result in tubular obstruction and renal failure. The cumulative effect of the release of intracellular muscle contents into the circulation can be a disseminated coagulopathy.

Hypercapnia may be the first sign of metabolic stimulation. It is associated with an increased oxygen demand, which is achieved by an increase in cardiac output following an increase in heart rate. However, tachycardia is limited to 200 beats/minute and so when the heart rate reaches the maximum, the increasing demand for oxygen results in arterial desaturation and cyanosis. With developing hypoxaemia, lactic acidosis occurs and the combined effects of raised bicarbonate (hypercapnia) and raised lactate can reduce the pH to about 6.7 (a potentially lethal acidosis). Throughout the whole episode, the metabolic stimulation causes hyperthermia which may reach 43°C within the first hour. Above this temperature, proteins begin to denature and irreversible cerebral damage occurs.

The speed of the reaction may be so fast that a dangerous metabolic/muscle imbalance occurs within 30 minutes, and death may occur within 1 hour.

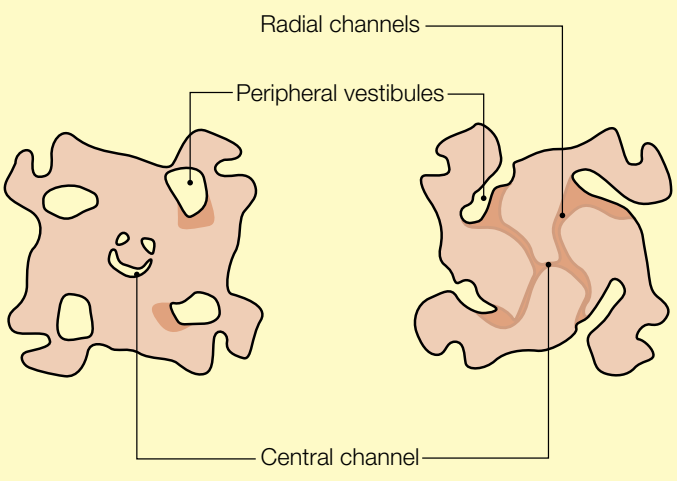
The incidence of MH may be as high as 1/6000 anaesthetics (Japan) or as low as 1/200,000 (UK). It depends on the use of the trigger drugs (suxamethonium and inhalational volatile vapours) and exposure to them. Thus, certain types of surgery (e.g. trauma and ear, nose and throat) are more likely to be associated with MH because of the selection of anaesthetic technique.

Pathophysiology

The acute episode is associated with a rise in intracellular ionic calcium. Recently, however, the demonstration of causative mutations in the *RYR1* gene on chromosome 19 has identified the abnormality predisposing to MH in the ryanodine calcium gate.

The ryanodine receptor (Figure 2) is a tetramer attached to the dihydropyridine voltage sensor in the T tubule in skeletal muscle (Figure 3). A mutation in a gene encoding for protein in this complex gene is intellectually satisfying especially as 15 gene mutations in the *RYR1* gene have 'causative' properties.

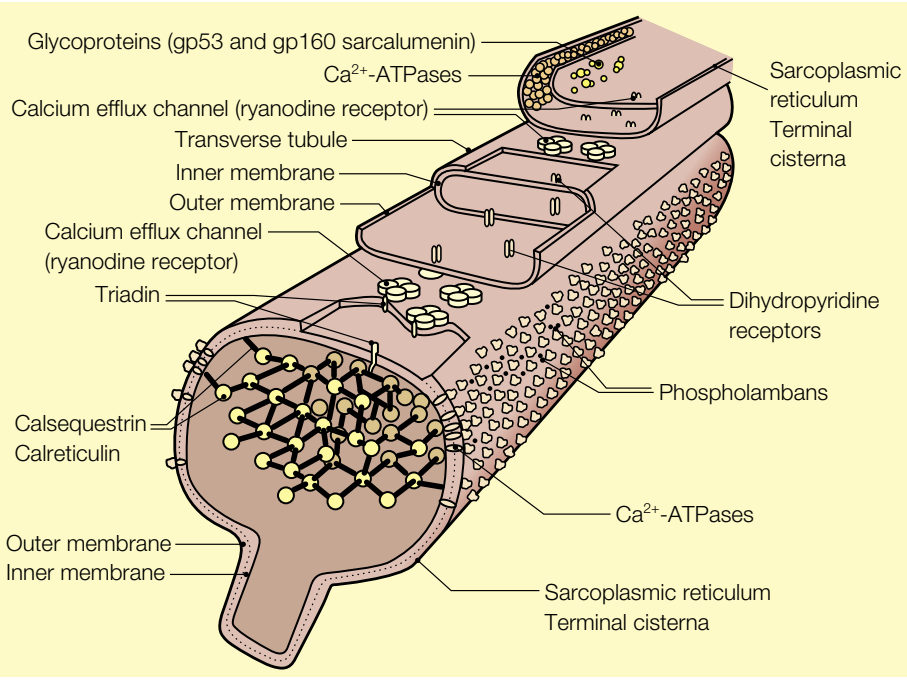
Ryanodine receptor



Cross-section of a computer-generated, three-dimensional reconstruction of the foot structure (calcium efflux channel) of skeletal muscle (ryanodine receptor). The reconstruction of the molecular interior shows that a single central channel leads outward through four radial channels to four peripheral vestibules which open to the sarcoplasm. This structural organization may allow the release of Ca^{2+} in the sarcoplasm at right angles to the central channel along the plane of the junctional gap

Triad

The relative positions of T tubule tetrads (dihydropyridine receptors), sarcoplasmic reticulum foot proteins (Ca^{2+} efflux channels or ryanodine receptors) and triadin are shown. Also shown are the proteins of the sarcoplasmic reticulum lumen, calsequestrin and calreticulin, and the glycoproteins gp53 and gp160 (sarcalumenin). The calcium ATPases and phospholamban pentamers are depicted on the outer surface of the sarcoplasmic reticulum. The ryanodine receptors occupy the junctional gap between the T tubule and sarcoplasmic reticulum. Triadin molecules co-localize with the ryanodine receptors in the junctional sarcoplasmic reticulum and serve to anchor calsequestrin adjacent to the sites of Ca^{2+} efflux from the sarcoplasmic reticulum. Dihydropyridine receptors are located in the T tubule junctional membrane opposite alternate ryanodine receptors. The T tubule tethers are not depicted



One of the problems in the genetics of MH is the apparent heterogeneity. Only 60% of families have an *RYR1* mutation. In one family the causative and defined gene mutation is on chromosome 1, and other genes on chromosomes 3, 5, 7 and 11 have been shown to co-segregate. It is perhaps surprising that there are so many causative mutations for MH in humans, whereas only one porcine mutation has been identified. It is found in three breeds of pig (Landrace, Pietrain, Poland China) as well as in some humans.

Pathopharmacology

MH is caused by two different types of chemicals (suxameth-onium and volatile inhalational vapours). Most of the work on inducing MH has been performed on susceptible pigs which are probably homozygous for MH due to inbreeding whereas most humans are heterozygous for the *RYR1* mutation.

If the *RYR1* mutation is the causative gene, and the evidence is good, it is difficult to understand how suxamethonium, which is a charged ionic compound, can penetrate the T tubule membrane and find a receptor on a membrane protein. Suxa-methonium causes increased masseteric muscle tone in 85% of normal subjects and it may be that people susceptible to MH are in the group that shows the most marked reaction to suxameth-onium owing to calcium lability within the sarcosplasm.

Other drugs that have been implicated in the induction of MH include phenothiazines, lidocaine (lignocaine), nitrous oxide, tricyclic antidepressants and ketamine, but the evidence has not been substantiated.

Management

Guidelines for the management of an MH crisis are given in Figure 4.

Guidelines for the management of a malignant hyperthermia crisis

- Presentation of malignant hyperthermia (MH) varies and the order of treatment may have to be modified. The steps below are intended as an aide memoire
- Know where dantrolene is stored in your theatre

Diagnosis: consider MH if
- Masseter muscle spasm occurs after suxamethonium
- Unexplained, unexpected tachycardia occurs with unexplained, unexpected increase in end-tidal CO_2

Early management
- Withdraw all trigger agents (i.e. all anaesthetic vapours)
- Install clean anaesthetic breathing system and hyperventilate
- Abandon surgery if feasible
- Give dantrolene, 1 mg/kg i.v. initially, and repeat as required up to 10 mg/kg
- Measure arterial blood gases, potassium and creatine kinase
- Measure core temperature
- Begin surface cooling avoiding vasoconstriction

Intermediate management
- Control serious arrhythmias with β-blockers
- Control hyperkalaemia and metabolic acidosis

Later management
- Clotting screen to detect disseminated coagulopathy
- Take first voided urine sample for myoglobin estimation
- Observe urine output for developing renal failure
- Promote diuresis with fluids/mannitol (20 mg dantrolene contains 3 mg mannitol)
- Repeat creatine kinase at 24 hours

Late management
- Consider other diagnoses and carry out appropriate investigations (e.g. vanillylmandelic acid (VMA), thyroid function tests, white cell count, chest radiography)
- Consider possibility of myopathy, neurological opinion, EMG
- Consider possibility of recreational drug ingestion (Ecstasy)
- Consider possibility of neuroleptic malignant syndrome
- Counsel patient and/or their family regarding implications of MH
- Refer patient to MH unit

Acute crisis

MH can occur rapidly during anaesthesia and many deaths have been reported within 1 hour of induction. The marked reduction in mortality since the 1960s, from 70% to 1%, is due to anaesthetists' greater awareness and knowledge of the condition and the better monitoring of all anaesthetized patients by oximetry, capnography, electrocardiography and pulse rate recording.

Early diagnosis may be sufficient to abort a crisis merely by withdrawing the causative drugs and installing a clean anaesthetic breathing system. Hypercapnia can be controlled by mechanically hyperventilating the lungs, and the developing hypoxaemia can be countered by increasing the inspired oxygen fraction.

The only specific drug to control MH is dantrolene, 1 mg/kg i.v. initially. It may have to be repeated up to 10 mg/kg to establish full control of the excessive calcium release from the sarcoplasmic reticulum (the calcium store in the muscle cell). Procainamide and glucocorticoids have also been used to control calcium release, but they are general membrane stabilizers and do not have any specific action on the sarcoplasmic reticular membrane.

The metabolic status of the patient must be monitored by measuring the arterial blood gases and plasma potassium repeatedly until the crisis is controlled. Blood should be kept for a later measurement of creatine kinase (CK), which indicates the degree of muscle breakdown. CK measurement should be repeated 12 hourly.

The earliest descriptions of MH recorded high body core temperatures as a consequence of prolonged metabolic stimulation. Today, owing to early diagnosis, the body core temperature seldom rises more than 1–2°C. Core temperature can help to monitor the progress of the acute crisis and should be recorded. In small children, who can develop rapid hyperthermia, body surface cooling could be considered using lukewarm water (cold water induces vasoconstriciton and heat retention).

Mainly as a consequence of the developing hyperkalaemia, the heart rhythm may become irregular. This can be controlled using β-adrenergic blockers. Hyperkalaemia should be controlled by dantrolene and the other measures mentioned above. Rising potassium can usually be controlled by dextrose/insulin, but in the worst case haemofiltration should be considered.

When MH is controlled, the pH stabilizes and begins to return to normal levels. If the pH remains low, an infusion of bicarbonate should be contemplated.

Late management
When muscle breakdown has been intense or prolonged, there is a danger of developing a disseminated intravascular coagulopathy (DIC). Any suggestion of oozing from cut surfaces or bruising should be investigated using a coagulation screen. Advice should be sought from a haematologist if a DIC develops.

The first voided specimen of urine should be tested for myoglobin using spectroscopy. Intense myoglobin-uria could herald the onset of renal tubular obstruction and renal failure, therefore all patients should be given a forced diuresis using a crystalloid load combined with an osmotic diuretic (e.g. mannitol).

A severe MH crisis can continue intermittently for several days with metabolic and body temperature instability. In these circumstances dantrolene, 25 mg q.d.s. may be given orally. Continuing renal failure may require haemodialysis before recovery.

Aftercare
There is often doubt about the diagnosis of MH, and the authors recommend that the patient is referred to an MH unit to consider whether a muscle biopsy using *in vitro* contracture testing (IVCT) is indicated. If the clinical diagnosis is confirmed by IVCT, family screening can be organized.

In 25% of families, the diagnosis of MH susceptibility can be made using DNA detection of one of the 15 known causative mutations in the *RYR1* gene on chromosome 19. In conjunction with other members of the European MH Group, the authors have published guidelines for DNA screening (see Further reading).

If MH is not confirmed, other causes of MH-like reactions should be sought including toxaemia, myopathy, thyroid disease, phaeochromocytoma, hypersensitivity to a drug or drug combination and neuroleptic malignant syndrome.

Management of anaesthesia
In the UK, 2500 MH-susceptible individuals have been identified. When they require surgery, they must inform the anaesthetist of their susceptibility (they are encouraged to wear an identification necklace). Anaesthesia can be conducted most easily using a local anaesthetic technique, though general anaesthesia can be conducted safely by avoiding known inducing agents. Prophylactic dantrolene is unnecessary. Modern anaesthetic techniques include the use of total intravenous administration and inhalational vapours can easily be avoided. Non-depolarizing relaxants act quickly enough for rapid intubation without the need for suxamethonium. ◆

ACKNOWLEDGEMENTS
The authors thank Dave Iles for permission to reproduce Figures 2 and 3 from Malignant Hyperthermia: A Molecular Genetic Study. CIP-Gegevens, Koninklijke Biblotheek, Den Haag, 1994.

The Association of Anaesthetists of Great Britain and Ireland are thanked for the Guidelines for the Management of a Malignant Hyperthermia Crisis, which they produced as a poster for the authors.

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Mechanisms of Drug Action not Involving Protein Binding

Barbara J Pleuvry

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Most drugs act by binding to proteins, but a few exert their effects by osmosis, bulk formation, interacting directly with nucleic acids or by altering the pH of a physiological fluid such as stomach contents or urine. The latter mechanism is also discussed under drug absorption and drug interactions elsewhere.

Drugs utilizing osmosis

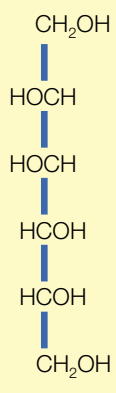
Osmosis is the physiological process by which water moves across a semipermeable membrane from one solution towards another that contains a higher solute concentration. Drugs that use this process are the osmotic diuretics (e.g. mannitol) and the osmotic laxatives (e.g. lactulose and the saline purgatives).

Osmotic diuretics

Mannitol (Figure 1) is a highly water-soluble compound that is not absorbed readily across membranes. It is given intravenously in relatively large doses so that it makes up an appreciable part of plasma osmolarity. Mannitol is unable to cross the blood–brain barrier or cross into the eye, therefore it can extract water from these compartments. It is used to treat cerebral oedema and glaucoma (raised intraocular pressure). Mannitol is filtered in the glomerulus of the kidney and very little is reabsorbed, thus increasing the osmotic pressure of the urine. Water is drawn into the renal tubules where they are most permeable to water (i.e. the proximal tubule, the descending limb of the loop of Henle and the collecting ducts). The increased osmotic pressure within the ducts reduces the passive reabsorption of water. The increased volume of urine reduces the dilution of sodium and thus the electrochemical gradient for its reabsorption, therefore sodium reabsorption is also reduced. Mannitol has been used to prevent acute renal failure because it can maintain a flow of urine even when the glomerular filtration rate is compromised. However, if the patient is unable to make urine, mannitol can cause cardiac failure or pulmonary oedema. Other osmotic diuretics include glycerol, isosorbide and urea, but mannitol is the most commonly used.

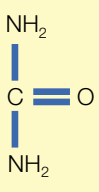
Osmotic diuretics

Mannitol

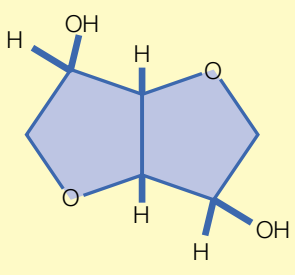


Glycerol

Urea



Isosorbide



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Osmotic laxatives

Osmotic laxatives increase the volume of fluid in the lumen of the gastrointestinal tract and accelerate the transference of the contents through the intestine to the colon. The excessive bulk of fluid in the colon causes evacuation about 1 hour later. Magnesium sulphate (Epsom salts) and magnesium hydroxide are virtually insoluble and remain in the intestine to exert an osmotic effect. Very little is absorbed in a healthy patient, but small children or patients with poor renal function can absorb enough to cause problems such as CNS depression, heart block or neuromuscular blockade. Lactulose is a disaccharide of fructose and galactose and is administered as an oral solution. Bacteria in the intestine split lactulose into the two component sugars, which are poorly absorbed. These are fermented to form lactic and acetic acids, which cause the osmotic effects required; this process takes several days. All osmotic laxatives can cause abdominal cramps.

Bulk laxatives

Bulk laxatives are polysaccharide polymers that are not broken down in the gut, but retain water, thus inducing peristalsis; examples include bran, agar and methylcellulose.

Faecal softeners and antifoaming agents

The addition of a surfactant to the gastrointestinal tract promotes evacuation by softening the faeces. An example is docusate sodium, which also has some mild stimulant activity on intestinal motility.

Several antifoaming agents are included in many commercial antacid mixtures to break up gas bubbles in the stomach. It is believed that small air bubbles trapped during swallowing can lead to gastric bloating and flatulence. Simethicone (dimeticone) is an effective antifoaming agent but there is no evidence that it is useful in treating gaseous intestinal distension.

Gel-forming substances

Compounds such as kaolin, pectin and attapulgite form semisolid gels within the intestine, cause resistance to flow and increased firmness of the stool. They are commonly used to treat diarrhoea, but they do not reduce the volume of liquid excreted and thus have little benefit other than the formation of a firmer stool. It has been suggested that they absorb bacterial toxins but there is no firm evidence to support this view.

Drugs affecting nucleic acids

The nucleic acids found in cells are deoxyribonucleic acid (DNA), which makes up the genetic codes, and the three ribonucleic acids (RNA), which co-operate to make specific proteins using the information provided by DNA. The three types of RNA are messenger (mRNA), transfer (tRNA) and ribosomal (rRNA). The nucleic acids are formed from a string of nucleosides: each nucleoside consisting of a nitrogen-containing base connected to a pentose sugar and a phosphate group. RNA and DNA are compared in Figure 2.

Comparison of DNA and RNA

	RNA	DNA
Pentose sugar	Ribose	Deoxyribose
Nitrogen-containing bases	Adenine Cytosine Guanine Uracil	Adenine Cytosine Guanine Thymine
Function	Perform protein synthesis directed by DNA	Stores genetic code controlling protein synthesis
Size and shape	100–50,000 base pairs Shape varies with degree of hydrogen bonding along strand Three types: mRNA, tRNA, rRNA	More than 45 million base pairs Paired strands coiled into a double helix

2

Many drugs used in the treatment of cancers target DNA. The anti-cancer antibiotic, bleomycin, causes fragmentation of the DNA strand following free radical formation. This prevents mammalian cell division.

Alkylating agents (Figure 3) covalently attach alkyl groups to other molecules by the formation of positively charged carbonium ions. The carbonium ions interact with electron-rich sites such as those found on DNA. Most clinically useful drugs have two alkylating groups so that they can form covalent cross-links between adjacent strands of nucleic acids. This cross-link hinders subsequent separation of the two strands and is more difficult to repair than a single alkyl bond.

Examples of alkylating agents

Alkylating agents	Comment
Cyclophosphamide	Alkylate N7 bond of the guanine base
Nitrosoureas (e.g. lomustine)	Lipid soluble, crosses the blood–brain barrier therefore useful for tumours of the brain and meninges
Busulfan (busulphan)	Selective effect on bone marrow Used in chronic granulocytic leukaemia
Cisplatin	Causes intrastrand cross-linking between the N7 and O6 atoms of adjacent guanine bases. Particularly useful for solid tumours of the testis

3

Acriflavine and other acridine topical disinfectants intercalate into the DNA causing increasing distance between base pairs leading to frame-shift mutations.

Some antibiotics inhibit bacterial protein synthesis by interfering with the function of RNA. For example tetracycline competes with tRNA by binding to the complementary base on mRNA preventing the production of essential proteins.

Agents changing the pH of compartments

Urine can be made more alkaline by sodium bicarbonate, sodium citrate or potassium citrate. The salts are metabolized and the cations are excreted with bicarbonate. The use of these for the treatment of weak acid overdose is discussed elsewhere, as is the use of ammonium chloride to acidify the urine for the treatment of weak base overdose.

Alkalization of the urine also decreases inflammation in the urinary tract and may have some antibacterial effects.

Antacids are used to neutralize gastric acid and increase gastric pH. They are present in many over-the-counter indigestion mixtures and include magnesium hydroxide, magnesium trisilicate and aluminium hydroxide gel. Sodium bicarbonate is also effective in the short term, but the carbon dioxide produced can cause belching and the stimulation of a secondary rise in gastric acidity. ◆

Mechanisms of Drug Interactions

Barbara J Pleuvry

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Any physician administering more than one drug to a patient must be aware of potential interactions. While many are trivial and unimportant some are life threatening. If in doubt, 'look it up'. The response of a patient to a drug can be modified by individual variation (e.g. age, obesity) and by interactions with other drugs, foods or chemicals ingested at the same time. There are several types of drug interaction (Figure 1), but many are theoretical or clinically trivial. Drug interactions are usually described as pharmacokinetic (one drug affects the absorption, distribution or excretion of another) or pharmacodynamic (changes in drug action occur in the area of the target tissue). The later includes the actions of agonists and antagonists at the same or different receptors.

An additional mechanism of drug interaction is when two drugs are mixed and one complexes with the other; this is really a pharmaceutical incompatibility. An example is the formation of a complex when thiopental (thiopentone) and suxamethonium are mixed in the same syringe. This is simple chemistry and no pharmacological principle is involved. However, pharmaceutical incompatibilities can occur in the body and may be manipulated for the patient's benefit. An example is the termination of the anticoagulant activity of the strongly acidic heparin by the strongly basic protamine sulphate. In addition, heavy metals can be chelated by chemicals and removed from the circulation or the gastrointestinal tract. A chelate is a complex formed between a metal and a compound that contains two or more potential ligands. The stability of the chelate varies with the metal and the ligand. Calcium has a higher affinity for oxygen ligands than for sulphur and nitrogen ligands, while mercury and lead have the opposite affinity. This allows drugs to be designed that will chelate only with a specific metal. Some chelating agents used in medicine are listed in Figure 2.

Classification of drug interactions

Pharmaceutical incompatibility

Pharmacodynamic interactions
- Interaction at or near the site of action

Pharmacokinetic interaction
- Interaction at the site of entry
- Interaction at or near storage sites
- Interaction at or near the site of metabolism
- Interaction at or near the site of excretion

1

Chelating agents

Chelating drug	Therapeutic use	Comments
Desferrioxamine	Iron poisoning	Has low affinity for iron in haemoglobin and cytochrome enzymes but high affinity for iron stored as ferritin and haemosiderin
Dicobalt edetate	Cyanide poisoning. May be used after large doses of sodium nitroprusside	Toxic
Penicillamine	Heavy metal poisoning Wilson's disease in which copper is deposited in the body	Also used in rheumatoid arthritis, but mechanism does not involve chelation
Sodium calcium edetate	Lead poisoning	Calcium in the molecule prevents hypocalcaemia
Tetracycline	Antibiotic	May chelate with ions in the intestine (e.g. calcium or iron) reducing absorption of the drug because the chelate is highly insoluble

2

Pharmacodynamic interactions

Pharmacodynamic interactions occur because of the presence of another drug at the site of drug action.

Additive or synergistic interactions

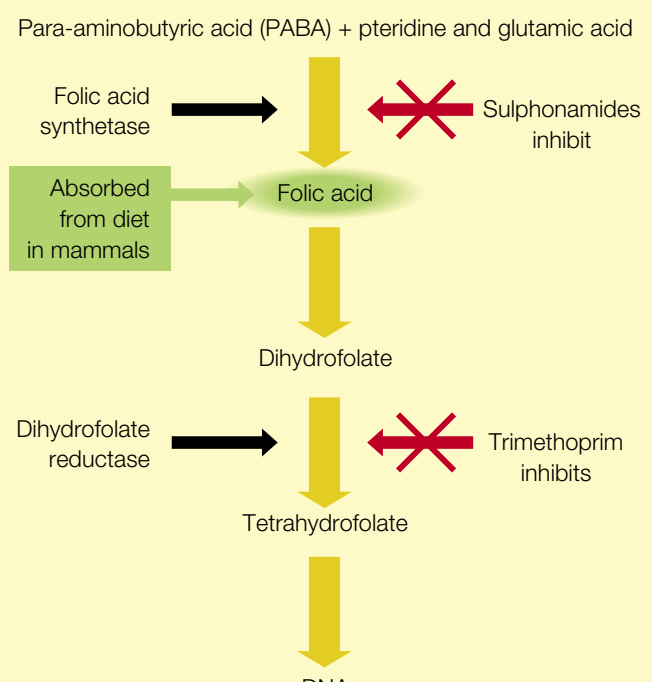
Additive or synergistic interactions occur when two drugs with similar pharmacological properties are given together. A commonly encountered example is ethanol combined with other sedative drugs such as benzodiazepine anxiolytics or histamine H_1-receptor antagonists used for travel sickness. Benzodiazepines alone have a high therapeutic index and while overdose may cause prolonged sedation they are seldom fatal. In contrast, a combination of benzodiazepine overdose with ethanol is often fatal.

Drugs with different therapeutic indications may have a common pharmacological action that is responsible for side-effects. Both the tricyclic antidepressants (e.g. amitriptyline), and antipsychotic drugs (e.g. thioridazine), possess muscarinic receptor antagonist properties. When combined or used with other antagonists at muscarinic acetylcholine receptors the enhancement of anticholinergic effects can result in heat stroke in hot, humid climates, or psychoses, in addition to dry mouth and blurred vision.

Aminoglycoside antibiotics (e.g. streptomycin) impair the influx of calcium ions into the neuron by chelating them, thus inhibiting acetylcholine release. This causes an enhancement of competitive neuromuscular blockade.

Synergy or potentiation is seen when sulphonamide antibiotics are combined with trimethoprim. Both drugs are bacteriostatic when given alone, but the combination is bactericidal (Figure 3).

Bacterial DNA pathway: site of action of antibiotics



Inhibition of a single enzyme by either sulphonamides or trimethoprim results in a bacteriostatic effect but inhibition of both enzymes is bactericidal

3

Drugs with similar adverse effects may also be additive, particularly with respect to ototoxicity (e.g. ethacrynic acid and streptomycin) or nephrotoxicity (tobramycin and cephalothin). However, not all combinations of similar drugs cause clinical problems. For example furosemide (frusemide) and streptomycin combinations do not result in enhanced ototoxicity.

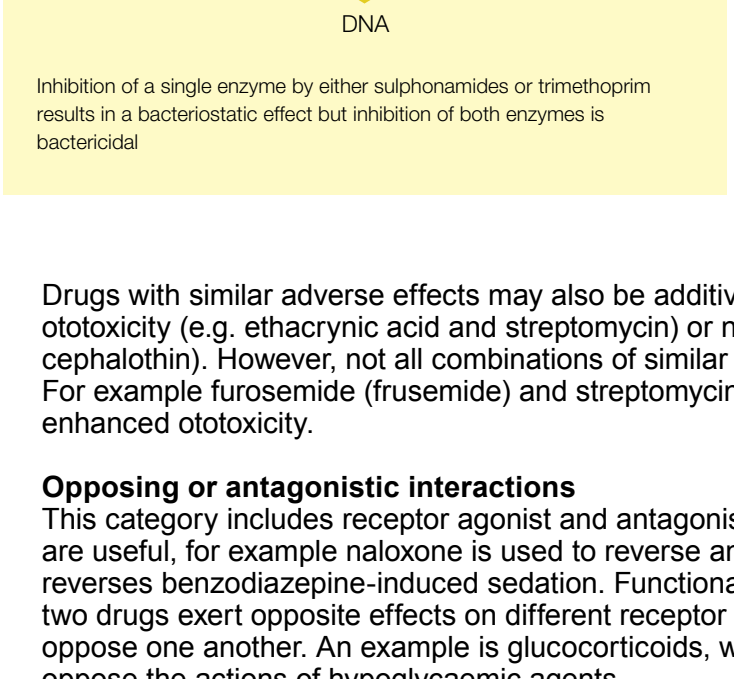
Opposing or antagonistic interactions

This category includes receptor agonist and antagonist inter-actions. Many of these are useful, for example naloxone is used to reverse an opioid overdose and flumazenil reverses benzodiazepine-induced sedation. Functional antagonisms also occur when two drugs exert opposite effects on different receptor systems and thus physiologically oppose one another. An example is glucocorticoids, which cause hyperglycaemia and oppose the actions of hypoglycaemic agents.

Alteration in drug transport mechanisms

Many drugs compete with each other for uptake at the site of action. The noradrenergic neuron is a prime site for this type of action (Figure 4). Indirectly acting sympathomimetic drugs such as amfetamine (amphetamine) derivatives need to be taken up into the neuron in order to release noradrenaline. Adrenergic neuron-blocking agents (e.g. guanethidine) that were formerly used as antihypertensive drugs, required uptake into the neuron to produce their effects. All these drugs use the noradrenaline reuptake mechanism. The tricyclic antidepressants inhibit this reuptake process and diminish the action of drugs requiring it. However, neither guanethidine nor amphetamine is widely used in modern therapeutics.

The noradrenergic neuron



4

Changes in fluid and electrolyte balance

Digitalis glycosides are the prime example of drugs that exhibit this type of interaction. Increased cardiac contractility is brought about by the inhibition of Na^+/K^+-ATPase causing a build up of Na^+ in the cardiac cell. This results in an increase in Na^+/Ca^{2+} exchange and a build-up of intracellular calcium and enhancement of contraction. In high doses this can lead to disturbances of cardiac rhythm. Plasma K^+ normally competes with digitalis for the binding site on Na^+/K^+-ATPase and thus the sensitivity of the enzyme to digitalis is increased if plasma K^+ is low. Digitalis may be used to treat heart failure and the oedema associated with the disease is often treated with diuretics. Both the loop diuretics and, to a lesser extent, the thiazide diuretics lower plasma K^+ and may thus increase digitalis toxicity. Lithium can take the place of sodium in a number of cellular processes, thus lithium toxicity is enhanced by low dietary salt.

Pharmacokinetic interactions

Absorption, distribution, metabolism and excretion of drugs can be modified by interaction with other drugs. There are many examples of these interactions in the literature and only some of the more important ones are mentioned here.

Absorption
Most interactions occur due to changes, usually reduction, in the absorption of orally administered drugs. If a drug is given acutely for a single-dose effect (e.g. analgesics, anxiolytics, hypnotics) then changes in the rate of absorption may alter the peak plasma concentration and the maximum therapeutic effect obtained. In contrast, when drugs are given chronically, it is usually the total amount of drug absorbed that is important rather than the rate of absorption.

The largest absorptive site in the gastrointestinal tract is the small intestine and thus drugs that enhance gastric emptying (e.g. the prokinetic agent metoclopramide) hasten drug absorption while drugs that inhibit gastric emptying (e.g. muscarinic acetylcholine receptor antagonists) slow absorption. This interaction has been exploited in anaesthesia when metoclopramide is used to increase the rate of onset of oral morphine administered as MST Continus tablets. The combined administration of paracetamol and metoclopramide has also been used to enhance the rate of drug absorption in the treatment of migraine.

The formation of insoluble chelates between tetracycline and a variety of divalent and trivalent ions has already been described (Figure 2). Fluoroquinolone antibiotics (e.g. ciprofloxacin, norfloxacin), which inhibit DNA topoisomerase II and prevent the supercoiling of DNA, also form poorly soluble chelates with these ions.

The effect of pH changes on drug absorption is discussed elsewhere. A rise in gastric pH due to H_2-receptor antagonists and antacids can markedly reduce the absorption of the anti-fungal agent ketoconazole but, in general, the effects of these drugs on absorption is small and variable because most drugs are absorbed in the small intestine rather than in the stomach.

The simultaneous presence of two anaesthetic gases in the lung may cause the 'second gas effect' in which the rapid absorption of one gas causes more gas to be delivered to the alveoli, enhancing absorption of the second anaesthetic. This phenomenon has been seen with 75% nitrous oxide and 1% enflurane when the plasma concentration of enflurane rises much faster in the presence of nitrous oxide.

Distribution
There are many theoretical drug interactions involving competition for plasma protein and tissue protein binding sites. While displacement of a drug from its binding site causes a transient increase in free (active) drug concentration, this is followed by increased elimination until a new steady state is reached. Few of these cause clinical problems, but there are a few well-documented exceptions. Both aspirin and the sulphonamides are given in large enough doses to cause displacement of other substances bound to albumin including bilirubin. This can be catastrophic in a jaundiced newborn baby in whom unbound bilirubin can penetrate the brain, causing basal ganglia disorders. Aspirin and sulphonamides can also change the ratio of free to bound phenytoin in the plasma, making dose adjustment more difficult and narrowing the therapeutic window.

Metabolism
The pharmacological actions of many drugs are terminated by metabolism that produces more water-soluble compounds that can be more readily excreted by the kidney. Most drug metabolism occurs in the liver (see Anaesthesia and Intensive Care Medicine 2:8: 322). Oxidation, reduction or hydrolysis of drugs (phase 1 reactions) occur in the endoplasmic reticulum often utilizing cyctochrome P450, a nonspecific enzyme system. A number of drugs and environmental pollutants can induce the P450 system making drug metabolism faster though the effect may take several days or even weeks to develop. Enzyme induction has been responsible for failure of oral contraception and ineffectiveness of corticosteroid or anticoagulant therapy. Each of the enzyme-inducing agents can also increase the metabolism of any other.

Some drugs have some selectivity for different isoforms of cytochrome P450 and they are responsible for more selective drug interactions. Grapefruit juice inhibits the activity of the CYP 3A3/4 isoform of cytochrome P450 that is responsible for the metabolism of a number of calcium channel blockers including felodipine, nifedipine, nimodipine and nitrendipine. Over two-fold increase in plasma concentrations of these drugs has been reported in patients drinking grapefruit juice, with a consequent decrease in blood pressure and an increase in side-effects, at least with felodipine.

Other drugs such as chloramphenicol inhibit cytochrome P450 enzymes, causing reduced metabolism and prolongation of drug activity. This may lead to toxicity if the drug has a low therapeutic index (e.g. phenytoin). Ketoconazole selectively inhibits the P450IIIA4 isoenzyme, which also metabolizes cyclosporin. This interaction is well known and transplant patients may need less than 25% of the dose of cyclosporin if ketoconazole is co-prescribed. Ketoconazole also appears to stop the metabolism of ketoconazole by the gut wall. Some other drugs inhibiting cytochrome P450 enzymes are listed in Figure 5.

Enzyme inhibitors involved in drug interactions

Drug	Enzyme inhibited	Comment
Allopurinol	Xanthine oxidase	Increases mercaptopurine toxicity
Ecothiopate and organophosphorus pesticides	Cholinesterase	Prolongation of suxamethonium neuromuscular blockade
Disulphiram and metronidazole[1]	Aldehyde dehydrogenase	Increase in blood aldehyde concentrations after alcohol ('antabuse reaction')
Erythromycin	Cytochrome P450IIIA	Inhibition of benzodiazepine metabolism
Phenelzine and tranylcypromine	Monoamine oxidase	Reduced destruction of tyramine from dietary sources causing hypertensive crisis

[1] Metronidazole also inhibits the enzyme responsible for the oxidation of the S(-) isomer of warfarin leaving the more potent anticoagulant within the body with a prolongation of bleeding time

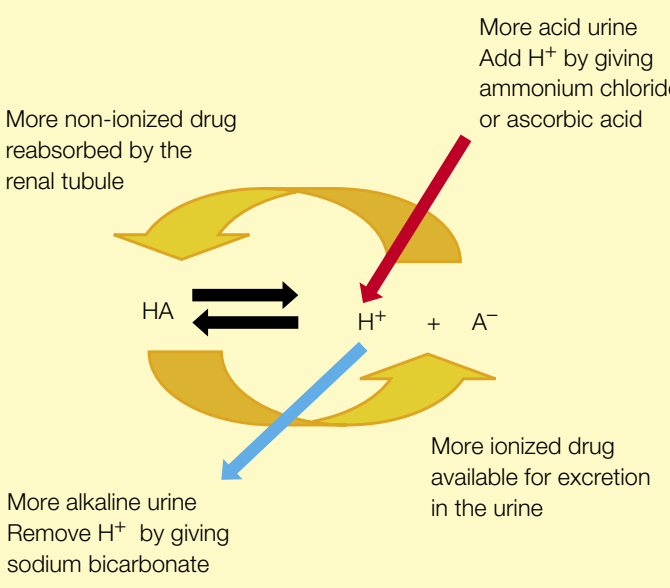
Not all drugs are metabolized by the cytochrome P450 enzymes. Concurrent drug therapy can inhibit other drug- metabolizing enzymes and result in toxicity. Some examples of enzyme inhibitors that have caused problems are listed in Figure 5. Monoamine oxidase inhibitors can cause a number of interactions at the noradrenergic nerve terminal (Figure 4). They prevent the breakdown of noradrenaline (norepinephrine) that is taken up into the nerve so that more is accumulated in the store. Indirectly acting sympathomimetic drugs, of which tyramine is only one, cause enhanced release of noradrenaline (norepinephrine), over-stimulation of the α_1-adrenoceptors and a potential hypertensive crisis.

Excretion
Inhalational anaesthetics are excreted in the expired air and this can be increased by the addition of carbon dioxide to the inhaled gas to stimulate ventilation. Most other drugs are excreted in the bile or urine. Renal excretion can be altered by changes in protein binding (discussed above), inhibition of tubular secretion, alteration in kidney blood flow or urinary pH.

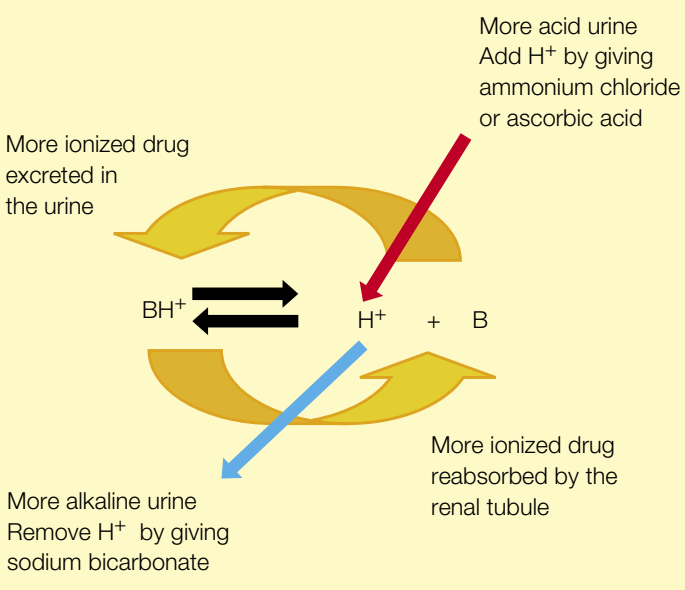
Probenecid is the classic example of a drug that was designed to compete with the active transport mechanism that secretes acids such as the penicillins into the renal tubule. Prolongation of the action of penicillin was essential in the early days when availability of the antibiotic was low and the price high. However, a number of other acidic drugs (e.g. aspirin, indomethacin, sulphonamides) share this property. Each can cause increases in the plasma concentrations of any other. Prostaglandins cause renal capillary vasodilatation, and prostaglandin production is inhibited by non-steroidal anti-inflammatory drugs, causing a reduction in renal blood flow. This is an important interaction for renally excreted drugs with a low therapeutic index, such as lithium. Changes in urinary pH affect the elimination of weak acids and weak bases. While this is not an important interaction for most drugs it can be used to enhance excretion of overdoses of susceptible drugs (Figure 6). ◆

Renal excretion of weak acids and bases

Renal excretion of a weak acid (e.g. aspirin)



Renal excretion of a weak base (e.g. amphetamine)



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Membranes: Action of Gases and Vapours

Barbara J Pleuvry

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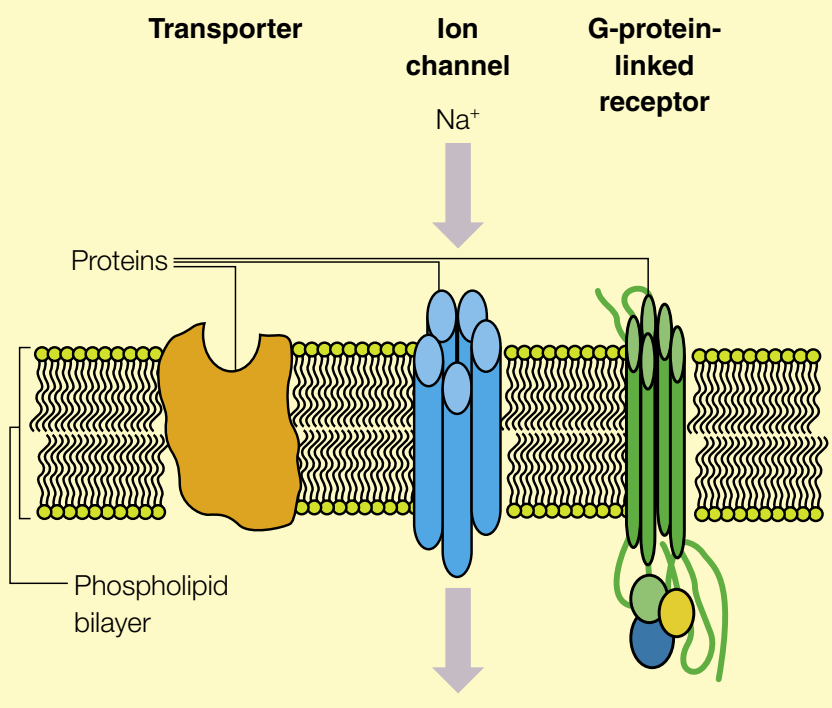
A plasma membrane surrounds all cells and separates the intracellular from the extracellular environment. The two environments have different compositions and the membrane's function is to maintain the intracellular environment while allowing movement of substances, such as respiratory gases, ions and glucose, into and out of the cell. The membrane is also required to regulate the cell's response to intracellular signalling via hormones and neurotransmitters. The membrane consists of a phospholipid bilayer with proteins embedded in it (Figure 1). Phospholipids are glycerides in which a group containing phosphoric acid and a base replaces one of the three organic residues. The base may be cholamine (in kephalin) or choline (in lecithin) and, with the phosphoric acid, results in a highly polar 'head' to the molecule. The rest of the organic residues are fatty acyl chains, such as arachidonic or linoleic acids, which are non-polar. The phospholipid molecules arrange themselves so that the polar heads face the internal and external aqueous media and the non-polar tails form the middle of the membrane sandwich. The proteins associated with the membrane may be associated with the internal or external surface of the membrane or embedded within the membrane. Like the phospholipid bilayer, embedded proteins have polar regions in contact with the aqueous media. There are five main classes of membrane proteins (Figure 2). Both membrane proteins and phospholipids may be targets for gases and vapours, several of which can cause anaesthesia (Figure 3).

Cell plasma membrane



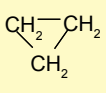
1

The five main classes of membrane proteins

1. Extrinsic protein bound by ionic forces to the internal or external surface of the lipid bilayer (e.g. cytoskeletal and extracellular matrix proteins)
2. Proteins anchored into the bilayer by a non-polar peptide (e.g. G-protein subunits)
3. Proteins with a single transmembrane span (e.g. synaptobrevin)
4. Proteins with several membrane spans (e.g. ion channels and G-protein-linked receptors)
5. Proteins linked to a glycolipid (e.g. acetylcholinesterase)

2

Some anaesthetic gases and vapours

	Minimum alveolar concentration	Formula
Inert gases		
• Xenon	71%	Xe
Non-organic gases		
• Nitrous oxide	1.02 atmospheres	N_2O
• Nitrogen	5 atmospheres	N_2
Hydrocarbons		
• Cyclopropane	9.3%	
Halogenated hydrocarbons		
• Halothane	0.75%	CF_3-CHBrCl
Ethers		
• Diethyl ether	1.9%	C_2H_5-O-C_2H_5
• Isoflurane	1.2%	CF_3-CHCl-O-CHF_2
• Desflurane	7%	CHF_2-O-CF_3
• Sevoflurane	2%	CH_2F-O-$CH(CF_3)_2$

3

Interactions with the membrane lipid bilayer

The cell membrane is permeable to water (probably via specialized water channels), lipid-soluble molecules (e.g. corticosteroid hormones), and gases (e.g. oxygen, carbon dioxide). Other polar molecules, such as glucose and amino acids, utilize specific transporter proteins (Figure 1).

The correlation of oil/gas partition coefficient with anaesthetic potency has been repeatedly confirmed for a range of compounds. Both the lipid bilayer and the integral proteins contain hydrophobic sites that could be the target of anaesthetic action.

Closely packed phospholipid heads, with their tails extended, exist in a gel-like state that is highly ordered and in which there is little movement. Transition from this state to a more fluid, liquid-like, state can be brought about by a small increase in temperature or by the insertion of small molecules, such as anaesthetic gases and vapours, into the bilayer. There is a positive correlation between the fluidization of the phospholipid head and anaesthetic potency. It is logical to assume that fluidization would be reversed by increases in pressure. Thus, the well-established pressure reversal of anaesthesia would be consistent with fluidization of the lipid bilayer being relevant to anaesthetic action. While changes in fluidity could cause a change in membrane function that equates with anaesthesia, most scientists have discarded this hypothesis. At anaesthetic concentrations the fluidization produced by anaesthetic agents is equivalent to that produced by a 1°C increase in temperature. Minor elevations of temperature do not cause anaesthesia, indeed cooling rather than heating increases anaesthetic potency. In addition, some alcohols that cause anaesthesia, do not appear to fluidize lipid bilayers and there is some structural dependency of some molecules with anaesthetic action, which is incompatible with a simple fluidization hypothesis.

Critical volume hypothesis

An observation that anaesthetics occupy space in membranes dependent on molar concentration and volume led to the hypothesis that anaesthesia occurred when the molecules of an anaesthetic agent occupied a critical volume within the membrane. At anaesthetic concentrations, membranes expand by a consistent 0.4% though their own volume is only 0.02%. It was proposed that such an expansion could disrupt the ion channels necessary for cell functioning. The observation that anaesthesia could be reversed by increasing the ambient pressure (so that the membrane could revert to its normal size) seemed to support the premise that membrane expansion was the key to anaesthesia. However Halsey's group demonstrated that pressure reversal was not the same for all anaesthetics. While the greatest difference in pressure reversal was seen with the intravenous agents, the anaesthetic vapours and gases did not show a common pattern. The differences were explained in terms of a multisite expansion hypothesis, which suggested that anaesthetic agents could expand in more than one site and that the physical properties of these sites varied. In addition, pressure and the anaesthetic might act on different sites (i.e. a physiological or functional antagonism). This hypothesis received much criticism on methodological and interpretative grounds but it introduced the idea of possible multiple sites of anaesthetic action.

Interactions with membrane proteins

Early experiments with the enzyme luciferase demonstrated that anaesthetic gases and vapours could inhibit the protein in parallel with anaesthetic potency. Subsequently, interactions with many types of protein have been demonstrated but have not been proven to be the definitive site of anaesthetic action.

Ion channels are particularly sensitive to anaesthetic action. General anaesthetics, like local anaesthetics, can block voltage-gated sodium channels but a diminution in axonal conduction occurs only in concentrations greater than that necessary to produce general anaesthesia. Similarly, inhalational anaesthetics can be shown to inhibit voltage-gated calcium channels and activate potassium channels. The type of channel affected varies from agent to agent and much of this work has been done *in vitro* or in the snail and therefore its relevance to anaesthesia in mammals is uncertain.

Ligand-gated ion channels (Figure 4) are probably the most popular candidates for the site of anaesthetic action. In general, the anaesthetics inhibit or block excitatory ligand-gated ion channels and enhance the sensitivity of inhibitory ion channels such as γ-aminobutyric acid receptor A ($GABA_A$). Blockade of the ion channel in the N-methyl-D-aspartate (NMDA) type of glutamate receptor by ketamine caused great excitement. However, ketamine is an atypical dissociative anaesthetic that most pharmacologists could accept to be acting by a mechanism not mirrored by other anaesthetics. Isoflurane also decreases the probability of the NMDA channel opening, and ethanol and diethyl ether have been shown to have some preferential depressant effects on NMDA receptors. Many anaesthetics including the inhalational gases and vapours can enhance GABA transmission via the $GABA_A$ receptor. Studies in molecular biology have shown that the presence of a particular domain, or binding site, is necessary for these potentiating effects of a given anaesthetic agent. Interestingly, the domain is not the same for all anaesthetics, indicating multiple modulatory sites on the $GABA_A$ receptor. Inhibition and/or block of excitatory neurotransmission within the CNS is a tempting explanation for anaesthesia, but until the biochemical basis of consciousness is elucidated nothing can be certain.

Ligand-gated ion channels sensitive to anaesthetic gases and vapours

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- Glycine
- Glutamate receptors
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FURTHER READING

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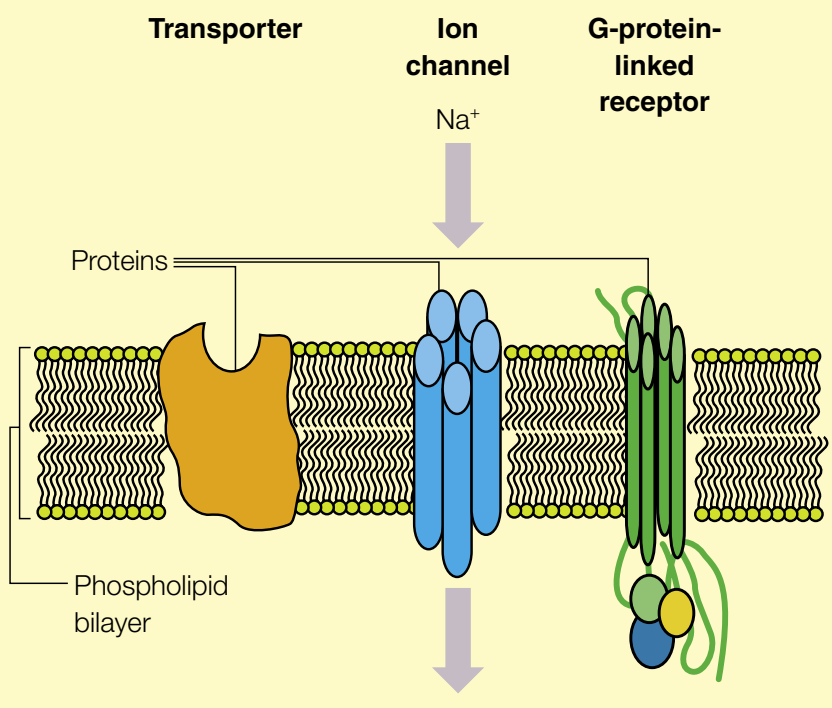

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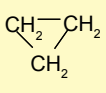
• Cyclopropane	9.3%	
Halogenated hydrocarbons		
• Halothane	0.75%	CF_3-CHBrCl
Ethers		
• Diethyl ether	1.9%	C_2H_5-O-C_2H_5
• Isoflurane	1.2%	CF_3-CHCl-O-CHF_2
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Methodology of Clinical Trials

Paul Coulthard

Paul Coulthard is Senior Lecturer and Honorary Consultant at the Central Manchester and Manchester Children's University Hospitals, which incorporates the Dental Hospital. He is Head of Oral and Maxillofacial Surgery and has a research interest in acute pain management.

Healthcare interventions should have a scientific basis provided by basic medical science and clinical research. This research evidence, together with clinical expertise integrated with an understanding of patient values, comprises evidence-based medicine. Clinical trials are scientific experiments that evaluate the effectiveness and safety of therapeutic interventions and are invaluable in guiding decisions about healthcare. The general term, clinical trial, encompasses controlled clinical trials and randomized controlled trials.

Study designs

Clinical research takes many forms.

Case studies or series observational studies are common, in which an intervention and outcome are described in one or more individuals. These may be useful in alerting clinicians to the feasibility or potential of a new treatment, but they lack a control group with which to compare the findings.

Retrospective studies look at patients who have already received a treatment. Outcomes may be compared with a control group but because randomization has not been used, matching or other statistical adjustments must be used to ensure that comparison groups are as similar as possible.

Prospective studies – in these studies, a defined group of patients receive a treatment and are followed over a period of time and the study may contain a control group.

Controlled clinical trial is a study that compares one or more intervention groups with one or more comparison (control) groups.

Randomized controlled trial or randomized clinical trial is an experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups. There is universal agreement that well-conducted randomized controlled trials constitute the best scientific evidence for treatment effectiveness.

Efficacy and effectiveness trials

Efficacy refers to whether an intervention works under ideal conditions in those who receive it. Comparing different surgical techniques is an example of an efficacy trial, where the investigators control the intervention, and therefore participant compliance is complete.

Effectiveness refers to whether an intervention works in practice. The intervention, such as novel analgesic or standard analgesic, may be accepted or rejected by the participant. An intention-to-treat analysis is one in which all the participants are analysed according to the intervention to which they were allocated, whether they received it or not. These analyses are favoured in assessments of effectiveness because they mirror the non-compliance and treatment changes that are likely to occur when the intervention is used in practice.

Phase I, II, III and IV trials

New drugs are evaluated in a series of clinical studies.

- A phase I trial is usually undertaken, following animal investigation, in healthy human volunteers to investigate the effect and metabolism of the novel compound. There is no control group.
- Phase II trials investigate the efficacy of a range of doses and are usually not randomized. If they are ineffective, further trials are not undertaken.
- A phase III trial is carried out if phase II trials show the new drug to be effective and safe. Typically they compare the effectiveness with placebo or an existing drug. These trials are usually randomized controlled trials.
- Phase IV trials are large studies to monitor the adverse effects of a new drug after its approval.

Parallel and cross-over design randomized controlled trials

In a parallel design, each group of participants is exposed to only one of the study interventions, for example, the new drug or placebo. This is the most common type of randomized controlled trial.

In a cross-over design, each participant is given each study intervention in successive periods. The order in which the participants receive each intervention is randomized. As each participant acts as his or her own control, fewer participants are required than for a parallel design.

Conducting a trial

Trial protocol: the research question should contribute something useful to existing knowledge and be developed following a thorough search of the existing sources of evidence, especially systematic reviews, to avoid duplication of work. The protocol also contains details of the background, scientific design and practical organization of the trial, including patient eligibility, treatments and outcome measures.

Ethics: the purpose of a research ethics committee in reviewing a proposed study is to contribute to safeguarding the dignity, rights, safety and well-being of the study participants. Informed consent is at the heart of ethical research and all studies must have appropriate arrangements for obtaining consent. Attention must also be given to systems to ensure confidentiality of personal information. When reviewing a research proposal, the research ethics committee also takes into consideration the principle of justice. This requires that the benefits and burdens of research be distributed fairly among all groups and classes in society, taking into account age, gender, economic status, culture and ethnic considerations. The principal investigator is the person designated as taking overall responsibility within the team of researchers for the design, conduct and reporting of the study, but research funders, the sponsor and the employing organization also have responsibilities.

Random allocation: the term random does not mean haphazard but rather that all participants have the same chance of being assigned to each of the study groups and allocation is not determined by the investigators, clinicians or study participants. Random number tables or computer-generated number sequences are the best way of doing this. By allocating the participants randomly, the characteristics of the participants are likely to be similar across groups at the start, and the investigators will be more able to quantify the impact of the intervention, with minimal effects from other factors, known and unknown.

Allocation concealment is the process used to prevent foreknowledge of group assignment in a randomized controlled trial. The allocation method should be impervious to any influence from the individual making the allocation by having the randomization process administered by someone who is not responsible for recruiting participants. Methods such as date of birth or case record numbers are open to manipulation because the treatment group is known when a patient is considered for entry into a trial and this knowledge may influence the decision to recruit that patient. Adequate methods include centralized randomization schemes and sealed envelopes each containing the name of the next treatment.

Blinding (masking) refers to keeping the investigators or participants ignorant of the group assignment. It is used to protect against the possibility that knowledge of assignment may affect patient response to treatment. A trial that is not blind is called an open randomized controlled trial, for example when surgery is compared with medication. In a single-blind randomized controlled trial, one group does not know the identity of the intervention that is given to each participant. In a double-blind randomized controlled trial, neither the investigator nor the participants know the identity of the intervention. To be successful, interventions must be indistinguishable to participant and investigators, therefore a placebo tablet must look, weigh and taste the same as the active medication. In a triple-blind randomized controlled trial, those evaluating the outcomes (data analysts and statisticians) do not know the identity of the intervention.

Bias is any factor or process that tends to deviate the results or conclusions of a trial away from the truth. Bias can be introduced into a trial voluntarily, but usually it is involuntary. Selection bias occurs when the outcomes of a trial are affected by systematic differences in the way in which individuals are accepted or rejected for a trial. With true randomization, all the study participants are given the same opportunity to be allocated or assigned to each of the study groups and this is the main appeal of the randomized controlled trial. However, other forms of bias can occur at any stage of the research process, for example, publication bias when editors accept manuscripts more favourably when the trial results are positive.

Sample size should be pre-specified. Patient variability means large numbers are needed in a trial. However, sample sizes are often not calculated and therefore small and important therapeutic effects may be missed. Reporting often lacks justification of sample size.

Trial quality

Good clinical practice: if trials are to benefit patients, they must be properly designed, conducted and appropriately analysed. Bodies such as the Association of the British Pharmaceutical Industry (ABPI) have played a key role in improving research quality. The ABPI has produced many useful guidelines including: *Good Clinical (Research) Practice, Good Clinical Trial Practice*, and the *ABPI Guidance Note: Patient Information and Consent for Clinical Trials*.

Research governance: clinical governance aims to improve the overall standards of clinical care in the UK National Health Service. A comparable strategy is in place to improve the quality of research practice in health and social care. The standards described in the *Research Governance Framework* offer a model for use by NHS staff using NHS resources, and research undertaken by industry, the charities, the research councils and UK universities.

The national research register is a database of continuing and recently completed UK research, funded by or of interest to the NHS. Over 76,000 research projects are included. This database is useful for identifying unpublished research, particularly important to those undertaking systematic reviews, and identifying and bringing together researchers between and across related areas of research.

Reporting trials: the reporting of randomized controlled trials and research in general is often incomplete. Ideally, the report of a trial should convey the relevant information to permit informed judgements to be made regarding the internal and external validity of the trial. The Consolidated Standards of Reporting Trials (CONSORT) statements checklist proposed in 1995 offers guidance in report presentation. Internal validity of the trial is the degree to which the trial design, conduct, analysis and presentation have minimized or avoided biased comparisons of the interventions under evaluation. External validity is the precision and extent to which it is possible to generalize the results of the trial to other settings. Several tools exist to evaluate the quality of trial reporting. ◆

FURTHER READING

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www.consort-statement.org

Modes of Drug Elimination

Barbara J Pleuvry

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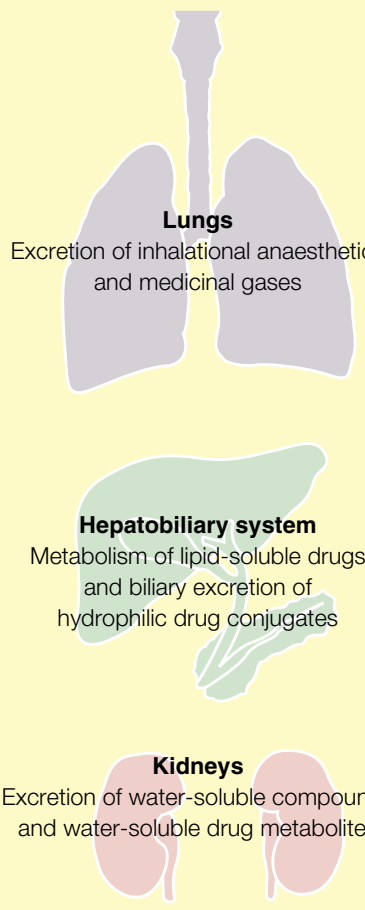
Drug elimination is the removal of a drug from the body by metabolism and/or excretion. The main routes for drug excretion (Figure 1) are the kidneys, hepatobiliary system and the lungs, the latter being important for inhalational anaesthetics and medicinal gases. The kidneys excrete polar compounds unchanged in the urine. In contrast, lipid-soluble compounds have to be metabolized to polar compounds before excretion in the urine. Most metabolism occurs in the liver, which can also be involved in elimination through biliary excretion. Removal of a drug from the blood or plasma is expressed as clearance. Total body clearance is calculated by dividing the amount that enters the systemic circulation by the area under its blood or plasma concentration–time curve. For most drugs the total body clearance is the sum of hepatic and renal clearance, but for some drugs clearance by the lungs is important (see below).

Organs of drug excretion



1

Drug metabolism

The liver is the organ with the greatest metabolic capacity, but the kidney, lungs and blood-borne enzymes may also contribute. The enzyme systems involved in drug elimination can be classified as phase 1 or phase 2. Phase 1 includes oxidation, reduction and hydrolysis, some examples of which are given in Figure 2. In the liver, many of these reactions are catalysed by the mixed function oxidase system, of which the most important group is the cytochrome P450 system. This is described in greater detail in *Anaesthesia and Intensive Care Medicine* **2:8:** 322. Drugs that are cleared or removed efficiently by the liver (e.g. morphine, lidocaine (lignocaine), imipramine) are restricted in their rate of elimination solely by liver blood flow. The elimination of these drugs is little affected by enzyme induction, hepatic disease, and changes in protein binding or competitive binding interactions. In contrast, drugs whose elimination depends on intrahepatic processes (e.g. phenytoin, warfarin) may be seriously affected by the above changes, but will be little affected by changes in liver blood flow.

Examples of phase 1 metabolic pathways

Oxidation

• Phenytoin	*p*-hydroxyphenytoin
• Ethanol	Ethanoic acid
• Midazolam	α-hydroxymidazolam

Reduction

• Halothane	Trifluoroethane
• Cortisone	Hydrocortisone

Hydrolysis

• Pethidine	Norpethidine
• Aspirin	Salicylic acid

2

Enzyme systems other than those included in the cytochrome P450 system are involved in phase 1 reactions, examples are cholinesterase in the hydrolysis of suxamethonium and alcohol dehydrogenase in the oxidation of ethanol. Phase 1 reactions do not necessarily result in the inactivation of the drug and there are numerous examples of pro-drugs and toxic metabolites of drugs (see *Anaesthesia and Intensive Care Medicine* **3:3:** 114). Phase 2 reactions occur when a drug or phase 1 metabolite has a group (e.g. amino, hydroxyl, thiol) that makes it susceptible to conjugation. The most common conjugate is glucuronide but conjugates with sulphate, glutamate, acetate and methyl groups also occur. Commonly, phase 2 products are pharmacologically inactive and are excreted via the biliary route or via the kidney in the urine. However, there are some important active phase 2 products such as morphine-6-glucuronide, which has significant opioid activity.

Glucuronide formation can occur in the gastrointestinal tract as mentioned above and in the kidney, placenta and skin. The blood and many tissues contain esterases that are important in the metabolism of drugs such as remifentanil (tissue esterase) and suxamethonium (cholinesterase). Extrahepatic metabolism accounts for 50% of the conjugation of propofol with glucuronide and sulphate.

First-pass effects

In contrast to the situation for phase 1 metabolism, the enzymes responsible for phase 2 metabolism are found in the liver and the gut in similar quantities. Therefore, when given orally, a drug that is metabolized principally by phase 2 reactions (e.g. morphine) may be extensively metabolized before reaching the systemic circulation. This is known as first-pass gut metabolism. Other orally administered drugs may undergo significant first-pass hepatic metabolism. Once absorbed from the intestine, the drug enters the portal circulation to the liver. If the drug has a high hepatic clearance (see *Anaesthesia and Intensive Care Medicine* **2:6:** 237), then little unchanged drug will reach the systemic circulation. The local anaesthetics and the β-adrenoceptor antagonist, propranolol, are examples of this type of drug.

First-pass effects can also apply to drugs given intravenously. When a drug is given by a fast intravenous bolus it reaches the pulmonary capillary bed in high concentration before it enters the systemic circulation. Highly ionized drugs remain in the blood stream, but lipid-soluble drugs may diffuse into lung tissue. If the drug is not extensively bound to proteins in the lung, this has little effect on distribution because the drug rapidly diffuses out again as plasma concentrations fall. Some drugs, particularly lipid-soluble basic drugs such as local anaesthetics, propranolol and fentanyl, bind to lung protein and significant quantities are removed from the blood in the first circulatory pass. However, the contribution of the lung to the metabolism of these drugs is probably small.

Biliary excretion and enterohepatic recycling

Although the liver is the main organ for drug metabolism it may also excrete unchanged drug in the bile. Like the kidney, the liver has a number of acid and base handling systems that transport drugs from the plasma to the bile. Hepatocytes can transport uncharged molecules into the bile and a number of drug conjugates are concentrated in the bile. When these compounds are returned to the intestine, lipid-soluble drugs may be reabsorbed, conjugated drugs may be hydrolysed and the original drug reabsorbed. This is known as enterohepatic recycling and it may occur repeatedly leading to a reservoir of drug. Figure 3 gives examples of drugs that undergo significant recycling by this route. Enterohepatic recycling is particularly important to maintain the effects of ethinyloestradiol. Oral dosing with broad-spectrum antibiotics can cause diarrhoea thus preventing recycling of ethinyloestradiol and consequent oral contraceptive failure. Polar drugs that are excreted in the bile (e.g. neuromuscular blocking agents) are not reabsorbed from the intestine and so, for these drugs, biliary excretion is a true method of drug elimination.

Drugs that undergo enterohepatic recycling

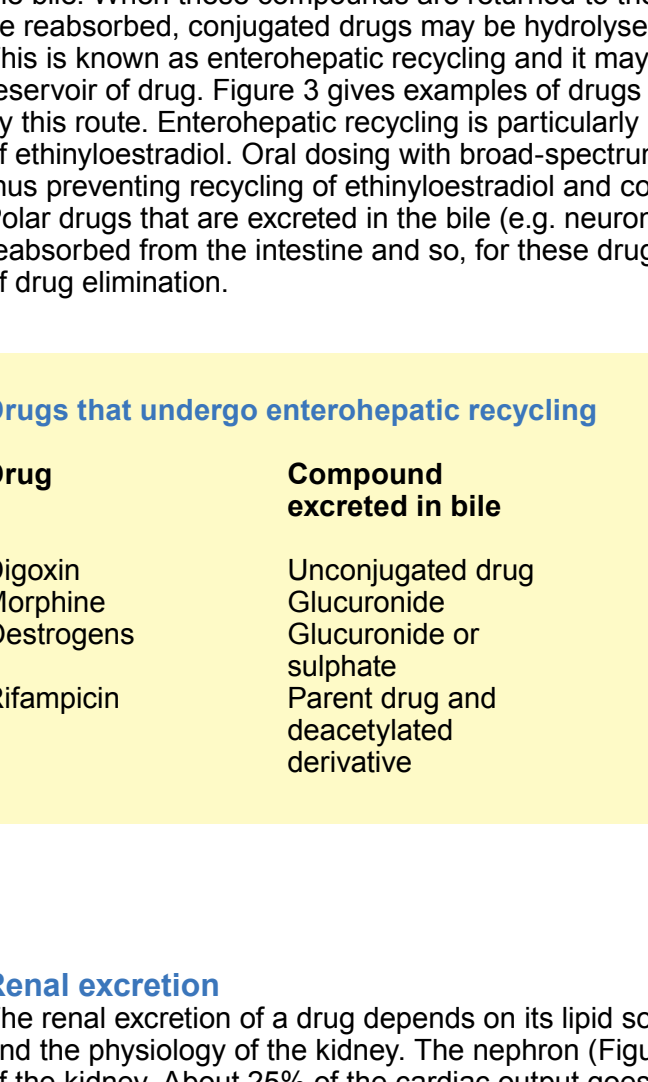
Drug	Compound excreted in bile	Fate in intestine
Digoxin	Unconjugated drug	Reabsorbed
Morphine	Glucuronide	Hydrolysed and reabsorbed
Oestrogens	Glucuronide or sulphate	Hydrolysed and reabsorbed
Rifampicin	Parent drug and deacetylated derivative	Parent drug reabsorbed and derivative excreted in the faeces

3

Renal excretion

The renal excretion of a drug depends on its lipid solubility, binding to plasma proteins and the physiology of the kidney. The nephron (Figure 4) is the basic anatomical unit of the kidney. About 25% of the cardiac output goes to the kidney and about 10% is filtered at the kidney. Drugs bound to proteins or cells are unable to pass across the glomerular membranes therefore only plasma water is filtered; the normal rate is about 125 ml/minute. This is measured by determining the clearance of creatinine, a catabolic product of amino-acid metabolism derived from muscle. Creatinine clearance is equal to the glomerular filtration rate. The drug concentration in the filtrate at this initial stage is the same as that in the plasma water. From the renal corpuscle the filtrate passes down the renal tubules. Meanwhile the blood from the glomerulus passes into the peritubular capillaries, which surround the proximal and distal tubules and the vasa recta that supplies the loop of Henle. In its passage down the tubules drug may be reabsorbed into the capillaries or drug may be added to the filtrate by active secretion.

Structure of a nephron



4

Active secretion
If the rate of excretion of a drug exceeds the rate of filtration of plasma water then active secretion of the drug is inferred. Active secretion occurs via a carrier mechanism and binding to plasma proteins does not inhibit it. Penicillin for example is 80% protein bound and thus only a small amount is filtered at the glomerulus. However, it is almost completely removed from the blood by secretion from the blood into the proximal tubule. Some drugs that are secreted into the proximal renal tubule are listed in Figure 5.

Some drugs actively secreted into the proximal renal tubule

Uric acid transport systems secrete organic acid drugs and metabolites
- Penicillins
- Glucuronide metabolites
- Probenecid
- Sulphate conjugates
- Salicylic acid
- Thiazide diuretics

Choline and histamine transport systems secrete organic bases
- Quaternary ammonium compounds (e.g. neuromuscular blocking agents)
- Morphine
- Pethidine

5

Passive diffusion across the renal tubule
Water is progressively reabsorbed as the filtrate passes down the nephron so that only 1% of the original filtrate emerges as urine. The amount of drug that is reabsorbed during its passage depends on its ability to permeate the tubule. Thus, highly lipid-soluble, non-polar drugs such as thiopental (thiopentone), phenytoin and inhalational anaesthetic agents pass through freely and little is lost in the urine. In contrast, polar drugs, provided they are too large to penetrate the water pores of the cells will be unable to be reabsorbed and will be voided in the urine. For these drugs, renal clearance approaches glomerular filtration rate. Examples include many neuromuscular blocking agents, polar metabolites and conjugates. The reabsorption of weak acid and bases depends on urinary pH, weak acids are more readily reabsorbed if the pH is acid and weak bases are more readily reabsorbed in alkaline urine. The adjustment of urinary pH to influence the excretion of certain drugs is discussed in *Anaesthesia and Intensive Care Medicine* **3:3:** 99.

Active reabsorption across the renal tubule
Drugs that resemble essential metabolites (e.g. levodopa, α-methyldopa, thyroxine) are actively reabsorbed. Uric acid is also actively reabsorbed and this can be inhibited by probenecid, which competes with uric acid for the active transport system. This is the basis of the use of probenecid for the treatment of gout.

Elimination via the lungs
The elimination of inhaled drugs by the lungs depends on alveolar ventilation, cardiac output and the degree of biotransformation of the agent. In general, the higher the alveolar ventilation the greater the rate of elimination of gases and volatile agents via the lungs. The administration of carbon dioxide to stimulate ventilation may decrease the time to recovery from inhalational anaesthetics.

An increase in cardiac output increases the concentration gradient between the vessel-rich compartment and the alveolar air, thus facilitating transfer of gases to the alveolar air and hastening elimination. Some inhalational anaesthetics (e.g. isoflurane, desflurane, nitrous oxide) are little metabolized and exhalation is the most important route of elimination. In contrast, halothane may be up to 20% metabolized and though recovery is due to exhalation, significant quantities of metabolite remain in the body. Some other agents can be smelt on the breath (e.g. ethanol, paraldehyde, thiols) but the quantity excreted by the lungs is insignificant.

Excretion by other routes
Non-ionized, lipid-soluble compounds can diffuse through the epithelial cells of glands and appear in sweat, saliva or tears. Saliva is usually swallowed, therefore it is not an effective mechanism for drug elimination. However, for some drugs, the concentration in saliva parallels concentrations in plasma so it can be used as an alternative fluid to measure drug concentrations when blood sampling is undesirable. Drugs may also be excreted in breast milk and some (e.g. ethanol) reach the same concentrations as in plasma. Since milk is a little more acidic than plasma there may be a tendency for some small concentrations of basic compound in breast milk. Quantitatively these routes of elimination are unimportant.

Some heavy metals such as arsenic and mercury are concentrated in hair or skin and this has been used by forensic scientists to detect cases of poisoning many years after the death of the subject. ◆

Neuromuscular Blocking Agents

Brian J Pollard

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Motor nerves that supply striated muscle have their cell body in the CNS and a single long axon. This axon divides repeatedly as it approaches the muscle and may supply few or many muscle fibres depending on the function of the muscle. The nerve does not make direct contact with the muscle fibre at the neuromuscular junction, the prejunctional nerve ending being separated from the postjunctional muscle endplate region by a narrow gap, the junctional cleft.

The nerve terminal is concerned with the synthesis, storage, mobilization, release and recycling of the neurotransmitter. Acetylcholine (ACh) is synthesized in a process involving the acetylation of choline, which itself enters the nerve terminal by an active transport system. The reaction is catalysed by the enzyme choline-acetyltransferase and is an energy-dependent process involving coenzyme A. The synaptic cleft is filled with a mucopolysaccharide basement membrane material in which acetylcholinesterase is distributed, though it is particularly concentrated in the folds of the postjunctional membrane. The postjunctional endplate region contains the recognition and binding sites for ACh and the mechanism to translate this event into an electrical impulse that can activate the contractile mechanism of the muscle.

The process of neuromuscular transmission follows the arrival of an action potential at the nerve ending. ACh is released from vesicles in the immediately available store and this is rapidly replenished from the reserve stores (transmitter mobilization). ACh crosses the junctional cleft and combines with the postjunctional receptors. It is necessary for two molecules of ACh to combine with each receptor system to initiate opening of the channel and the binding of the first ACh molecule facilitates the binding of the second. Once the channel is open, sodium travels down its concentration gradient leading to local depolarization of the muscle membrane.

There are about 10,000 receptors per μm^2 located on the shoulders of the junctional folds. Each receptor unit has five glycoprotein subunits with a central cation channel passing through the postjunctional membrane. In each receptor, two of the glycoprotein subunits, the α subunits, are identical and each carries one ACh recognition site. The others are the β, α and either α in the adult or γ in the fetus (and in various other species). The α subunit also binds other agonists, toxins and reversible antagonists. Although the two α subunits have an identical amino-acid sequence, they are functionally different by virtue of their different positions in the receptor unit.

Receptors also exist on the prejunctional nerve endings, which subserve a feedback or modulating function controlled by ACh or other physiological mediators.

A number of potential sites of action exist for agents to modify neuromuscular transmission:

- inhibition of ACh release (e.g. botulinum toxin, gentamicin)
- prevention of ACh combination with postjunctional receptors (e.g. pancuronium)
- inhibition of choline uptake (e.g. hemicholinium)
- inhibition of ACh synthesis (e.g. triethylcholine)
- action at prejunctional receptors (e.g. tubocurarine)
- inhibition of acetylcholinesterase (e.g. neostigmine).

Not all of these mechanisms are clinically relevant, though drugs that affect neuromuscular transmission probably act at more than one site. Several mechanisms take place and result in potential inhibition of neuromuscular transmission as follows.

Receptor occlusion – any chemical substance that binds to either one or both ACh recognition sites can produce neuromuscular block by physically preventing ACh from binding and therefore the channel from opening. It is currently believed that the major component of the action of the clinical neuromuscular blocking agents (NMBAs) takes place through this mechanism.

Closed channel block – any bulky molecule binding near the channel opening may act like a lid, physically obstruct the mouth of the channel and impede the passage of cations. This binding will take place irrespective of whether the channel is open or closed.

Open channel block – any positively charged molecule may enter the channel once it has been opened. The presence of another molecule within the channel lumen will reduce current flow by physically obstructing the flow of ions through the channel. It is unlikely that channel block is of major importance in the clinical situation.

Prejunctional receptors – the existence of prejunctional receptors for ACh (nicotinic and muscarinic), noradrenaline (α- and β-adrenergic), and a number of other humoral mediators at the neuromuscular junction has been known for over 40 years. The physiological function of most of these receptors is unclear though it seems likely that the NMBAs may also modify neuromuscular transmission by their action on prejunctional receptors.

Membrane effects – the normal functioning of the channel depends on the integrity of the phospholipid cell membrane. A substance that dissolves in the lipid bilayer membrane, or which binds elsewhere in the vicinity of the receptor complex, may disturb the fluidity of the membrane and thereby influence the function of the channel.

Neuromuscular blocking agents

There are two ways to prevent the normal action of ACh at the neuromuscular junction. In the first, the binding site is occupied by an agent (an antagonist) that does not itself produce depolarization but prevents the access of ACh. In the second, the binding site is occupied by an agent that produces depolarization (an agonist) but the depolarization is prolonged and the receptor mechanism is thus rendered insensitive for a longer period of time.

Depolarizing neuromuscular blocking agents

Succinyldicholine (suxamethonium) is the only depolarizing agent in current clinical use. Normally the endplate is depolarized by ACh for only a very short period of time before it becomes repolarized. The persistent depolarization from succinyldicholine inactivates the voltage-gated sodium channels in the muscle membrane immediately adjacent to the motor endplate, resulting in a temporary insulating zone of electrical inexcitability around the endplates through which impulses cannot pass.

Succinyldicholine is the NMBA with the most rapid onset and the shortest duration of action. It has many unwanted side-effects, however. The most important are raised intracranial, intra-abdominal and intraocular pressures, hyperkalaemia, postoperative myalgia, bradycardia and the potential to trigger an episode of malignant hyperthermia. It has an active metabolite, succinylmonocholine, which is an NMBA with a potency about 20% of that of succinyldicholine. Being metabolized by plasma cholinesterase, its action is prolonged in patients who have a deficiency of that enzyme. All of these problems have stimulated the search for a non-depolarizing agent devoid of such side-effects and with a similar rapidity of onset and brevity of action.

Non-depolarizing neuromuscular blocking agents

Antagonists comprise the non-depolarizing NMBAs. These bind in a reversible manner to the ACh recognition sites on the α subunits, prevent ACh binding and activation of the receptor. In the presence of a non-depolarizing agent, a dynamic equilibrium exists that favours either the agonist (ACh) or the antagonist depending on their relative concentrations within the junction. The non-depolarizing agents are all large, bulky molecules with nitrogen with one, two or three positive charges. It was originally believed that there had to be two quaternary nitrogen moieties separated by a distance of about 1 nm and the early molecules conformed to this ideal. Some of the more recent molecular structures, however, are monoquaternary with more variable inter-onium distances. Although many of the NMBAs have been discovered and developed in a largely empirical manner, the more recent ones have evolved into precise pharmacological agents, with more precise receptor selectivity and minimal side-effects. Although not yet obtained, the development of an ultra-short-acting non-depolarizing agent with a very rapid onset to replace suxamethonium is on the horizon.

Since the introduction of these agents into clinical practice in 1942, many non-depolarizing relaxants have been synthesized, only a small number of which have found their way into regular clinical practice. A summary of their basic pharmacodynamic data is given in Figure 1.

Pharmacodynamic properties of the non-depolarizing neuromuscular blocking agents

	ED_{95} (mg/kg)	Onset time (minutes)	Duration (minutes)	Elimination half-life (minutes)
Alcuronium	0.25	5–6	60	200
Atracurium	0.23	3–5	25–35	20
Cisatracurium	0.05	4–6	30–35	
Doxacurium	0.03	7–10	60–80	130
Gallamine	2.4	4–7	45–60	135
Metocurine	0.28	5–6	60–80	220
Mivacurium	0.08	3–5	18–22	17
Pancuronium	0.06	3–4	50–60	130
Pipecuronium	0.05	4–6	40–60	138
Rapacuronium	1.1	1–2	18–22	
Rocuronium	0.3	2–3	30–40	120
Tubocurarine	0.5	4–7	50–70	200
Vecuronium	0.04	3–5	20–30	60

1

Long-acting agents

Tubocurarine was the first NMBA to enter clinical practice. It is extracted from *Chondodendron tomentosum*. Its use has declined and it is no longer available in the UK. Tubocurarine undergoes minimal metabolism and is excreted unchanged in both bile and urine. The possession of two separate routes of elimination led to it being used safely for patients with either impaired liver function or impaired renal function though its clearance is reduced in these situations. Tubocurarine is a potent antagonist at autonomic ganglia, and hypotension commonly follows its administration, with a reduction in both cardiac output and systemic vascular resistance. Tubocurarine may also release histamine at clinical doses and this may exaggerate the hypotension caused by block of autonomic ganglia. Skin flushing is common and bronchospasm may be seen in susceptible patients.

Metocurine, a relaxant produced by the methylation of the hydroxyl groups of tubocurarine, has enjoyed some popularity particularly in North America. It is about twice as potent as tubocurarine though its rate of onset and duration of action are similar. Side-effects are fewer than with the parent compound, though at higher doses autonomic block appears, resulting in hypotension. The potential for histamine release is much less than that of tubocurarine

Alcuronium is a bisquaternary compound synthesized from the naturally occurring alkaloid, toxiferine. It entered clinical practice in 1961. From the mid-1980s, its popularity began to decline and it was withdrawn from clinical use in the UK in 1999. Alcuronium is almost entirely renally excreted as the unchanged molecule and the clearance is therefore considerably prolonged in patients with renal impairment. A weak antagonist at autonomic ganglia, it may produce hypotension though this is not as marked as that with tubocurarine. The heart rate can be expected to rise by 5–10% owing to its weak vagolytic action.

Gallamine was the first synthetic, and the only trisquaternary, NMBA. It was popular during the 1950s and 1960s, but its use has declined. Gallamine is not metabolized but excreted unchanged in the urine. It is therefore an unwise choice in patients with impaired renal function. The most notable side-effect is a dose-related tachycardia caused by its potent vagolytic action. It does not often cause histamine release.

Pancuronium was the first steroid-based NMBA in clinical use. It is metabolized in the liver to the 3-OH, 17-OH, and 3,17-diOH derivatives though only the 3-OH compound has been detected in man. This metabolite possesses neuromuscular blocking activity with a potency of about 40% that of the parent compound. Pancuronium and its metabolites are excreted by the kidneys. In patients with impaired renal or hepatic function, the duration of action of pancuronium may be prolonged. Onset time is about 3–4 minutes and increasing the dose to 0.1 mg/kg reduces the onset time to about 2 minutes. Higher doses last proportionately longer, and accumulation can be observed following repeated doses. The blood pressure is well maintained and tachycardia, hypertension and an increased cardiac output may occasionally be seen resulting from block of cardiac vagal receptors and increased release of noradrenaline together with its decreased re-uptake from sympathetic nerve fibres. Pancuronium appears to be devoid of any propensity to release histamine.

Doxacurium is a bisquaternary benzylisoquinolinium substance with a chemical structure similar to atracurium. Its ED_{95} of 0.03 mg/kg makes it the most potent NMBA available. Its onset of action is slow (up to 10 minutes) with a duration of about 60 minutes. The onset can be shortened to about 3–4 minutes by increasing the intubating dose to 0.08 mg/kg, but the administration of such a high dose produces a block that may last up to 150 minutes. Doxacurium is excreted principally by the kidneys and its duration of action is therefore prolonged in patients with impaired renal function. Doxacurium has no effects on heart rate, blood pressure or cardiac output and it does not release histamine.

Pipecuronium belongs to the steroid family and was developed in Hungary in 1980. Its onset of action is about 4–6 minutes and this can be shortened to about 2–3 minutes by the administration of a larger bolus dose. Pipecuronium undergoes very little metabolism and most of the administered dose is recovered from the urine. Its action is extended in renal failure. Pipecuronium is almost devoid of cardiovascular side-effects and histamine release does not appear to be a problem.

Intermediate-acting agents

Atracurium is an ester with two positively charged nitrogen atoms and four asymmetric centres, giving a total of 16 possible stereoisomers. It was developed to exploit a novel method of metabolism – the Hofmann elimination reaction. Atracurium is metabolized by esterases in the plasma (< 1%) and the liver (about 60%), the remainder by the Hofmann reaction. Atracurium is unstable at body temperature and pH, and is stored in ampoules at 4°C at a pH of 3. Breakdown products of atracurium include laudanosine and acrylates. Laudanosine produces convulsions in certain laboratory animals and the acrylates are highly reactive, potentially hepatotoxic substances. No problems of toxicity have been reported in man, however. The duration is about 25–40 minutes and is little changed by renal or hepatic dysfunction. This reliable and predictable action has made it the drug of choice for many short-to-intermediate procedures. One of the key features of atracurium is its lack of cardiovascular effects though bradycardia has been reported, which is particularly noticeable when using a high-dose narcotic technique. Histamine release may be a problem when using doses in excess of about 0.5–0.6 mg/kg.

Cisatracurium is a single isomer preparation of the main active ingredient in atracurium. It is about three times more potent than atracurium though it has a slightly slower onset. Cisatracurium has been shown to possess greater cardiovascular stability than atracurium and, like atracurium, it is unaffected by renal or hepatic disease. Accumulation following repeated doses or a continuous infusion does not occur. Biotransformation of cisatracurium produces laudanosine and acrylates, as does atracurium, but because of its increased potency, there is less potential for accumulation of the metabolites.

Vecuronium is a synthetic steroid-based agent and, like pancuronium, it breaks down to 3-OH, 17-OH and 3,17-diOH compounds. The 3-OH derivative is also an NMBA with a potency of about 50–70% that of vecuronium. Vecuronium is eliminated through the kidneys both as the parent compound and as its breakdown products. Accumulation has been reported following larger doses, especially in the presence of renal failure. The duration of action of vecuronium may also be prolonged in liver failure. The onset of action of vecuronium is about 3–5 minutes and this can be reduced to about 2 minutes by increasing the intubating dose. An intermediate-acting agent, its duration of action is about 20–30 minutes and spontaneous recovery is reliable. Vecuronium is almost devoid of cardiovascular side-effects and this has made it a popular relaxant, particularly in those with compromised cardiovascular systems. Like atracurium, its lack of vagal action may unmask a bradycardia from surgical stimulation. There is very little histamine release at normal clinical doses.

Rocuronium is another steroid-based NMBA. Its important feature is its rapid onset with increased doses (Figure 2). The pattern of onset of rocuronium differs slightly from the other agents in that there is a faster initial phase. Intubation is thus possible after only 60 seconds with doses greater than 0.45 mg/kg. Accumulation has not been reported following repeated doses or with use by infusion. Rapid and satisfactory reversal can be accomplished by the use of routine clinical doses of neostigmine. Most of a dose of rocuronium is taken up by the liver and secreted into the bile though a significant amount is excreted in the urine. It is mainly eliminated unchanged. Rocuronium is almost devoid of cardiovascular side-effects and histamine release, has negligible ganglion-blocking actions and minimal effect on the vagus.

Onset characteristics of rocuronium

Dose (mg/kg)	Time to intubation (seconds)
0.3	120–150
0.45	90
0.60	60
0.90	45

2

Short-acting agents

Mivacurium belongs to the benzylisoquinolinium (atracurium) family and is the only non-depolarizing NMBA to be metabolized by plasma cholinesterase. Under circumstances in which the activity or quantity of plasma cholinesterase is reduced, the duration of action of a dose of mivacurium is prolonged. This includes patients with impaired renal function. The onset can be accelerated by increasing the intubating dose such that 0.25 mg/kg has an onset time of about 2.5 minutes. Recovery, once it has begun, is rapid and complete and unlike the other non-depolarizing agents, the duration of action is little affected by increasing the dose. It is often unnecessary to use an anticholinesterase agent to antagonize a mivacurium block, but if clinically indicated, reversal is rapidly secured with a routine dose of neostigmine. A transient fall in blood pressure and flushing in the arm used for venepuncture may sometimes be seen, particularly with larger doses, due to the release of histamine. Administering the mivacurium bolus more slowly over about 15–30 seconds can reduce these phenomena.

Rapacuronium is the newest of the NMBAs. It has not (at January 2001) been released for general use in the UK and so experience is limited. It has the most rapid onset of the non-depolarizing agents, a dose of 1.5 mg/kg producing good intubating conditions almost, but not quite, as rapidly as succinylcholine, 1 mg/kg. It seems likely that it will prove to be an acceptable alternative to succinylcholine for rapid-sequence induction. Its recovery profile is similar to that of mivacurium with a recovery index of about 6 minutes and spontaneous recovery to 90% in about 18–20 minutes. Onset and recovery at the larynx is more rapid than at the thumb. Although spontaneous recovery is considerably slower than with succinyl-choline, adequate reversal from a rapacuronium block has been reported using a routine dose of neostigmine after about 2–3 minutes. Recent reports have appeared of bronchospasm following rapacuronium administration which have led to its withdrawal in the USA. Some patients exhibit a tachycardia amounting to a rise in the heart rate of about 10–12%.

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Non-opioid Analgesics

Barbara J Pleuvry

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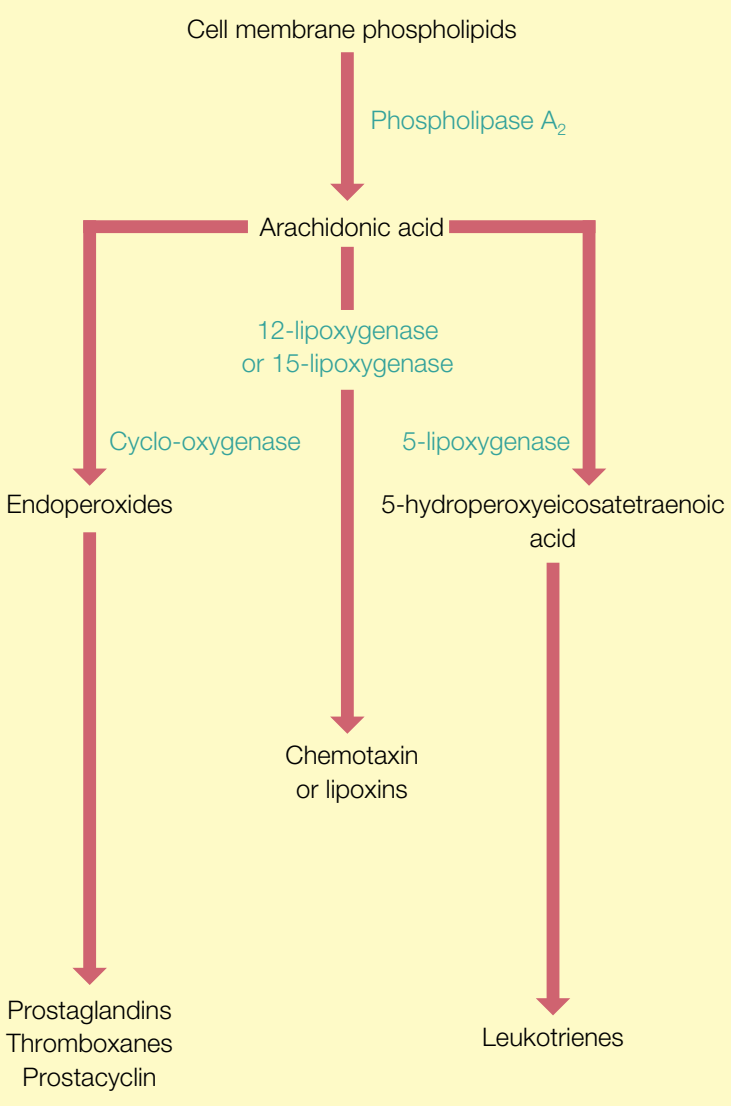
Non-steroidal anti-inflammatory drugs (NSAIDs)

Sodium salicylate, a chemical manipulation of the glycoside salicin obtained from extracts of willow bark, was introduced in 1875 to treat rheumatic fever. Acetylsalicylic acid (aspirin) was introduced about 25 years later and since then many anti-inflammatory analgesics have been marketed. Although paracetamol was first used clinically at the end of the 19th century, it was only when it was recognized as the active metabolite of both acetanilide and phenacetin (two compounds now withdrawn because of unacceptable toxicity), that it achieved popularity. Paracetamol possesses analgesic and antipyretic activities comparable with aspirin but is anti-inflammatory only in high doses therefore it should not be included as a NSAIDs.

The first convincing hypothesis to explain the anti-inflammatory, antipyretic and analgesic activity of NSAIDs was proposed in the early 1970s by Vane and colleagues. It was observed that NSAIDs inhibit the production and release of prostaglandins in all cell types tested. Prostaglandins together with the thromboxanes and leukotrienes are part of a group of arachidonic acid metabolites called the eicosanoids. Arachidonic acid is a twenty-carbon atom fatty acid containing four double bonds, and it is usually found esterified in the phospholipids in cell membranes. A number of stimuli, such as antigen/antibody reactions and general cell damage, can cause activation of phospholipase (A_2 and/or C) and liberate arachidonic acid. Once liberated, arachidonic acid is rapidly metabolized by a number of enzyme systems including cyclo-oxygenase (COX) and several lipoxygenases (Figure 1).

Metabolism of arachidonic acid



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Prostaglandins and pain

Of all products of COX activity, the prostaglandins of the E series (PGEs) and prostacyclin (PGI_2) are most likely to have a role in inflammatory pain. They sensitize nociceptors to other noxious stimuli such as bradykinin and 5-hydroxytryptamine (5-HT) and they can produce pain. NSAIDs are inhibitors of COX. A second isoform of COX (cyclo-oxygenase 2 or COX-2) is induced by inflammation. This enzyme is susceptible to NSAIDs and it is likely that the anti-inflammatory action of these agents is due to COX-2 inhibition. It has been suggested that COX-1 inhibition is responsible for many of the side-effects of NSAIDs when used for their anti-inflammatory properties. Aspirin, and to some extent indomethacin and sulindac, are relatively selective for COX-1, while ibuprofen and piroxicam are less selective. Ibuprofen is preferred to aspirin for the treatment of inflammatory diseases because of its relative lack of side-effects. Although paracetamol inhibits COX-1 and COX-2 within the CNS, its lack of useful anti-inflammatory effects has been attributed to the weakness of its COX inhibition in the presence of high concentrations of peroxides that are found in inflammatory states. Alternatively, co-factors necessary for the inhibition of COX by paracetamol are not present in the inflamed tissues.

Pain that has no obvious inflammatory component is also sensitive to NSAIDs. It is unlikely that peripheral inhibition of COX has a role in this type of analgesic activity and there is debate as to whether inhibition of COX at any site is relevant. However, there may be a role for prostanoids in pain transmission in the spinal cord.

Non-selective COX inhibitors

There are at least 50 different NSAIDs or related drugs marketed for their analgesic, antipyretic and anti-inflammatory activity, all have significant adverse effects (Figure 2).

Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs)

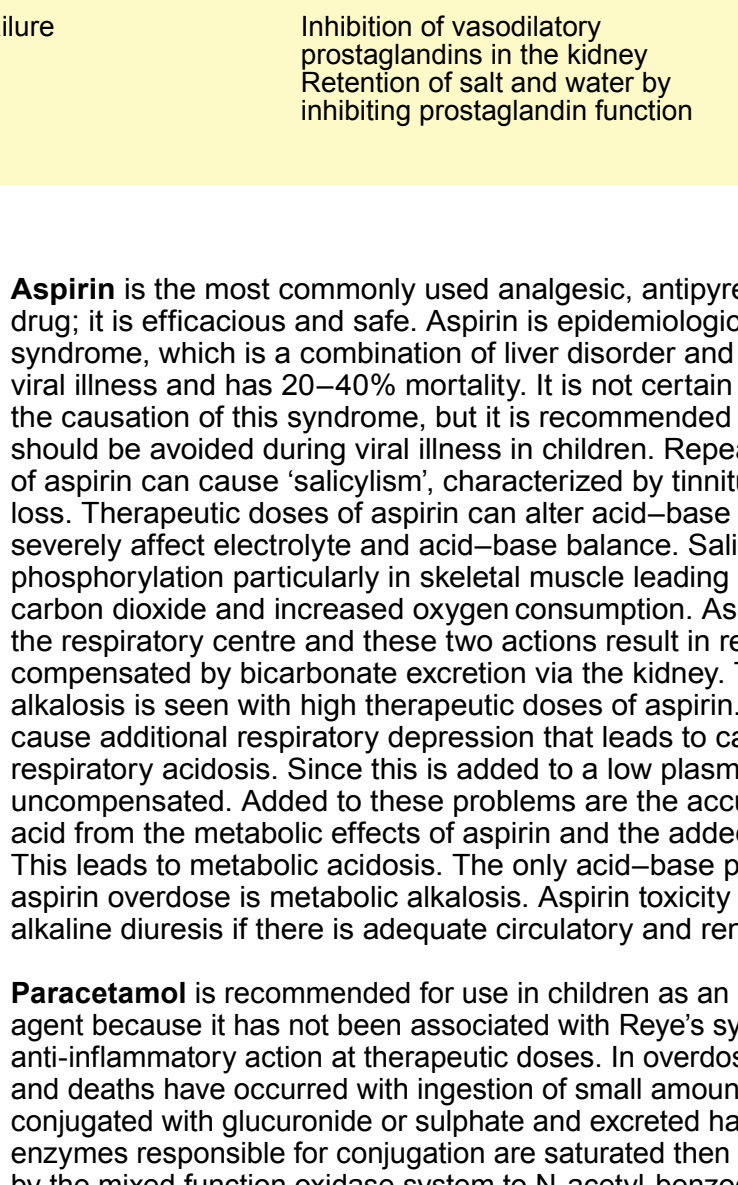
Adverse effects	Proposed mechanism	Comments
Gastrointestinal intolerance and ulceration	Inhibition of cytoprotective PGI_2 and PGE_2 in the gastric mucosa	Less of a problem with p-aminophenol derivatives (e.g. paracetamol)
Hypersensitivity reactions	Diversion of arachidonic acid synthesis down the leukotriene pathway	Relatively rare; more common with acetylated salicylates
Reduced platelet aggregation	Blockade of thromboxane formation	Particular problem with aspirin, a non-reversible inhibitor of COX Can be useful in thromboembolic disorders
Inhibition of uterine motility (delayed parturition)	Inhibition of PGE and F series which stimulate the uterus before birth	May be useful for inhibition of preterm labour
Renal failure	Inhibition of vasodilatory prostaglandins in the kidney Retention of salt and water by inhibiting prostaglandin function	Mainly a problem in patients with congestive heart failure, hepatic sclerosis or chronic renal disease Analgesic nephropathy with chronic NSAID consumption

2

Aspirin is the most commonly used analgesic, antipyretic and anti-inflammatory drug; it is efficacious and safe. Aspirin is epidemiologically linked to Reye's syndrome, which is a combination of liver disorder and encephalopathy following a viral illness and has 20–40% mortality. It is not certain that aspirin is implicated in the causation of this syndrome, but it is recommended that aspirin administration should be avoided during viral illness in children. Repeat ingestion of high doses of aspirin can cause 'salicylism', characterized by tinnitus, vertigo and hearing loss. Therapeutic doses of aspirin can alter acid–base balance, and toxic doses severely affect electrolyte and acid–base balance. Salicylates uncouple oxidative phosphorylation particularly in skeletal muscle leading to an increased production of carbon dioxide and increased oxygen consumption. Aspirin also directly stimulates the respiratory centre and these two actions result in respiratory alkalosis that is compensated by bicarbonate excretion via the kidney. This compensated respiratory alkalosis is seen with high therapeutic doses of aspirin. Toxic doses of aspirin cause additional respiratory depression that leads to carbon dioxide retention and respiratory acidosis. Since this is added to a low plasma bicarbonate it will be uncompensated. Added to these problems are the accumulation of pyruvic and lactic acid from the metabolic effects of aspirin and the added acid from the drug itself. This leads to metabolic acidosis. The only acid–base problem not associated with aspirin overdose is metabolic alkalosis. Aspirin toxicity can be treated with forced alkaline diuresis if there is adequate circulatory and renal function.

Paracetamol is recommended for use in children as an analgesic and antipyretic agent because it has not been associated with Reye's syndrome although it has little anti-inflammatory action at therapeutic doses. In overdose, paracetamol is hepatotoxic and deaths have occurred with ingestion of small amounts. Normally paracetamol is conjugated with glucuronide or sulphate and excreted harmlessly (Figure 3). If the enzymes responsible for conjugation are saturated then paracetamol is metabolized by the mixed function oxidase system to N-acetyl-benzoquinoneimine. This toxic metabolite is conjugated with glutathione. If glutathione is depleted then the toxic metabolite accumulates and binds with cell macromolecules to cause cell death. Liver and kidney cells are the usual targets for this effect and signs of liver or renal toxicity occur 24–48 hours after ingestion of the drug. Early treatment of paracetamol overdose with N-acetylcysteine (within 12 hours) to complex with the reactive metabolite of paracetamol can save life. Both paracetamol and aspirin are commonly available as combination analgesics with weak opioid agonists.

Metabolism of paracetamol



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Ibuprofen and naproxen are both propionic acid derivatives. Naproxen has greater efficacy and, consequently, more adverse effects than ibuprofen, but its longer half-life makes twice daily administration feasible.

Other NSAIDs are listed in Figure 4 with their clinically relevant differences. Phenylbutazone can cause agranulocytosis and is seldom used. Indomethacin is still used for inflammatory conditions, especially ankylosing spondylitis and osteoarthritis, although gastrointestinal disturbances and CNS effects (e.g. confusion, headache) reduce its usefulness.

Characteristics of the most important non-steroidal anti-inflammatory drugs (NSAIDs)

Drug	Elimination half-life (hours)	Comments
Aspirin (acetylsalicylic acid)	Varies with dose (4 hours with low doses) Saturation kinetics above 4 g/day	Relatively selective for COX-1 (> 100-fold). Inhibits platelet aggregation in low doses
Diclofenac	1–2	Gastrointestinal bleeding and ulceration. Elevation of hepatic aminotransferases. Equally effective on both COX enzymes
Etodolac	7	May have some COX-2 selectivity. Fewer gastrointestinal problems
Ibuprofen	2	Reversible inhibitor of COX. Selectivity for COX-1 (15-fold)
Ketorolac	4–6	Somnolence and headache. Superior to aspirin for chronic pain states. Topically useful for eye inflammation
Mefenamic acid	2–4	Gastrointestinal discomfort, inflammation of the bowel. Haemolytic anaemia. No advantages over other NSAIDs
Meloxicam	Variable (about 50 hours)	May have some COX-2 selectivity. Fewer gastrointestinal problems
Nabumetone	3	Some gastrointestinal irritation. Useful for patients with allergic hypersensitivity to NSAIDs. Equally effective on both COX enzymes
Naproxen	14	More efficacious than ibuprofen, but more adverse gastrointestinal effects. Equally effective on both COX enzymes
Oxaprozin	40–60	Similar to ibuprofen. Long half-life allowing once daily dosage
Paracetamol	2–4	Not anti-inflammatory at therapeutic doses. Hepatotoxicity can occur with single doses of 10–15 g. COX-1 selectivity 7.5-fold
Piroxicam	Variable (about 50 hours)	Gastrointestinal disturbances. Reduces renal clearance of lithium. More than 100-fold selective for COX-1

Selective COX inhibitors

Two premises have led to the development of COX-2 selective drugs. Firstly, that inhibition of COX-1 is responsible for the undesirable actions of NSAIDs such as gastric irritation and renal injury. Secondly, that COX-2 inhibitors retain the anti-inflammatory, analgesic and antipyretic actions of the NSAIDs. Some existing NSAIDs (e.g. meloxicam, etodolac, nimesulide) have selectivity for COX-2. Meloxicam has fewer gastrointestinal side-effects than comparator NSAIDs but the equivalence of dose has been questioned. These compounds lose their selectivity for COX-2 at higher doses. Epidemiological studies of ulcer complications indicate that nimesulide offers no advantages with respect to the non-selective COX inhibitors.

Two highly selective COX-2 inhibitors (celecoxib, rofecoxib) have recently been introduced. Both caused significantly less gastric mucosal injury than non-selective NSAIDs in patients without gastrointestinal pathology. However, some caution has been expressed over these findings. Chronic treatment with selective COX-2 inhibitors in patients with pre-existing gastrointestinal injury or inflammation may show a significant increase in damage. COX-2 appears to have an important role in promoting the healing of ulcers.

Celecoxib and rofecoxib are analgesic, antipyretic and anti-inflammatory, but whether they will be as effective as non-selective agents in all inflammatory condition awaits the outcome of long-term clinical trials. The elimination half-life of celecoxib is 8–10 hours (longer for rofecoxib) such that once a day dosage is recommended. Celecoxib is an inhibitor of the P450 (CYP2D6) isoenzyme, therefore plasma concentrations of other drugs (antidepressants, antipsychotic, antiarrhythmic drugs) that are a substrate for this enzyme may be increased. Celecoxib is teratogenic in several animals and is therefore contraindicated in pregnancy. In one trial of postoperative dental pain, rofecoxib, in the dose used, was found to be superior to celecoxib and equivalent to ibuprofen.

Drugs used to treat arthritis

Osteoarthritis

Pain that worsens on movement, is the most common presenting feature of osteoarthritis. In uncomplicated disease, paracetamol is acceptable as first-line pain therapy because osteoarthritis has only a minor inflammatory component. NSAIDs are also prescribed for osteoarthritis, but gastrointestinal side-effects limit their usefulness. New developments concerned with COX-2 selective NSAIDs may be beneficial (see above), but await further study.

Cartilage destruction is one of the major processes of osteoarthritis progression. NSAIDs and other drugs have different effects on cartilage metabolism. Paracetamol and the NSAIDs treat the symptom of pain and not the disease itself. Indeed NSAIDs have been implicated in the more rapid progression of osteoarthritis. Simplistically relieving pain may lead to increased usage and further damage, but there are complex links between prostanoids and metaloprotinases that cause cartilage breakdown. Some specific chondroprotective agents (e.g. chondroitin, glucosamine, hyaluronic acid) have been examined in the hope of delaying or reversing the progress of the disease. Adequate long-term trials are required before their place in therapy can be defined.

Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease in which the immune system invades the synovial cells and destroys cartilage in the joint. The pain of rheumatoid arthritis tends to be worse when rested. It is an inflammatory disease therefore NSAIDs used to be the mainstay of therapy, but they did not retard the development of the disease and, because high doses are needed to obtain an anti-inflammatory effect, patients suffered from gastrointestinal side-effects. Recently, the use of disease-modifying anti-rheumatic drugs (DMARDs) has been recommended at an early stage of the disease. If given early, DMARDs can stabilize the joint function at a near-normal stage rather than when it has become disabled. None of the drugs included in this group (Figure 5) are analgesic in any classical sense.

Tumour necrosis factor (TNF) has a central role in the pathological inflammatory response associated with rheumatoid arthritis and two approaches have been tried to decrease TNF activity. Etanercept contains soluble TNF receptors and has been shown to have beneficial effects, including pain reduction, in patients with rheumatoid arthritis, both as monotherapy and as an adjuvant to methotrexate. Similar studies with infliximab, a preparation of anti-TNF-α antibodies, have been reported.

Disease-modifying anti-rheumatic drugs (DMARDs) and their use in rheumatoid arthritis

	Mechanism	Unwanted effects	Comment
Azathioprine	Immunosuppressant Interferes with purine synthesis and inhibits lymphocyte proliferation	Bone marrow suppression Nausea, vomiting and diarrhoea are common. Skin eruptions	Reserved for patients with disease that is refractory to other DMARDs
Chloroquine and hydroxychloroquine	Suppresses lysosomal enzymes and inhibits interleukin-1 release but many reports are contradictory	Irreversible retinopathy with high doses. Gastrointestinal intolerance	Less effective than other DMARDs. Used only for mild disease or when other DMARDs are too risky
Cyclophosphamide	Immunosuppressant Decreases T and B lymphocytes	Bone marrow depression. Infertility. Infection risk	Only used (unlicensed) for patients with life-threatening complications of rheumatoid arthritis
Cyclosporin	Immunosuppressant Suppresses the synthesis and release of interleukin-1 and interleukin-2	Dose-related hypertension and nephrotoxicity	Used when other treatments have failed
Gold	Unknown. May affect B and T lymphocyte function	Wide-ranging toxicity Eczema and mouth ulcers common. Diarrhoea with auranofin	Oral gold (auranofin) is less toxic than parenteral gold but probably less efficacious
Leflunomide	Pro-drug. Inhibits pyrimidine pathway. Reduced B and T cell proliferation	Teratogenic. Abdominal pain	New class of drug, still under development
Methotrexate	Immunosuppressant Changes the balance between pro-inflammatory and anti-inflammatory cytokines	Nausea and stomatitis common Haematological toxicity rare with low doses (which are used in rheumatoid arthritis)	Most effective DMARD currently available. Relatively fast onset of action (1 month)
Penicillamine	Not certain; chelates divalent cations. Impairs antigen presentation	Nausea, rashes, leucopenia and thrombocytopenia. Bone marrow aplasia	Clinical use is declining due to toxicity
Sulfasalazine (sulphasalazine)	Unknown; combines an anti-inflammatory with antibacterial molecules	Low rate of serious adverse effects (leucopenia and thrombocytopenia) Gastrointestinal intolerance common	Better tolerated than gold. Formerly the first-line therapy in the UK. Onset between 6 and 12 weeks

Anti-migraine drugs

Migraine is a common, notoriously under-treated, neurological condition characterized by intense unilateral headache, nausea and vomiting. The diagnostic criteria for migraine adapted from the International Headache Society are given in Figure 6.

The pathological changes associated with migraine are uncertain. The suggestion that the aura is caused by vasoconstriction and the headache by vasodilatation is too simplistic. The headache appears to involve the activation of the trigemino-vascular system resulting in a neurogenic inflammatory response characterized by dural vasodilatation and plasma extravasation, resulting in pain. Migraine is thought to occur when inappropriate antidromic activation of the trigeminal nerve releases neuropeptide transmitters such as substance P and calcitonin gene-related peptide into the blood vessel wall. These peptides cause vasodilatation and oedema leading to sensitization of the trigeminal nerve causing pain and reflex activation of the facial nerve, which leads to extracranial vasodilatation and release of vasoactive intestinal peptide, all of which contribute to the migraine syndrome.

Diagnostic criteria for migraine

One or more focal neurological dysfunction signs make up the aura that may last up to 1 hour; the signs may be visual, motor or autonomic

- Some migraine attacks do not proceed beyond the aura and not all migraine attacks are preceded by an aura
- Untreated attacks last 4–72 hours

The headache has two of the four characteristics

- unilateral
- pulsating
- severe enough to disturb activities
- aggravated by movement

Associated symptoms (at least one present)

- nausea or vomiting
- intolerance of light
- intolerance of noise

Until the early 1990s, NSAIDs, paracetamol (discussed above), or ergot alkaloids supplemented with anti-emetics (e.g. metoclopramide) were used to treat migraine. Metoclopramide enhances the absorption of the analgesic by stimulating gastric motility. Combination analgesics were used in more severe cases. Ergot alkaloids were found to be effective anti-migraine drugs in the 1920s. The vasoconstrictor agent ergotamine was most commonly used. However, the ergot alkaloids are very non-selective pharmacological agents interacting with most of the receptors so far described for 5-HT, noradrenaline and dopamine. Following the hypothesis that 5-HT was crucially involved in migraine, more selective drugs were synthesized, resulting in sumatriptan, which had selectivity as an agonist at the 5-HT_1 family of receptors, and a particular affinity for the 5-$HT_{1B/1D}$ receptor. Sumatriptan is effective for the acute treatment of migraine and tends to reduce the nausea and vomiting as well as the headache. However, its oral bioavailability is low and the drug has a short half-life of 2 hours. The drug may cause constriction of the coronary blood vessels and is contraindicated in patients with pre-existing coronary artery disease.

Recently introduced triptans include zolmitriptan, naratriptan and rizatriptan, which have better oral bioavailability and longer half-lives. Although sumatriptan is often considered to be a selective 5-$HT_{1B/1D}$ receptor agonist, it and many other drugs in this group have affinity for 5-HT_{1F} receptors. Agonist drugs selective for 5-HT_{1F} receptors, such as LY-334370, prevent the dural plasma protein extravasation that is seen in migraine. This compound lacks the vasoconstrictor action of 5-$HT_{1B/1D}$ receptor agonists, and thus should be free of this adverse effect if current clinical trials show it to be effective in migraine.

Prophylactic treatment for migraine is recommended for patients who have three or more severe attacks per month. Figure 7 summarizes the drugs that have been found to be effective, though only 60–70% of patients benefit. The exact mechanism of the anti-migraine effects of these drugs is unknown and may be independent of their main therapeutic or pharmacological classification.

Prophylactic treatment for migraine

Drug group	Action in migraine prophylaxis	Efficacy	Unwanted effects
α_2-adrenoceptor agonists (e.g. clonidine)	?	Doubtful	Sedation
β-adrenergic antagonists (e.g. atenolol, propranolol, timolol)	Not related to β-adrenoceptor antagonism. Some β-blockers are inactive	50–70% patients obtain more than 50% reduction in attacks	Contraindicated in asthma
5-HT receptor antagonists (e.g. methysergide, cyproheptadine, pizotifen)	Could be 5-HT antagonism, but many other receptors affected	60–80% patients obtain more than 50% reduction in attacks. Useful for cluster headaches	Nausea, vomiting. Retroperitoneal fibrosis with methysergide on long-term therapy
Monoamine oxidase inhibitors (e.g. phenelzine, isocarboxazide)	Ability to increase endogenous 5-HT?		Orthostatic hypotension, insomnia and nausea
Tricyclic antidepressants (e.g. amitriptyline, nortriptyline)	Not correlated with antidepressant activity. Blockade of 5-HT transporter?	Particularly useful for mixed (migraine plus tension) headaches	Cardiac arrhythmias
Calcium channel blockers (e.g. flunarizine, diltiazem)	?	Effectiveness questioned by recent studies	Frequent constipation, orthostatic hypotension

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Non Steroidal Anti-Inflammatory Drugs

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Living tissues respond to noxious insults with a cascade of energy-consuming reactions evolved to limit damage. Inflammatory disease results from the inappropriate manifestation of this defence reaction; major symptoms are vasodilatation, erythema, raised temperature, pain, oedema and loss of normal function.

The characteristics of the inflammatory response that indicate involvement of endogenous chemical mediators are: similar syndrome, latency to onset, reversible nature and suppression by chemical antagonists.

Major classes of endogenous chemicals mediating acute inflammation include:
- fatty acid oxidation products (e.g. prostaglandins (PGs))
- kinins (e.g. bradykinin)
- lysosomal enzymes (e.g. neutral proteases)
- oxygen-derived products (e.g. superoxide radicals)
- pro-inflammatory cytokines (e.g. interleukin 1)
- vasoactive amines (e.g. histamine).

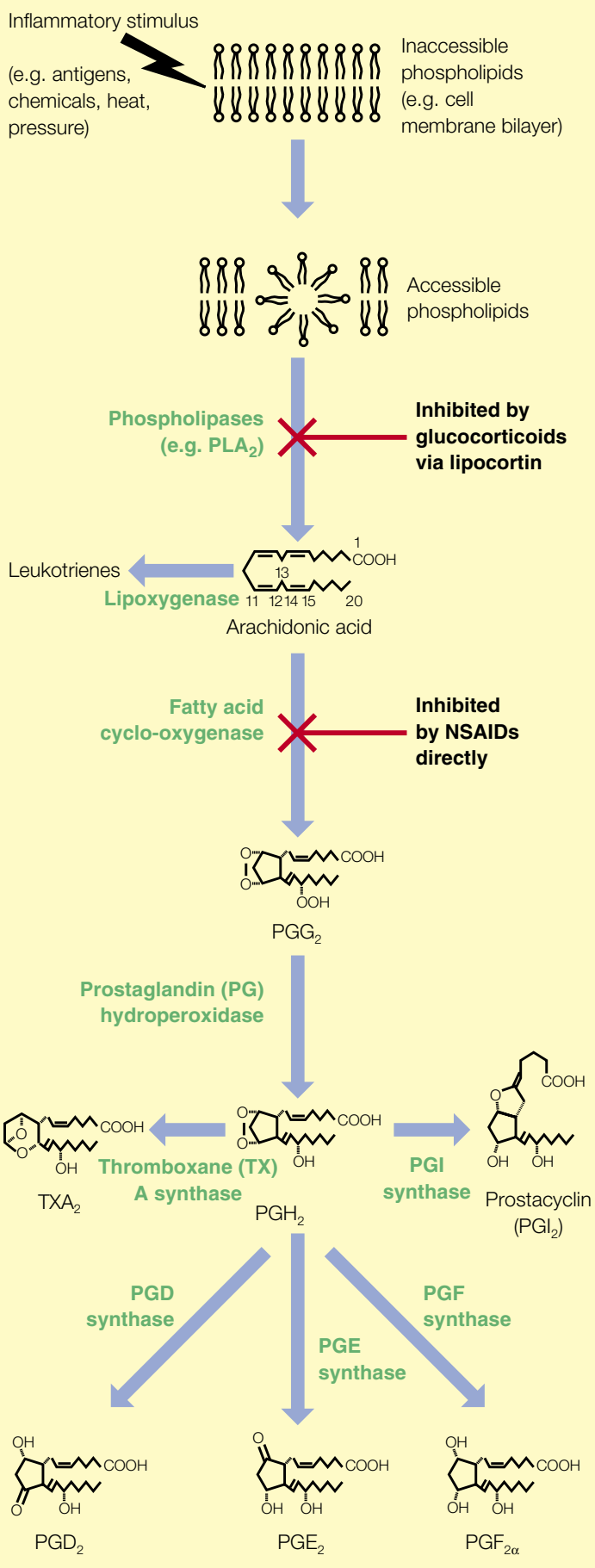
Drugs inhibiting the biological activities of these mediators alleviate the symptoms of inflammation; therefore there are several different pharmacological groups of anti-inflammatory drugs. This article describes the non-steroidal anti-inflammatory drugs (NSAIDs), the group most widely used.

Nature of NSAIDs
Numerous NSAIDs are available from several chemical classes. Many are weak organic acids, which partly determines their absorption, distribution, excretion and toxicity. Their pharmacological effects and mechanisms of action are also similar. Despite these similarities, the anti-inflammatory and adverse effects of selected NSAIDs vary between patients; choice should be determined by individual patient tolerance.

Aspirin (acetylsalicylic acid), a prodrug producing salicylic acid on hydrolysis, is used as a typical or 'type' compound to describe the pharmacology of salicylic acid derivatives (salicylates) in particular and NSAIDs, including non-salicylates (e.g. ibuprofen, naproxen, meloxicam) in general. This practice is based on the extensive knowledge acquired from the long and widespread use of salicylates, initially as plant extracts (e.g. *Salix*, *Spirea*) and since 1899 as the synthetic drug aspirin, though there are differences between aspirin as 'type' compound and other NSAIDs (see below).

Over the last 10 years, the role in which aspirin serves as a reference for other NSAIDs has altered from one of typical drug to one of comparison. This change followed the discovery of two isoforms of cyclo-oxygenase (COX), the enzyme activity inhibited by NSAIDs (Figure 1), and the development of drugs more selective for COX-2 than for COX-1.

Formation of biologically active oxygenated products of arachidonic acid via cyclo-oxygenase



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Mechanism of action
Microsomal enzymes metabolize free (unesterified) 20-carbon, unsaturated (eicosanoic) fatty acids to a range of oxygenated products, eicosanoids (Figure 1). The rate-limiting step in this pathway is the availability of free fatty acids. During inflammation, phospholipase activity is enhanced and the release of free fatty acids increased from previously unavailable phospholipid stores. COX activity forms hydroperoxidated (15-OOH) fatty acid endoperoxides (e.g. PGG_2 from arachidonic acid, the most abundant fatty acid in man). The 15-OOH endoperoxides are chemically unstable and are converted, under the influence of hydroperoxidase then synthase activity, to progressively more stable products, which include prosta-glandins mediating inflammation, hyperalgesia and pyrexia. The established therapeutic uses of NSAIDs are attributable to their ability to inhibit COX activity, thereby reducing endogenous concentrations of biologically active eicosanoids (e.g. PGE_2, thromboxane A_2 (TXA_2)).

The enzyme prostaglandin endoperoxide synthase possesses both COX and hydroperoxidase activities. Two isoforms have been identified as different gene products with distinct cellular locations and COX activities:
- COX-1 constitutively expressed in a wide variety of cells
- COX-2 induced by inflammatory stimuli and growth factors.

The isoforms are similar in structure and enzymatic activity: both are homodimeric, glycosylated membrane proteins with a highly conserved catalytic domain with the NSAID binding site in a narrow hydrophobic channel. Classical NSAIDs (aspirin, ibuprofen, naproxen) are not selective and inhibit both COX-1 and COX-2 activities. NSAIDs bind reversibly, with the exception of aspirin, which covalently acetylates serine in position 530. NSAIDs inhibit COX activity by preventing abstraction of hydrogen from arachidonic acid carbon atom 13, thereby blocking peroxidation at carbon atoms 11 and 15. Hydroperoxidase activity appears unaffected.

Substitution of valine in COX-1 by isoleucine in COX-2 at positions 434 and 523 increases the size and changes the shape of the NSAID binding site channel in COX-2. These differences have been exploited in the development of highly selective COX-2 inhibitors (e.g. celecoxib, rofecoxib).

Therapeutic effects
The commonly sought therapeutic effects of NSAIDs are:
- symptomatic relief from inflammation in musculoskeletal disorders
- analgesia, particularly when associated with inflammation
- antipyresis.

All can be attributed to inhibition of prostaglandin production. Prostaglandins of the E family (PGEs) are important mediators of inflammation, hyperalgesia and pyrexia. Lowering concentrations of prostaglandins with NSAIDs results in reduced:
- vasodilatation, vascular permeability, chemotaxis and oedema (giving relief from inflammation)
- sensitization of nociceptors and hyperalgesia (analgesia)
- disruption to central neurons regulating core temperature (antipyresis).

In addition to the typical actions of NSAIDs listed above, aspirin also inhibits thrombus formation and helps prevent cardiothrombotic disease (e.g. ischaemic stroke, myocardial infarction). Although aspirin is hydrolysed rapidly in the body to salicylic acid, it does appear briefly in the presystemic circulation and irreversibly inhibits COX-1 in platelets. The major platelet product lost is TXA_2, a potent platelet aggregator and vasoconstrictor. Platelets are not nucleated and are unable to express new enzyme. The balance of COX products regulating cardiovascular events shifts towards the major prostaglandin from nucleated vascular endothelial cells, prostacyclin (PGI_2) an anti-aggregation agent and vasodilator.

Other applications for NSAIDs are being researched, including prevention of diabetic cataracts and treatment of multi-infarct dementia, Alzheimer's disease and gastrointestinal cancers. At present, these are unlicensed indications.

Adverse effects
Some of the adverse effects of NSAID therapy are shown in Figure 2; the list is not exhaustive and does not include therapeutic overdose toxicity. Preparations containing aspirin should not be given to children because of an association with Reye's syndrome. Loss of prostaglandins acting as autacoids (e.g. maintaining local blood flow) is often a contributory factor to the adverse effects of NSAIDs, but the overall causes are usually complex. Reduced metabolism of free fatty acids by COX may result in increased formation of inflammatory, bronchoconstrictor leukotrienes via the lipoxygenase pathway (Figure 1). Physiochemical properties of acidic NSAIDs can contribute directly to cell damage.

Some adverse effects of NSAID therapy

System	Adverse effect	Putative mechanisms
Gastrointestinal	Discomfort	Chemical irritancy
	Nausea	Back diffusion of gastric acid
	Diarrhoea	Loss of homeostatic prostaglandins
	Ulceration	Ischaemia
	Bleeding	Gastric barrier breakdown
Renal	Fluid retention	Loss of homeostatic prostaglandins
	Sodium retention	
	Renal failure	
Cardiovascular	Exacerbation of hypertension	Secondary to renal disturbances
	Exacerbation of congestive heart failure	
Pulmonary	Exacerbation of asthma	Loss of homeostatic prostaglandins Increase in leukotriene production
Blood	Haemorrhage	Decreased prothrombin Decreased thromboxane A_2

Early appreciation that the adverse effects of aspirin can be attributed to loss of prostaglandins with autacoid or homeostatic function has led to a search for NSAIDs selectively inhibiting inflammatory prostaglandins. Discovery of isoforms of COX has resulted in the development of highly selective COX-2 (*versus* COX-1) inhibitors as NSAIDs with a lower risk of gastrointestinal damage (e.g. celecoxib, rofecoxib). This advantage is reduced if patients take low-dose aspirin as a relatively selective COX-1 inhibitor for the prevention of cardiothrombotic disease; celecoxib and rofecoxib do not protect against ischaemic cardiovascular events.

Therapeutic use of highly selective COX-2 inhibitors is associated with changes in renal function (e.g. sodium retention, oedema and increases in blood pressure) indicating that renal COX-2 is constitutive and its products physiologically desirable. In the stomach, COX-2 products are implicated in adaptive cytoprotection and ulcer repair. Consequently, drugs like rofecoxib can exacerbate severe congestive heart failure and impair gastric ulcer healing. ◆

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Opioid Mechanisms and Opioid Drugs

Barbara J Pleuvry

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The analgesic property of opium was described 6,000 years ago by the Sumerians who lived in the south of Mesopotamia. However, it was only in the 1950s that an understanding of how it might work began to emerge. Observations of structure–activity relations between morphine and the natural or synthetic compounds that shared its analgesic action suggested the existence of opioid receptors. Morphine, one of the active compounds extracted from opium, is an agonist at opioid receptors and the discovery of the opioid antagonist naloxone gave scientists an important tool to uncover the natural role of opioid receptors in the body. Morphine and related opioid analgesics possess a number of properties other than analgesia (Figure 1) and morphine analogues are available that have selectivity for a few of these properties (e.g. dextromethorphan is a selective cough suppressant). This suggested to researchers that there might be more than one opioid receptor.

It has now been established by cloning and protein sequencing that there are three separate opioid receptors μ, δ and κ. All three receptors are members of the G-protein-coupled superfamily of receptors. In 1997, the International Union of Pharmacology (IUPHAR) reclassified opioid receptors as OP_1 (δ), OP_2 (κ) and OP_3 (μ) corresponding to the cloned receptors. Each receptor has a different distribution throughout the CNS. Some regions, such as the dorsal horn of the spinal cord, express μ, δ and κ receptors while others, such as the thalamic nuclei, express the μ receptor only. Three families of endogenous ligands for these receptors have been described, the enkephalins, the dynorphins and the endorphins. The characteristics of the opioid peptides are summarized in Figure 2. The enkephalins are pentapeptides (Figure 3) while the dynorphins and the endorphins contain a longer sequence of amino acids. Each family of opioid peptides is derived from its own precursor though dynorphins all have a leu-enkephalin sequence and endorphins have a met-enkephalin sequence at the proximal end of the molecule.

While only three opioid receptors have been cloned at the time of writing, this is not proof that subtypes of these receptors do not exist. There is evidence of subtypes of all three receptors, which may represent alternative splicing of the opioid receptor clones.

Earlier studies suggested an σ opioid receptor that mediated the psychotomimetic effects of some opioid analgesics (e.g. pentazocine). Cloning studies have confirmed the existence of this receptor but it is not now considered to be opioid in nature, because naloxone is an inconsistent antagonist. Nevertheless, some opioid drugs bind to σ receptors as does phencyclidine and its analogue ketamine.

Some pharmacological actions of opioid drugs

Analgesia
- Main use although less effective in neuropathic pain syndromes
- May be useful to prevent breathing attempts in ventilated patients

Constipation
- Site of action both CNS and peripheral. A troublesome side-effect when analgesic activity is required, however, useful for the treatment of diarrhoea
- Poorly absorbed opioids (diphenoxylate and loperamide) exert a local effect preventing fluid accumulation in the intestine; loperamide is so little absorbed that it can be sold over the counter

Emesis
- Undesirable in all instances
- Site of action chemosensitive trigger zone in the area postrema on the floor of the fourth ventricle
- Not separable from analgesic activity with current drugs
- N.B. Opioids also depress the vomiting centre

Euphoria
- Abuse potential
- Mediated by μ receptors

Tolerance and dependence
- Can be detected within 12–24 hours
- Tolerance occurs most readily to analgesia, respiratory depression, emesis and euphoria and less readily to constipation

Cough suppression
- Heroin, codeine and pholcodine are used as cough suppressants
- Dextromethorphan has selectivity for this action

Miosis
- Little tolerance to this effect so may be seen in addicts; caused by stimulation of the oculomotor nerve nucleus

Antidiuretic effect
- N.B. κ agonists have a diuretic action

Sedation
- Usefulness depends on the circumstances

1

Endogenous opioid peptides

	Enkephalins	**Dynorphins**	**Endorphins**
Precursor	Pro-enkephalin A	Prodynorphin	Pro-opiomelanocortin (N.B. ACTH comes from the same precursor and both are released during stress)
Example	Methionine-enkephalin Leucine-enkephalin	Dynorphin A	β-endorphin
Distribution	Widespread in CNS and periphery	Widespread in CNS and periphery	Anterior pituitary gland and a pathway from the hypothalamus to the periaqueductal grey
Opioid receptor preferentially activated	δ	κ	μ, κ and δ
Metabolism	Rapid via enkephinase and other peptidases	Rapid	Slow

2

Amino-acid sequence of some opioid peptides

Met-enkephalin
Tyr-Gly-Gly-Phe-Met

Leu-enkephalin
Tyr-Gly-Gly-Phe-Leu

Dynorphin A
Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Trp-Asp-Asn-Gln

β-endorphin
Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu

3

Opioid mechanisms in pain pathways

Figure 4 shows the areas of the pain pathway where the endogenous opioid receptors are found. Opioid receptors are found at the level of the nociceptors. Opioid drugs acting at peripheral opioid receptors on sensory nerves can relieve inflammatory pain. μ, κ and δ receptors all appear to be present at this site.

Acting through an inhibitory G-protein, μ receptor activation inhibits adenylyl cyclase activity, thus preventing nociceptor sensitization by inflammatory mediators such as prostaglandin E_2 that involves the activation of adenylyl cyclase. Agonists at κ and δ receptors do not share this mechanism of activity, instead they are able to prevent bradykinin-induced release of noxious mediators from sympathetic nerves. These findings have led to the use of peripheral application of opioid drugs to treat inflammatory pain.

Most of the opioid receptors in the dorsal horn of the spinal cord are μ receptors though δ and κ receptors are present. At this site, both μ and δ agonists inhibit pain transmission though the role of κ receptor activation in pain control is more controversial. At the neuronal level, μ and δ opioid receptor activation causes a decrease in adenylyl cyclase activity, which in turn opens potassium channels (hyperpolarization) and closes calcium channels. Both these actions result in decreased release of a pain neurotransmitter, probably glutamate and/or substance P.

High concentrations of opioid receptors are found in the periaqueductal grey, nucleus raphe magnus and nucleus reticularis gigantocellularis and systemic morphine induces analgesia at these sites. The limbic system also contains opioid receptors and drugs acting at this point are believed to reduce the affective component of pain.

Opioid receptors are found at other sites (e.g. thalamus, cortex), which may be relevant to nociceptive control. However, concentration in other areas such as the tractus solitarius is more likely to be related to respiratory effects.

The opioid antagonist naloxone does not affect pain threshold or produce any other effects in a normal individual, indicating that opioid systems are not tonically active. However, it does prevent stress-induced analgesia and can make an existing pain condition worse. Naloxone has been useful to treat thalamic pain syndromes, but this is thought to be due to an effect on local blood flow rather than an analgesic action.

Site of endogenous opioid receptors

4

Analgesic opioid drugs

Agonists at m opioid receptors

Most of the analgesia produced by clinically useful analgesics is mediated via the μ opioid receptor as are most of the side-effects. Thus, the development of drugs having greater μ selectivity than morphine (e.g. sufentanil) has not resulted in large reductions in adverse effects. Nevertheless, the μ opioid analgesics now available have useful differences in pharmacokinetic properties that have had a significant beneficial effect on patient comfort and safety. Some of the more important μ opioid agonist analgesics are compared in Figure 5.

μ agonist analgesics

	Elimination half-life (hours)	Metabolites	Comments
Alfentanil	1.5–3.5	None active	Short duration of action of single doses but multicompartment distribution means this advantage is lost when given as an infusion
Fentanyl	1.5–5.5	None active	High potency and lipid solubility allow for transdermal administration. Also possesses local anaesthetic activity which may contribute to analgesia when used via the intrathecal or epidural route
Methadone	9–87	Active metabolite, but not clinically important	Firmly bound to proteins in tissues. Slow release results in mild but protracted withdrawal syndrome
Morphine	2–3	Morphine-6-glucuronide contributes significantly to analgesia in chronic use	Morphine-6-glucuronide contributes significantly to analgesia in chronic use. Poorly absorbed orally. Incidence of vomiting probably greater than other opioids
Oxycodone	2–3	None active	Can be given orally alone or in combination with non-steroidal anti-inflammatory drugs (NSAIDs). May be given as pectinate to provide sustained release (suppository)
Pethidine (meperidine)	3–5	Norpethidine (stimulatory effects)	Anticholinergic effects. Local anaesthetic activity Excitement or convulsions more common Interaction with monoamine oxidase inhibitors
Remifentanil	0.16–0.35	None active	Rapid metabolism allows intravenous infusions for total intravenous anaesthesia, but analgesia ceases on termination of infusion
Sufentanil	2.5–3.5	Not reported in humans	High potency and lipid solubility allow for transdermal administration

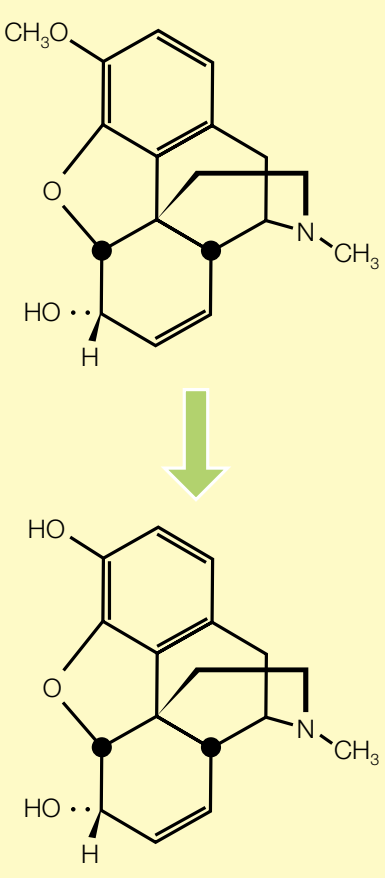
5

Weak and partial agonists at m opioid receptors

Codeine, dihydrocodeine and dextropropoxyphene have a maximum analgesic action below that of morphine. They are often called weak agonists, because there are no data indicating whether or not they are true partial agonists at μ opioid receptors. They cause less tolerance and dependence than the drugs in Figure 1. Codeine (Figure 6) and possibly dihydrocodeine are pro-drugs that are metabolized to morphine, which accounts for most of their pharmacological effects. Dextropropoxyphene is metabolized to norpropoxyphene, which may contribute to toxicity with repeated doses. It has been suggested that combinations of either codeine or dextropropoxyphene with aspirin produce a higher degree of analgesia than either drug given alone.

Buprenorphine is a true partial agonist at μ opioid receptors. Its oral bioavailability is poor and it is usually administered sublingually or by intramuscular injection. Buprenorphine has significant respiratory depressant activity. Once administered, reversal by naloxone is uncertain because of the slow dissociation of the drug from the opioid receptor. It has been suggested that naloxone may increase the agonist activity of a high dose of buprenorphine. The mechanism of this effect has been ascribed to the bell-shaped dose–response relationship proposed for the analgesic action of buprenorphine (Figure 7).

Codeine metabolized to morphine



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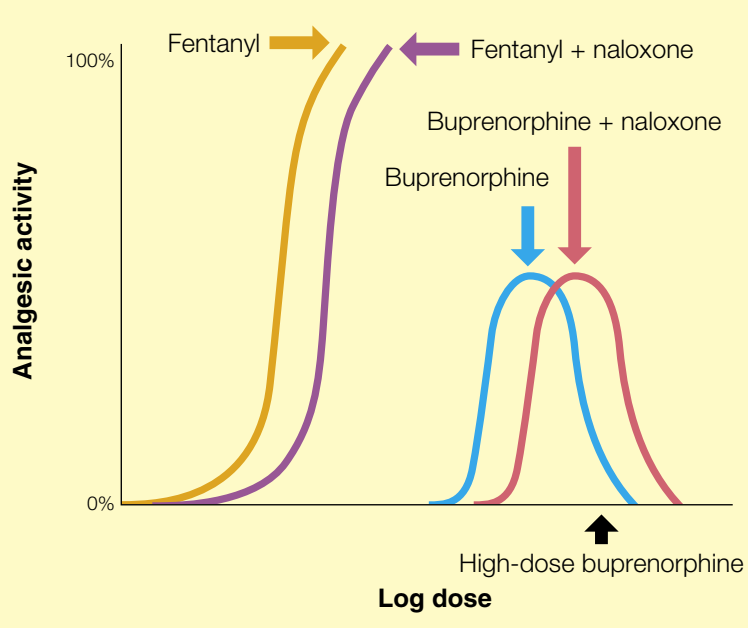
Effect of naloxone on the log dose-response relationships to fentanyl and buprenorphine



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Drugs acting at both k and μ opioid receptors

Pentazocine, nalbuphine and butorphanol were originally thought to be κ opioid receptor agonists and μ opioid receptor antagonists. However, they all produce respiratory depression, a property not associated with full κ agonists at least in experimental animals. It is now believed that they are probably partial agonists at both receptor types though the degree of agonist activity varies from drug to drug. Which receptor is involved in their analgesic activity is unclear. All three drugs have elimination half-times of about 3 hours. Pentazocine, like its predecessor nalorphine, produces more intense dysphoria and psychotomimetic effects than nalbuphine and butorphanol. Only the l-isomer of the racemate pentazocine combines with opioid receptors, the d-isomer having particular affinity for the σ, non-opioid, receptor. In addition, nalbuphine and butorphanol are not associated with cardiovascular stimulation. Nalbuphine is a more effective μ receptor antagonist than pentazocine and exhibits a well-documented ceiling effect on respiratory depression. Butorphanol has marked sedative actions. The abuse liability of these drugs is significantly less than that of morphine.

Meptazinol and tramadol

Meptazinol (elimination half-life about 2 hours) combines partial agonist activity at μ opioid receptors with activation of muscarinic cholinoceptors. In animals its analgesic action is sensitive to both naloxone and muscarinic antagonists. Meptazinol is rapidly metabolized in the neonate and was recommended for used in labour. Meptazinol is dysphoric in high doses and induces vomiting in a high proportion of patients, which is not surprising in view of its cholinomimetic properties. Both these effects have resulted in a marked decline in its use. It was originally claimed that meptazinol had selectivity for the μ_1 subgroup of receptors and this resulted in a lack of respiratory depressant activity (assuming this to be the property of μ_2 receptors). However, not all experts believe in this receptor subdivision and the cholinomimetic actions of the drug tend to reduce any opioid-induced respiratory depression.

Tramadol is a weak μ agonist with even weaker activity at κ and δ subtypes of opioid receptor. It inhibits the neuronal reuptake and promotes the release of both noradrenaline and 5-hydroxytryptamine. It has been used for over 20 years in Germany, but has been available in the UK only since 1994 and in the USA since 1995. It appears to produce minimal tolerance and dependence and relatively little respiratory depression. Tramadol is not useful in severe pain and the chief adverse effects are nausea and dizziness. Like other monoamine reuptake inhibitors, tramadol may lower seizure threshold. Its elimination half-life is about 6 hours.

Analgesic usefulness of selective opioid receptor agonists

A number of selective κ agonists have been tested as potential analgesics. Enadoline is a selective κ-opioid agonist that produces analgesia but lacks typical opioid side-effects such as constipation, respiratory depression, vomiting and dependence. Enadoline has been used for postsurgical pain in clinical studies but has given conflicting results. Enadoline, 25 mg, had no useful effect after dental surgery, but was equivalent to morphine, 10 mg, after abdominal or pelvic surgery. The reasons for these differences in effectiveness are unknown. Trials of enadoline that demonstrated a significant analgesic effect were terminated because of dose-limiting neuropsychiatric effects; a problem that appears to recur in compounds with opioid κ receptor activity.

These typical adverse effects of κ agonists can be reduced by the use of compounds that have limited access to the brain. Asimadoline is a peripherally acting κ opioid that has been shown to be antinociceptive in visceral models of pain. In the periphery, agonists at κ receptors are able to prevent bradykinin-induced hyperalgesia. Asimadoline is an effective anti-arthritic drug, attenuating both the joint damage and pain associated with adjuvant-induced arthritis in the rat and it is now on clinical trial for the treatment of osteoarthritis. Fedotozine is another κ agonist that has been used clinically, with some success, in irritable bowel syndrome and functional dyspepsia. However, these beneficial effects may not always be mediated via the κ receptor. Fedotozine does not appear to have the diuretic action seen with other κ agonists.

The original ligands for the δ receptor were the enkephalins and highly selective ligands were developed based on the enkephalin peptide structure, but no commercially useful drug appeared. Non-peptide δ agonists have been synthesized and show promise in animal studies but await trials in humans. TAN-67 has been reported to mediate both spinal and supraspinal antinociceptive activity via the δ_1 subgroup of opioid receptors. As with the κ opioid agonists mentioned above, δ agonists may have clinical applications not associated with classical analgesic activity. TAN-67 reduces infarct size and is cardioprotective in a rat model of coronary artery occlusion and re-perfusion.

In summary, while selective agonists at non-μ subtypes of opioid receptors exert analgesic properties, their clinical use may be limited to specific pathologies where pain relief is just one component of their beneficial action.

Pain and opioid sensitivity

The standard method of postsurgical pain control is the parenteral administration of opioids. Patient-controlled analgesia (PCA) is widely used to tailor opioid administration to an individual patient by titrating to an effective drug concentration and maintaining analgesia at that level. However, the ideal opioid for PCA, that has a fast onset of action, high efficacy, moderate duration of action and few side-effects does not exist. Morphine is the standard opioid against which others are judged and there is often little credible evidence that other drugs have significant advantages. In severe pain, partial agonists may be ineffective if the ceiling to their effect occurs at low doses. In many instances, postoperative pain is poorly controlled. The main reasons are poor routine evaluation of pain severity, the use of lower than recommended doses of analgesics and discrepancies in pain assessment between the patient and the medical or nursing staff. It has been suggested that education rather than new drugs or better delivery would cause the greatest improvements in the management of acute pain.

The parenteral use of opioids is a popular method of providing analgesia in obstetrics though it is associated with various adverse effects on the fetus, including low Apgar scores and neurobehavioural deficits. Avoiding additional opioids after the first stage of labour can reduce these effects, but this may lead to inadequate pain relief. Spinal opioids are ineffective in labour. In chronic pain syndromes, neuropathic pain is often opioid insensitive.

The routes used to administer opioid drugs are listed in Figure 8.

Routes of administration for opioid drugs

Route	Advantages	Disadvantages
Oral immediate release	• Convenient • Can be administered by patient or family • Low bioavailability, unpredictable absorption	• Side-effects may limit analgesic doses • Patient must be able to swallow
Oral modified release	• Convenient • Can have once-daily dosage • Can be administered by patient or family	• Some preparations have a slow onset • Dose titration is necessary initially • Unsuitable for acute pain
Topical	• May be effective for skin lesions when systemic opioids have failed	• Only effective if broken or inflamed skin • Occlusive dressings are required
Transdermal patches	• Does not require the patient to swallow • Can have a long duration of analgesic effect • Avoids first-pass metabolism	• Slow onset of analgesia • Only suitable for very lipid-soluble opioids (e.g. fentanyl) • Difficult to adjust dose rapidly • Action is not terminated by patch removal • Expensive
Transdermal iontophoresis	• Faster onset of analgesia than patches • Dose can be adjusted by current control	• Hardware (possibly bulky) needed for administration • Expensive
Oral transmucosal	• Avoids inactivation in the gut (especially buprenorphine) • Action can be terminated by removal of the drug (no depot formation)	• Absorption may be erratic • Drug can be swallowed accidentally
Rectal	• Relatively easy to use if oral route is unavailable • Inexpensive	• Not widely acceptable to patient and family • Absorption can be slow
Intranasal and inhalational	• Avoids injections	• Advantages for only a limited number of patients
Subcutaneous infusion	• Can be used without intravenous access • Can be used for patient-controlled analgesia (PCA)	• Limited volume can be administered • Requires nursing and pharmacy care • Local irritation can occur • Expensive apparatus
Intravenous infusions	• Rapid pain relief • Easy to titrate dose • Suitable for PCA	• Requires intravenous access • Possibility of infection • Requires nursing input • Apparatus expensive
Spinal (intrathecal or epidural)	• May be effective when other routes are not	• Pruritus, urinary retention and infection at catheter site • Expensive • Requires expert attention

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Other Targets for Analgesic Drugs

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The basic science behind conventional analgesics is discussed in *Anaesthesia and Intensive Care Medicine* **2:11:** 450 and 455. However, other transmitters and modulators appear to influence pain perception and many potential analgesics are being investigated. Many of these substances are peptides (e.g. enkephalins) and some basic differences between peptide neuro-transmission and transmission by traditional neurotransmitters such as noradrenaline (norepinephrine) and γ-aminobutyric acid are shown in Figure 1.

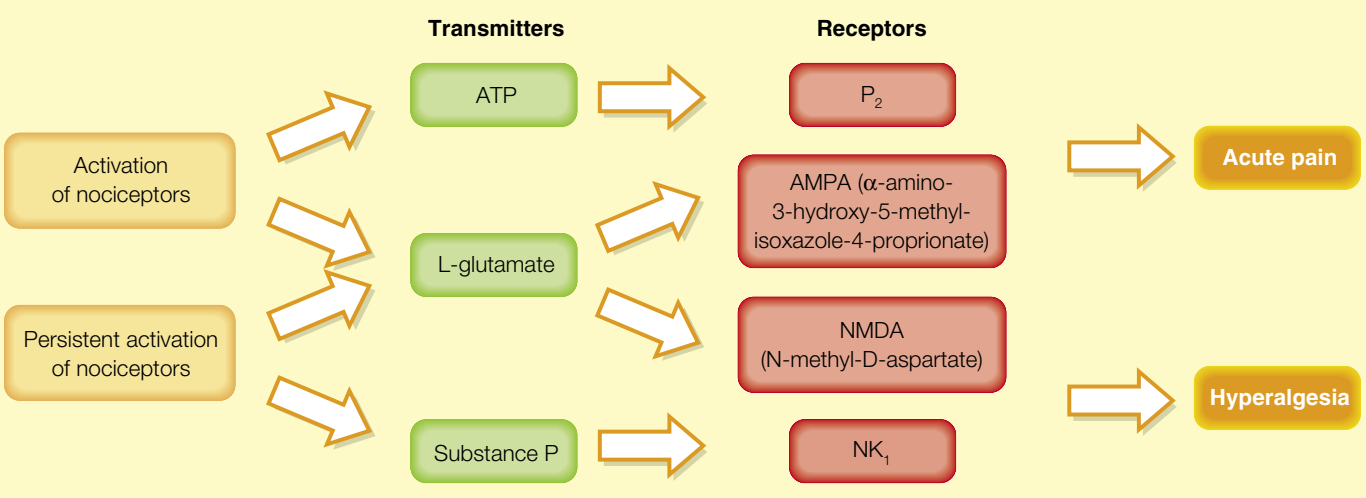
Comparison of peptide and non-peptide (traditional) neurotransmitters

Peptide	Non-peptide
• High molecular weight > 200 daltons (e.g. endorphins)	• Low molecular weight < 200 daltons (e.g. noradrenaline (norepinephrine))
• Synthesized by the genetic material of the neuron No necessity to take up specific precursors	• Precursor taken up into the neuron
• Many products possible from precursor gene by selective DNA splicing, selective cleavage of pro-hormone or post-translational modification (e.g. pro-opiomelantocortinyields both ACTH and endorphins)	• Only one product obtained from the precursor in an individual neuron
• Once released, enzymes are required for termination of activity	• May be metabolized by enzymes or taken up into neurons or glia

1

Individual modulators will be discussed, but Figure 2 illustrates the relationship between these compounds at one site in the pain pathway.

Pain transmission in the spinal cord



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Acetylcholine

Cholinomimetic drugs (e.g. oxotremorine) and anticholinesterase agents that prevent the breakdown of acetylcholine have long been known to have analgesic activity. Neostigmine given intrathecally had significant analgesic activity in man, but adverse effects, such as prolonged motor block and nausea and vomiting, reduced its usefulness. If intrathecal neostigmine is combined with another analgesic, such as morphine, lower doses of each drug can be used to achieve the same analgesic effect, with a consequent reduction in the adverse effects of the individual agents. Epidural neostigmine combined with lidocaine (lignocaine) significantly increased the duration of pain relief compared with lidocaine alone, without increasing the incidence of adverse effects. The adverse effects of neostigmine can also be reduced, while maintaining the analgesic effect, by injecting the compound locally (intra-articularly) in patients undergoing knee arthroscopy. In the periphery, neostigmine appears to activate muscarinic receptors to acetylcholine to produce analgesia and the effect has been reversed experimentally by atropine.

Nicotinic receptors are also involved in cholinergic analgesia because nicotine is an effective analgesic acting within the CNS. In the dorsal horn of the spinal cord, nicotinic receptors have an important role in the modulation of persistent pain and neurogenic inflammation. Although nicotine has unacceptable adverse effects, continued interest in the therapeutic potential of cholinergic analgesia has been stimulated by the isolation of epibatidine from the skin of the Ecuadorian poison arrow frog. Epibatidine is significantly more potent than nicotine as an analgesic and rapidly enters the brain after intravenous administration. However, it also showed unacceptable adverse effects, in particular, disruption of motor activity. Neuronal nicotinic acetylcholine receptors are pentameric ligand-gated ion channels that exist in several different subunit combinations, which exert different physiological functions. One of these subunit combinations (α4,β2 subtype) is responsible for analgesic activity and a selective agonist (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) has been developed that has a greater separation between analgesic and motor effects than nicotine and epibatidine. Safety trials of the compound in humans are planned.

Adrenaline (epinephrine) and noradrenaline (norepinephrine)

In some patients, the sympathetic nervous system is responsible for continuing pain and persistent hyperalgesia and pain can be abolished by local anaesthesia of sympathetic ganglia or by depletion of noradrenaline (norepinephrine) by substances such as guanethidine. Antagonists at α_1-adrenoceptors, but not at β-adrenoceptors can also provide relief. No simple test is available to predict the success of sympathetic interventions.

Both α_1- and α_2-adrenoceptor binding sites are found in the parts of the brainstem controlling pain modulation. While α_1-receptor activation increases responses, α_2-receptor activation decreases responses to pain by preventing the release of substance P in the spinal cord. Intrathecal and epidural administration of α_2-agonists (e.g. dexmedetomidine, clonidine) have been receiving attention as potential treatments for pain in humans. The chief drawbacks to α_2-agonists as analgesics are the concurrent sedative and hypothermic properties. There is clearly summation, if not synergy, between opioids and α_2-agonists; a reduction in adverse effects might therefore, result from combinations of the two classes of drug.

5-hydroxytryptamine (5-HT)

5-HT is released from mast cells and blood platelets during tissue damage. In high concentrations it elicits pain directly and it is involved in inflammatory hyperalgesia. However, whether 5-HT causes pain or analgesia depends on the location and the receptors involved (Figure 3) and thus applications of agonist or antagonists as analgesics will rely on localization of effects.

5-HT receptors and pain

Receptor	Location	Analgesic activity
5-HT_1	Peripheral nociceptors	Antagonists
	Brainstem	Agonists
5-HT_2	Peripheral nociceptors	Antagonists
	Brainstem	Agonists
5-HT_3	Nociceptors	Antagonists
	Dorsal horn	Agonists
5-HT_4	Nociceptors (visceral?)	Antagonists

3

A particularly important site of pain control is a descending inhibitory control, which constitutes one of the gating mechanisms that control pain transmission in the dorsal horn, and carries tryptaminergic fibres from the brainstem. Direct application of 5-HT to the spinal cord is analgesic and 5-HT uptake inhibitors have analgesic properties. Some patients with chronic pain obtain relief with antidepressant drugs that prevent the reuptake of 5-HT, suggesting that underactivity of tryptaminergic systems may contribute to their problem. Prevention of 5-HT reuptake contributes to the analgesic activity of the weak opioid drug tramadol, and ritanserin, a 5-HT_2-receptor-blocking drug, antagonizes the antinociceptive activity of tramadol suggesting that this subtype of 5-HT receptor may be important with respect to 5-HT actions on pain pathways. Agonists at $5\text{-HT}_{1B/1D}$-receptors prevent the sensitization of caudal trigeminal neurons in response to dural vasodilatation. This action is relevant to the successful use of triptans (see *Anaesthesia and Intensive Care Medicine* **2:11:** 460) to treat a migraine attack.

γ-aminobutyric acid (GABA)

GABA, the major inhibitory neurotransmitter in the brain, has a widespread distribution. In most areas of the brain, such as the periaqueductal grey, GABA agonists at either GABA_A or GABA_B receptors appear to be analgesic. However, when applied to the nucleus reticularis gigantocellularis, in contrast to other brain areas, agonists at GABA_A receptors facilitate pain while antagonists are analgesic. Whether identifying the vast number of subtypes of the GABA_A receptor will allow separation of the two opposing activities of GABA_A agonists on pain transmission remains to be seen. Nevertheless the overall effect of systemic administration of GABA_A agonists in man is analgesia.

In neuropathic pain there is an up-regulation of GABA_B receptors as a consequence of loss of inhibitory neurons caused by the excitotoxicity of excessive glutamate release. In these conditions, the GABA_B agonist baclofen is analgesic, though tolerance to this action develops quickly. For this reason, baclofen is not an effective analgesic in man except in the treatment of trigeminal neuralgia. A more potent GABA_B agonist has been developed (CGP 44532), which is a more effective analgesic than baclofen and appears to retain this activity after chronic administration. This may be a more promising candidate for analgesic activity in humans.

Gabapentin

Gabapentin was synthesized as a structural analogue of GABA but does not bind to any known GABA receptor. It appears to have a specific interaction with the α2δ subunit of the voltage-dependent calcium channel. The analgesic actions of gabapentin are of value in hyperalgesic states and the drug has been used successfully to treat neuropathic pain. A significant part of gabapentin's activity is spinal, though supraspinal activity cannot be ruled out. Gabapentin and its analogues may have some advantages over drugs such as morphine and amitriptyline in the treatment of mechanical allodynia because they block both static and dynamic components of the pain.

Excitatory amino acids

L-glutamate is released in areas of the spinal cord containing primary afferent terminals. There are a number of receptors for glutamate that can be subdivided into the inotropic receptors, NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-isoxazole-4-proprionate) and kainate, L-AP4 (L-2-amino-4-phosphonobutyrate) and metabotropic receptors, of which eight have been cloned. It is likely that AMPA receptors are involved in primary pain transmission (Figure 2). Thus, acute pain control strategies should focus on the AMPA receptor in the spinal cord.

The ion channel associated with the NMDA receptors is blocked by magnesium ions at normal resting potentials. When the neuronal membrane is depolarized by a primary pain transmitter the magnesium ion block of the NMDA receptors is removed. This results in the synaptic potential being prolonged by NMDA receptor activation, resulting in a hyperalgesic or allodynic state. Both direct NMDA receptor antagonists and NMDA channel blockers such as dizocilpine (MK 801) can reduce hyperalgesia in animal models of neuropathic pain. However, preventative treatment is necessary with the NMDA receptor antagonists to achieve this effect. In contrast to the analgesic actions of excitatory amino-acid antagonists in the spinal cord, supraspinally they reduce analgesia.

What is important, however, is whether modulation of excitatory amino-acid transmission can provide analgesia in humans. Flupirtine, a non-opioid centrally acting analgesic has been shown to function as a weak NMDA antagonist. Ketamine is a dissociative anaesthetic first described as an analgesic in 1965. Subsequently it was shown to block the channel gated by NMDA and, in view of the experimental evidence suggesting that an NMDA receptor might be involved in hyperalgesia and wind-up pain, there have been a number of trials assessing the efficacy of ketamine in the treatment of chronic pain conditions. While some patients benefited from ketamine treatment, the drug does not seem to be effective in all types of chronic pain. When used alone as an analgesic, the psychotomimetic effects of ketamine are common and probably preclude its use as a sole agent. A reduction in dose, and thus side-effects, can be obtained by combining NMDA antagonists with opioids for the treatment of chronic pain states. Low-dose ketamine has been used as an adjuvant to other pain control procedures in postoperative pain.

NMDA antagonists also prevent the induction of tolerance to the analgesic action of morphine, though both preventative treatment and a single dose of the channel blocker, dizocilpine, can reverse morphine tolerance. Dextromethorphan was introduced over 40 years ago as an alternative to morphine, but preliminary studies demonstrated that, although it had little analgesic activity, it was an effective antitussive. Subsequently, dextromethorphan was shown to have some NMDA-receptor-blocking action and has analgesic actions in animal models of neuropathic pain. In human trials, dextromethorphan alone was shown to have little useful analgesic activity in neuropathic pain but, when combined with morphine, it has a potential for preventing the development of tolerance. A combination tablet for moderate-to-severe cancer pain containing dextromethorphan and morphine has been submitted to the US Food and Drug Administration for approval.

Since magnesium ion normally blocks the NMDA-receptor-operated channel, it follows that magnesium should exert some analgesic activity. Indeed, an inverse relationship between pain experienced and serum magnesium concentration has been observed in women in labour, and in patients with myocardial infarction, pancreatitis and burns. Studies have demonstrated that magnesium sulphate reduces analgesic requirements in the perioperative period.

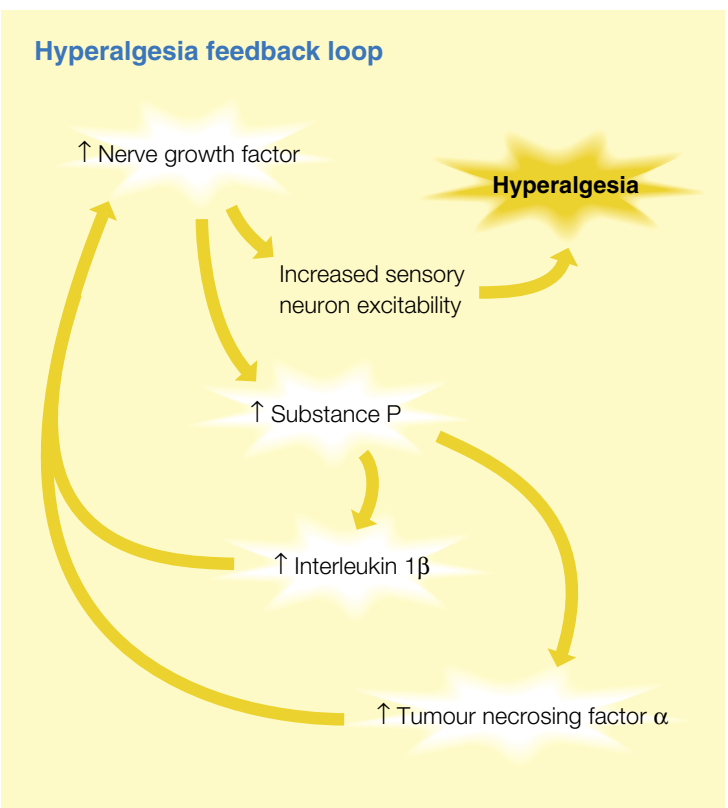
Bradykinin
Bradykinin is proteolytically cleaved from plasma and tissue kininogen at the site tissue of injury and is the most potent pain-producing substance so far described. It interacts with at least two receptors known as B_1 and B_2. B_2 is the most abundant and appears to be responsible for nociceptor excitation. While selective B_2-antagonists, presently available, are too short-lived to be clinically useful, a non-selective bradykinin receptor antagonist D-Arg [4-hydroxy-Pro^3-D-Phe^7] bradykinin has produced encouraging results in clinical trials for the treatment of pain from burns. The fact that this antagonist is non-selective may be advantageous, because it is now apparent that B_1-receptors are expressed during chronic inflammation and contribute to hyperalgesia. A selective B_1-antagonist has been developed des-Arg^9[Leu^8] bradykinin, which inhibits hyperalgesia in animals. Both these receptors are potential targets for analgesic therapy.

Tachykinins
The tachykinins, substance P, neurokinin A and neurokinin B, all play a role in pain transmission, and antagonists at all three receptors, NK_1, NK_2 and NK_3, are under investigation as potential analgesics. Substance P is released in the area of the nociceptor during pain initiation but it is associated with the flare response rather than nociceptor stimulation. Substance P and neurokinin A are released within the dorsal horn of the spinal cord in response to noxious stimulation of the primary afferent nerves. Neurokinin A, which stimulates NK_2 receptors, is a likely candidate as a primary pain transmitter because NK_2-receptor antagonists are more effective in inhibiting C-fibre evoked activity than substance P antagonists (NK_1 antagonists). Substance P plays a role in wind-up pain and selective NK_1-receptor antagonists attenuate wind-up pain and the increase in spinal neuron excitability induced by repetitive C-fibre activity and peripheral inflammation. Nevertheless the NK_1-receptor antagonist CP-99,994 has been shown to provide significant analgesia after dental surgery though ibuprofen provided a better and longer-lasting effect. Neurokinin B acts on NK_3-receptors that also appear to be involved in hyperalgesic states, though they have selectivity for hyperalgesic states initiated by thermal rather than mechanical stimuli.

Cholecystokinin
Within the CNS, the cholecystokinin (CCK) group of peptides has been found predominantly in dorsal horn neurons and has been suggested as an endogenous antagonist of opioid (i.e. morphine)-induced analgesia. Inflammatory pain exhibits an enhanced sensitivity to morphine and is associated with a decrease in CCK in the spinal cord. Nerve section induces CCK and the pain produced is relatively insensitive to morphine. While there are other explanations for this observation, CCK antagonists can restore morphine sensitivity in neuropathic pain. CCK and opioid peptides have parallel distributions in many brain areas associated with pain perception and it may be that the two systems reciprocally modulate CCK-enkephalin release. There appears to be a critical balance between opioid and CCK systems in the control of pain, and their interrelationship depends not only on the tone of both systems, but also on the exact nature of the pain-inducing stimulus. It is likely that manipulation of the balance between them using antagonists at either CCK-A or CCK-B receptors may benefit an individual patient, but will not provide an all-embracing analgesic without side-effects. Nevertheless, preliminary studies combining the CCK antagonist proglumide with opioids for the treatment of cancer pain have shown promise. It has also been shown that proglumide enhances the analgesic action of morphine in chronic pain and may prevent the development of tolerance to opioids.

Somatostatin
Somatostatin, which has been localized in interneurons in the superficial layers of the dorsal horn, produces analgesia by a mechanism distinct from that shown by opioids. Although there is some controversy about the anti-nociceptive activity of somatostatin in the experimental animal, intrathecal infusions of somatostatin itself or the stable analogue, octreotide, have been used successfully to treat cancer pain in humans that was refractory to opioids.

Nerve growth factor (NGF)
During inflammation there is increased synthesis of NGF and the subsequent increase in sensory neuron excitability and promotion of axon sprouting contribute to hyperalgesia. NGF increases the content of mediators such as calcitonin gene-related peptide and substance P in sensory nerves making greater quantities available for release. Substance P in turn up- regulates the production of tumour necrosing factor α (TNFα) and the interleukin, IL-1β, which completes the feedback loop by increasing the synthesis of NGF. The development of drugs that break this loop (Figure 4) could be a route to novel analgesic and anti-inflammatory compounds. There is some early evidence that anti-NGF antibodies may be potential analgesics in the treatment of neuropathic pain because some studies have indicated that anti-NGF did not prevent nerve regeneration.



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Nociceptin (orphanin FQ)
Nucleic acid probes based on the δ opioid receptor resulted, not only in the cloning of the μ and κ opioid receptor, but also in a new sequence of a novel G-protein-linked receptor that failed to bind classical opioid ligands. The distribution of this orphan (opioid-receptor-like: ORL) suggested that it might have a role in somatosensory processing. The endogenous ligand of this receptor was isolated by two separate groups and was named nociceptin or orphinan FQ. In the spinal cord, nociceptin consistently produces analgesic effects, but supraspinally it appears to exert an anti-opioid effect.

Leukotrienes
The D4 and B4 variant leukotrienes, which are products of arachidonic acid metabolism via the lipoxygenase pathway, appear to have a role in nociceptor sensitization. The evidence suggests that their actions are indirect via the release of other noxious mediators (e.g. prostanoids, substance P). These two leukotrienes have relative selectivity for the BLT and CysLT1 receptors, respectively. The CysLT1 receptor antagonists, zafirlukast and pranlucast, are used in the treatment of asthma, but analgesic uses in humans have not been reported.

Adenosine and adenosine triphosphate (ATP)
Although adenosine and ATP are primarily involved in energy metabolism, they have a wide range of other unrelated pharmacological effects including modulation of nociceptive transmission. Receptors for adenosine were originally designated as P_1-purinoceptors for adenosine and P_2-purinoceptors for ATP. Subsequently, the P_1-receptors have been subdivided and renamed A_1, A_{2a}, A_{2b} and A_3: all are G-protein-linked receptors. Analgesia occurs in neuropathic pain with low doses of adenosine and it appears to involve mainly the A_1-receptor. However, a highly selective adenosine A_1-receptor agonist (WAG 994) was shown to be poorly analgesic in postoperative dental pain when used in doses that did not produce adverse effects. In contrast, enhanced pain perception seen with high concentrations of adenosine is mediated largely through the A_2-receptor.

Large quantities of ATP can be released by tissue damage and produce sharp transient pain. This action is thought to be due to a direct action on ion channels via the ATP-sensitive purine (P_2) receptor and can be blocked by specific P_2-antagonists such as suramin. A subgroup of P_2-receptors, P_{2X}, is selectively expressed in small-diameter sensory neurons. Selective antagonists at this receptor may be potential analgesic drugs. ATP can be selectively released from the dorsal horn of the spinal cord and can cause fast depolarization of dorsal horn neurons (Figure 2).

Cannabinoids
Cannabis extracts have been available for centuries and their analgesic properties are well known. However, the absence of well-controlled clinical trials has meant that no useful clinical analgesics have emerged from them. The most abundant cannabinoid found in extracts is Δ^1 tetrahydrocannabinol (sometimes referred to as Δ^9 because of an alternative numbering system) which mediates an analgesic effect via the CB_1 cannabinoid receptor. An endogenous ligand for the cannabinoid receptor has been isolated and is an arachidonic acid derivative known as anadamide. The cannabinoid system appears to be tonically active because cannabinoid antagonists cause hyperalgesic responses.

In addition, cannabinoid agonists reduce hyperalgesia and inflammation by a peripheral action on CB_1-receptors though CB_2-receptors may also be involved at this site. Nabilone, a cannabinoid analogue, has shown analgesic activity in patients with intractable pain caused by multiple sclerosis.

Vanilloids
Capsaicin, responsible for the pungent taste of red peppers, binds to receptors found in polymodal nociceptors causing initial stimulation and subsequent inhibition. The inhibitory effect of capsaicin on pain perception is believed to involve the depletion of a number of peptides such as substance P and CCK. The initial stimulation of nociceptors causes an intense burning sensation that has limited its usefulness as an analgesic. This problem has been avoided by administering a local anaesthetic before topical capsaicin in the treatment of complex regional pain syndromes and neuropathic pain. Nine out of 10 patients obtained relief lasting 1–18 weeks. In lower doses, capsaicin cream has been used to treat residual limb pain in traumatic amputees.

Voltage-operated sodium channels
Several use-dependent sodium channel blockers, including carbamazepine and mexiletine, can relieve neuropathic pain. Sodium channels accumulate in large-diameter peripheral nerves at the site of nerve injury and it has been suggested that abnormal sodium channel activity may be associated with nerve damage and related pain. System administration of local anaesthetic drugs such as lidocaine (lignocaine) and mexiletine appear to be effective only in pain due to nerve damage, and there is little evidence that they should be used in other types of pain such as cancer pain.

Not all sodium channel blockers have the same effect on pain transmission. For example, bupivacaine reduces the dorsal horn neuronal responses to repetitive C-fibre stimulation while lamotrigine appears to increase wind-up in these neurons. Whether these differences between sodium channel blocking drugs result from selectivity for subtypes of sodium channel or other unrelated properties awaits investigation. The sodium channels expressed by sensory neurons are highly resistant to tetrodotoxin block. This opens the way to the rational design of selective sodium channel blockers. There is strong evidence for a role for the tetrodotoxin-resistant sodium channel (PN3/SNS), which is predominantly localized in the dorsal route ganglia, in hyperalgesia and allodynia.

Voltage-operated calcium channels
Verapamil, the L-type voltage-operated calcium channel blocker, has been shown to enhance the postoperative analgesia-sparing effects of epidural bupivacaine in patients undergoing abdominal surgery. Flunarizine, which produces a non-selective block of calcium channels, has also been reported to have antinociceptive properties. Certain types of sea snails contain ω conotoxins, which are blockers of N, P and Q-type calcium channels. Ziconotide (SNX 111), a synthetic derivative of ω conotoxin MVIIA, produces analgesia in animal models of acute persistent and neuropathic pain The compound is now on clinical trial and has been successful in the treatment of a patient with intractable brachial plexus avulsion. Although dose-dependent adverse effects were seen, such as dizziness, blurred vision and lateral gaze nystagmus, these could be resolved with dose reduction without the return of pain. The pharmacokinetics of ziconotide mean that relatively expensive drug-delivery systems are necessary and that may limit its use in the treatment of chronic pain.◆

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Overview of Hormone Therapy

Alex Pleuvry

Alex Pleuvry is an Independent Pharmaceutical Consultant. He qualified in pharmacy from the University of London, and spent most of his career in the pharmaceutical industry. His particular area of interest is the chemotherapy and hormone therapy of cancer.

A hormone is a substance, produced in a ductless organ, which is secreted directly into the blood and thence conveyed to a second organ, where it exerts its biological effect. Some neurotransmitters and 'local hormones' may be encompassed by this definition, but are beyond the scope of this article.

The range of natural hormones is demonstrated in Figure 1. Most natural hormones are peptides or steroids. Those produced by the hypothalamus, anterior and posterior pituitary, pancreas and parathyroid are peptides. The thyroid produces iodo-amino acids (T3 and T4) and the peptide calcitonin. Hormones produced by the adrenal cortex, placenta and gonads are steroids.

Natural hormones

Source	Hormone	Target
Hypothalamus	Growth hormone-releasing factor (GHRF)	Anterior pituitary, GH
	Somatostatin	Anterior pituitary, GH
	Thyrotrophin-releasing hormone (TRH)	Anterior pituitary, thyrotrophin
	Corticotrophin-releasing factor (CRF)	Anterior pituitary, ACTH
	Gonadotrophin-releasing hormone (GnRH) or luteinizing hormone-releasing hormone (LHRH)	Anterior pituitary/follicle-stimulating hormone (FSH) and LH
	Prolactin-releasing factor (PRF)	Anterior pituitary/Prolactin
Anterior pituitary	Growth hormone (GH)	Regulates growth
	Thyrotrophin	Thyroid/T3 and T4
	Adrenocorticotrophin (ACTH)	Adrenal cortex, corticoids
	FSH	Ovary, oestrogen, progestogen
	LH	Ovary, oestrogen and progestogen or testis, testosterone
	Prolactin	Mammary gland, milk production
Posterior pituitary	Antidiuretic hormone (ADH)	Kidney tubules
	Oxytocin	Mammary gland, milk expression Uterus, post-partum contraction
Thyroid	Thyroxine (T4)	Regulation of metabolism, growth and development
	Tri-iodothyronine (T3)	Regulation of metabolism, growth and development
	Calcitonin	Control of plasma calcium
Parathyroid	Parathyroid hormone	Control of plasma calcium
Pancreas	Insulin	Reduction in blood sugar
	Glucagon	Liver: stimulation of glucose breakdown but inhibition of glycogen synthesis and glucose oxidation
	Somatostatin	Local control of insulin and glucagon release
Adrenal cortex	Mineralocorticoids (e.g. aldosterone)	Control of water and electrolyte balance
	Glucocorticoids (e.g. hydrocortisone, corticosterone)	Control of carbohydrate and protein metabolism
Ovary	Oestrogens	Promotes proliferative phase of endometrial regeneration Promotes formation of progesterone receptors in target tissue
	Progesterone	Promotes secretory phase of endometrial regeneration Maintenance of pregnancy
Placenta	Gonadotrophins, oestrogens, progesterone	Maintenance of pregnancy
Testis	Testosterone	Maturation of male sexual organs and development of secondary sexual characteristics Maintenance of spermatogenesis Anabolic effects

1

Hormones combine with receptors that belong to several different superfamilies of receptors. For example, insulin binds with tyrosine kinase-linked receptors and the steroid and thyroid hormones link with receptors that regulate gene transcription. Somatostatin receptors show significant homology with opioid receptors, which may explain the analgesic action of somatostatin analogues such as octreotide. Several hormones also have a functional role as neurotransmitters (e.g. somatostatin, calcitonin).

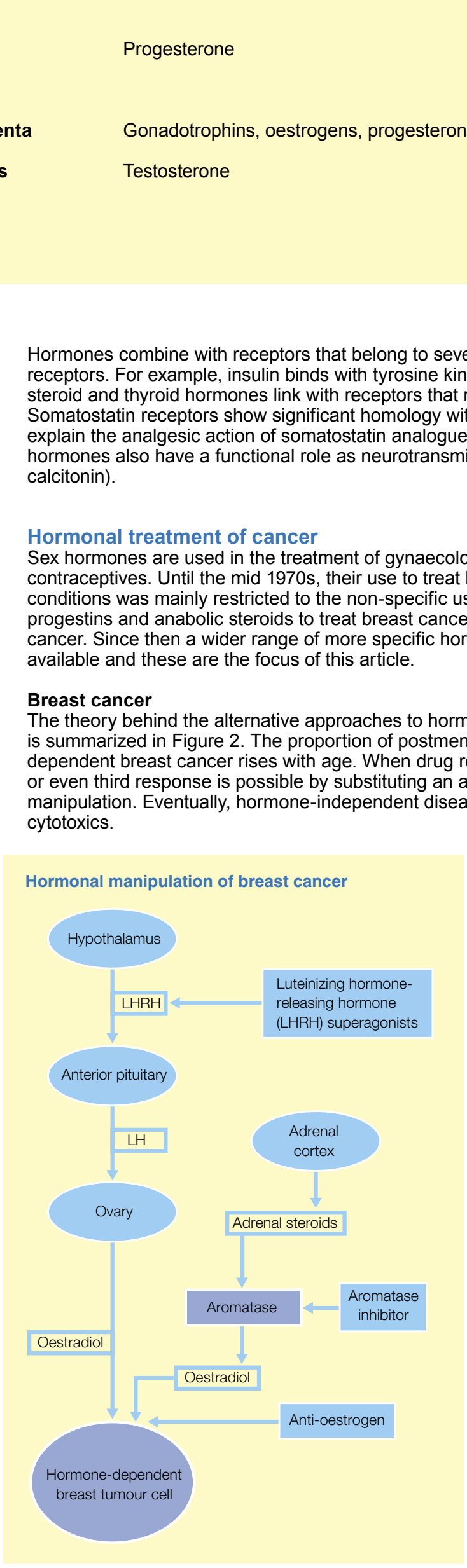
Hormonal treatment of cancer

Sex hormones are used in the treatment of gynaecological disorders and as oral contraceptives. Until the mid 1970s, their use to treat hormone-dependent malignant conditions was mainly restricted to the non-specific use of androgens, oestrogens, progestins and anabolic steroids to treat breast cancer and stilboestrol for prostate cancer. Since then a wider range of more specific hormonal agents has become available and these are the focus of this article.

Breast cancer

The theory behind the alternative approaches to hormonal treatment of breast cancer is summarized in Figure 2. The proportion of postmenopausal patients with hormone-dependent breast cancer rises with age. When drug resistance occurs, a second or even third response is possible by substituting an alternative type of hormonal manipulation. Eventually, hormone-independent disease develops, which requires cytotoxics.

Hormonal manipulation of breast cancer



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Anti-oestrogens: the nuclei of hormone-sensitive breast cancer cells contain receptor proteins (ER) that specifically bind oestradiol. This activates the interaction of the hormone-receptor complex with specific regions of DNA resulting, eventually, in tumour cell growth. The binding of oestradiol to the receptor is competitively inhibited by anti-oestrogens (e.g. tamoxifen) which thus inhibit tumour cell proliferation. Tamoxifen is also associated with increased levels of growth inhibitory factor (TGF-β), decreased levels of TGF-α and increased levels of sex hormone-binding globulin (SHBG), which reduces free oestradiol concentrations. Tamoxifen also has some partial agonist effects, which may cause endometrial or ovarian changes, resulting in a higher than expected incidence of endometrial cancer following long-term treatment.

Tamoxifen is not only the most widely used anti-oestrogen but also the most widely used hormonal agent in the treatment of breast cancer. Several simple tamoxifen analogues were developed, mainly involving halogen substitutions, but the development of most of these simple analogues for breast cancer has ceased, though raloxifene is used in the treatment of osteoporosis. Today, the main use of tamoxifen is in the adjuvant treatment of early breast cancer, typically for 5 years, to reduce the recurrence rate. More recently, it has been approved by the FDA for the prevention of breast cancer in women at high risk.

Fulvestrant is the first of a new class of oestrogen receptor down-regulator that targets and degrades oestrogen receptors. Phase III trials of fulvestrant (ICI 182780) have demonstrated a broader range of activity, including effectiveness in tamoxifen-resistant patients, and a longer duration of effect than current endocrine agents. It was approved by the FDA in April 2002.

Aromatase inhibitors: in postmenopausal women with hormone-dependent breast cancer, the principal source of oestrogen is through aromatization of adrenal steroids. The enzyme aromatase, a member of the cytochrome P450 group found in peripheral tissues and breast tumours, converts androstenedione into oestrone and testosterone into oestradiol. The early inhibitors (e.g. aminoglutethimide) were non-specific, inhibiting other cytochrome P450 enzymes resulting in reductions in cortisol and aldosterone synthesis. The more recently introduced new generation of specific aromatase inhibitors (e.g. anastrozole) show a higher degree of selectivity, are well tolerated and can be administered orally. They are used clinically in the treatment of postmenopausal women with advanced breast cancer but are unsuitable for premenopausal women. Trials are in progress to test their efficacy in earlier disease.

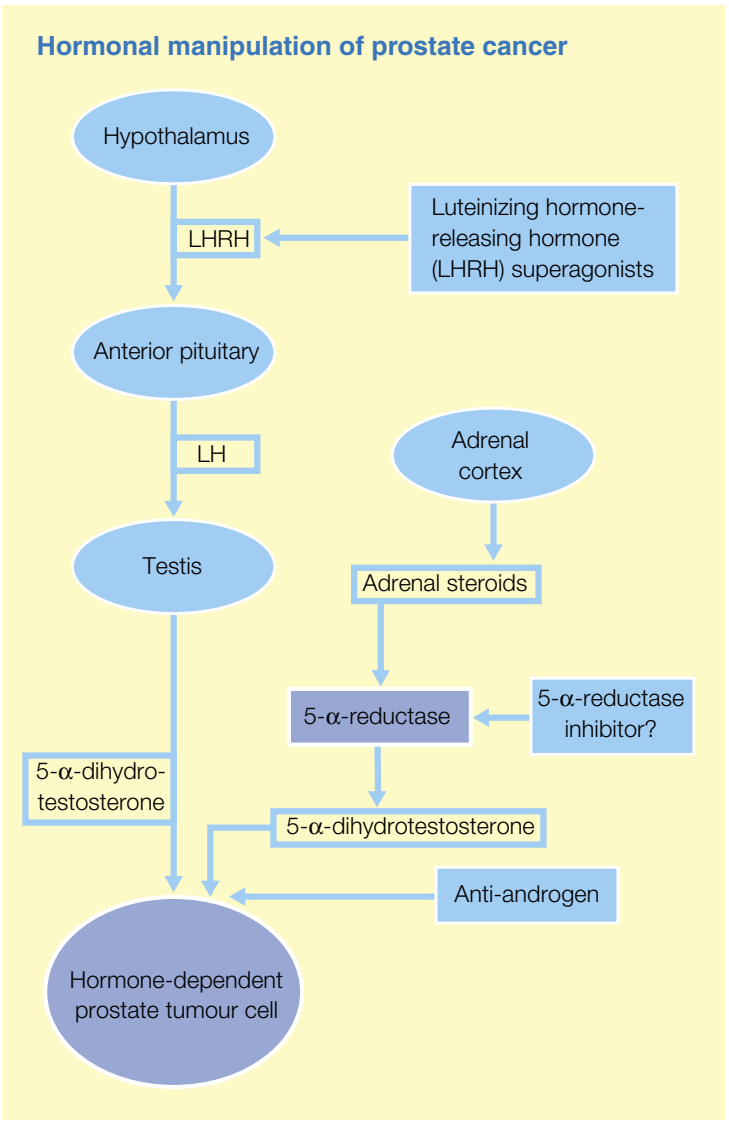
Luteinizing hormone-releasing hormone (LHRH) agonists: physiologically, LHRH is released in a pulsatile manner by the hypothalamus and binds to the LHRH receptors on the anterior pituitary gland causing release of follicle-stimulating hormone (FSH) and LH. The latter acts on the ovary to secrete oestrogen. The potent analogues of LHRH, the most widely used being goserelin and leuprorelin, occupy the LHRH receptors and down-regulate them. New receptors are synthesized but the constant presence of the analogue causes them to be occupied immediately and disappear. The result is that oestrogen levels fall to castrate levels. These LHRH analogues are used in the treatment of women with functioning ovaries but are unsuitable for postmenopausal women.

Progestins and anti-progestins: progestins have long been used as second- or third-line non-specific therapy in breast cancer. The discovery of the progestin receptor suggested a role for an anti-progestin (e.g. mifepristone) in breast cancer, but clinical results have been disappointing.

Prolactin inhibition: observation that the dimethyl-benzanthracene (DMBA) rat tumour model of breast cancer was strongly prolactin dependent led to the development of bromocriptine. However, clinical results were disappointing because oestrogen dependence is significantly more relevant in human breast cancer than prolactin dependence.

Prostate cancer

The theory behind the alternative approaches to hormonal treatment of prostate cancer is summarized in Figure 3. At diagnosis, most patients have hormone-dependent disease, but hormonal treatments fail eventually with the appearance of hormone-refractory disease. The traditional treatments for metastatic prostate cancer were an oestrogen (e.g. stilboestrol) which was found to have cardiovascular consequences, or bilateral orchidectomy. Use of both has declined since the appearance of the LHRH analogues and anti-androgens.



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Anti-androgens: the Leydig cells of the testis, under the influence of LH secreted by the pituitary, produce 95% of total androgen as testosterone. Most of the testosterone is serum bound to SHBG or albumin but the remaining 2–3% free form is the functionally active substance that passes into the prostate gland where it is converted by 5-α-reductase to the more potent androgen dihydrotestosterone (DHT). DHT binds to androgen receptors in the cell nucleus, activating prostatic cell functions. The anti-androgens inhibit the binding of DHT to the androgen receptor thus inhibiting prostatic cell growth. The early inhibitors, notably cyproterone, were also steroidal progestins and were therefore non-specific, resulting in side-effects. Flutamide is a more specific non-steroidal anti-androgen but the more recently introduced bicalutamide is better tolerated. The controversy over the merits of combination use of anti-androgen with LHRH analogue (maximal androgen blockade (MAB); also known as combined androgen blockade (CAB)) in advanced prostate cancer continues but the trend is for bicalutamide to be increasingly used in the treatment of earlier stages of the disease.

LHRH agonists and antagonists: in prostate cancer, the action of LHRH analogues is analogous to that in breast cancer (discussed above) except that, because the pituitary is prevented from producing LH, testosterone production from the testis falls to castrate levels.

It could be argued that an LHRH antagonist might be more efficient because it would block LHRH receptors directly. There would be no release of testosterone at the start of treatment, thus avoiding the testosterone flare associated with the super-agonists, and perhaps the efficacy would be equivalent to that of a combination of a superagonist and an anti-androgen. The early antagonists suffered considerable toxicity problems but abarelix proceeded to phase III trials in prostate cancer. However, it was rejected by the Food and Drug Administration because of concerns about the reliability of duration of efficacy.

5-α-reductase inhibitors: the adrenal glands are secondary sources of androgens accounting for 5% of total testosterone and this encouraged the development of 5-α-reductase inhibitors, notably finasteride, which has proved effective in treating benign prostatic hypertrophy but not prostate cancer.

Neuroendocrine tumours
The somatostatin analogues, octreotide and lanreotide, are used in treating the symptoms of carcinoid tumours and VIPomas.

Corticosteroids
The main use of the glucocorticoids in cancer is as supportive therapy in conjunction with cytotoxic chemotherapy but they are also used to reduce intracranial pressure in the treatment of brain cancer (primaries and metastases) as well as to inhibit lymphocyte proliferation in the treatment of lymphomas and leukaemias.

Drug interactions relevant to anaesthesia

The hormonal anticancer agents are remarkably free from drug interaction problems, in contrast with the cytotoxic anticancer agents. In some, but not all, patients the anticoagulant effects of warfarin are markedly enhanced in the presence of tamoxifen. This may require dose reduction of the anticoagulant. The opposite occurs when anticoagulants are administered with the first-generation aromatase inhibitor aminoglutethimide, therefore the dose of the anticoagulant may need increasing.

Challenges for the formulator

The LHRH analogues and somatostatin analogues are peptides that if given orally would be destroyed in the gastrointestinal tract. Initially these analogues were administered by daily subcutaneous injection, which was inconvenient for patients with consequent compliance problems. Nasal sprays have been used but the major advance was the development of 1-month depot subcutaneous injections using lactide-glycolide co-polymer technology. 3-month (and longer) injectable depots have also been marketed. Recently a surgically implantable depot containing a LHRH analogue has been developed to last for 12 months. An injectable gel formulation has also been developed. ◆

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Overview of Pharmacokinetics

Norman Calvey

Norman Calvey was formerly Senior Research Fellow in the University Department of Anaesthesia, Liverpool, UK. He qualified in science and medicine from Liverpool University and has worked in Departments of Pharmacology and Anaesthesia. His research interests include pharmacokinetics and drug isomerism.

The term pharmacokinetics is derived from the Greek words *pharmakon* (drug) and *kinesis* (movement), and is commonly used with reference to two related concepts. It can be used to refer to the disposition of drugs by absorption, distribution, metabolism and excretion. It is also used to describe a mathematical approach to the behaviour of drugs; various constants or parameters are derived from the analysis of plasma concentrations [C] at various times after drug administration. This review is mainly concerned with the latter aspect of pharmacokinetics.

Pharmacokinetic parameters

The parameters that best describe the behaviour of drugs in the body are volume of distribution (V) and clearance (CL). V represents the apparent volume available for drug disposition; CL reflects the ability of the body to eliminate drugs. The half-life ($t_{½}$) can be derived from values for V and CL.

Volume of distribution

V is the apparent volume into which a drug is distributed at equilibrium; it represents the volume that would contain the drug if its concentration throughout the body was the same as in plasma. It is partly determined by physical properties (e.g. lipid solubility, plasma/tissue binding), as well as physiological factors (regional blood flow, plasma protein concentration).

In healthy adults, V for different agents ranges from 5 litres to more than 1000 litres. Drugs can be divided into three main groups. Compounds with a V of 5–50 litres are extensively bound to plasma proteins (e.g. warfarin) or localized in extracellular fluid (e.g. muscle relaxants). Drugs with a V of 50–500 litres are widely distributed in most tissues (e.g. local anaesthetics, opioid analgesics). When V is greater than 500 litres, there is extensive tissue localization and binding (e.g. digoxin). V is increased in the newborn and in pregnancy, and may be affected by renal and cardiac failure.

Clearance

CL was originally defined as the volume of plasma from which a drug must be entirely eliminated within a set time in order to account for its removal from the body. It also represents the rate of drug elimination (mg/minute) per unit of [C] (mg/ml). The rate of drug elimination is normally proportional to [C], therefore CL is usually constant. Several sites (e.g. liver, lung, kidney, plasma) may be involved in the elimination of a single drug; CL is the sum of these individual clearances.

Renal clearance: in many instances, both CL and renal clearance (CL_R) can be directly measured. When CL_R is greater than 70% CL, drug accumulation may occur in patients with renal insufficiency (or during renal transplantation).

Hepatic clearance: most drugs are cleared from the body by the liver (by metabolism and/or biliary excretion). In steady-state conditions, hepatic clearance (CL_H) is dependent on blood flow (Q) and the extraction ratio (ER); thus, $CL_H = Q \times ER$. The ER (which has a value between 0 and 1) reflects the ability of the liver to remove drugs from the circulation.

Alternatively, CL_H can be considered in terms of Q and $CL_{intrinsic}$ (defined as the ability of the liver to irreversibly eliminate drugs) as 'capacity-limited' or 'flow-limited' clearance.

- In capacity-limited elimination, $CL_{intrinsic}$ is relatively low compared with Q, and $CL_H \approx CL_{intrinsic} \times f$, where f is the fraction of unbound drug. In these conditions, $CL_{intrinsic}$ is rate-limiting; CL_H is relatively low and is not altered by changes in Q, but is modified by changes in $CL_{intrinsic}$ (due to enzyme induction, inhibition, age, malnutrition or disease), as well as protein binding. This type of elimination occurs with many common drugs (e.g. diazepam, warfarin, phenytoin).
- In flow-limited elimination, $CL_{intrinsic}$ is relatively large compared with Q, and $CL_H \approx Q$. In these conditions, Q is rate-limiting; CL_H is dependent on and determined by Q (21 ml/kg/minute in adults), but is relatively insensitive to changes in hepatic enzyme activity or plasma protein binding. This type of elimination is involved in the clearance of most β-adrenoceptor antagonists, opioid analgesics and local anaesthetics.

Clearance by other routes: some drugs are predominantly eliminated from the body by non-renal and non-hepatic routes. For example, some anaesthetic drugs are esters (e.g. remifentanil, suxamethonium, mivacurium and esmolol) and are predominantly eliminated from the body by hydrolysis; in these instances, values for CL may be greater than hepatic and or renal blood flow.

Half-life

Half-life ($t_{½}$) is the time required for [C] to decrease by 50% during the terminal phase of decline. It is approximately related to V and CL by the expression:

$$t_{½} = k \times \frac{V}{CL}$$

where k is a constant (ln (natural logarithm) 2; 0.693). Consequently $t_{½}$ is a hybrid pharmacokinetic parameter, and depends on the primary parameters V and CL. Alterations in $t_{½}$ may reflect changes in V and or CL, and differences between the $t_{½}$ of drugs do not necessarily reflect changes in drug elimination.

When drugs are administered in identical oral doses at intervals that are equal to their $t_{½}$, steady-state concentrations are reached after about 4–5 $t_{½}$s. This delay can be avoided by an initial loading dose. Drugs are often given orally at intervals that are about equal to their $t_{½}$s; this usually provides an acceptable compromise between the decline in drug concentrations after each dose, and the maintenance of an acceptable [C]. Nevertheless, $t_{½}$s may be a poor indication of the duration of drug action.

Context-sensitive half-times: when drugs are given by intra-venous infusion, computer-derived values for their context-sensitive half-time (CSHT) are a better indication of their disposition and activity than $t_{½}$s. The CSHT can be defined as the time required for the plasma concentration to decrease by 50% at the end of a specified period of infusion.

For some drugs (e.g. remifentanil), the CSHT (3–5 minutes) is independent of the duration of infusion; its effects are rapidly reversible, even after prolonged infusions. In other instances (e.g. alfentanil, midazolam, propofol) the CSHT is initially relatively constant, but increases 2–3 times after infusions of 6–8 hours. By contrast, in these conditions the CSHT of fentanyl increases 10–12 times, and its effects may persist for several hours after the termination of prolonged infusions.

CSHTs are a useful indication of the disappearance of drug activity after infusions of different durations, and may therefore be of considerable value in total intravenous anaesthesia.

Compartmental analysis

In compartmental analysis, a suitable pharmacokinetic model is used to describe drug disposition and elimination; values for V, CL, and other constants are then derived from the parameters of the model. The pharmacokinetics of many drugs were originally interpreted by a simple, one-compartment open model, which has limitations. Two- and three-compartment open models are now used to describe the behaviour of drugs after intravenous administration.

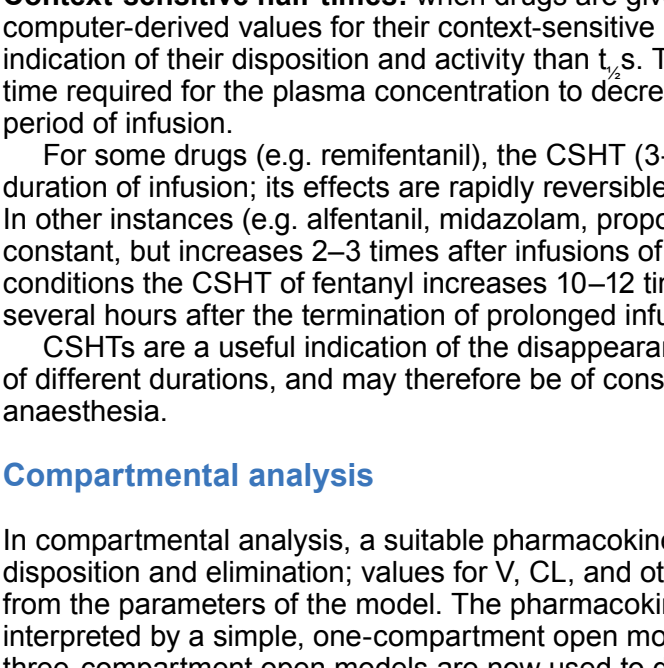
Two-compartment models

After intravenous injection of most drugs, there is an initial rapid decrease in [C] (distribution phase) followed by a slower decline (elimination phase). When ln [C] is plotted against time, the decrease in [C] can be resolved into two exponential components by extrapolation (Figure 1). The terminal decline in [C] is extended to the ordinate, which it intersects at point B. Subtraction of the extrapolated values from the initial data points gives a series of residual points, reflecting the initial phase of exponential decline (defined by the line that intercepts the ordinate at A). Both the distribution and elimination phases have characteristic slopes (α and β) and half-lives ($t_{½\alpha}$ and $t_{½\alpha}$); their intercepts (A and B) represent the amount that each half-life contributes to the decrease in [C].

The decline in [C] can be interpreted in terms of a two- compartment open pharmacokinetic model (Figure 2). The compartments have no physiological meaning; their parameters and constants are determined solely by the behaviour of the drug in the body. The model is a theoretical concept that accounts for the observed decline in [C].

Values for A, α, B and β are used to derive the parameters of the model (e.g. CL, V, k_{12}, k_{21}, k_{10}). V is represented by two different expressions (V_{area} and V_{ss}); V_{area} overestimates V when CL is high. V_{ss} (i.e. V at steady state) is preferable, because it is independent of CL.

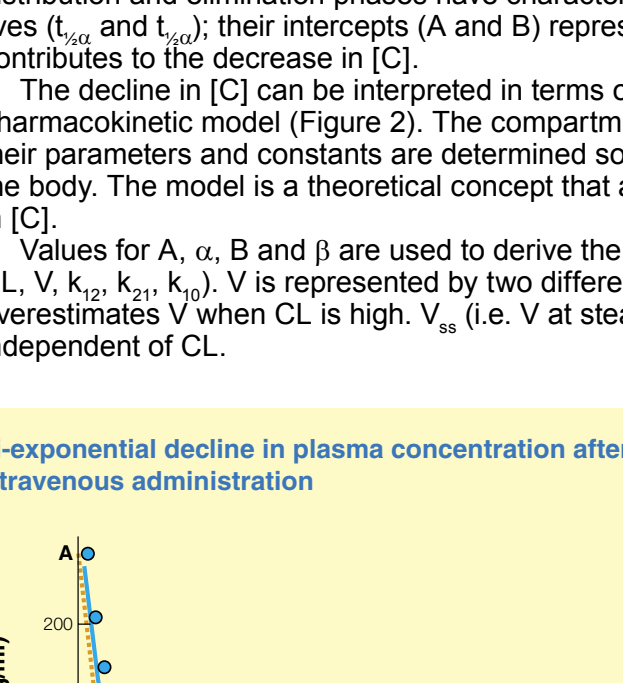
Bi-exponential decline in plasma concentration after intravenous administration



Data points correspond to plasma concentration at different times after drug administration. The terminal decline in concentration is extrapolated to the ordinate which it intersects at point B. The extrapolated values are subtracted from the data points to give a series of residual values, representing the initial phase of exponential decline which intersects the ordinate at point A. α and β represent the slopes of the distribution and elimination phases of exponential decline.

1

Two-compartment open pharmacokinetic model



k_{10} is the elimination rate constant; k_{12} and k_{21} are the rate constants controlling drug transfer between the central and peripheral compartments

2

Three-compartment models

In many instances, three-compartment models provide a better interpretation of the data (e.g. with opioids, muscle relaxants, intravenous anaesthetics). The decline in [C] is resolved into three exponential components; values for the intercepts (A, B and C) and the slopes (α, β and γ) of the components are obtained and interpreted by a three-compartment open model, with administration into and elimination from the central compartment.

Other models

Pharmacokinetic–pharmacodynamic models

When drugs act reversibly, there is often a close correlation between their [C] and pharmacological effects. Nevertheless, after intravenous administration there is usually a short delay between the rise in [C] and the onset of their action; during recovery, the fall in [C] commonly precedes their offset. This phenomenon of hysteresis or temporal disequilibrium can be rationalized by the addition of a minute, distinct, effect or 'biophase' compartment, with individual rate constants, to the central compartment of a pharmacokinetic model. The rate constant (k_e or k_{eo}) characterizes the disequilibrium between the central compartment and the biophase during the onset and offset of drug action. In these conditions, there is a hysteresis-free relationship between their biophase concentration and pharmacological effects.

Pharmacokinetic–pharmacodynamic models of this type have been developed for muscle relaxants, opioids, and intravenous anaesthetic agents, and may have a role in the development of closed-loop control systems.

Physiological models

Physiological models are more complex than pharmacokinetic models; they depend on the interpretation of drug distribution in terms of organ or tissue spaces with defined volumes, perfusion characteristics and partition coefficients. Individual compartments may have 'flow-limited' or 'membrane-limited' characteristics (depending on whether blood flow or transmembrane transport is the limiting factor governing drug transfer).

These complex models are based on the detailed analysis of anatomical and physiological data, and depend on numerous assumptions; consequently, their resolution may be extremely difficult. Nevertheless, they have a number of distinct advantages. They can be used to predict changes in drug concentration in different tissues in relation to [C]; in addition, they can take account of physiological changes produced by drugs or occurring during anaesthesia (e.g. alterations in cardiac output, blood volume, regional blood flow and renal function).

The disposition of several drugs, including thiopental (thiopentone), lidocaine (lignocaine), and some inhalational anaesthetics, has been described in terms of physiological perfusion models.

Non-compartmental methods

Non-compartmental methods do not depend on the assumptions inherent in compartmental models, though they can be used to derive values for CL and V_{ss}. CL is derived from the relationship:

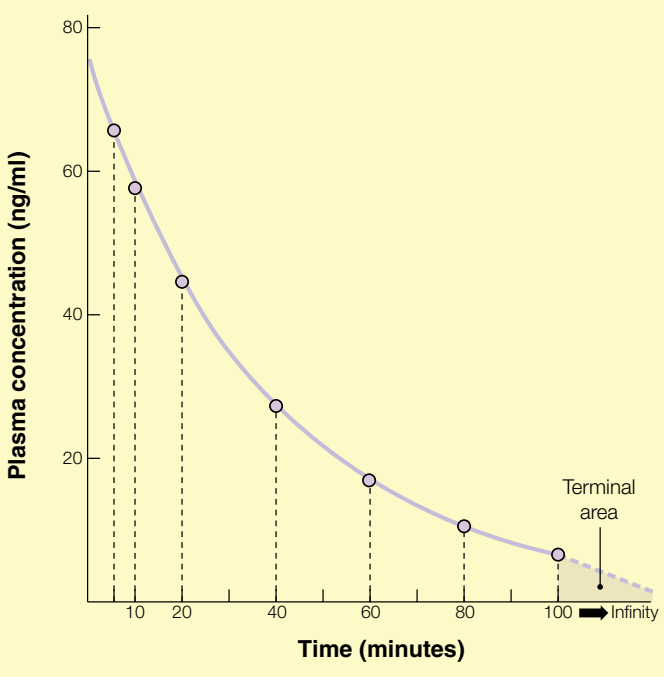
$$CL = \frac{Dose}{AUC}$$

where AUC is the area under the plasma concentration–time curve between time zero and infinity. The AUC can be estimated by the 'trapezoidal rule', which depends on the measurement and summation of the area of each trapezoid between successive sampling times and the corresponding values for [C] (Figure 3). The terminal area between the final [C] versus time, and time infinity is estimated from the expression:

$$\text{terminal area} = (\text{final [C]} \times t_{1/2}) \div 0.693$$

V_{ss} is then calculated as the product of CL and the mean residence time (i.e. the mean time that each drug molecule resides in the body).

Determination of the area under the curve by the trapezoidal rule



The plasma concentration–time curve is divided into a series of trapezoids subtended by the time of each sample and its corresponding plasma concentration. The area under the curve (AUC) is the sum of the area of each trapezoid and the terminal area

Constant plasma concentrations of drugs

A number of intravenous dose regimens have been used to produce constant [C] of drugs; most of these depend on an initial bolus, followed by a continuous infusion. In one regimen, a bolus dose of (V × required [C]) is given, followed by a continuous infusion of (CL × required [C]) (mg/minute). This method depends on accurate values for V and CL, and may cause transiently high [C].

Recently, combinations of a bolus dose, an exponentially declining initial infusion, and a maintenance infusion (the bolus, elimination and transfer method) have been used to produce a constant [C]. The bolus is designed to fill the central compartment to the required [C]; the exponentially declining infusion compensates for the distribution of the drug to peripheral compartments. The maintenance infusion equals the rate of drug elimination. This method has been used with computer-controlled programmed infusion devices in open-loop and closed-loop control systems.

Non-linear pharmacokinetics

In pharmacokinetic analysis, it is generally assumed that drug disposition and elimination are exponential, first-order processes. In these conditions, $dX/dt = -kX$, where X is the amount of drug in an organ or compartment, and k is a rate constant. These assumptions are not always correct. The enzymic reactions involved in drug metabolism can be saturated by high substrate concentrations (Michaelis–Menten kinetics); similarly, physiological systems that depend on carrier transport can be saturated. Consequently, metabolism and transport occur at maximal, constant rates that are independent of drug concentration (i.e. $dX/dt = -k$). Other biological processes (e.g. protein binding) can also be saturated.

This type of kinetics is known as non-linear, saturation, or zero-order kinetics, and occurs when drugs are eliminated by enzymic or transport processes. In practice, the phenomenon is relatively uncommon, because most drugs are potent agents and their plasma concentrations are relatively low. Nevertheless, non-linear kinetics occurs with ethyl alcohol, salicylates and phenytoin, and after large or repeated doses of thiopental (thiopentone) (e.g. during cerebral resuscitation). It also occurs in drug overdosage; it is unclear whether this reflects saturation of hepatic metabolism or drug toxicity.

Non-linear pharmacokinetics typically reduces V and CL, and prolongs the $t_{1/2}$ of drugs; similarly the AUC is disproportionately raised. By contrast, when drugs are subject to first-order kinetics, V, CL and $t_{1/2}$ are all independent of dose.

Population pharmacokinetics

Population pharmacokinetics results in the derivation of pharmacokinetic parameters that describe drug disposition in an entire population.

Individual data from a large number of subjects are integrated into a single population model, that depends on certain assumptions (e.g. identical individual and population concentration profiles). Individual variability (irrespective of its cause) is incorporated in the model by statistical techniques.

Differences between individual pharmacokinetic constants and population values are then assessed in terms of fixed effects (e.g. age, weight, CL_R, CL_H) and random effects (unexplained variability). Population pharmacokinetics generally attempts to interpret variability in terms of measurable characteristics or fixed effects.

Bioavailability

Bioavailability can be defined as the proportion of the oral dose that is present in the systemic circulation. It is usually derived from the AUC (Figure 3). After intravenous administration, drugs have a fractional bioavailability of 1 (i.e. 100%); consequently, the bioavailability of oral drugs (%) is defined as:

$$\frac{\text{AUC after oral administration}}{\text{AUC after intravenous administration}} \text{ ¥ } 100$$

Many drugs have a high oral bioavailability (e.g. diazepam, phenytoin, warfarin). In general, they are acid-stable, extensively absorbed agents with little first-pass metabolism (i.e. they are not significantly degraded by the gut wall or the liver before they reach the systemic circulation).

In contrast, other drugs have a low oral bioavailability, because of:

- gastrointestinal instability or degradation
- poor absorption
- significant first-pass metabolism.

Some drugs are unstable in gastric acid or are degraded in the small intestine (e.g. benzylpenicillin, heparin, polypeptides). Others are poorly absorbed, usually because of their limited lipid solubility (e.g. neostigmine, glycopyrrolate, gentamicin). Finally, drugs with significant first-pass metabolism have a low bioavailability, because they are extensively broken down by the gut and/or the liver (e.g. morphine, propranolol, lidocaine (lignocaine)).

In some instances, there are variations in the oral bioavailability of different preparations of a single drug. These differences are sometimes related to their *in vitro* dissolution characteristics. When CL_H is dependent on blood flow, any reduction in perfusion may increase systemic bioavailability. Similarly, drugs that inhibit microsomal enzymes (e.g. cimetidine), physiological changes (old age) and pathological factors (hepatic cirrhosis) can impair drug metabolism and affectbioavailability.

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Pharmacodynamics: Concentration–Response Relationships and Hysteresis

Barbara J Pleuvry

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Much of the theory regarding drug concentration–response relationships is derived from experiments using *in vitro* preparations bathed in physiological solutions to which known quantities of drugs can be added. Using this system, the responses of the tissue can be related directly to the concentration in the bathing fluid and the characteristic sigmoid log concentration–response relationship can be obtained. Different conditions apply *in vitro*. It is usually feasible to measure only the plasma concentrations of a drug rather than its concentration at the site of action. Thus, a direct relationship between plasma concentration and effect is only obtainable when a drug such as heparin exerts its effect within the plasma. Therefore, plasma concentrations of a drug may not be a good indicator of drug response for several reasons.

Maximum responses
If the drug is a full agonist, it is capable of producing the maximum response that activation of that receptor can produce. Concentrations of drug above this maximum concentration will have no further effect.

Irreversible effects
If the drug acts irreversibly then the response to its administration will outlast its plasma concentration. Some drugs of this type are listed in Figure 1.

Examples of irreversible drugs

Drug	Pharmacological action	Mechanism of recovery
Aspirin	Inhibition of cyclo-oxygenase	Synthesis of new cyclo-oxygenase. Inhibition of enzyme in platelets requires new platelet production
Phenelzine	Non-selective inhibitor of	Synthesis of new enzyme monoamine oxidase
Phenoxybenzamine	α-adrenoceptor blockade	Synthesis of new receptors
Sarin (nerve gas)	Cholinesterase inhibition	Synthesis of new enzyme
Selegiline	Suicide inhibitor of monoamine oxidase B	Synthesis of new enzyme

1

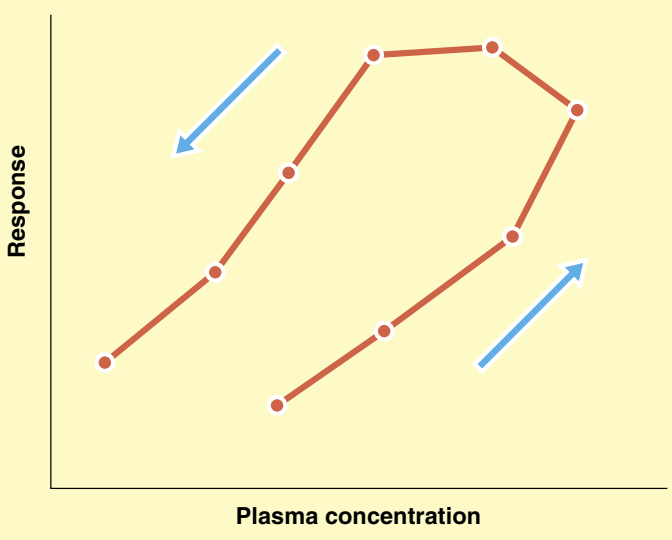
Complex responses
Many drug responses are integrated physiological changes, for example, a fall in blood pressure after a β-adrenoceptor antagonist (e.g. propranolol). This response involves inhibition of renin release from the kidney, a fall in cardiac output, inhibition of noradrenaline release and a reduction in sympathetic output from the CNS. Each component might be directly related to plasma concentration, there is no direct relationship to the final integrated response. Hysteresis may also affect the individual components of the response.

Hysteresis

Most drugs have to move into the biophase (site of action) and then occupy receptors or bind with enzymes before they can exert their effect. When the plasma concentration declines the effects are reversed, but there is a lag phase before observed effects follow the changes in plasma concentration. This phenomenon is known as hysteresis, which may be defined as 'the retardation or lagging of an effect behind the cause of the effect'. The two main reasons for the lag phase are limited access to the site of action or slow receptor kinetics.

Limited access
A few drugs reach the biophase rapidly; they include the highly lipid-soluble compounds that penetrate through cell membranes rapidly (e.g. intravenous anaesthetic agents). These agents would be expected to show little hysteresis though inter-individual variation in the concentration–effect relationship for thiopental (thiopentone) has been ascribed to differences in effect-hysteresis. More significant hysteresis is seen with ionized compounds or poorly lipid-soluble compounds (e.g. morphine). This is sometimes termed anticlockwise hysteresis (Figure 2) because the arrows relating time to the concentration–effect relationship run in an anticlockwise direction.

Anticlockwise hysteresis loop



Concentration–response measurements are made at various times after a dose. The arrows show the direction of time

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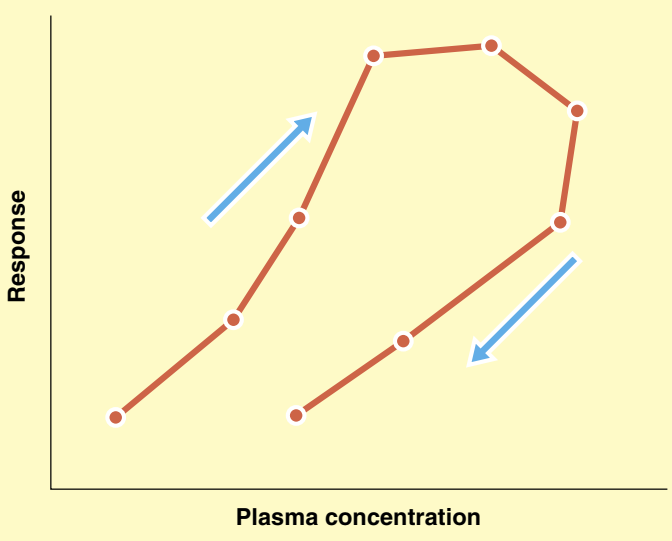
Even drugs whose site of action is outside the CNS can exhibit hysteresis. The slow onset of pancuronium has been ascribed to the slow movement of the ionized compound from the capillary to the junctional cleft. A recent study has demonstrated marked anticlockwise hysteresis with single rectal doses of diclofenac, a weak acid, indicative of the effective biophase being within the CNS. The delay to peak analgesia was 300 minutes after administration while the peak plasma concentration was 60 minutes. The authors highlighted the possible dangers of co-administration of patient-controlled morphine where high morphine use during the time of peak diclofenac plasma concentrations could lead to persistent high concentrations of the active metabolite morphine-6-glucuronide during the peak analgesic activity of the diclofenac. This would predispose the patient to respiratory depression.

It is important that hysteresis should be incorporated into pharmacokinetic and pharmacodynamic modelling of intravenous infusion protocols and the use of context-sensitive half time is a step in the right direction (see *Anaesthesia and Intensive Care Medicine* **2:6:** 250c).

Slow receptor kinetics
The best example of a drug that binds slowly to its receptors is buprenorphine, which may take minutes rather than seconds to reach equilibrium. It is difficult to distinguish this type of hysteresis from limited access hysteresis.

Tolerance
Tolerance describes the phenomenon where the effect of a drug declines despite its continuing presence. On a short time scale, such as a few minutes, this situation is sometimes called desensitization or tachyphylaxis and on a longer time scale, such as days or weeks, the term tolerance is preferred. An example is shown in Figure 3, in which, in contrast to Figure 2, the arrows indicating time on the concentration–response relationship rotate clockwise. Some authors call this clockwise hysteresis, but in order to do this it is necessary to use an alternative definition of hysteresis. A less physics-based definition would be 'Failure of one of two related phenomena to keep pace with the other. Any situation in which the value of one depends on whether the other is increasing or decreasing'.

Clockwise hysteresis loop



Concentration–response measurements are made at various times after a dose. The arrows show the direction of time

3

Tolerance or desensitization can occur as a result of the mechanisms listed in Figure 4. ◆

Mechanisms of desensitization and tolerance

Mechanism	Example
Conformational change in receptors • Binding of agonist but no channel opening • Uncoupling from second messenger system • Loss of modulator binding site	 Nicotinic receptors at the neuromuscular junction β-adrenoceptors and opioid receptors? Benzodiazepine site on $GABA_A$ receptor
Loss of receptors	β-adrenoceptors (slow process) and many hormone receptors
Physiological adaptation	Acetazolamide
Increased metabolism	Many anticonvulsants induce the enzymes responsible for their own metabolism
Exhaustion of mediators	Indirectly acting sympathomimetics (e.g. amfetamine (amphetamine))

4

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Pharmacogenetics: Familial Variation in Drug Response

Maria Alvarez

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Genetically determined variability in drug response is an important clinical problem. It is responsible for the lack of therapeutic effect in some individuals and also explains the idiosyncratic drug reactions that occur in a few individuals. In the future it may be possible to prescribe drugs on an individual basis, to obtain the maximum benefit and to avoid side-effects.

Early genetic observations suggested that the biotransform-ation of foreign compounds by the human body might be governed by inheritance laws. In 1957, it was postulated that hereditary variations occurred in response to drugs and the term pharmacogenetics was used to describe these phenomena. Variation in genotype contributes to variation in pharmacodynamic and pharmacokinetic characteristics of drugs among individuals. Some inborn errors are rare, to the extent that only 1/100,000 people might be affected, others are classical genetic polymorphisms in which the abnormal gene has a frequency of more than 1% in the general population. Many genes are subject to polymorphic variation. In some cases inheritance patterns can determine abnormal responses to drugs used during anaesthetic practice (Figure 1). Much of the work in the field of pharmacogenetics concentrates on polymorphisms in human metabolic enzymes.

Pharmacogenetic diseases relevant to anaesthesia and their inheritance patterns

Inheritance patterns	Protein affected	Response
Autosomal recessive	N-acetyltransferase	Slow/rapid acetylators
Autosomal recessive	Methaemoglobin reductase	Methaemoglobinaemia
Autosomal recessive	Cytochrome P450	Impaired hydroxylation
Autosomal autonomous	Plasma cholinesterase	Suxamethonium apnoea
Autosomal dominant	Ryanodine receptor	Malignant hyperthermia
Autosomal dominant	Porphobilinogen deaminase	Intermittent porphyria

1

Drug metabolism and genetic polymorphism
The main purpose of drug metabolism is to convert lipid-soluble molecules into more polar compounds that can be excreted. The metabolic process is usually divided into two steps:
- phase 1 reactions (non-synthetic or functionalization reactions)
- phase 2 reactions (synthetic or conjugation reactions).

Phase 1 normally results in the oxidation of the parent drug by a non-specific enzyme system, sited in the hepatic endoplasmic reticulum and known as the ‘mixed function oxidase system’. Key components of this system are the cytochrome P450-dependent mono-oxygenases. Phase 2 involves sulphation, glucuronidation or acetylation of unchanged drugs or the products of phase one metabolism. Although most compounds are primarily metabolized by liver enzymes, some agents such as suxamethonium are hydrolysed in plasma by cholinesterase and others are metabolized by different tissues including the gut, kidney and lung. Since the early stages of pharmacogenetics, advances in genotyping technology have been outstanding, one of the most significant steps was the description of variability in drug oxidation mediated by the cytochrome P450 system.

Polymorphisms affecting phase 1 reactions
Most cytochrome P450-mediated drug oxidation in man is catalysed by cytochrome P450 CYP3A4 or cytochrome P450 CYP2D6; both found in liver. CYP3A4 is active primarily in the metabolism of naturally occurring antibiotics, while CYP2D6 metabolizes drugs targeted to the CNS and is also found in brain tissue. Cytochrome P450 determines the biological half-life of most drugs in current clinical use. Therefore, individuality in the expression of its isozymes has therapeutic consequences including:
- no drug effect owing to rapid metabolism and clearance
- lack of pro-drug activation (e.g. conversion of codeine to morphine)
- impaired metabolism leading to accumulation of the drug and toxic side-effects
- activation to toxic products (e.g. paracetamol to N-acetyl-p-benzoquinone immine).

CYP2D6 is not expressed in about 6% of the Caucasian population, which as a consequence, has an altered ability to metabolize a wide range of drugs including β-blockers, antiarrhythmics, tricyclic antidepressants, neuroleptics, opioid analgesics, laudanosine, nitrates, anti-emetics and many other compounds.

Other genetically polymorphic P450 genes include CYP2C19, which normally metabolizes diazepam, CYP2C9, the low activity allele of which is responsible for warfarin toxicity, and CYPIBI for which the phenotypic consequences of variation are not fully understood (see *Anaesthesia and Intensive Care Medicine* **2:8:** 322).

The genes that encode the major enzymes of alcohol metabolism, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), also exhibit functional polymorphism. The variability in ALDH activity might explain individual and ethnic differences to alcohol intolerance and the variation in susceptibility to ethanol and acetylaldehyde related tissue and organ damage.

Polymorphisms affecting phase 2 enzymes
Phase 2 enzymes including glutathione S-transferase, N-acetyl transferase, sulphotransferase and UDP-glucuronyl transferase (involved in the metabolism of propofol), are also polymorphic and although the consequences of their variability are of less significance than those affecting P450 isozymes both effects can be synergistic.

Polymorphic N-acetylation, due to the presence of multiple alleles at the *NAT2* gene, divides the human population into three possible genotypes:
- homozygote (rapid/rapid)
- heterozygote (slow/rapid)
- homozygote (slow/slow).

These genotypes give rise to two phenotypes: rapid and slow acetylators. This phenomenon applies to drugs including isoniazid, hydralazine, nitrazepam and sulphonamide. For a given dose, slow acetylators have a higher plasma concentration of the drug.

Marked ethnic differences are seen in the distribution of allelic variants of many drug metabolizing enzymes. An example is the presence of the ultra-rapid metabolizer gene, which occurs at frequencies of 20%, 7% and 1.5% in Ethiopian, Spanish and Scandinavian populations, respectively.

Malignant hyperthermia
Malignant hyperthermia is a disorder of the skeletal muscle with an autosomal dominant pattern of inheritance. There is a significant association between susceptibility for the condition and inheritance of DNA markers for the gene coding for ryanodine receptor protein (*RYR1*); about 20 mutations of this gene have been found. Other genetic loci are also associated with malignant hyperthermia in individual families, including a mutation for the gene coding for the dihydropyridine receptor, responsible for excitation–contraction coupling in skeletal muscle. Malignant hyperthermia can be pharmacologically triggered by volatile agents and suxamethonium. For management of the disorder see page 222.

Suxamethonium apnoea
Some people experience prolonged respiratory muscle paralysis following administration of the short-acting depolarizing muscle relaxant suxamethonium, also known as succinylcholine. The cause is a variation in plasma cholinesterase (an enzyme that normally hydrolyses suxamethonium) activity, which is an inherited trait. The pattern of inheritance is autosomal autonomous, with a penetrance between dominant and recessive, so the phenotype is determined by the contribution of each gene. At least four allelic variants of this gene have been identified and are described in more detail elsewhere.

Acute intermittent porphyria
Haem is required for haemoglobin and the cytochromes, including cytochrome P450 function oxidase system. In the UK, 1/10,000 people carry a gene that codes for a defective enzyme (porphobilinogen deaminase) in the haem synthesis pathway. This produces an inborn error of metabolism known as acute intermittent porphyria. Normally patients have no symptoms but acute attacks can be triggered by drugs, including barbiturates, benzodiazepines, cephalosporins, thiazide diuretics and sulphonamides. The result is an increase in the activity of δ-aminolaevulinic acid synthetase with overproduction of δ-aminolaevulinic acid and porphobilinogen which causes abdominal pain, motor neuritis, anxiety and psychosis. It can be fatal.

Hereditary methaemoglobinaemia
The main route for regenerating haemoglobin from methaemoglobin is NADH methaemoglobin reductase, if this enzyme is defective the methaemoglobinaemia produced by oxidizing drugs such as nitrites, nitrates, prilocaine and sulphonamides is prolonged and severe. The reducing agent used to regenerate haemoglobin is methylene blue. ◆

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Pharmacokinetic Analysis

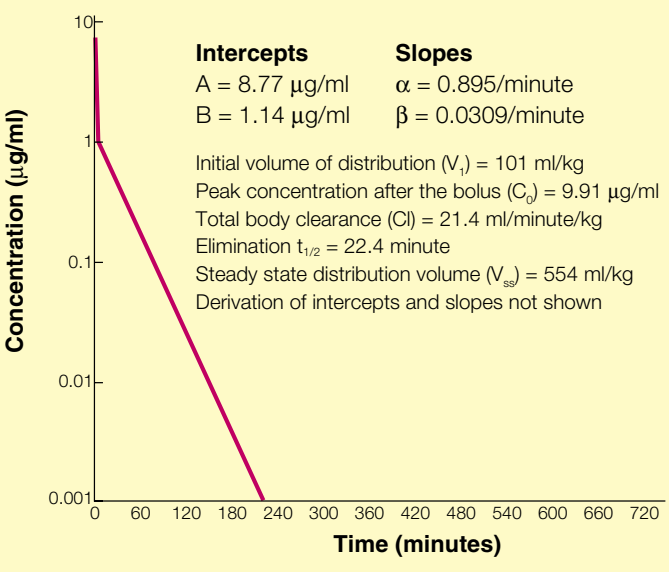
Iain Glen

Iain Glen qualified in veterinary medicine at Glasgow University and became a lecturer in veterinary anaesthesia. Until recently he was a clinical specialist in anaesthesia at AstraZeneca and was closely involved in the development of Diprivan and the Diprifusor target- controlled infusion system.

The purpose of pharmacokinetic analysis is to obtain information on the distribution and elimination of a drug to facilitate the formulation of optimum dosing guidelines. The process involves the administration of a known amount of drug, the collection and analysis of serial blood samples at timed intervals and the use of these data to derive a pharmacokinetic model characterized by a unique set of parameters for each drug. This article explains the rationale behind the derivation of the most important parameters and shows how these parameters influence drug behaviour using lidocaine (lignocaine) and propofol as examples.

Concept of 'compartments'
In pharmacokinetics, a compartment refers to organs or tissues for which the rates of uptake and clearance are similar. For most drugs, the curve for blood or plasma concentration (on a log scale) over time after a bolus injection resembles that in Figure 1. The curve initially falls steeply (distribution phase) as there is rapid movement from the blood into tissues. Thereafter, distribution equilibrium is established as return of drug from well-perfused tissues is balanced by continuing distribution to less well-perfused peripheral tissues, and the slope of this second (elimination) phase represents the rate of removal of drug from the body.

Bi-exponential decline in plasma concentration of lidocaine (lignocaine) after a 1 mg/kg bolus



Source of data: Schnider. *Anesthesiology* 1996; **84:** 1043.

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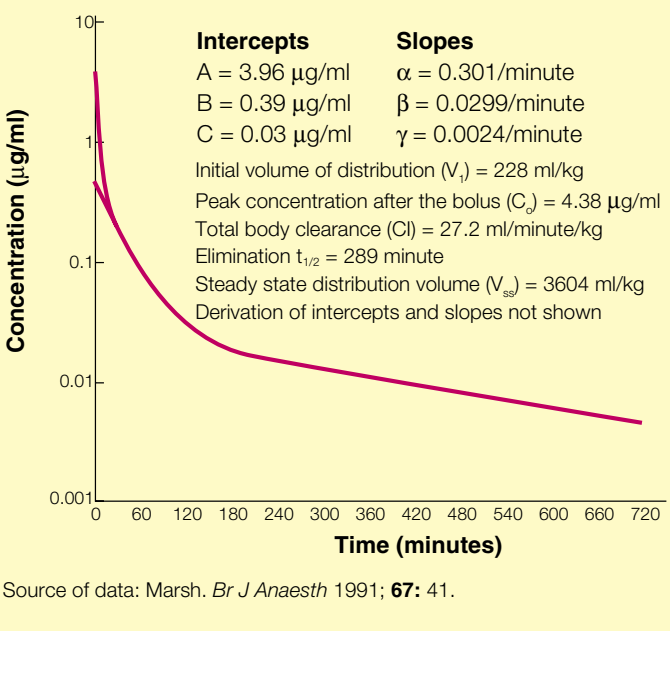
The two phases are characterized by two exponential terms and from the concentration–time profile, the intercepts A and B and the slopes α and β can be derived. The number of exponentials needed to describe the blood concentration–time curve determines the number of compartments required to characterize the behaviour of a drug. From the primary parameters (A, B, α and β), compartmental model parameters (V_1, k_{10}, k_{12}, k_{21}) can be calculated. The concentration profiles of many anaesthsetic drugs are best described by three phases and therefore a three-compartment model. In these models there are two distribution phases (a rapid and a slower phase) before the terminal elimination phase.

The parameters that best describe the behaviour of a drug are the volumes of distribution (V_1, V_{ss}) and total body clearance (Cl). Loading dose is determined by the initial volume of distribution (V_1) and the maintenance dose by Cl. In the following examples, blood concentration profiles following an intravenous bolus dose of 1 mg/kg of lidocaine (lignocaine) (two-compartment model, Figure 1) or 1 mg/kg of propofol (three-compartment model, Figure 2) are illustrated. The modelling techniques assume linear kinetics – the blood concentration achieved at any time is directly proportional to the dose given.

Tri-exponential decline in blood concentration of propofol after a 1 mg/kg bolus



Source of data: Marsh. *Br J Anaesth* 1991; **67:** 41.

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Volumes of distribution
V_1, also called the central compartment distribution volume, indicates the apparent space needed to explain the relationship between a given dose and the resulting peak concentration, rather than an actual anatomical volume. The lower the concentration achieved with a given dose, the larger is V_1 and *vice versa*. At equilibrium, drug is distributed throughout all body tissues and the volume required to explain the concentration observed in blood at this time is the steady-state distribution volume (V_{ss}); it equals the sum of the volumes of individual compartments.

$$V_1 \text{ (ml/kg)} = \frac{\text{Dose (μg/kg)}}{\text{A+B (μg/ml) (or A+B+C for a three-compartment model)}}$$

$$C_0 \text{ (μg/ml) (the peak concentration after the bolus)} = \frac{\text{Dose (μg/kg)}}{V_1 \text{ (ml/kg)}}$$

Clearance
The clearance of a drug is a principal determinant of its rate of elimination and is a more useful parameter than elimination half-life ($t_{½}$). Creatinine clearance is an index of renal function. Drug clearance is expressed in units of volume divided by time and is defined as the hypothetical volume of blood from which the substance is completely removed per unit time. If the clearance of a drug is 500 ml/minute, and its concentration in blood is 10 μg/ml, then the amount of drug removed over that minute will be 5000 μg (i.e. 5 mg). If drug is being infused to maintain a steady-state concentration in blood, then the amount required to compensate for clearance is 5 mg/minute. If no further drug is being administered, the amount of drug removed each minute will decrease exponentially with time as the concentration in blood falls. At a given value of Cl, the rate of elimination from the central compartment (k_{10} or k_{el}), which is the rate at which the drug concentration falls as drug is removed each minute, is dependent on V_1:

$$k_{10} \text{ (per minute)} = \frac{\text{Cl (ml/minute/kg)}}{V_1 \text{ (ml/kg)}}$$

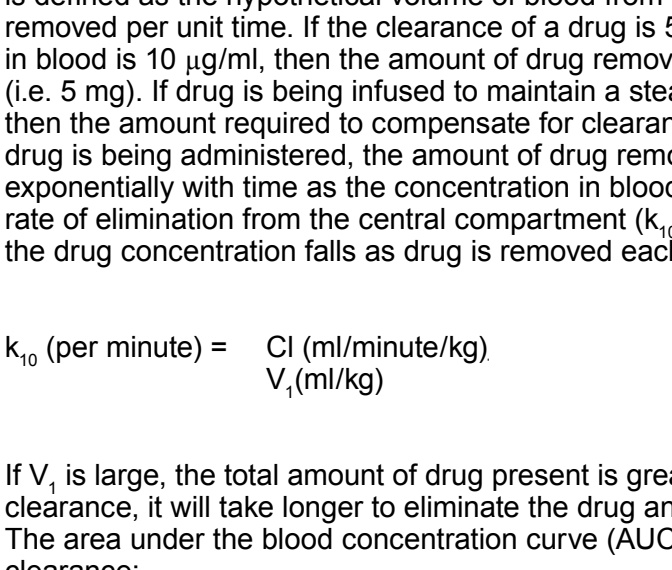
If V_1 is large, the total amount of drug present is greater, such that with constant clearance, it will take longer to eliminate the drug and the value of k_{10} will be smaller. The area under the blood concentration curve (AUC) can also be used to estimate drug clearance:

$$\text{Cl (ml/minute/kg)} = \frac{\text{Dose (μg/kg)}}{\text{AUC (minute/μg/ml)}} \qquad \text{AUC} = \frac{A}{\alpha} + \frac{B}{\beta}$$

Clearance mechanisms: many drugs are cleared by more than one process (e.g. hepatic metabolism and renal excretion) and clearance is the sum of individual organ clearances. In the same way as cardiac output can be determined by the Fick equation as oxygen consumption divided by the difference in oxygen content between arterial and mixed venous blood, the clearance of a drug by an organ such as the liver or kidney is indicated by an arterio-venous concentration difference across the organ. If most of the drug present in arterial blood is cleared by a single transit through an organ the extraction ratio approaches 1 and the drug is said to have a high extraction ratio. Clearance by hepatic metabolism or renal excretion is dependent on the product of blood flow to the organ and the extraction ratio. Thus, a change in organ blood flow will have the greatest effect on the clearance of drugs that are highly extracted by that organ.

Compartmental models
The models most widely applicable to anaesthetic drugs are two- or three-compartment open mamillary models (Figure 3). Drug is administered into the central compartment (V_1) and elimination occurs from this compartment with a rate constant of k_{10}. Distribution occurs from V_1 to a peripheral compartment V_2 (or peripheral compartments V_2 and V_3) with k_{12} and k_{21} being the intercompartmental distribution rate constants.

Two-compartment model for lidocaine (lignocaine)



Source of data: Schnider. *Anesthesiology* 1996; **84:** 1043.

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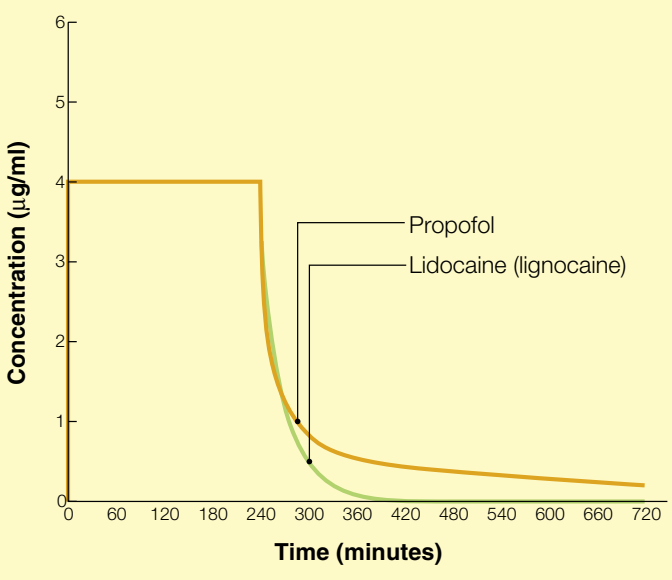
In Figure 1, lidocaine (lignocaine) concentrations show an initial short distribution phase followed by a log-linear elimination phase. With propofol (Figure 2) the initial distribution phase lasts longer and is followed by a second distribution phase before the flatter part of the curve (elimination phase) occurs. Metabolism of propofol occurs throughout and the last phase indicates metabolism constrained by the slow return of drug from the periphery. Parameters derived from the intercepts and slopes for these agents have been added to Figures 1 and 2. As the same dose (1 mg/kg) was given with both drugs, the higher initial peak concentration for lidocaine (lignocaine) reflects its lower V_1. Both drugs have high values for clearance, close to hepatic blood flow, and are thus highly extracted agents, despite a marked difference in elimination $t_{½}$ attributable to the much larger V_{ss} of propofol. The intercepts, A, B and C derived from the concentration profile also provide useful information on the contribution of each $t_{½}$ to the decrease in concentration following a bolus dose. In the case of lidocaine (lignocaine), 88% of the decrease occurs during the initial distribution phase. With propofol, 90% and 8.9% occurs during the first and second distribution phases, respectively. Thus, with propofol, the concentration has fallen well below effective concentrations before the slower terminal phase is reached.

Computer simulation

Some aspects of the behaviour of a drug can be derived from pharmacokinetic data, but computer simulation is required to understand the likely consequences of any dosing scheme. V_1, k_{10}, k_{12}, and k_{21} (plus k_{13} and k_{31} if a three-compartment model is required) are the parameters required as inputs for pharmacokinetic simulation programs or the control of an infusion with a target-controlled infusion system. Examples of computer simulation programs that can be obtained via the Internet are PK-SIM, RUGLOOP and STANPUMP (http://anesthesia.stanford.edu/pkpd) and TIVA TRAINER (www.eurosiva.org). They allow possible dosing strategies to be examined and do not require an understanding of the mathematics behind the derivation of the parameters. Figure 4 shows the predicted rates of decline in blood concentrations after a 4-hour infusion of propofol or lidocaine (lignocaine) designed to maintain a blood concentration of 4 μg/ml. Despite the difference in elimination $t_{½}$ between the two agents this simulation shows that the 4-hour context-sensitive half-time (CSHT; the time required for the concentration to fall to 50% of the starting concentration) is similar for the two agents. Predicting the recovery time with propofol depends on the percentage reduction required from the starting concentration to reach the 'waking concentration' and this may be more or less than the 50% of the CSHT. Another merit of computer simulation is the ability to predict the time of peak effect of a drug by the addition of an 'effect compartment' to the model with $t_{½}$ k_{e0} describing the rate that drug concentrations in the biophase equilibrate with those in blood. Such simulations demonstrate the more rapid onset of alfentanil in comparison with fentanyl. ◆

Predicted propofol and lidocaine (lignocaine) concentrations after a 4-hour infusion



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Pharmacokinetic Variation

Iain Glen

Iain Glen qualified in veterinary medicine at Glasgow University and became a lecturer in veterinary anaesthesia. Until recently he was a clinical specialist in anaesthesia at Astra Zeneca and was closely involved in the development of Diprivan and the Diprifusor target- controlled infusion system.

The consequence of pharmacokinetic variation is that the administration of a given dose of a drug will result in a range of different drug concentrations in a population of patients. If the concentration is low, lack of efficacy may result and if the concentration is high, side-effects may be increased. An understanding of possible sources of variation in the pharmacokinetic behaviour of a drug can help to ensure that in an individual patient the most appropriate dose to achieve a desired clinical end-point is selected. Variation in the response to a given concentration of drug at the effector site is also important in predicting the overall response to the administration of a particular dose.

Measuring pharmacokinetic variability
Information on pharmacokinetic variability is usually obtained after administration of a drug by serial measurement of its concentrations in blood. In this way, the mean time–concentration profiles, and inter-individual variability at particular time points, can be examined. More sophisticated studies may use the principles of population pharmacokinetic analysis whereby a small number of blood samples are collected from a large and diverse population of patients. Analysis of the data obtained quantifies inter- and intra-patient variability and attempts to link variation to patient characteristics, organ function or co-administered drugs.

Predictions of the likely effect of pathophysiological changes on pharmacokinetic variability may also be obtained from studies in experimental animals, where the contribution of individual organs to total body clearance can be investigated by looking at arteriovenous concentration differences across a particular organ such as the liver or kidney. *In vitro* systems, incorporating recombinant human drug-metabolizing enzymes have been used to investigate drug metabolism and to predict the likelihood of possible pharmacokinetic interactions with other drugs.

Physiological models
Physiological models have been used to predict how blood and tissue concentrations of a drug change with time. These models require detailed information on the mass of different tissues, their blood flow as a proportion of cardiac output and partition coefficients. Once established they can be used to predict the influence of changes in physiological parameters and have particular benefits when modelling drugs the pharmacological effects of which include changes, for example in cardiac output, which could influence their own disposition. One of the earliest models was developed by Price and his colleagues in 1960 and used to demonstrate the importance of redistribution to the termination of the effect of a bolus dose of thiopental (thiopentone). This model also explained the reduced dose requirements of patients in haemorrhagic shock because the fraction of the dose received by the brain was then high and its rate of removal slow, owing to the decreased blood flow to other tissues. Recently, another model for thiopental (thiopentone) disposition in man has predicted greater peak arterial concentrations in patients with low versus high cardiac output and in those who are lean versus the obese. Changes with gender and age were relatively minor. This model indicates that differences in basal cardiac output may explain much of the variability between patients in early thiopental (thiopentone) disposition. As increasingly sophisticated models are developed they may be incorporated in desktop computer simulation programs or in whole-body anaesthesia simulators for teaching and training.

Sources of pharmacokinetic variability

The four main processes that determine the pharmacokinetic behaviour of a drug are absorption from the site of administration, distribution within the body, metabolism and excretion. In many patients, age, weight, physiological changes caused by pregnancy or disease processes, drug interactions, and the effects of anaesthesia and surgery may also affect pharmacokinetics. Assay sensitivity or the duration of sampling may also account for variable results.

Absorption
Gastrointestinal absorption may be slowed by atropine or opiates, which inhibit gastrointestinal motility, or accelerated by metoclopramide, which hastens gastric emptying. Peak blood concentrations of some orally administered drugs are normally limited by first-pass metabolism in the liver. In elderly patients, a reduction in hepatic blood flow may reduce this first-pass effect leading, for example, to increased blood concentrations of propranolol. First-pass metabolism of drugs metabolized by cytochrome P450 (e.g. midazolam, diazepam) may be reduced by inhibitors of this enzyme (e.g. itraconazole, grapefruit juice) leading to increased bioavailability of the hypnotic agents. The addition of a vasoconstrictor to local anaesthetic drugs injected into tissues or the epidural space reduces their systemic uptake leading to prolongation of the local block and a reduction in the peak concentrations obtained in blood. Central neuraxial blockade produces circulatory changes (vasodilatation in regions denervated by the block and compensatory vasoconstriction in other areas) such that differences may occur in venous drug concentrations depending on the sampling site, with values closer to arterial concentrations in vasodilated regions.

Distribution
The initial volume of distribution (V_1) is not simply the circulating blood volume but includes tissues that equilibrate rapidly with the blood concentration. The peak concentration reached after a bolus or short infusion of thiopental (thiopentone) or propofol, is influenced by body weight, changes in blood volume and the mass of rapidly equilibrating tissues, and cardiac output. The greater the cardiac output, the greater the dilution of blood entering the pulmonary artery during the administration of a bolus or short infusion. Thus, peak blood concentrations in the systemic situation may be decreased, and dose requirements increased, when cardiac output is increased, for example with anxiety or hyperthyroidism, in young children compared with adults, and in the later stages of pregnancy. Conversely, a decrease in cardiac output leads to less initial dilution, higher peak concentrations and slower redistribution to peripheral tissues.

The overall volume of distribution at steady state (V_{ss}) depends on the mass of tissue available, the physicochemical nature of the drug (lipid-soluble drugs have a greater V_{ss} than water-soluble agents) and protein binding. Only unbound drug can diffuse across cell membranes, but the total amount of drug in some tissues may be greater than in others because of binding to tissue components. A reduction in plasma albumin is commonly associated with hepatic or renal failure. This leads to decreased plasma binding, an increased free drug concentration and more rapid distribution of drug from plasma, thus increasing V_{ss}.

Muscle mass is greater and adipose tissue mass smaller in men compared with women. Thus, when compared on a ml/kg basis, water-soluble drugs have larger distribution volumes in men and highly lipid-soluble drugs (e.g. diazepam, propranolol) have larger distribution volumes in women. A decline in lean tissue mass with age occurs in men and women.

Metabolism
Drug metabolism occurs primarily in the liver. Drugs such as propranolol or propofol that show total body clearance values close to hepatic blood flow (i.e. about 1.5 litre/minute) are known as high-extraction drugs (Figure 1). For these drugs, clearance depends on liver blood flow and is minimally affected by changes in plasma protein binding because virtually all drug passing through the liver is extracted, whether bound or not. With low-extraction drugs (e.g. phenytoin, warfarin) hepatic clearance is limited by drug-metabolizing enzyme activity and the extent of protein binding influences hepatic clearance. With these drugs, the hepatic extraction ratio is less than the free fraction and any decrease in plasma binding (and increase in free fraction) as a consequence of disease or displacement by a more highly bound drug, can increase their hepatic clearance.

Factors influencing hepatic clearance

Highly extracted drugs
Clearance = Hepatic blood flow (e.g. propranolol)

- Clearance affected by changes in hepatic blood flow
- Enzyme induction/inhibition or changes in protein binding have minimal effect

Poorly extracted drugs
Clearance << Hepatic blood flow (e.g. warfarin)

- Clearance affected by changes in hepatic metabolic activity, enzyme induction or inhibition
- Changes in protein binding may affect clearance

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Intrinsic hepatic clearance of agents metabolized by cytochrome P450 may be increased by the induction of this enzyme by drugs such as phenobarbital (phenobarbitone), phenytoin or alcohol or decreased by a reduction in hepato-cellular mass or by drugs such as cimetidine, erythromycin or disulfiram, which inhibit this enzyme. With drugs such as propofol, with high intrinsic clearance (principally glucuronidation), impairment of hepatic function leads to little difference in hepatic elimination because the normal liver has a great reserve of metabolic capacity. Variability in the clearance of midazolam has been attributed to inter-individual genetic differences in the activity of the P450 isoform CYP3A.

Excretion
In patients with renal failure, drugs excreted by the kidney, including digoxin, some antibiotics and neuromuscular blocking drugs, show decreased clearance, closely parallel to that of creatinine. In general, a reduction in protein binding has only a small effect on renal excretion. Diuretic drugs increase the excretion rate of renally cleared drugs.

Weight and gender
Some gender-related changes in drug distribution are mentioned above. Where a clear relationship between body weight and volume of distribution or clearance of a drug has been demonstrated, reduced variability can be expected by dosing on a mg/kg basis. In obese patients, the increase in total body weight correlates with an increase in propofol clearance. Clearance of midazolam is not increased in obese volunteers and it would be more appropriate to adjust infusion rates based on ideal as opposed to total weight. A recent model for remifentanil advocates scaling of V_1 to age and lean body mass. Women have less efficient clearance of drugs such as propranolol, temazepam and lidocaine (lignocaine). Gender has little effect on the kinetics of remifentanil or propofol, though a recent study described a 10% increase in propofol clearance in elderly women compared with elderly men.

Age
Some drug-metabolizing enzymes are immature in neonates. In general, drugs that have high intrinsic clearance are relatively unaffected by immature metabolic pathways whereas drugs with lower intrinsic clearance (e.g. thiopental (thiopentone)) are affected to a greater extent. Maturation usually occurs rapidly and infants are likely to show an increase in V_1 and clearance relative to adults. In elderly patients, the usual trend is a decrease in V_1 and clearance, which may be related to a decline in hepatic blood flow. With midazolam, a reduction in clearance in elderly men leads to a prolongation of the elimination half-life following intravenous dosing and increased bioavailability of an oral dose. Similar differences were not found between elderly and young women. Remifentanil and propofol show age-related decreases in clearance and central volume of distribution. The albumin concentration in plasma, and thus plasma protein binding, tends to be reduced in elderly patients, with the increased free fraction leading to enhanced distribution to extravascular tissues. Reduced renal function with advancing age reduces the clearance of drugs that are normally excreted by the kidney.

Pregnancy
In later pregnancy, cardiac output increases and plasma volume increases by 50% in the third trimester. A reduction in plasma protein binding favours distribution into extravascular tissues. These changes may explain the larger V_{ss} and longer elimination half-life of thiopental (thiopentone) in patients undergoing caesarean section.

Pathological conditions
The magnitude of any effect (decreased clearance) depends on the importance of hepatic metabolism or renal excretion for each drug. Impairment of hepatic metabolic activity is likely to have the greatest effect on drugs such as theophylline, pancuronium and vecuronium, which in healthy patients have low intrinsic hepatic clearance. Increased V_{ss}, decreased clearance and increased elimination half-life have been observed with diazepam in patients with alcoholic cirrhosis, whereas the pharmacokinetics of propofol are not significantly affected by moderate cirrhosis.

Renal excretion is important for a number of commonly used neuromuscular blocking drugs with 50–60% of pancuronium and 20–30% of the administered dose of vecuronium eliminated by this route. The elimination of both atracurium, by Hofmann degradation, and remifentanil, metabolized by circulating and tissue esterases, is independent of hepatic and renal function and is unaffected by renal or hepatic failure.

When propofol is used as a sedative in ICU patients over several days, clearance values are similar to those seen during anaesthesia. A longer elimination half-life has been seen in ICU patients, possibly related to the longer period of sampling, but this is unlikely to delay recovery after long infusions.

Smoking and alcohol
Smoking induces cytochrome P450, thereby increasing the clearance of drugs metabolized by oxidative pathways in the liver. High alcohol intake also induces drug metabolizing activity such that dose requirements may be increased but much of this effect may be related to pharmacodynamic changes in alcoholic patients. As alcoholism progresses towards liver failure, the enhancement of hepatic metabolism is reversed.

Other drugs
A number of examples of drugs affecting the absorption, distribution or metabolism of other drugs have been given above. In general, these are drugs that affect volume of distribution by changes in cardiac output or changes in their unbound fraction; or that affect clearance by inducing or inhibiting hepatic enzyme activity. Anaesthetic drugs with negative inotropic effects (e.g. halothane), slow the peripheral distribution of other agents by reducing cardiac output, thus tending to increase the blood concentration of co-administered agents. Such drugs also reduce the clearance of highly extracted drugs (e.g. lidocaine (lignocaine), propofol, fentanyl, propranolol) by reducing hepatic blood flow. A drug such as propofol, at high concentrations, could reduce its own clearance, thus contributing to intra-patient variability in kinetics at different depths of anaesthesia. The co-administration of alfentanil and propofol leads to elevated concentrations of both.

Anaesthesia and surgery
The haemodynamic effects of anaesthetic drugs may alter the distribution and clearance of other agents. In addition, the haemodynamic response to painful stimuli, as a result of inadequate anaesthesia, may modify drug distribution and reduce hepatic and renal blood flow. During abdominal surgery, pressure on major blood vessels may result in temporal variation in drug distribution and clearance. In anaesthesia for cardiopulmonary bypass, a transient decrease in drug concentrations in blood can be expected with haemodilution at the onset of bypass. However, because the greatest amount of drug is present in peripheral compartments rather than the circulation, equilibration across compartments restores blood concentrations. Induced hypothermia reduces hepatic metabolic efficiency leading to an increase in drug concentration if a constant administration rate is maintained. With both thiopental (thiopentone) and propofol an increase in unbound fraction has been observed.

Predicting the effects of pharmacokinetic variation

Predicting the clinical consequences of observed changes can be complex because of the interrelationship between different pharmacokinetic parameters. The blood concentration achieved after the intravenous administration of a given loading dose is principally dependent on the initial volume of distribution:

$$\text{Concentration} = \frac{\text{Dose}}{\text{Volume}}$$

Thus, any factor that decreases V_1 increases the peak blood concentration and *vice versa*. As the duration of drug administration increases and steady-state conditions are approached, the rate of infusion required to maintain a particular drug concentration is principally dependent on the clearance of the drug:

Rate of infusion = concentration at steady state x clearance

If clearance is increased, the infusion rate required is increased and *vice versa*.

Distribution occurs not only within V_1 but also to peripheral tissues (V_2 and possibly V_3 if a three-compartment model is appropriate). The sum of these volumes is V_{ss}. Elimination half-life ($t_{½}$) is influenced by the total volume of drug to be cleared (V_{ss}) and the rate of clearance. Elimination half-life is increased if V_{ss} is increased in the presence of unchanged clearance or if clearance is decreased with no change in V_{ss}. Alterations of V_{ss} and clearance in the same direction may have little influence on elimination half-life depending on the magnitude of the respective changes. The elimination half-lives of many drugs used in anaesthesia are a poor indicator of duration of action. With drugs whose kinetics fit multicompartment models, blood concentrations may have declined below effective levels before the terminal phase becomes dominant in the elimination profile. A more useful descriptor for comparing different drugs is the context sensitive half time (CSHT), which is the time required for the blood concentration to fall to 50% of the concentration that has been maintained for a specified duration. This descriptor emphasizes the importance of the duration of administration and takes account of the significant contribution of continuing distribution in lowering the blood concentration. Elimination half-life is independent of duration of administration whereas estimations of CSHT for fentanyl indicate that recovery is rapid after short infusions but delayed after prolonged administration.

Implications for target controlled infusion
Target controlled infusion systems, such as *Diprifusor* for the administration of propofol, use a pharmacokinetic model that represents an average patient. The amount of drug delivered at a given target concentration setting is standardized to the body weight of the patient but the blood concentration achieved varies between patients, such that titration of the target setting to the requirement of each patient is required. With target controlled infusion, a steady-state blood concentration is achieved more rapidly and titration is facilitated by the ability to make proportional changes to the blood concentration in a controlled manner.

Managing pharmacokinetic variability

Pharmacokinetic variability is a feature of biological variability and it is impossible to adjust dosage to achieve the effect desired in every patient. Pharmacokinetic and pharmacodynamic variability can be accounted for, if a drug can be titrated to achieve a desired effect. An understanding of potential sources of pharmacokinetic variability can guide the direction in which titration may be required. Drugs for which the therapeutic effect cannot be achieved by individual dose titration and for which the therapeutic margin is small may require therapeutic monitoring of drug concentrations. ◆

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Pharmacological Control of Blood Sugar

Leonard Best

Leonard Best is Senior Lecturer in Cell Physiology at Manchester University. He obtained his BSc in Biochemistry at Sheffield University and his PhD in Endocrinology at Aston University. His research interests include the physiology of the pancreatic β cell, mechanisms of glucose sensing by islet cells and hypothalamic neurons and glucose toxicity.

Under normal physiological circumstances, the blood glucose concentration is controlled by circulating hormones. Normal fasting blood glucose concentrations are 3.3–5.6 mmol/litre. A significant fall below this range induces the release of glucagon from the pancreatic islet α cells. This hormone stimulates glucose synthesis from certain metabolic intermediates and causes the breakdown of glycogen to glucose in the liver, from which the glucose is released into the blood. Cortisol released from the adrenal cortex in response to stress or starvation also raises hepatic glucose output. Following a meal, and largely as a result of raised blood glucose levels, the pancreatic islet β cells release insulin. This hormone stimulates glycogen synthesis in the liver and promotes glucose uptake into peripheral tissues (predominantly skeletal muscle and adipose tissue). Insulin also stimulates the metabolic disposal of glucose in peripheral tissues, notably glycogen synthesis in muscle and glucose conversion to triglyceride in adipose tissue. Administration of insulin and glucagon, together with a wide variety of pharmacological agents, can be used in the treatment of abnormal blood glucose homeostasis (Figure 1).

Agents that affect blood glucose concentration

Agents that lower blood glucose
Insulin – stimulates glucose uptake and metabolism in peripheral tissues
Hypoglycaemic sulphonylureas – stimulate insulin release
Meglitinides – stimulate insulin release
Biguanides – have insulin-like action
Thiazolidinediones – have insulin-sensitizing action
α-glucosidase inhibitors – inhibit digestion of starches to glucose in gut

Agents that raise blood glucose
Glucagon – stimulates hepatic glucose output
Diazoxide – inhibits insulin release

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Diabetes mellitus

A major clinical application for agents that influence blood glucose levels is the treatment of diabetes mellitus. Diabetes is a common condition. In the UK, there are about 1.4 million diagnosed cases, representing about 3% of the population, and it is likely that an additional 1 million individuals have undiagnosed diabetes. The incidence of diabetes mellitus is increasing, possibly by 4–5% per year. At present, it is the fourth most common cause of death in developed countries. Diabetes mellitus is a heterogeneous condition, but consists of two principal types. Type I diabetes is also known as insulin-dependent diabetes, but is often referred to as juvenile-onset diabetes, because it is usually manifest before the age of 40 years (most commonly between 10 and 16 years). Type II, non insulin-dependent diabetes, is commonly referred to as maturity-onset diabetes, because it usually appears in those over 40. About 80–90% of diabetic patients are not insulin dependent.

Aetiology

Both types of diabetes result from insufficient insulin, but their aetiology is distinct. Type I diabetes is the result of an auto-immune condition whereby the body mounts an immunological attack specifically on the insulin-producing pancreatic β cells. This results initially in impaired function and eventually in destruction of the β cells. The initial trigger for the autoimmune response is unknown, but it is likely that a combination of genetic susceptibility and environmental factors (possibly including viral infections) plays an important role.

Type II diabetes is thought to result from impaired β cell function and reduced insulin release in response to a rise in blood glucose concentration. This condition is also often associated with obesity and with insulin resistance, where the sensitivity of peripheral tissues (notably skeletal muscle, adipose tissue and the liver) to insulin is reduced. Susceptibility involves a genetic predisposition, while age, poor diet, high body weight and sedentary lifestyle are contributory factors. Some pharmacological agents exert diabetogenic actions and can precipitate or unmask diabetes mellitus. These include immunosuppressive drugs, certain diuretics, glucocorticoids and some oral contraceptives. Diabetes can also be precipitated by pregnancy.

Symptoms and complications

Insufficient insulin release or impaired insulin action results in hyperglycaemia. This leads to glucosuria, polyuria and thirst. Type I diabetes is often associated with ketoacidosis, where fat is broken down to free fatty acids, which are then converted in the liver to ketoacids (acetoacetate, β-hydroxybutyrate). These substances provide an alternative energy supply to tissues starved of glucose through lack of insulin. However, their formation can result in a significant fall in blood pH, leading to functional and metabolic disturbances, and in extreme cases, coma.

Long-term complications are discussed on page 317. In general, their incidence and severity increases with inadequate control of hyperglycaemia, and it seems likely that they arise, at least in part, as a consequence of prolonged exposure of tissues and/or the microvasculature to raised glucose levels. This phenomenon has been termed glucose toxicity. Thus, the major objective in the treatment of diabetes is the long-term control of blood glucose levels.

Treatment

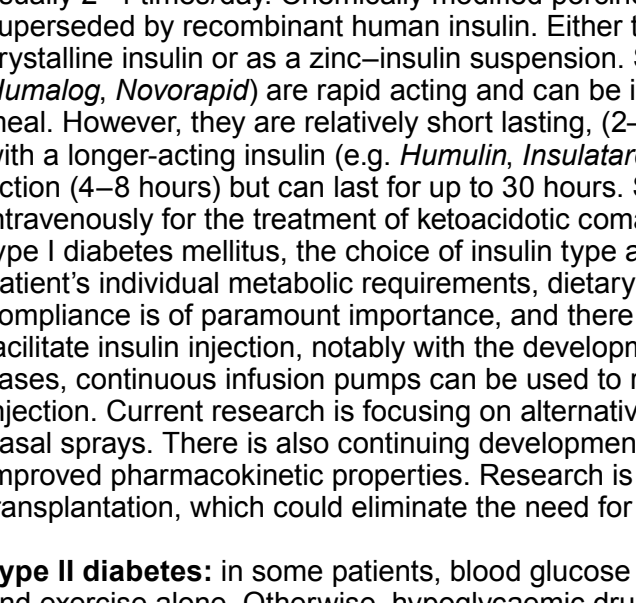
An important factor in the management of both types of diabetes is diet, which should be low in fat and simple sugars with a relatively high proportion of complex carbohydrate. Such a diet provides a limited rate of glucose absorption from the gut and avoids large increases in glycaemia. Physical exercise should be encouraged because it increases glucose uptake and utilization in peripheral tissues, especially skeletal muscle, and thus has an insulin-sparing action. Exercise also reduces body weight and blood pressure and improves cardiovascular function, all of which are of benefit in diabetes.

Type I diabetes: treatment almost invariably involves subcut-aneous insulin injection, usually 2–4 times/day. Chemically modified porcine insulin is gradually being superseded by recombinant human insulin. Either type can be administered as soluble crystalline insulin or as a zinc–insulin suspension. Soluble insulin preparations (e.g. *Humalog*, *Novorapid*) are rapid acting and can be injected 5–30 minutes before a meal. However, they are relatively short lasting, (2–8 hours) and may require mixing with a longer-acting insulin (e.g. *Humulin*, *Insulatard*), which has a slower onset of action (4–8 hours) but can last for up to 30 hours. Soluble insulin can be injected intravenously for the treatment of ketoacidotic coma. For the day-to-day treatment of type I diabetes mellitus, the choice of insulin type and mixture is determined by the patient's individual metabolic requirements, dietary and exercise regimens. Patient compliance is of paramount importance, and there has been considerable effort to facilitate insulin injection, notably with the development of pen-type injectors. In some cases, continuous infusion pumps can be used to reduce or eliminate the need for injection. Current research is focusing on alternative routes of administration such as nasal sprays. There is also continuing development of chemically modified insulins with improved pharmacokinetic properties. Research is directed at the possibility of islet transplantation, which could eliminate the need for insulin therapy.

Type II diabetes: in some patients, blood glucose levels can be controlled by diet and exercise alone. Otherwise, hypoglycaemic drugs can be used. There are several classes of oral hypoglycaemic agent that act in different ways, most commonly by stimulating insulin output from the pancreas or by enhancing glucose uptake and utilization by peripheral tissues. They can be used individually or, more commonly, combined in a stepwise manner to optimize glycaemic control. For example, sulphonylureas are potent drugs and therefore are preferable for use in more severely hyperglycaemic patients with little or no insulin resistance. On the other hand, the biguanides, thiazolidinediones and α-glucosidase inhibitors may be of greater value in the treatment of mildly hyperglycaemic patients and those with insulin resistance. Oral hypoglycaemic drugs may also be used in combination with insulin therapy to reduce insulin requirement.

Hypoglycaemic sulphonylureas – the first-generation sulphonylureas, tolbutamide and chlorpropamide, are largely obsolete and second-generation drugs, including glibenclamide (also called glyburide in the USA), gliclazide and glipizide, are in widespread use. Recently developed third-generation sulphonylureas (e.g. glimepiride) are more selective and show fewer side-effects. Sulphonylureas act by directly stimulating insulin release from the pancreatic β cell. The drug binds to a specific protein on the cell surface (the sulphonylurea receptor, SUR1; Figure 2) which forms part of a potassium channel (the K_{ATP} channel). Sulphonylurea binding to the SUR results in closure of the channel which depolarizes the β cell membrane. This leads to opening of voltage-sensitive calcium channels and calcium entry into the cell which is the trigger for insulin release. Some sulphonylureas, especially third-generation drugs, may also increase insulin sensitivity. Side-effects of the sulphonylureas include nausea, skin rash and hypoglycaemia. The latter is caused by excessive insulin release and can be prolonged.

The pancreatic β cell K_{ATP} channel complex



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Meglitinides (e.g. repaglinide, nateglinide) act in a similar manner to the sulphonylureas, exerting a direct stimulatory effect on insulin release from the pancreatic β cells. Side-effects include nausea and skin rashes, but because meglitinides have a more rapid action and shorter duration than sulphonylureas, they may elicit a more physiological insulin profile during meals with a reduced tendency to provoke hypoglycaemia.

Biguanides – metformin, the most commonly used biguanide, lowers blood glucose levels in a number of ways, including reduced hepatic glucose output and increased glucose uptake into muscle and adipose tissue. Biguanides may also impair glucose absorption from the gut and reduce hyperlipidaemia**.** Side-effects include stomach upsets and nausea.

Thiazolidinediones are a relatively new class of drug that include rosiglitazone, troglitazone and pioglitazone. Thiazolidinediones increase the sensitivity of tissues to insulin, thereby counteracting the insulin resistance often associated with type II diabetes. Their mechanism of action involves binding to the nuclear peroxisome proliferator-activated receptors (PPAR). This alters the transcription of genes involved in carbohydrate and fat metabolism, ultimately increasing insulin-mediated glucose disposal in peripheral tissue (especially skeletal muscle). Side-effects include headaches, oedema and weight gain.

α-glucosidase inhibitors (e.g. acarbose) impair the enzymatic hydrolysis of complex carbohydrates in the gut, thereby reducing the rate of glucose liberation and absorption into the blood following a meal. Side-effects include diarrhoea.

Hypoglycaemia

Hypoglycaemia is a potentially hazardous side-effect in the treatment of diabetes mellitus, both with insulin injection and hypoglycaemic sulphonylureas. Precipitating factors include missing a meal and unaccustomed exercise. In severe cases, hypoglycaemia can result in coma and rapid action must be taken to restore blood sugar levels. This can be achieved by oral glucose (3–4 lumps of sugar with water) if the patient is conscious or by intravenous infusion (50 ml of 50% glucose solution) if unconscious. A number of hyperglycaemic agents are also available.

Glucagon is a peptide hormone and can be injected by any route (subcutaneous, intramuscular, intravenous) for the treatment of acute hypoglycaemia if glucose administration is impossible. Glucagon acts by mobilizing liver glycogen and thus increasing hepatic glucose output.

Diazoxide is usually reserved for the treatment of chronic hypoglycaemia caused by excessive insulin release. This can be the result of an insulinoma or prolonged hypoglycaemia and hyperinsulinaemia in infancy (PHHI) which is relatively rare. PHHI is characterized by a constantly high output of insulin and is thought to result from a genetic defect in the sulphonylurea receptor whereby the β cell is permanently depolarized and thus actively secreting. Diazoxide is given orally and raises blood glucose levels by a direct inhibition of insulin release from the pancreatic β cell. The drug binds to the sulphonylurea receptor associated with the K_{ATP} channel (Figure 2) but, in contrast to the sulphonylureas and meglitinides, this results in activation of the potassium channel thereby hyperpolarizing the cell membrane and preventing calcium entry and insulin release.

Anaesthetic management

For the anaesthetic management of the diabetic patient see elsewhere. ◆

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Pharmacological Effects of Drug Degradation Products

Barbara J Pleuvry

Barbara J Pleuvry is Senior Lecturer in Anaesthesia and Pharmacology at the University of Manchester, UK. She is a pharmacist by first degree but has been involved in teaching pharmacology to postgraduates and undergraduates for over 30 years. Her research interests include pain, analgesia and anticonvulsant drugs.

Most drugs are lipophilic and can cross biological membranes to their site of action. However, lipophilicity hinders their elimination from the body, therefore metabolism of these drugs to more polar compounds that can be excreted via the kidney is essential to terminate their action. Generally metabolites are inactive, but sometimes drugs are converted into metabolites that are pharmacologically active. A pro-drug is inactive in its own right but is metabolized in the body to an active compound. Alternatively, the parent drug may be active and then metabolized into another active drug that may have beneficial or adverse effects.

Pro-drugs

Many pro-drugs were discovered long after the drug had been introduced into therapeutics. For example, phenacetin was introduced into therapeutics in 1887 and was widely used as an analgesic. It was not until 1949 that paracetamol was recognized as the active metabolite and began to take over the market share from phenacetin, which was then being implicated in analgesic abuse nephropathy.

Other drugs have been designed as pro-drugs because they confer therapeutic advantages. Parkinson's disease is associated with a loss of dopamine from the nigrostriatal tracts and can be treated by replacing dopamine. However, dopamine is poorly absorbed, therefore its precursor, inactive levodopa, is given and it is converted to dopamine within the body.

Zidovudine is converted to its active triphosphate metabolite only in cells containing reverse transcriptase, which is present only in cells infected with the human immunodeficiency virus. Some other pro-drugs are listed in Figure 1.

Pro-drugs

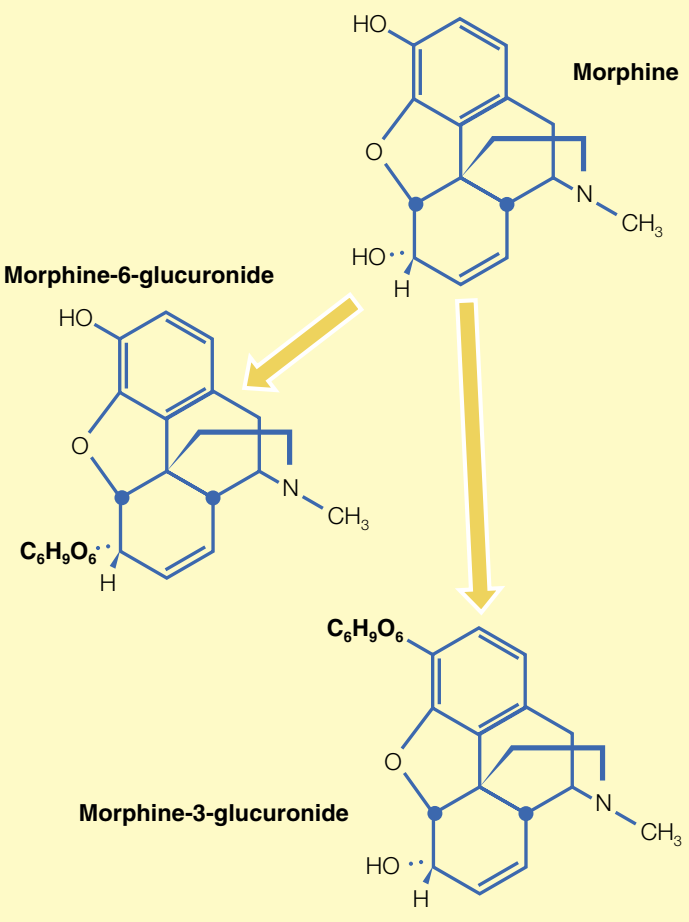
Pro-drug	Active metabolite	Comment
• Azathioprine	Mercaptopurine	Immunosuppressant
• Cyclophosphamide	Phosphoramide mustard	Converted to an alkylating agent by the liver Reduces potential intestinal toxicity
• Enalapril	Enalaprilat	Angiotensin converting enzyme inhibitor Active metabolite can be given only intravenously because it is not absorbed orally
• Cortisone	Hydrocortisone	Cortisone is better absorbed orally
• Sulphasalazine	5-aminosalicylic acid	Metabolized to active agent by bacteria in the large intestine Gives a local anti-inflammatory action in ulcerative colitis
• Aciclovir	Aciclovir triphosphate	Metabolized by herpes viruses and the host viral infected cell
• Benorylate	Salicylic acid and paracetamol	Parent drug is highly lipid soluble Conversion occurs in the liver so intestinal toxicity of acid is reduced

1

Drugs where parent and metabolite have similar pharmacological activity

The opioid analgesic morphine is a typical example of this type of drug. Morphine has an elimination half-time of 3 to 4 hours and it is metabolized in the liver to glucuronides (Figure 2). Morphine-6-glucuronide is a more potent analgesic than the parent drug and may contribute significantly to the therapeutic actions of morphine. Glucuronides are excreted in the urine, therefore the dose of morphine may require reduction in cases of renal failure. It has been suggested that the analgesic effects of morphine-6-gluronide are mediated by a splice variant of the μ opioid receptor but no significant clinical difference between the pharmacological actions of the parent and metabolite have been reported. In contrast, morphine-3-glucuronide has been reported to have some opioid antagonistic properties but the importance of this in the overall activity of morphine is unclear.

Metabolism of morphine



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Benzodiazepines are renowned for being metabolized to active compounds, often with longer half-lives that the parent drug. Diazepam has a half-life of 20–40 hours and is metabolized to nordiazepam with a half-life of over 60 hours. Nordiazepam has its own active metabolite of oxazepam with a half-life of 8–12 hours. Oxazepam is conjugated with glucuronide before excretion and this final metabolite is devoid of pharmacological action. These active metabolites may contribute significantly to the hangover effects of these anxiolytics and some clinicians prefer to use compounds that are metabolized only to inactive compounds (e.g. oxazepam, lorazepam).

Two antidepressant compounds, imipramine and amitriptyline, are metabolized to desmethylimipramine and nortriptyline, respectively, which have antidepressant actions of their own.

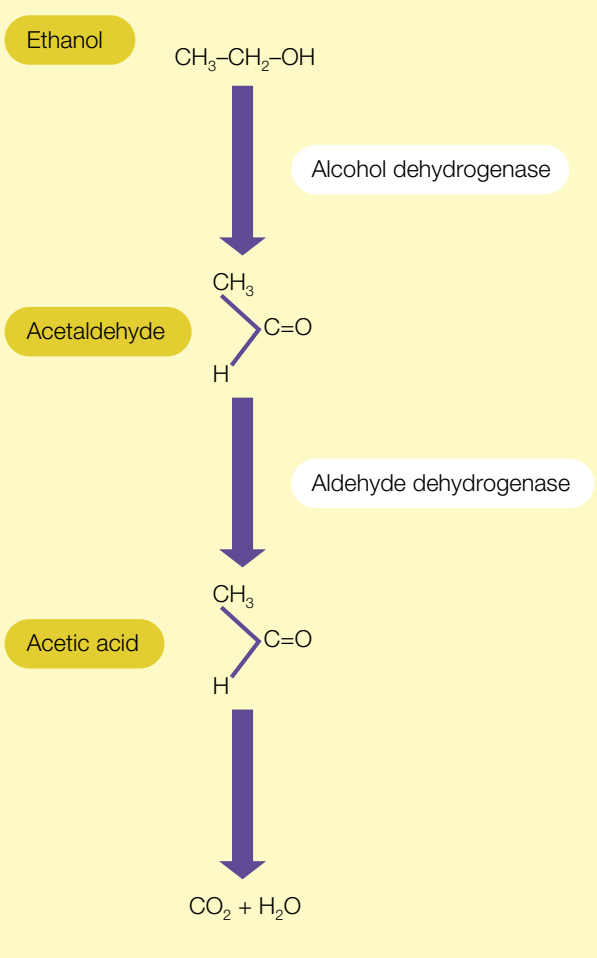
Drugs producing toxic metabolites

In therapeutic doses, paracetamol is conjugated with glucur-onide or sulphate and excreted harmlessly. If the enzymes responsible for conjugation are saturated, then paracetamol is metabolized by the mixed function oxidase system to N-acetyl-benzoquinoneimine. This toxic metabolite is conjugated with glutathione. If glutathione is depleted then the toxic metabolite accumulates and binds with cell macromolecules to cause cell death, particularly in the liver and kidney.

The toxic effects of inhalational anaesthetics may be related to their metabolites in that the most metabolized ones, methoxyflurane and halothane, are associated with renal and hepatic toxicity, respectively. Methoxyflurane is mainly of historical interest. Up to 70% of the inhaled drug was metabolized to free fluoride and oxalic acid. Both these metabolites are nephrotoxic and the incidence of toxicity was such that the popularity of methoxyflurane waned rapidly. Halothane is not normally metabolized to fluoride ion, but its oxidative metabolite, trifluoroacetyl chloride can be covalently bonded to some hepatic proteins, which may, in susceptible individuals, act as antigens. Hepatotoxicity results from the antigen/antibody reaction. Despite the rarity of this problem, it eroded the popularity of halothane and preference is now given to less metabolized agents, which are not thought to pose a similar threat.

Another anaesthetic, ethanol, has an active metabolite acetaldehyde (Figure 3).

Metabolism of ethanol



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Acetaldehyde produces headache and vomiting, a property that is used in the use of disulphiram in ethanol aversion therapy. Disulphiram inhibits aldehyde dehydrogenase causing a build-up of the aldehyde whenever ethanol is consumed.

Methanol, a common industrial solvent, is metabolized by the same pathway, but the metabolites (formaldehyde and formic acid) have significantly greater toxicity than the equivalent ethanol metabolites. Methanol intoxication can result in blindness. The affinity of ethanol for alcohol dehydrogenase is 100-fold greater than the affinity of methanol for the enzyme. Thus, ethanol can be used competitively to inhibit the metabolism of methanol in cases of methanol poisoning. Similarly, ethanol can be used to treat ethylene glycol toxicity. Ethylene glycol is metabolized by the same route, yielding nephrotoxic metabolites. ◆

Pharmacological Modulation of Myocardial Function, Vascular Resistance and Blood Pressure: Drugs used During Cardiopulmonary Resuscitation

Roger Small

Roger Small is Reader in Pharmacology in the School of Biological Sciences at Manchester University. He qualified with a BSc in Pharmacy from Manchester University and his research interests have focused on the electrophysiology and pharmacology of smooth muscle, notably that of the airways.

This article describes the pharmacology of modulators of cardiac function, antihypertensive drugs, vasopressor drugs and agents used during cardiopulmonary resuscitation. The present discussion of drugs used to modulate myocardial function includes inotropic agents and anti-anginal drugs; the pharmacology of antidysrhythmic drugs will be addressed in a future issue.

Modulators of myocardial function

Positive inotropic agents

Inotropic agents increase myocardial contractility and thus increase cardiac output.

Cardiac glycosides

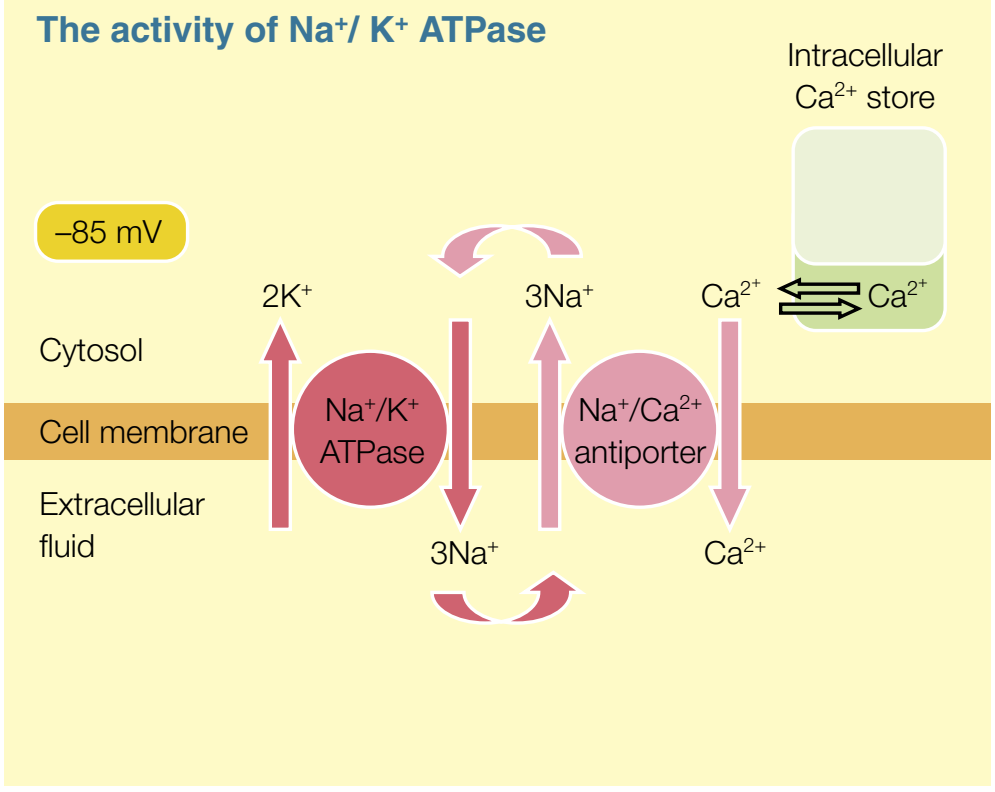
Digoxin is a cardiac glycoside; it binds to the extracellular surface of the α-subunit of plasmalemmal Na^+/K^+ ATPase (Figure 1) and inhibits this transporter. Na^+/K^+ ATPase utilizes the energy derived from the hydrolysis of ATP to transport $2K^+$ ions into the cell while extruding $3Na^+$ ions. The enzyme is thus electrogenic and helps to generate the transmembrane potential of the cell. The activity of Na^+/K^+ ATPase is intimately linked to that of the Na^+/Ca^{2+} antiporter. Na^+ ions extruded by the activity of Na^+/K^+ ATPase are transported back into the cell by the Na^+/Ca^{2+} antiporter. During this process Ca^{2+} is extruded into the extracellular fluid. By regulating the cytosolic concentration of Ca^{2+}, the Na^+/Ca^{2+} antiporter helps to control the content of the intracellular Ca^{2+} store (Figure 1). Digoxin-induced inhibition of Na^+/K^+ ATPase results in cellular depolarization, increased cytosolic Na^+ and, thus, inhibition of the Na^+/Ca^{2+} antiporter. Ca^{2+} ions that would have been extruded by the antiporter are redirected to the intracellular Ca^{2+} store. Treating a contracting cardiac muscle cell with digoxin results in a larger rise in the cytosolic free Ca^{2+} concentration and thus more forceful contraction. The shape of the action potential is not significantly altered by digoxin, therefore the positive inotropic action of the glycoside results from increased release of Ca^{2+} from the (more completely filled) intracellular store rather than from increased cellular influx of Ca^{2+}.

Digoxin depresses conduction through the atrioventricular (AV) node. The mechanisms underlying this effect include depolarization of nodal cells, the activation of baroreceptors (triggered by a rise in blood pressure secondary to increased cardiac output) or the direct stimulation of central vagal centres. The latter two effects increase vagal tone to the AV node. In addition, digoxin may directly sensitize the nodal cells to acetylcholine.

The depressant action of digoxin on the AV node is exploited in the treatment of supraventricular arrhythmias (e.g. atrial fibrillation). Digoxin may convert atrial tachycardia into atrial flutter, or atrial flutter into atrial fibrillation. However, conduction through the AV node is depressed, therefore a slower and more stable ventricular rate is achieved. The positive inotropic action of digoxin is exploited in the treatment of congestive cardiac failure in patients remaining symptomatic despite optimal treatment with angiotensin converting enzyme (ACE) inhibitors (see below) and diuretics. Digoxin does not increase the life expectancy of patients with congestive cardiac failure. It does, however, suppress symptoms and reduce the patients' need for hospitalization.

Digoxin has a low therapeutic index (about 2:1). Signs of toxicity include nausea and vomiting, disturbances of vision (acuity and colour) and ventricular tachydysrhythmias. The tachydysrhythmias result from increased automaticity of Purkinje fibres, which thus act as ventricular ectopic foci. The toxicity of digoxin is increased by hypokalaemia (e.g. the use of diuretics that promote K^+ excretion and conditions such as secondary hyperaldosteronism). The treatment of digoxin toxicity includes stopping its administration and correcting any hypokalaemia (KCl tablets or intravenous infusions containing KCl + NaCl or KCl + glucose). Ventricular tachydysrhythmias may be controlled by propranolol or phenytoin. Digoxin-specific antibody fragments (e.g. *Digibind*) may be given by intravenous infusion in order to neutralize the glycoside.

The activity of Na^+/K^+ ATPase



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Inhibitors of cyclic nucleotide phosphodiesterase: cyclic nucleotide phosphodiesterase catalyses the hydrolysis of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP) to yield the less biologically active AMP or GMP, respectively. There are several isoenzymes of phosphodiesterase, which have different substrate specificity (cAMP or cGMP), tissue distribution and sensitivity to inhibitors. The activity of phosphodiesterase type 3 is strongly expressed in cardiac muscle, its inhibition leads to an increase in the cAMP content of cardiac muscle and thus an increase in the rate and force of contraction.

Enoximone and milrinone are selective inhibitors of phosphodiesterase type 3. When used to treat congestive cardiac failure, they may have some haemodynamic benefit. However, they tend to induce ectopic beats and tachydysrhythmias. By inhibiting phosphodiesterase type 3 in vascular smooth muscle, they cause vasodilatation, headache and hypotension. They do not increase the life expectancy of patients with cardiac failure.

Sympathomimetic inotropes

Dopamine is a metabolic precursor of noradrenaline and adrenaline. It is a neurotransmitter in the brain and, possibly, in the periphery. Dopamine is a directly acting agonist at α_1- and β_1-adrenoceptors. It is also an indirectly acting sympathomimetic, because it can displace noradrenaline from neuronal storage vesicles. It can also activate dopamine D_1-receptors in the renal vasculature. Dopamine produces a mixture of effects on the cardiovascular system. The force of cardiac contraction is increased owing to the activation of cardiac β_1-adrenoceptors. Vasodilatation (D_1-receptor activation) may occur in the renal and mesenteric vascular beds while vasoconstriction (activation of α_1-adrenoceptors) may occur elsewhere.

Dopamine is used in the treatment of cardiogenic shock following myocardial infarction or cardiac surgery. It has a short half-life (2 minutes), and is therefore administered by intravenous infusion into a central, rather than a peripheral, vein. At relatively low dose rates (e.g. 2–5 μg/kg/minute) renal perfusion may be improved. Higher dose rates yield a better improvement in cardiac output, but the renal vasodilator action may be lost as a consequence of α_1-adrenoceptor activation.

Dobutamine is an agonist that acts directly on adrenoceptors. It is relatively selective for the α_1-adrenoceptor but may also activate the β_1-adrenoceptor. It increases the force of cardiac contraction with relatively little effect on cardiac rate. Why dobutamine should have little chronotropic effect is poorly understood. Dobutamine has a half-life of about 2 minutes. It is administered by intravenous infusion in order to improve cardiac output in septic shock or in cardiogenic shock associated with myocardial infarction, cardiac surgery or cardiac myopathy.

Xamoterol is a partial agonist at β_1-adrenoceptors. Its use is restricted to the treatment of mild heart failure. In moderate or severe cardiac failure, increased sympathetic neural tone plays a more important role in maintaining cardiac output. Xamoterol is contraindicated in this situation, because, as a partial agonist at β_1-adrenoceptors, it reduces the effects of neurally released noradrenaline (a full agonist) and may thus aggravate the condition.

Dopexamine is a directly acting agonist at both β_2-adrenoceptors and dopamine D_1-receptors. By activating the relatively small number of cardiac β_2-adrenoceptors it can improve cardiac output. It may improve renal perfusion by the activation of dopamine D_1-receptors. Dopexamine is used in the treatment of chronic heart failure or heart failure secondary to cardiac surgery; it is administered by infusion into a central vein or a large peripheral vein.

Anti-anginal drugs

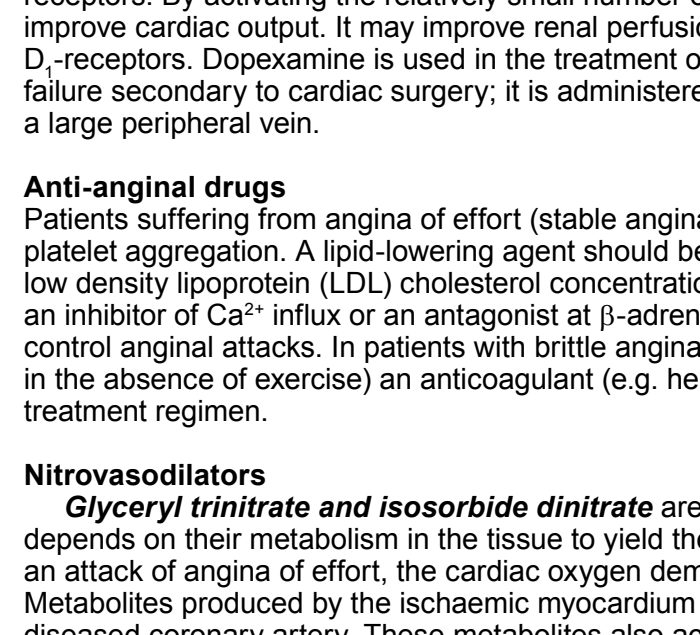
Patients suffering from angina of effort (stable angina) should receive aspirin to inhibit platelet aggregation. A lipid-lowering agent should be prescribed if the patient's plasma low density lipoprotein (LDL) cholesterol concentration is elevated. A nitrovasodilator, an inhibitor of Ca^{2+} influx or an antagonist at β-adrenoceptors may be prescribed to control anginal attacks. In patients with brittle angina (when attacks are experienced in the absence of exercise) an anticoagulant (e.g. heparin) should be added to the treatment regimen.

Nitrovasodilators

Glyceryl trinitrate and isosorbide dinitrate are prodrugs; their biological activity depends on their metabolism in the tissue to yield the active principle (Figure 2). During an attack of angina of effort, the cardiac oxygen demand exceeds the oxygen supply. Metabolites produced by the ischaemic myocardium evoke maximal dilatation of the diseased coronary artery. These metabolites also activate the sensory nerve terminals that mediate the sensation of anginal pain. Since myocardial ischaemia itself promotes maximal dilatation of the diseased coronary artery, that artery cannot represent a major site of action for the nitrates in relieving the anginal attack. Low doses of organic nitrates dilate capacitance veins. As a result, the venous filling pressure of the heart is reduced. Since the myocardial fibres are less stretched at the end of diastole and they contract less forcibly (Starling law), stroke volume is reduced. This is partly compensated for by a reflex tachycardia. Nevertheless, a fall in cardiac output occurs. The main effect of the nitrates in alleviating an attack of angina of effort is to reduce the cardiac work rate by reducing the preload. In this way, the imbalance between cardiac oxygen demand and supply is restored. In higher doses, the organic nitrates also dilate arterioles, and thus reduce peripheral resistance and cardiac afterload. Nitrate-induced arteriolar dilatation also corrects the imbalance between cardiac oxygen demand and supply, by reducing the cardiac work rate. The organic nitrates may also dilate collateral vessels in the ischaemic myocardium, thus improving blood flow distal to the point of occlusion in the diseased artery. Glyceryl trinitrate is ineffective if swallowed because it is metabolized to inorganic nitrate in the liver. It is administered as sublingual tablets, a buccal spray, transdermal patches, an ointment or as an intravenous injection. The duration of action of the sublingual tablets is 20–30 minutes.

Isosorbide dinitrate is effective when swallowed and its activity depends on its metabolism to the mononitrate form. It can be administered by a variety of routes. The duration of action of the sustained-release tablets can be up to 12 hours. For this reason the development of tolerance (depletion of tissue SH groups) is more likely than for glyceryl trinitrate. Side-effects of the nitrates include skin flushing, sweating, throbbing headache, orthostatic hypotension and reflex tachycardia.

Vasodilatation induced by organic nitrates



GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate

2

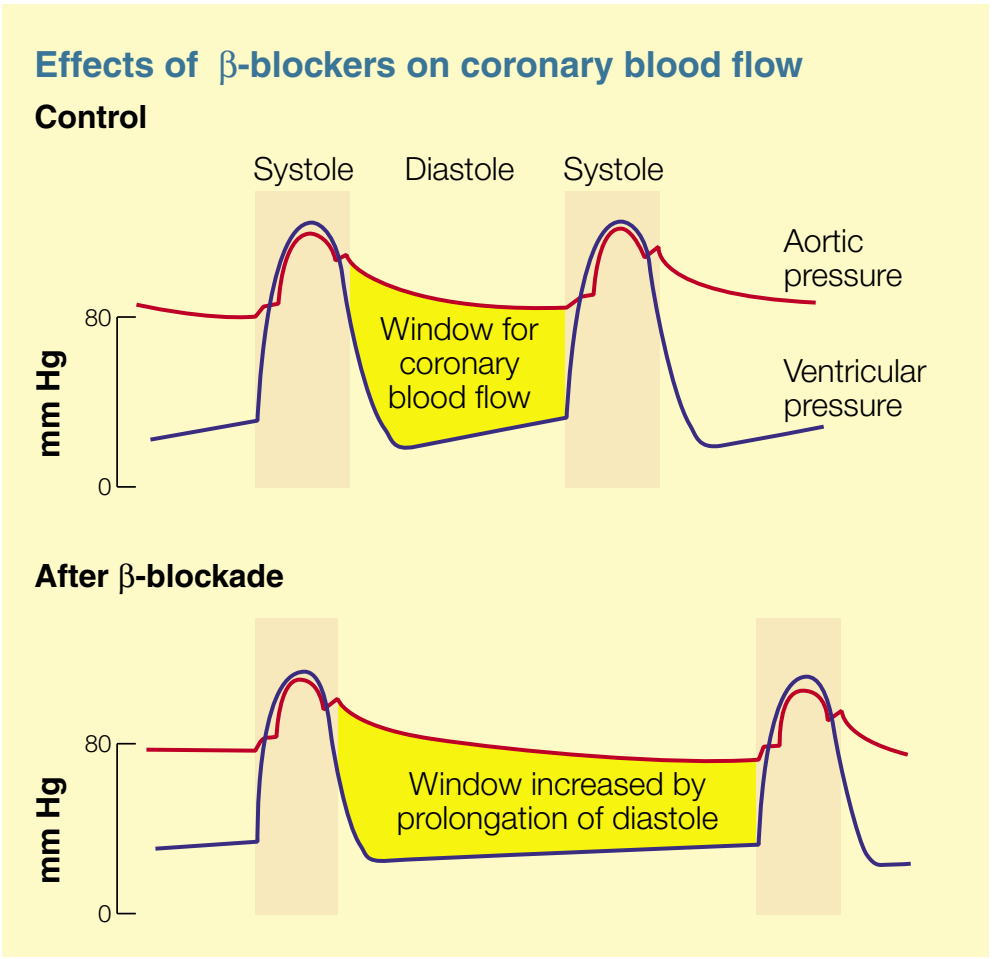
Ca^{2+} influx inhibitors

Nifedipine, verapamil and diltiazem – nifedipine (a dihydropyridine), verapamil (a phenylalkylamine) and diltiazem (a benzothiazepine) each inhibit the cellular influx of Ca^{2+} through the L-type voltage-sensitive Ca^{2+} channel. The binding site for nifedipine is on the extracellular surface of the α-subunit of the L-type Ca^{2+} channel. For this reason, blockade of the L-type channel by nifedipine shows no dependency on the frequency at which the channel opens (i.e. no use-dependency). However, binding of nifedipine to the L-type channel is enhanced if the resting membrane potential of the cell is relatively low, a situation in which a significant proportion of the channels will be in an inactivated state. The resting membrane potential of vascular smooth muscle is about –50 mV while that of the ventricular myocardium is about –85 mV, therefore nifedipine will preferentially bind to the L-type channels of vascular smooth muscle. For this reason, nifedipine is more potent in depressing the activity of vascular smooth muscle than that of cardiac tissue. The principal effect of nifedipine in relieving angina of effort is to dilate both arterioles and capacitance veins. By this means, cardiac preload and afterload are both reduced. The cardiac work rate is reduced and the imbalance between cardiac oxygen demand and supply is corrected.

Verapamil and diltiazem each have a binding site on the α-subunit of the L-type Ca^{2+} channel at its intracellular surface. These drugs can gain access to their binding sites only by passing through the open pore of the L-type Ca^{2+} channel. Thus, their activity is dependent on the frequency of channel opening (use-dependent action). Since the L-type Ca^{2+} channels of cardiac tissue open more often than those of vascular smooth muscle, verapamil and diltiazem are more potent in depressing the activity of cardiac tissue than that of vascular smooth muscle. The principal effect of these drugs in relieving angina of effort is to reduce the rate and force of cardiac contraction directly. They may secondarily reduce cardiac afterload by dilating arterioles. By reducing the cardiac work rate, the imbalance between cardiac oxygen demand and supply is corrected. Side-effects of the inhibitors of Ca^{2+} influx are described below.

Antagonists at β-adrenoceptors

Propranolol and atenolol – sympathetic neural tone to the heart is increased during physical exercise. Noradrenaline, released from the nerves, activates β_1-adrenoceptors to increase the rate and force of cardiac contraction. Propranolol and atenolol act as antagonists at β-adrenoceptors. Propranolol has approximately equal affinity for β_1- and β_2-adrenoceptors whereas atenolol is relatively selective for β_1-adrenoceptors. By competing with noradrenaline for occupancy of the cardiac β_1-adrenoceptors, these agents attenuate the cardiac effects of exercise. Cardiac work rate is thus reduced and, in the patient with angina of effort, the imbalance between cardiac oxygen demand and supply is corrected. Coronary blood flow is relatively low during systole because the contracting ventricular muscle tends to compress the arteries that run through it. Most of the coronary blood flow therefore occurs during diastole. By reducing cardiac rate, the antagonists at β-adrenoceptors prolong diastole. Improved coronary blood flow may thus contribute to their anti-anginal effects (Figure 3). Side-effects of the antagonists at β-adrenoceptors are described below.



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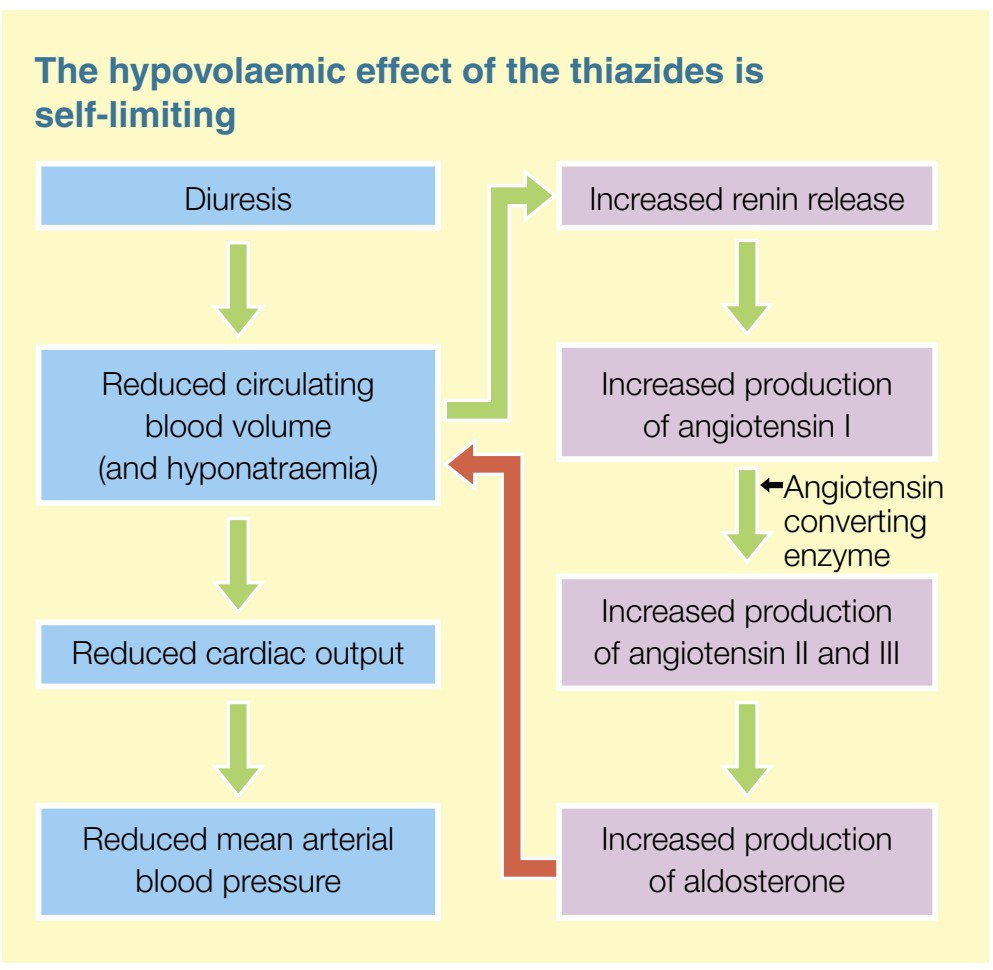
Antihypertensive drugs

Thiazide diuretics

Bendrofluazide (bendroflumethiazide) and chlortalidone (chlorthalidone) inhibit Na^+ and water reabsorption in the renal distal convoluted tubule. The resultant diuresis leads to a reduction in circulating blood volume thereby lowering cardiac output and mean arterial blood pressure. However, the resultant hyponatraemia and reduced renal blood perfusion activate the renin–angiotensin system so that the thiazide-induced effect on circulating blood volume and plasma Na^+ concentration is self-limiting (Figure 4). Despite this, the reduction in mean arterial blood pressure is maintained. The sustained hypotensive effect results from thiazide-induced opening of K^+ channels in the plasmalemma of arteriolar smooth muscle cells with resultant arteriolar dilatation and reduced peripheral resistance. Side-effects of the thiazides include hypokalaemia (stimulation of Na^+/K^+ exchange in the renal collecting ducts), aggravation of gout (competition with uric acid for active secretion into the renal proximal convoluted tubule), hyperglycaemia and impotence (reversible on cessation of treatment and of low incidence). A low dose of thiazide (e.g. bendrofluazide (bendroflumethiazide), 2.5 mg/day) produces a near-maximal lowering of blood pressure with little biochemical disturbance. Higher doses do not confer additional advantage.



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Antagonists at β-adrenoceptors

Propranolol and atenolol: the mechanism by which these agents reduce blood pressure may involve a reduction in cardiac output (blockade of cardiac β_1-adrenoceptors), a reduction in renin release (blockade of β_1-adrenoceptors on renal juxtaglomerular cells), a central action involving reduced outflow of sympathetic neural impulses to the periphery, or a combination of these actions. Side-effects of the antagonists at β-adrenoceptors include the aggravation of bronchial asthma (blockade of β_2-adrenoceptors on airways smooth muscle), the precipitation of cardiac failure (blockade of cardiac β_1-adrenoceptors), and aggravation of both Raynaud's phenomenon (cold hands) and claudication. The antagonists at β_1-adrenoceptors also mask the sympathetically mediated sweating and tremor that warns the insulin-dependent, diabetic patient of impending hypoglycaemia. Propranolol is relatively lipid soluble, can cross the blood–brain barrier and may induce vivid dreams. Atenolol is more water-soluble and is less likely to cross the blood–brain barrier.

Ca^{2+} influx inhibitors

Nifedipine, verapamil and diltiazem: the antihypertensive action of nifedipine stems mainly from its ability to dilate arterioles and thus to reduce peripheral resistance. In contrast, the antihypertensive actions of verapamil and diltiazem involve a direct reduction in cardiac output and a fall in peripheral resistance owing to arteriolar dilatation. Side-effects of nifedipine include flushing, headaches, dizziness and ankle swelling. Verapamil and diltiazem may also cause constipation, bradycardia, heart block and precipitation of cardiac failure.

ACE inhibitors

Captopril and enalapril: the ACE inhibitors are used to control hypertension when thiazides and β-adrenoceptor antagonists have failed to produce adequate lowering of blood pressure, are contraindicated or are poorly tolerated. ACE inhibitors can cause a profound fall in blood pressure, therefore the first dose (e.g. captopril, 12.5 mg) is best given at bedtime. ACE catalyses the conversion of angiotensin I to angiotensin II (vasoconstrictor and stimulant of aldosterone secretion), and is also responsible for the inactivation of bradykinin (a vasodilator). The hypotensive effects of the ACE inhibitors thus result from reduced production of angiotensin II and reduced metabolic inactivation of bradykinin. Side-effects of ACE inhibitors include angioedema and a dry cough, both triggered by the accumulation of bradykinin. ACE inhibitors interfere with the renin–angiotensin system, therefore they may act synergistically with thiazide diuretics. ACE inhibitors should be avoided in patients with renal artery stenosis, because they can reduce glomerular filtration to a level that promotes renal failure.

Antagonists at the angiotensin II receptor

Loasartan and valsartan compete with angiotensin II for occupancy of its receptors on vascular smooth muscle. The resultant arteriolar dilatation leads to a fall in peripheral resistance and thus a fall in mean arterial blood pressure. Unlike the ACE inhibitors, they do not inhibit the metabolism of bradykinin and therefore do not cause angioedema or dry cough. In view of the risk of precipitating renal failure, great caution should be exercised when using angiotensin II antagonists in patients with renal artery stenosis.

Antagonists at α-adrenoceptors

The α_1- and α_2-adrenoceptors found in vascular smooth muscle mediate vasoconstriction. The plasmalemma of the noradrenergic nerve terminal bears α_2-adrenoceptors, which mediate inhibition of noradrenaline release. These presynaptic or prejunctional receptors are activated during the noradrenergic neurotransmission process and exert negative feedback control over transmitter release.

The use of non-selective antagonists at α-adrenoceptors results in a fall in peripheral resistance and thus a fall in blood pressure. This hypotensive effect is accompanied by a reflex tachycardia as a result of baroreceptor activity. However, blockade of the α_2-adrenoceptors on noradrenergic neurons supplying the heart augments noradrenaline release at that site, thus accentuating the reflex tachycardia. For this reason, antagonists at both the α_1- and α_2-adrenoceptors find little use in the treatment of essential hypertension.

Prazosin is a competitive antagonist that is relatively selective for the α_1-adrenoceptors. It lowers blood pressure by blocking α_1-adrenoceptors on arterioles and thus reducing peripheral resistance. Its hypotensive effect is accompanied by an acceptable degree of reflex tachycardia. It is used to control hypertension when other therapies have proved ineffective or unacceptable. Side-effects include postural hypotension and retrograde ejaculation of seminal fluid into the bladder resulting from blockade of α_1-adrenoceptors in the smooth muscle of the bladder neck.

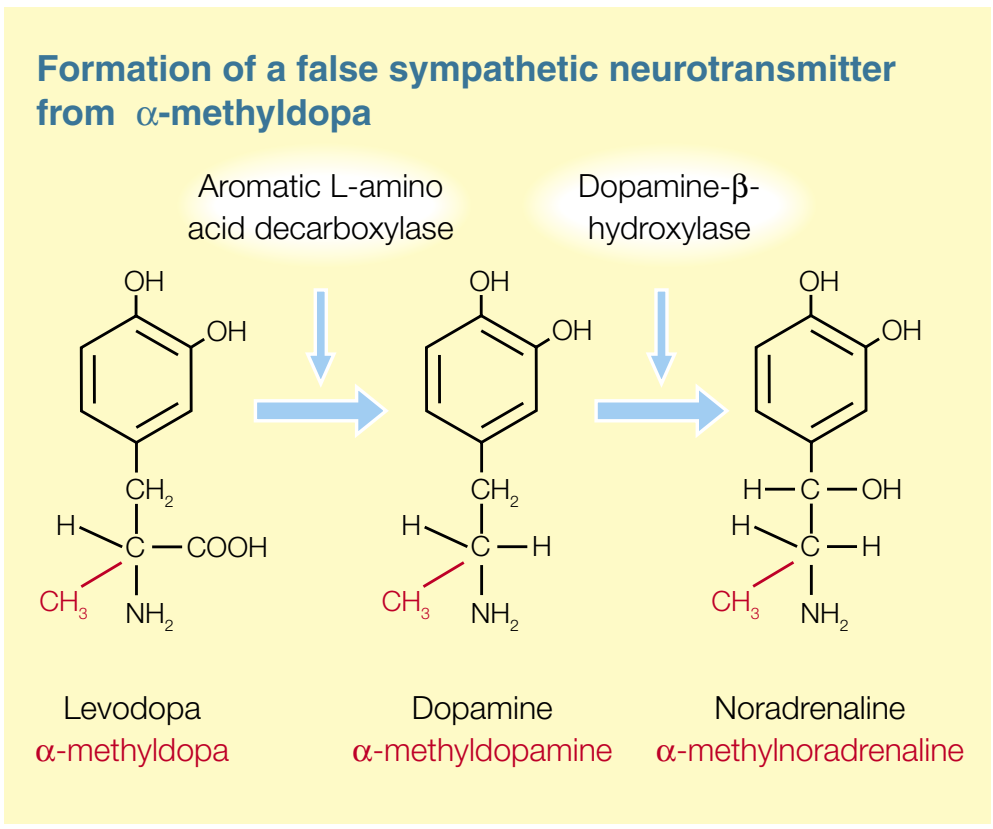
Phenoxybenzamine is an alkylating agent and an irreversible antagonist at both α_1- and α_2-adrenoceptors. It is used (in conjunction with an antagonist at α-adrenoceptors) to prevent hypertensive crises during the surgical removal of a phaeo-chromocytoma or in the long-term management of inoperable phaeochromocytoma.

Phentolamine is a competitive antagonist at both α_1- and α_2- adrenoceptors. It is sometimes used used as a diagnostic test for phaeochromocytoma. In the presence of excessive amounts of circulating catecholamines, the test dose of phentolamine induces a greater fall in blood pressure than otherwise expected.

Centrally acting antihypertensive drugs

Methyldopa is a prodrug, requiring metabolic conversion to yield its active principle, α-methylnoradrenaline (Figure 5). α-methylnoradrenaline is handled by the noradrenergic neuron in the same way as noradrenaline. It is retained in the granular storage vesicles and may be released into the junctional or synaptic cleft when the neuron terminal is invaded by a nerve action potential. α-methylnoradrenaline is thus said to function as a false transmitter. Measured at postjunctional α_1- or α-adrenoceptors, the potencies of noradrenaline and α-methylnoradrenaline are approximately equal. However, measured at the α_2-adrenoceptors on the noradrenergic neuron terminal, the potency of α-methylnoradrenaline exceeds that of noradrenaline. Thus, release of this false transmitter from the nerve terminal causes exaggerated feedback inhibition of neurotransmitter release. The noradrenergic neurotransmission process is therefore inhibited.

Methyldopa is actively transported into the CSF and brain. It inhibits noradrenergic neurotransmission within the medullary centres that regulate blood pressure. The outflow of sympathetic nerve impulses to the heart and blood vessels is reduced and blood pressure therefore falls. Methyldopa is considered safe for antihypertensive use in patients suffering from bronchial asthma and in toxaemia of pregnancy. Side-effects include drowsiness, depression, and salt and water retention. In about 20% of patients, methyldopa induces antibodies to rhesus antigens on erythrocytes (positive Coomb's test). In less than 1% of patients this may lead to haemolytic anaemia.



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Clonidine is a potent, directly acting agonist at the 2-adrenoceptors on the noradrenergic neuron terminal. Its mechanism of hypotensive action is similar to that of -methylnoradrenaline. Side-effects include drowsiness, depression, and salt and water retention. Sudden withdrawal of clonidine may provoke a hypertensive crisis.

Ganglion-blocking drugs

Trimetaphan camsylate: the nicotinic acetylcholine receptor in autonomic ganglia is a ligand-gated cation channel. Trimetaphan acts as an antagonist of acetylcholine at this receptor, not by competing with acetylcholine for occupancy of its binding site, but by blocking the cation channel pore. The blockade of transmission through sympathetic ganglia produced by trimetaphan leads to arteriolar dilatation, a fall in peripheral resistance and thus a fall in blood pressure. Trimetaphan is administered by intravenous infusion to lower blood pressure in certain types of surgery, particularly if a bloodless field of operation is required.

Other antihypertensive drugs

Hydralazine is a vasodilator and thus lowers blood pressure by reducing peripheral resistance. Its mechanism of action may involve interference with the ability of the intracellular second messenger, inositol trisphosphate, to induce the release of Ca^{2+} from the endoplasmic reticulum of the vascular smooth muscle cell. Side-effects include reflex tachycardia and fluid retention. It also tends to induce an autoimmune condition similar to systemic lupus erythematosus.

Sodium nitroprusside is a vasodilator that lowers blood pressure by reducing peripheral resistance. Its mechanism of action is similar to that of the organic nitrovasodilators (Figure 2). Sodium nitroprusside is useful in the emergency lowering of blood pressure. The effects of an intravenous infusion are seen within 1–2 minutes, but the hypotensive effect wanes rapidly when the infusion is stopped. Sodium nitroprusside is metabolized in the blood and liver to form thiocyanate. Accumulation of this toxic metabolite limits the time for which the drug may be infused.

Vasopressor agents

Sympathetic block is a hazard of spinal or epidural anaesthesia. The hypotension that results from sympathetic block may be treated using sympathomimetic vasoconstrictor agents. These drugs acivate α_1-adrenoceptors (and in some cases 2-adrenoceptors) on vascular smooth muscle either directly or indirectly. The resultant arteriolar constriction increases peripheral resistance and thus restores blood pressure. However, this effect may occur at the expense of reduced perfusion of vital organs, such as the kidney. Sympathomimetic agonists that are not substrates for the neuronal uptake process for noradrenaline (e.g. methoxamine, phenylephrine and metaraminol) may evoke a long-lasting elevation of blood pressure.

Noradrenaline acid tartrate (norepinephrine bitartrate): noradrenaline is the neurotransmitter of most postganglionic sympathetic neurons. It also has a transmitter role in the CNS. Noradrenaline is a directly acting agonist at all types of adrenoceptor. It not only evokes vasoconstriction, but also stimulates the heart.

Methoxamine hydrochloride is a directly acting agonist exhibiting selectivity for 1- and α2-adrenoceptors. It thus has no direct stimulant effect on the heart. Its vasoconstrictor action is useful in the correction of hypotension associated with tachycardia.

Phenylephrine hydrochloride is a directly acting agonist exhibiting selectivity for the α1- adrenoceptor. It has no direct stimulant effect on the heart.

Metaraminol is a directly acting agonist at both α- and β-adrenoceptors. It evokes vasoconstriction and stimulates the heart.

Ephedrine hydrochloride has little direct action on adrenoceptors. Ephedrine is a substrate for the neuronal noradrenaline uptake process. Ephedrine stoichiometrically (molecule for molecule) displaces noradrenaline from its storage vesicles. Much of the displaced noradrenaline escapes to activate the postjunctional adrenoceptors and mediate the (indirect) sympathomimetic effect of ephedrine. The noradrenaline released by ephedrine evokes vasoconstriction and stimulates the heart. This makes ephedrine particularly useful when hypotension is associated with bradycardia. The vasoconstrictor action of ephedrine may be susceptible to tachyphylaxis (depletion of neuronal noradrenaline stores) and is reduced when the neuronal uptake process is inhibited (e.g. abuse of cocaine).

Adrenaline (epinephrine) is the principal hormone secreted by the chromaffin cells of the adrenal medulla. It may also have neurotransmitter and neuromodulatory roles within the CNS. Adrenaline (epinephrine) is a directly acting agonist at both - and β-adrenoceptors. It is vital in the treatment of anaphylactic shock. Features of this condition include laryngeal oedema, bronchospasm and profound hypotension. Treatment consists of securing the airway and administering oxygen. Restoration of blood pressure is attempted by laying the patient flat with both feet raised. Adrenaline (epinephrine), 500 µg, is administered by intramuscular injection every 5 minutes until improvement occurs. In the severely ill patient, adrenaline (epinephrine), 500 µg for an adult, may be given by slow intravenous injection at a rate of 100 µg/minute, the infusion being terminated when improvement is observed. Adrenaline reduces capillary permeability and thus prevents further fluid loss to the interstitial compartment. It also restores blood pressure by increasing cardiac output (direct cardiac stimulation) and peripheral resistance (arteriolar constriction). These useful vascular and cardiac effects of adrenaline are mediated through the activation of α- and β-adrenoceptors, respectively. Adjunctive measures include the slow intravenous injection of an antagonist at histamine H1-receptors (e.g. chlorpheniramine) or the intravenous injection of hydrocortisone.

Agents used in cardiopulmonary resuscitation

Adrenaline (epinephrine), 1 mg injected into a central or peripheral vein, is used in the management of cardiac arrest. If a peripheral vein is used, the adrenaline (epinephrine) injection is followed by normal saline, 20 ml, to promote drug entry into the circulation. The adrenaline challenge is repeated every 2–3 minutes until resuscitation is successful or is abandoned. This treatment aims to evoke arteriolar constriction (α-adrenoceptor activation), and increase the rate and force of cardiac contraction (β-adrenoceptor activation). These effects of adrenaline maintain systemic vascular resistance, and help to promote cerebral and coronary blood flow.

Atropine is a competitive antagonist at the various subtypes of muscarinic acetylcholine receptor. There is little evidence to suggest that atropine is useful in the treatment of asystolic cardiac arrest. However, by antagonizing the effects of acetylcholine on the sinoatrial node and the AV node, atropine improves sinus automaticity and AV conduction, respectively. It is useful in the management of hypotension associated with sinus, atrial or nodal bradycardia. Side-effects include blurred vision, dry mouth, urinary retention and acute confusional states.

Calcium: for most cases of cardiac arrest, there is little evidence to suggest that the intravenous injection of Ca^{2+} salts has any beneficial effect. Indeed, high plasma concentrations of Ca^{2+} can be detrimental to the ischaemic myocardium and can impair recovery from cerebral ischaemia. For this reason, Ca^{2+} is administered during resuscitation only if there is evidence of dissociation between the electrical and mechanical activity of the myocardium. Such dissociation may result from severe hyperkalaemia, severe hypocalcaemia or overdose with Ca^{2+} influx inhibitors. In such cases, $CaCl_2$ may be administered by rapid intravenous injection. However, if some cardiac output exists, the injection should be given slowly to minimize the risk of slowing the heart and inducing arrhythmias.

FURTHER READING

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Pharmacological Treatment of Respiratory Tract Infections

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The treatments in this article are those recommended in edition 42 of the British National Formulary. Any treatment should take into account factors such as the patient's history, the treatment situation (community or hospital-based medicine) and whether a bacteriological diagnosis has been made (causative microorganism; presence or absence of drug-resistant strains).

Bacterial infections

Epiglottitis caused by *Haemophilus influenzae*

The currently recommended treatment for epiglottitis caused by *H. influenzae* is intravenous cefotaxime or chloramphenicol.

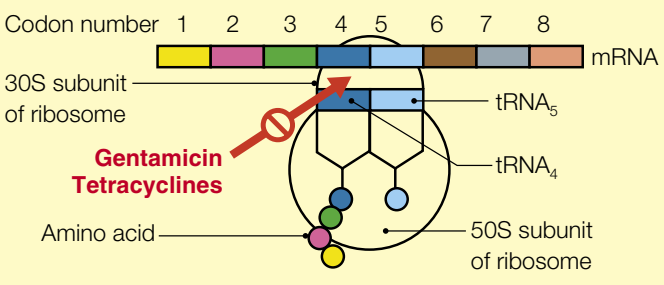
Cefotaxime is a third-generation cephalosporin. Its mechanism of antibacterial action is similar to that of penicillin. The cephalosporins and penicillins are structural analogues of D-alanyl-D-alanine. As such they are able to inhibit the transpeptidase reaction in the biochemical pathway by which the peptidoglycan of the bacterial cell wall is synthesized. The transpeptidase reaction occurs outside the cell membrane and involves the formation of peptide cross-links between the tetrapeptide side-chains of muramic acid molecules. The cell wall outside the cell membrane normally protects the bacterium from the osmotic effects of its environment, therefore interruption of cell wall synthesis by penicillins and cephalosporins leads to bacterial swelling and lysis. In contrast to bacteria, mammalian cells have a cell membrane only and do not possess a cell wall. The antibacterial action of penicillins and cephalosporins thus exhibits selectivity with a qualitative, biochemical basis.

Compared with the second-generation cephalosporins, cefotaxime has less activity against Gram-positive bacteria but more activity against Gram-negative bacteria. It has some activity against pseudomonads. Following its intravenous administration, cefotaxime is widely distributed throughout the body and is able to cross the blood–brain barrier. Its plasma half-life is 2 hours and excretion is mainly by renal tubular secretion. The unwanted effects of cefotaxime include diarrhoea and allergic reactions.

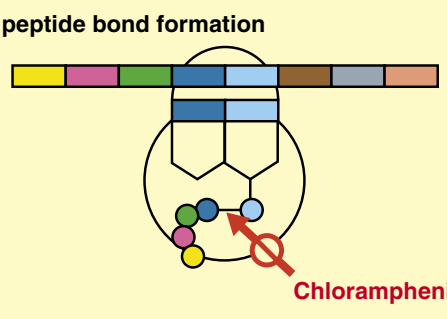
Chloramphenicol has such serious haematological effects that its systemic use should be reserved for the treatment of life-threatening conditions. Epiglottitis caused by *H. influenzae* can lead to obstruction of the respiratory tract in which case treatment with intravenous chloramphenicol may be justified. Chloramphenicol binds to the 50S subunit of the bacterial ribosome, thereby inhibiting the transpeptidation step in bacterial protein synthesis (Figure 1). To some extent chloramphenicol can also bind to the 70S ribosomes in mammalian cells and may thus inhibit mitochondrial protein synthesis. The antimicrobial action of chloramphenicol therefore exhibits selectivity with a quantitative, biochemical basis. Chloramphenicol has a wide spectrum of bacteristatic activity against both Gram-negative and Gram-positive organisms. However, it exerts bactericidal activity against *H. influenzae*. Resistance to chloramphenicol reflects the bacterial production of the enzyme chloramphenicol acetyltransferase.

Mechanisms by which some antibiotics interfere with bacterial protein synthesis

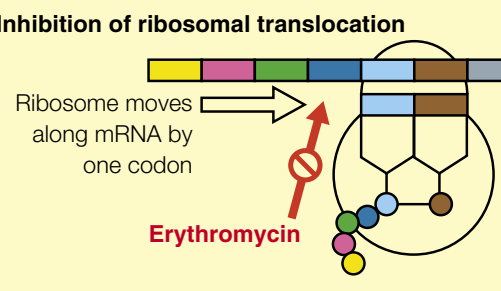
Impairment of function of 30S subunit of ribosome



Inhibition of peptide bond formation



Inhibition of ribosomal translocation



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Following its intravenous administration, chloramphenicol is widely distributed throughout the body and penetrates the CSF. Its plasma half-life is 2 hours. Chloramphenicol is mainly biotransformed in the liver but about 12% is excreted unchanged in the urine. The most serious unwanted effect of chloramphenicol is aplastic anaemia, which may prove fatal in 1/50,000 patients. In neonates, chloramphenicol should be administered with particular care, because the immature liver and kidney may not be able to biotransform the drug adequately leading to inadequate excretion of the unchanged drug. The resultant high plasma concentrations of chloramphenicol may cause 'grey baby' syndrome.

Exacerbations of chronic bronchitis

Streptococcus pneumoniae and *H. influenzae* are commonly causative in chronic bronchitis. *Staphylococcus aureus* is a less common cause. Exacerbations of chronic bronchitis may be treated with a broad-spectrum penicillin (e.g. ampicillin, amoxicillin (amoxycillin)), a tetracycline (e.g. tetracycline, oxytetracycline, doxycycline) or a macrolide antibiotic (e.g. erythromycin, azithromycin, clarithromycin).

Ampicillin and amoxicillin (amoxycillin; a derivative of ampicillin) interfere with bacterial cell wall synthesis as described above for cefotaxime. They are effective against certain Gram-positive and Gram-negative organisms. Both are inactivated by β-lactamases including those produced by *Staph. aureus*. Therefore, most staphylococci are resistant to ampicillin and amoxicillin (amoxycillin). About 15% of strains of *H. influenzae* are also resistant to these β-lactam antibiotics. However, amoxicillin (amoxycillin) can be prescribed (in the form of co-amoxiclav) in combination with the β-lactamase inhibitor, clavulanic acid. This renders amoxicillin (amoxycillin) effective against strains of *Staph. aureus, H. influenzae* and *Klebsiella* that would otherwise be resistant.

Ampicillin and amoxicillin (amoxycillin) are both absorbed from the gastrointestinal tract though absorption of ampicillin may be impaired by the presence of food in the stomach. Both agents have a plasma half-life of 80 minutes. Ampicillin is excreted in the bile and both agents are actively secreted into the urine. Unwanted effects of both include diarrhoea, maculopapular rashes and the allergic reactions characteristic of penicillins. Co-amoxiclav can cause cholestatic jaundice.

The tetracyclines are broad-spectrum antibiotics that are actively accumulated by susceptible microorganisms. Bacteria can become resistant to the tetracyclines by developing active extrusion processes that reduce the antibiotic concentration within the microbial cell. By binding to the acceptor site on the 30S subunit of the bacterial ribosome, the tetracyclines prevent the binding of aminoacyl-tRNA and interrupt protein synthesis (Figure 1). The tetracyclines have a similar effect on the 70S ribosomes in the mitochondria of mammalian cells. For this reason, the antibacterial action of the tetracyclines has selectivity with a quantitative rather than a qualitative biochemical basis. The tetracyclines exert bacteriostatic effects against a wide range of Gram-positive and Gram-negative microorganisms including *Mycoplasma pneumoniae, Rickettsia, Chlamydia* and some protozoa.

Absorption of tetracyclines from the gastrointestinal tract is variable. Only 30% of an oral dose of chlortetracycline is absorbed. For tetracycline and oxytetracycline this rises to 60–80%. For doxycycline and minocycline, absorption is virtually complete. The tetracyclines tend to form chelates with metal ions, therefore their absorption from the gastrointestinal tract is inhibited by ingestion of Ca^{2+} (dairy products), Al^{2+}, Mg^{2+} (antacids) and ferrous sulphate. Following absorption, the tetracyclines are widely distributed throughout the body and can cross the placenta to reach the fetus. They are excreted in the bile (the main route for doxycycline) and in the urine.

Unwanted effects include gastrointestinal disturbances (of which the worst is pseudomembranous colitis), skin rashes, allergic reactions and hepatotoxicity. Tetracycline-induced inhibition of protein synthesis may lead to the accumulation of nitrogenous waste products in the blood and aggravate renal failure. Tetracyclines should not be prescribed to pregnant women or children under 12 years of age because they form chelates with calcium ions causing bone deformities and staining of teeth.

Macrolide antibiotics (erythromycin, azithromycin, clarithromycin) bind to the 50S subunit of the bacterial ribosome, thus inhibiting the translocation step in bacterial protein synthesis (Figure 1). This antibacterial action may be bacteriostatic or bactericidal depending on the antibiotic, its concentration and the target microorganism. The binding site for the macrolides on the subunit of the bacterial ribosome is identical to that of chloramphenicol, and competition may occur. Erythromycin is effective against many Gram-positive and some Gram-negative organisms. Its action is similar to that of penicillin and it is useful in patients who are allergic to penicillin. Azithromycin is more effective than erythromycin against *H. influenzae*. The same is true for the active metabolite of clarithromycin.

The macrolides are absorbed from the gastrointestinal tract and are widely distributed in the body, though they do not cross the blood–brain barrier. The plasma half-life of erythromycin is 90 minutes and significantly longer for clarithromycin and azithromycin. Azithromycin is relatively resistant to biotransformation but erythromycin is deactivated in the liver and clarithromycin is converted to an active metabolite. Unwanted effects of the macrolides include gastrointestinal disturbances. Erythromycin has also been reported to cause skin rashes and cholestatic jaundice.

Uncomplicated, community-acquired pneumonia

Uncomplicated community-acquired pneumonia is caused by *S. pneumoniae* (30–50% of cases), *H. influenzae* (5–15%), *M. pneumoniae* (0–20%, according to a 4-year cycle of epidemics), *Chlamydia pneumoniae* (about 10%) and *Staph. aureus* (about 3%, increasing during epidemics of influenza or measles). *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are relatively uncommon causes of community-acquired pneumonia.

Uncomplicated, community-acquired pneumonia may be treated with amoxicillin (amoxycillin) or ampicillin. Erythromycin may be used if the patient is allergic to penicillins or an atypical pneumonia is suspected. If the patient has no history of chest infection, the causative organism is probably *S. pneumoniae* and it may be better to use benzylpenicillin, a highly potent penicillin, rather than amoxicillin (amoxycillin) or ampicillin. Benzylpenicillin is bactericidal against some Gram-positive cocci and bacilli and some Gram-negative cocci. It is hydrolysed by gastric acid, therefore it is administered by intravenous or intramuscular injection. It is widely distributed throughout the body but does not penetrate the CSF unless the meninges are inflamed. It is eliminated by renal tubular secretion. Its unwanted effects are characteristic of the penicillin group and mainly comprise hypersensitivity reactions.

Staph. aureus produces β-lactamase and pneumonia caused by this organism is best managed by adding flucloxacillin, a lactamase-resistant penicillin, to the treatment regimen. Flucloxacillin is resistant to gastric acid but is nevertheless poorly absorbed after oral administration. Food further impairs absorption of flucloxacillin from the gastrointestinal tract but it can be administered by intramuscular or intravenous injection. Protracted treatment with flucloxacillin (over 2 weeks) has been associated with cholestatic jaundice.

Severe community-acquired pneumonia of unknown aetiology

A macrolide antibiotic (e.g. erythromycin) in combination with cefuroxime or cefotaxime is recommended for the treatment of severe, community-acquired pneumonia of unknown aetiology. Cefuroxime is a second-generation cephalosporin that is relatively resistant to β-lactamase. Compared with the first-generation cephalosporins, cefuroxime is less effective against Gram-positive organisms but more effective against Gram-negative organisms. Cefuroxime can be administered orally or parenterally. It is widely distributed in the body and can cross the blood–brain barrier. Its plasma half-life is 90 minutes. Cefuroxime is mainly eliminated by active secretion in the kidney. If *Staph. aureus* is suspected as a cause of this type of pneumonia, flucloxacillin should be added to the treatment regimen.

Suspected atypical pneumonia
Suspected atypical pneumonia may be treated with a macrolide antibiotic (e.g. erythromycin). If *C. pneumoniae* or *M. pneumoniae* is the suspected cause a tetracycline may be used as an alternative to a macrolide. If *Legionella pneumophila* is suspected to be the causative microorganism, rifampicin should be added to the treatment with a macrolide. Rifampicin is an antibiotic that directly interferes with DNA-dependent RNA polymerase in bacteria but does not affect the homologous enzyme in the nuclei of mammalian cells. It enters phagocytic cells and is therefore active against intracellular microorganisms. It is bactericidal against a variety of bacteria including *L. pneumophila* and *Mycobacterium tuberculosis*. However, resistance to rifampicin can develop quite quickly through the production of an altered DNA-dependent RNA polymerase.

Rifampicin is suitable for oral administration and is widely distributed throughout the body. The plasma half-life is 1–5 hours and rifampicin is excreted partly in the bile (as metabolites) and partly in the urine. Rifampicin imparts an orange–red colour to secretions such as tears and urine. Unwanted effects of rifampicin include hepatotoxicity and gastrointestinal disturbances. It induces hepatic microsomal enzymes and may therefore reduce the efficacy of oestrogen-containing oral contraceptives, corticosteroids, sulphonylureas, warfarin and phenytoin.

Hospital-acquired pneumonia
Hospital-acquired pneumonia may be caused by *K. pneumoniae* (10–20% of cases), *P. aeruginosa* (10–15%), *S. pneumoniae* (about 10%), *Staph. aureus* (about 10%) or *H. influenzae* (about 5%). *M. pneumoniae* is a relatively uncommon cause.

A broad-spectrum cephalosporin, such as cefotaxime or ceftadizime, is indicated for the treatment of hospital-acquired pneumonia. If *P. aeruginosa* infection is suspected, ceftadizime may be particularly useful. Ceftadizime is a third-generation cephalosporin with good activity against *P. aeruginosa* and other Gram-negative bacteria. It is administered by intramuscular or intravenous injection and has a plasma half-life of 1.5 hours. It is not metabolized. An anti-pseudomonal penicillin (e.g. ticarcillin or piperacillin) may be used as an alternative to ceftadizime. Ticarcillin is a carboxypenicillin that is effective against *P. aeruginosa* and other Gram-negative bacteria. Absorption of ticarcillin from the gastrointestinal tract is poor and it is administered by intravenous infusion. Piperacillin is a ureidopenicillin with a broad spectrum of antibacterial activity. It is more active than ticarcillin against *P. aeruginosa.* Like ticarcillin, it is poorly absorbed from the gastrointestinal tract and is administered by the intramuscular or intravenous routes. Both ticarcillin and piperacillin are susceptible to β-lactamase. They can be administered together with a β-lactamase inhibitor such as clavulanic acid (ticarcillin) or tazobactam (piperacillin). In the presence of tazobactam, piperacillin is the penicillin that exhibits the broadest spectrum of antimicrobial activity.

When hospital-acquired pneumonia causes severe illness, an aminoglycoside such as gentamicin can be added to the treatment regimen. The aminoglycoside antibiotics enter susceptible bacterial cells by an oxygen-dependent transport process. For this reason they have little effect against anaerobic organisms. Once inside the aerobic bacterial cell, the amino-glycosides bind irreversibly to the 30S subunit of the bacterial ribosome, distorting the subunit so that reading of codons on the mRNA strand is impaired and protein synthesis is interrupted (Figure 1). This leads to the eventual disruption of the bacterial cell membrane.

Gentamicin is a highly polar, water-soluble base that is poorly absorbed from the gastrointestinal tract. It is administered by intramuscular or slow intravenous injection. Its distribution is restricted to the extracellular compartment and it penetrates the CSF poorly. Gentamicin is excreted by glomerular filtration. Its unwanted effects are dose-related and include ototoxicity and nephrotoxicity. The likelihood of these unwanted effects is increased with renal impairment.

Tuberculosis
Treatment of tuberculosis requires specialized knowledge, particularly if the infection involves extrapulmonary tissue or drug-resistant organisms. The Joint Tuberculosis Committee of the British Thoracic Society has recommended that the treatment of tuberculosis should comprise an initial phase lasting for 2 months and should involve the use of at least three antitubercular drugs. The object of this initial phase of treatment is to reduce the infecting population of mycobacteria as quickly as possible, to minimize the chance of resistant strains emerging. The recommended drugs include rifampicin, isoniazid, pyrazinamide and ethambutol. Ethambutol may be omitted if the risk of isoniazid resistance is low. After the initial phase, the continuation phase of therapy comprises the administration of rifampicin and isoniazid in combination for 4 months. Where resistant organisms are suspected, the continuation phase may involve alternative antitubercular drugs (only first-line agents are considered in this article). Where extrapulmonary infection is present the continuation phase of treatment may require extension.

Rifampicin is described above. It forms a crucial part of any treatment regimen for tuberculosis.

Isoniazid is a prodrug that exerts a highly selective action against mycobacteria. It is able to diffuse into mammalian cells to reach intracellular microorganisms. Isoniazid is actively accumulated by tubercle bacilli and, following its conversion to an active metabolite, interferes with the synthesis of mycolic acid and thus cell wall synthesis. Mycolic acids are unique to mycobacteria and this helps to explain the selectivity of action not only of isoniazid but also of pyrazinamide and ethambutol (see below). Isoniazid is bacteriostatic for resting microorganisms but bactericidal towards those that are rapidly dividing. If isoniazid is used in the absence of any other antitubercular drug, resistance develops rapidly. The most common resistance mechanism is reduced conversion of the prodrug into its active metabolite. However, cross-resistance between isoniazid and other antitubercular drugs does not occur.

Isoniazid is well absorbed from the gastrointestinal tract and widely distributed in the body. It readily penetrates the CSF and readily diffuses into cell interiors. It is acetylated in the liver at a rate that is genetically determined. Slow acetylators are more likely to develop unwanted effects such as peripheral neuropathy and hepatitis. The likelihood of isoniazid-induced peripheral neuropathy can be reduced by the co-administration of pyridoxine.

Pyrazinamide is relatively specific for mycobacteria. Its bactericidal action involves interference with the gene that encodes for mycobacterial fatty acid synthase. This leads to interruption of mycolic acid synthesis and thus the synthesis of the bacterial cell wall. The action of pyrazinamide proceeds best at a slightly acidic pH. Furthermore, *Mycobacterium tuberculosis* normally resides in an acidic phagosome within a macrophage. These conditions are ideal for the action of pyrazinamide. However, resistance to pyrazinamide develops rapidly when it is used in the absence of any other antitubercular drug.

Pyrazinamide is well absorbed from the gastrointestinal tract and is widely distributed throughout the body. It readily penetrates the CSF. Its plasma half-life is 9–10 hours. It is excreted by renal glomerular filtration mainly in the form of metabolites. Unwanted effects include hyperuricaemia, arthralgia and hepatic dysfunction.

Ethambutol is relatively specific for mycobacteria. It is taken up by mycobacterial cells and, after a delay of about 24 hours, it produces a bacteriostatic effect. This involves interference with the activity of arabinosyl transferase enzymes that are involved in cell wall synthesis. Resistance to ethambutol develops rapidly if used in the absence of any other antitubercular drug and results from changes in the gene that encodes for arabinosyl transferase.

Ethambutol is well absorbed from the gastrointestinal tract and can penetrate the CSF. Its plasma half-life is 3–4 hours. Ethambutol is partly metabolized but is mainly excreted unchanged in the urine. Unwanted effects include optic neuritis leading to reduced visual acuity and reduced ability to differentiate between red and green. These changes in vision are reversible, provided that the drug is withdrawn at an early stage. Ethambutol should be avoided, or its dose reduced, if there is renal insufficiency.

Fungal infections of the respiratory tract

Aspergillosis and cryptococcosis
Anti-asthma drugs, including inhaled or oral glucocortico-steroids, are indicated for allergic bronchopulmonary aspergillosis and for patients with well-developed aspergillomas. In the latter case, excision of these balls of fungal hyphae may be practicable. Where *Aspergillus* or *Cryptococcus* infections have disseminated from the respiratory tract to reach other tissues, or where there is a danger of this happening, ampho-tericin by slow intravenous injection is the treatment of choice.

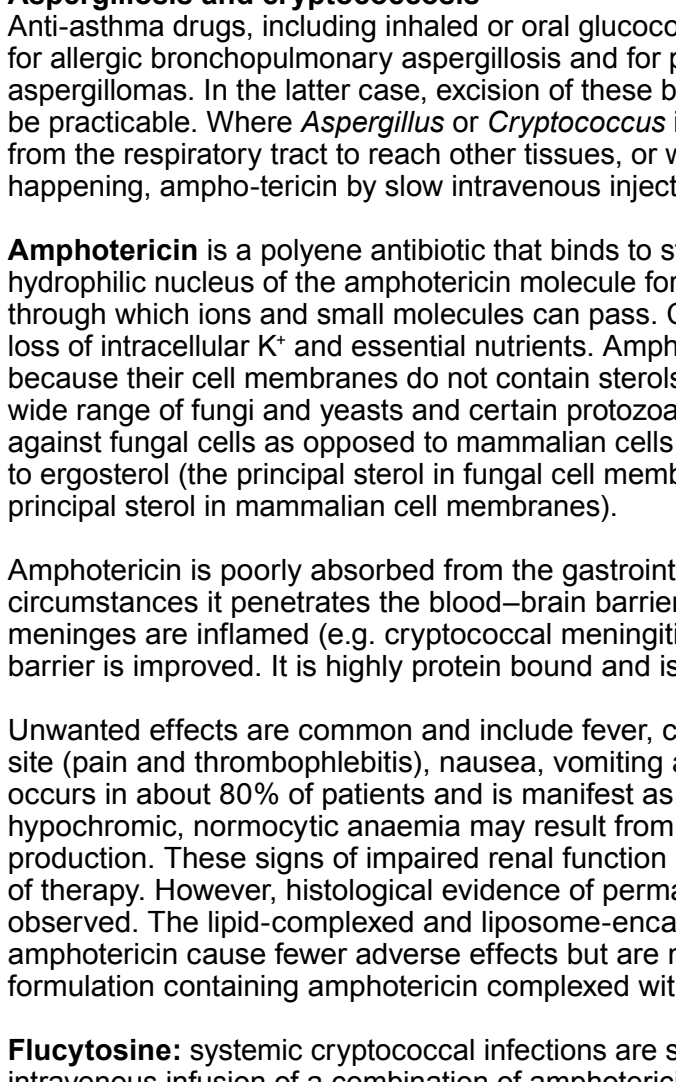
Amphotericin is a polyene antibiotic that binds to sterols in cell membranes. The hydrophilic nucleus of the amphotericin molecule forms a pore in the cell membrane through which ions and small molecules can pass. Cell death may result from the loss of intracellular K^+ and essential nutrients. Amphotericin does not affect bacteria because their cell membranes do not contain sterols. However, it is effective against a wide range of fungi and yeasts and certain protozoa. The drug exhibits some selectivity against fungal cells as opposed to mammalian cells because it binds more avidly to ergosterol (the principal sterol in fungal cell membranes) than to cholesterol (the principal sterol in mammalian cell membranes).

Amphotericin is poorly absorbed from the gastrointestinal tract. Under normal circumstances it penetrates the blood–brain barrier poorly. However, when the meninges are inflamed (e.g. cryptococcal meningitis) penetration of the blood–brain barrier is improved. It is highly protein bound and is slowly excreted by the kidney.

Unwanted effects are common and include fever, chills, irritation at the injection site (pain and thrombophlebitis), nausea, vomiting and tinnitus. Renal toxicity occurs in about 80% of patients and is manifest as uraemia and hypo-kalaemia. A hypochromic, normocytic anaemia may result from suppression of erythropoietin production. These signs of impaired renal function usually resolve on cessation of therapy. However, histological evidence of permanent renal damage is often observed. The lipid-complexed and liposome-encapsulated formulations of amphotericin cause fewer adverse effects but are more expensive than the standard formulation containing amphotericin complexed with a bile salt.

Flucytosine: systemic cryptococcal infections are sometimes treated by the intravenous infusion of a combination of amphotericin and flucytosine. This combination widens the antifungal spectrum and reduces the likelihood that resistance to flucytosine will develop. Flucytosine is a fluorinated pyrimidine and acts as a prodrug. It is taken up by both mammalian and fungal cells. Within the fungal cell, flucytosine is de-aminated to form 5-fluorouracil. This is metabolized to form 5-fluorodeoxyuridylic acid which acts as an inhibitor of thymidylate synthase (Figure 2). Fungal DNA synthesis is therefore impaired. Equivalent metabolism of flucytosine does not occur within mammalian cells, therefore the antifungal activity of flucytosine exhibits a high degree of distributional selectivity. Flucytosine is widely distributed throughout body fluids including the CSF. 80–90% is excreted unchanged in the urine.

Metabolism of 5-flucytosine by fungal cells



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Itraconazole and fluconazole: as an alternative to amphotericin, systemic infection with *Aspergillus* may be treated with oral itraconazole. Similarly, systemic infection with *Cryptococcus* may be treated with oral or intravenous fluconazole. Itraconazole and fluconazole are second-generation (triazole) imidazole, anti-fungal drugs. Their activity against *Cryptococcus* is greater than that against *Aspergillus*. These imidazole derivatives are inhibitors of sterol 14-α-demethylase, a microsomal cytochrome P450-dependent enzyme system. Itraconazole and fluconazole thus impair the synthesis of fungal ergosterol and cause the accumulation of 14-α-methylsterols in the fungal cell membrane. This disturbs the way in which phospholipids are arranged in the cell membrane, impairs the activity of membrane-associated enzymes such as Na^+/K^+-ATPase and thus inhibits fungal growth. The inhibitory action of these imidazole derivatives against fungi rather than mammalian cells exhibits selectivity with a quantitative biochemical basis.

Absorption from the gastrointestinal tract is good in the case of fluconazole but variable for itraconazole. Fluconazole enters most body fluids including the CSF; itraconazole does not enter the CSF. Fluconazole is excreted largely unchanged in the urine (90%) and faeces (10%). Itraconazole undergoes extensive hepatic metabolism and its inhibition of cytochrome P450 enzymes leads to the possibility of many drug interactions. Unwanted effects of these agents include nausea, headache and, more rarely, exfoliative skin lesions and hepatitis.

Viral infections of the respiratory tract

Respiratory syncytial virus (RSV)

Palivizumab: prophylaxis against RSV for at-risk infants can be provided by the humanized, monoclonal anti-IgG antibody, palivizumab. It acts to prevent the entry of RSV into host cells. Unwanted effects following its intramuscular injection include irritation at the injection site, fever and nervousness.

Ribavirin: treatment of RSV infection in infants may involve the administration of ribavirin as an aerosol. The drug may reduce the time for which mechanical ventilation is required, but there is little evidence to suggest that it reduces mortality or respiratory deterioration. Ribavirin is a purine nucleoside analogue. It inhibits a wide range of DNA and RNA viruses by mechanisms that have yet to be elucidated. It is taken up by host cells and converted to the mono-, di- and tri-phosphate derivatives by host cell enzymes. The monophosphate inhibits inosine 5'-phosphate dehydrogenase and interrupts guanosine triphosphate (GTP) synthesis and therefore nucleic acid synthesis. The triphosphate inhibits GTP-dependent 5'-capping of viral mRNA. Ribavirin therefore inhibits RSV by altering cellular nucleotide pools and by inhibiting viral mRNA.

Ribavirin is taken up by cells, therefore its apparent volume of distribution is large. Its binding to plasma proteins is negligible. It is eliminated by metabolism in the liver and by renal excretion as unchanged drug and its metabolites. Unwanted effects of ribavirin administered by aerosol include conjunctival irritation, rash and a transient worsening of pulmonary function; anaemia and haemolysis are less common. Ribavirin is teratogenic, therefore women of child-bearing age should avoid exposure to the aerosol.

Influenza

Vaccination provides the mainstay of prophylaxis against influenza. However, both the type A and the type B influenza viruses are constantly changing their complements of haem-agglutinin and neuraminidase and thus their antigenic properties. It is therefore important to use vaccine that has been prepared against the currently prevalent strain, or strains, of the virus. Such vaccines are recommended for use only in patients judged to be at high risk, including those suffering from chronic respiratory disease, chronic cardiac disease, chronic renal failure or diabetes mellitus. Other at-risk patients include those who are immunocompromised, those over 65 years of age and residents in long-stay homes for the elderly. The preparation of influenza vaccines involves growing the relevant viral strains on the chorioallantoic membranes of hens' eggs and therefore their use is contraindicated in those who are allergic to eggs.

Amantadine may be used as a prophylactic agent in outbreaks of influenza caused by the type A virus but not those caused by the type B virus. Prophylaxis provided by amantadine is reserved for unimmunized patients while their vaccination takes effect. It may also be used for at-risk patients in whom the vaccine is contraindicated or, during epidemics, for protecting essential healthcare workers from infection. In the type A virus, amantadine interferes with the action of viral M_2 protein. This protein acts as an ion channel that is important in the early stages of viral replication and in the budding of new viral particles from the infected host cell. Amantadine thus has dual actions against the type A virus. It is well absorbed from the gastrointestinal tract and has a large apparent volume of distribution. Amantadine is eliminated mainly by excretion unchanged in the urine. Its unwanted effects include dizziness, insomnia and slurred speech.

Zanamivir is a sialic acid derivative that is effective against influenza viruses. However, the National Institute for Clinical Excellence has recommended that it should not be used to treat adult sufferers of influenza who are otherwise healthy. It should be reserved for times when influenza is circulating in the community and then only for at-risk patients who are able to commence treatment within 48 hours of the onset of symptoms. Zanamivir specifically inhibits the neuraminidases of influenza viruses A and B. The budding of new viral particles from the infected host cell is thus prevented and their spread within the respiratory tract is reduced. Zanamivir is administered by inhalation. Its unwanted effects include skin rashes, gastrointestinal disturbances and bronchospasm. It should be administered with caution if there is a history of bronchial asthma or chronic obstructive pulmonary disease.◆

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Pituitary, Adrenal and Thyroid Dysfunction

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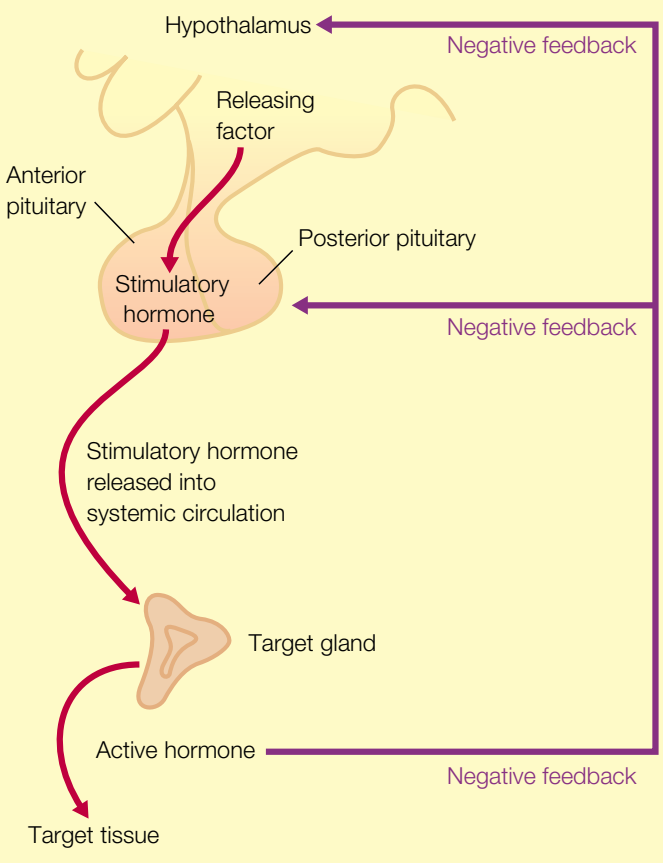
The hypothalamo-pituitary unit

The hypothalamus is located inferior to the thalamus. It synthesizes or regulates all the hormonal products of the pituitary gland. The pituitary releases regulatory hormones controlling a variety of physiological functions including growth, sodium regulation and milk secretion. The pituitary is divided into two distinct regions; the anterior lobe (adenohypophysis or pars distalis) and the posterior lobe (neurohypophysis or pars nervosa). The posterior pituitary stores and secretes oxytocin and vasopressin, which are synthesized in neurons located in the paraventricular and supraoptic nuclei of the hypothalamus. The axons of these neurons pass down the pituitary stalk into the posterior lobe of the pituitary where the peptide hormones are stored. The hypothalamus regulates the anterior pituitary by releasing regulatory factors into the hypothalamo-hypophyseal portal system from where they pass to the anterior lobe.

Feedback loops and dysfunction: regulation of hypothalamo-pituitary function is hierarchical and dependent on feedback loops. A typical stimulatory pathway (Figure 1) involves a releasing factor secreted by the hypothalamus stimulating the anterior pituitary to release a stimulatory hormone into the general circulation where it stimulates the target gland to release the active hormone. Increasing plasma concentrations of this hormone inhibit further secretion of the hypothalamic releasing factor and the stimulatory hormone, restoring the plasma concentration to basal levels. If there is a breakdown in this feedback system, chronic stimulation or inhibition may occur, resulting in unregulated secretion of hormones.

Negative feedback control of hypothalamo-pituitary axis



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Adrenal gland

The two adrenal glands are situated superior to the kidneys. They each weigh 4–5 g and are divided into two distinct regions, the outer cortex which comprises 90% of the gland and the inner medulla. The cortex is responsible for the synthesis of three steroid groups (mineralocorticoids, glucocorticoids, androgens); catecholamines are the main product of the medulla.

The adrenal cortex comprises three zones. The zona glomerulosa, which synthesizes the main mineralocorticoid aldosterone, is the outermost zone. Below that lies the zona fasciculata which secretes the glucocorticoids, primarily cortisol, and then the zona reticularis which secretes androgens (dehydroepiandrosterone and androstenedione). All adrenal steroids are derived from cholesterol and are produced by a series of hydroxylations. The specificity of steroid product in each zone is determined by the presence or absence of hydroxylase enzymes. Thus, cells in the zona glomerulosa that possess 18-hydroxylase are able to convert corticosterone to aldosterone, but lack 17α-hydroxylase, which is essential for the synthesis of cortisol and androgens. Conversely, cells in the fasciculata and reticularis lack 18-hydroxylase and cannot produce aldosterone.

Cortisol synthesis is regulated by corticotrophin releasing hormone (CRH) which stimulates pituitary secretion of adrenocorticotrophin (ACTH), leading to cortisol release. This is pulsatile in nature, reaching a peak in the early hours before waking. ACTH stimulates the rate-limiting conversion of cholesterol to pregnenolone by binding to adrenocortical cells, activating cAMP and phosphoprotein kinases. Aldosterone synthesis is stimulated by high plasma [K^+] and angiotensin II, which stimulates the rate-limiting conversion of cholesterol to pregnenolone and the 18-hydroxylation of corticosterone to aldosterone.

Hydroxylase enzyme deficiency

Defects in hydroxylase enzyme activity lead to metabolic errors in steroid synthesis. There are six categories of congenital adrenal hyperplasia (Figure 2), transmitted by autosomal recessive disorders, which result in low concentrations of cortisol, high concentrations of ACTH and varying degrees of genital ambiguity. In Types I, II and III which are characterized by deficiency of the enzymes 21α-hydroxylase (I and II) and 11β-hydroxylase, steroid synthesis is shifted towards androgen production and as a result girls are born with ambiguous genitalia. In Types IV–VI the defects occur earlier in the synthesis pathway, resulting in a reduction in androgen synthesis and thus female or ambiguous genitalia in boys.

Chromosomal and phenotypic sex mismatch in hydroxylase enzyme deficiency

Enzyme deficiency	21α-hydroxylase		11β-hydroxylase		17α-hydroxylase		3β-hydroxysteroid dehydrogenase		P450 scc side-chain cleavage	
Type	I and II		III		IV		V		VI	
Chromosomal sex	XX	XY	XX	XY	XX	XY	XX	XY	XX	XY
Phenotypic sex	Ambiguous	Male	Ambiguous	Male	Female	Female /ambiguous	Female	Ambiguous	Female	Female

2

Adrenal insufficiency

Addison's disease was first described by Thomas Addison in 1855. This rare condition (39/1,000,000 in the UK) arises through tuberculosis (20%) or autoimmune disease (80%). Clinical features (e.g. tiredness and weakness) are often non-specific, but patients may present with acute features such as shock, malaise, vomiting and postural hypotension. Other features include skin pigmentation (80–90% of cases) caused by excess melatonin or vitiligo (depigmentation in 10–20% of cases). Acute adrenal crisis may occur following infection, trauma, surgery, dehydration owing to lack of salt, vomiting or diarrhoea. Abdominal pain may occur accompanied by weakness, apathy and confusion. Hypotension, shock, fever, vomiting and tachycardia are common; shock and coma may lead to death in untreated cases.

Measurement of plasma cortisol and ACTH, or the cortisol response to ACTH are necessary to diagnose primary adrenal insufficiency. Metyrapone, 2–3 g orally (overnight test) or 750 mg every 4 hours for six doses (3-day test), is used to assess secondary adrenal insufficiency caused by pituitary ACTH deficiency because it blocks the conversion of 11-deoxycortisol to cortisol by inhibiting 11β-hydroxylase, thereby stimulating ACTH by removing negative feedback on the pituitary. ACTH then stimulates an increase in plasma 11-deoxycortisol in normal individuals (> 0.19 μmol/litre the following morning). Treatment includes glucocorticoid replacement therapy (hydrocortisone) in all patients and replacement of mineralocorticoids (9α-fludrocortisone) in some.

Adrenal excess

Hyperaldosteronism: primary hyperaldosteronism (Conn's syndrome) results in excessive aldosterone secretion and accounts for up to 2% of hypertensive cases. In most instances (70%) it arises through a unilateral adenoma, though bilateral hyperplasia of the zona glomerulosa may also be the cause. In both cases the result is severe hypertension and hypokalaemia. Trilostane, which inhibits 3β-hydroxysteroid dehydrogenase/delta 5–6 isomerase, blocks the 3β-dehydrogenation of preg-nenolone to progesterone and 17-hydroxypregnenolone to 17-hydroxyprogesterone, reduces aldosterone production. Secondary hyperaldosteronism arises as a consequence of renal artery stenosis leading to excessive renin secretion and inappropriately high plasma aldosterone concentrations owing to reduced renal blood flow. Angioplasty relieves the stenosis. ACE inhibitors are inadvisable because glomerular filtration is maintained in the affected kidney by high angiotensin II levels.

Cushing's syndrome was first described clinically by Harvey Cushing in 1932. It is a group of related disorders in which there is excessive glucocorticoid secretion. Some are ACTH-dependent while others are ACTH-independent. In the ACTH-dependent forms, which include most spontaneous cases (83%), excessive ACTH secretion either by the pituitary (Cushing's disease is four times more likely in women) or an ectopic tumour (bronchial and gastrointestinal carcinomas, neuroendocrine tumours of pancreatic islets) stimulates the adrenal gland to secrete glucocorticoids. In the ACTH-independent form adenomas (1.5–6 cm) and carcinomas (> 6 cm, usually in children) of the adrenal result in unregulated glucocorticoid secretion. However, the most common cause is the therapeutic (mis)use of synthetic glucocorticoids or ACTH. The glucocorticoids have a variety of permissive roles throughout the body therefore their excess results in many diverse clinical features. These include weight gain, central obesity, 'moon' face, muscle weakness, backache, malaise, depression or psychosis, hirsutism, striae, hypertension and sexual dysfunction.

Diagnosis – the common underlying feature of all forms of Cushing's syndrome is an inappropriately high plasma cortisol concentration. However, a single measurement of plasma cortisol is of little diagnostic value because it has a normal diurnal variation, being higher in the early morning. Cortisol may also be influenced by other factors, including stress, alcohol, depression, obesity and coma. Cushing's syndrome may also be intermittent. A more useful approach is to determine whether the plasma ACTH or plasma cortisol levels can be suppressed by the normal feedback loops.

An initial screening of plasma ACTH differentiates between the dependent and independent forms. Normal plasma ACTH falls in the range 2–11 pmol/litre; in the ACTH-independent form, plasma ACTH is suppressed below 2 pmol/litre, in the ACTH-dependent pituitary form plasma levels are modestly elevated at 4–40 pmol/litre, whereas in ectopic forms the levels may exceed 600 pmol/litre. Further confirmation can be achieved using the dexamethasone suppression test.

In the overnight low-dose test, dexamethasone, 1 mg, is given orally at 11 p.m. and plasma cortisol measured the following morning. Dexamethasone suppresses ACTH therefore this results in a low cortisol level (< 0.137 μmol/litre) in normal individuals, but those with Cushing's syndrome display high levels (> 276 μmol/litre). The 2-day test involves dexamethasone, 0.5 mg orally, administered every 6 hours for 2 days. 24-hour urine samples are collected before dexamethasone and during the second day of treatment. Normal individuals show a sup-pression of urinary 17-hydroxycorticosteroid to less than 10 μmol/24 hours. The high-dose test is useful in differentiating between a pituitary and ectopic source of ACTH. In the single dose form, a baseline plasma cortisol measurement is obtained in the morning, then dexamethasone, 8 mg, is given orally at 11 p.m. followed by a second plasma cortisol sample the following morning. In those with a pituitary tumour (Cushing's disease), plasma cortisol is suppressed by more than 50% whereas those with an ectopic tumour show little or no suppression. In the 2-day test dexamethasone, 2 mg orally, is administered every 6 hours. In most cases, those with a pituitary tumour show more than 50% suppression of urinary 17-hydroxy-corticosteroid while those with an ectopic tumour show little suppression.

Thyroid gland

The normal adult thyroid gland comprises two lobes joined by an isthmus. It originates as an outpouching of the floor of the pharynx, lying over the second and third tracheal rings, and comprises numerous spherical follicles of epithelial cells enclosing a colloid space. Interspersed between follicles are calcitonin-secreting parafollicular or C cells and connective tissue.

The principal hormonal products of the thyroid are tri-iodothyronine (T3) and thyroxine (T4), which are synthesized from tyrosine and iodine (Figure 3). Inorganic iodide is actively transported into the follicular cells where it is oxidized by thyroid peroxidase and linked to tyrosine to form 3-monoiodotyrosine and 3,5-diiodotyrosine. Further oxidation occurs in the colloid space to produce the biologically active 3',3,5-triiodotyrosine (T3) and 3'5',3,5-tetraiodotyrosine (thyroxine, T4). T3 and T4 are stored in the colloid space bound to thyroglobulin before reuptake into the follicular cell by endocytosis, where they are uncoupled from thyroglobulin by proteolysis and released into the circulation. Although both T3 and T4 are synthesized in the thyroid, most circulating T3 is produced by conversion of T4 in the kidney, liver and heart. The circulating concentration of T4 (65–155 nmol/litre) is 50 times that of T3 (1.5–2.9 nmol/litre); both are predominantly bound to the plasma protein thyroxine binding globulin, with 15% bound to albumin.

Physiological actions of T3 and T4

- Fetus – brain and skeletal growth
- Metabolic rate – increases oxygen consumption and heat production via Na^+:K^+-ATPase
- Cardiovascular effects – increases cardiac contractility
- Sympathetic effects – increases cardiac β-adrenergic receptors and decrease α-adrenergic receptors
- Pulmonary effects – maintains hypoxic and hypercapnic drive in respiratory centre
- Gastrointestinal effects – stimulate gut motility
- Skeletal effects – increase bone turnover
- Neuromuscular effects – essential for normal development of the CNS
- Lipid and carbohydrate effects – stimulate gluconeogenesis and glycogenesis
- Endocrine effects – decrease half-life of many hormones (e.g. cortisol) and drugs

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Activity of the thyroid gland is regulated by the hypothalamic thyrotrophin-releasing hormone (TRH) and the anterior pituitary thyroid-stimulating hormone (TSH). TRH is synthesized in the supraoptic and supraventricular nuclei of the hypothalamus and is released into the hypothalamo-hypophyseal portal system in a pulsatile fashion about every 1.8 hours. TRH release is also stimulated by low plasma T3 and T4 concentrations, vasopressin, α-adrenergic catecholamines, exposure to cold (in the newborn); it is inhibited by high plasma T3 and T4 concentrations, α-adrenergic blockers and hypothalamic tumours. TRH stimulates secretion of TSH from the anterior pituitary, which acts as the primary regulator of thyroid function, stimulating thyroid cell growth and changes in morphology, thereby accelerating thyroglobulin resorption (Figure 4). It also increases iodide uptake and metabolism, thyroglobulin mRNA and lysosomal activity releasing free T3 and T4 from thyroglobulin. These actions are mediated via the TSH receptor (TSH-R) which activates both cAMP and phospholipase C. TSH secretion is also stimulated by low T3 concentrations and is inhibited by high T3 and T4 concentrations, somatostatin, dopamine, dopamine agonists (e.g. bromocriptine) and gluco-corticoids. The thyroid hormones exert long-term effects with slow onset owing to their genomic mode of action. T3 is the active form of the hormone; T4 is converted to T3 inside the target cell by 5'-deiodinase where it binds to the T3 receptor that is part of the nuclear receptor family.

Circulating TSH and T4 and the TSH response to TRH administration in hypothyroidism

	Primary hypothyroidism	Secondary hypothyroidism	Hypothalamic hypothyroidism	Non-thyroid origin
TRH	Exaggerated TSH response	No TSH response	Normal or delayed TSH response	Normal or low TSH response
TSH	High	Low	Low	Normal or low
T4	Low	Low	Low	Low

T4, thyroxine; TRH, thyrotrophin-releasing hormone; TSH, thyroid-stimulating hormone

4

Hypothyroidism
Hypothyroidism arises through several mechanisms, including iodine deficiency (the most common cause of goitre), auto-immunity (the most common cause in non-iodine-deficient areas), surgery, radioiodine therapy or excessive iodine intake (e.g. chronic ingestion of proprietary cough medicines). Congenital failure of the hypothalamo–pituitary–thyroid axis is less common (1/4,000 births), but acquired hypothyroidism, especially primary hypothyroidism occurs in 2–4% of women (10 times less common in men).

The symptoms of hypothyroidism in newborns include respiratory difficulty, jaundice, cyanosis, poor feeding and retardation of bone development. In children, the main features are retarded growth and mental development, though precocious puberty may occur. Adults typically show fatigue, cold intolerance, weight gain, constipation and menstrual irregularities. Skin is cool, rough and dry, face and hands are puffy and the voice is hoarse. In severe untreated cases the end-stage is myxoedema coma, which is typified by progressive weakness, hypothermia, hypoventilation, hypoglycaemia, hyponatraemia, shock and death. Coma may be precipitated by heart failure, pneumonia, pulmonary oedema or administration of sedative or narcotic drugs.

Hypothyroidism is treated with levothyroxine (T4) which is readily converted to T3. Doses vary from 0.05 to 0.2 mg/day depending on body weight and age. Myxoedema coma is an acute medical emergency often requiring mechanical ventilation. Levothyroxine is administered intravenously, because of poor absorption in these patients, and adrenal support may also be required in case of autoimmune adrenal disease or pituitary insufficiency.

Hyperthyroidism
Hyperthyroidism occurs in 1.8% of the adult population, mainly in women (10:1). It is usually caused by autoimmune thyroid disease, commonly Graves' disease, though there are other rarer causes. Classical Graves' disease is typified by hyperthyroidism, goitre, eye signs (exophthalmos, lid retraction) and dermopathy (pretibial myxoedema). The cause of autoimmunity in Graves' disease is not fully understood, but there appears to be a familial component. T lymphocytes are sensitized to antigens in the thyroid, stimulating B lymphocytes to synthesize antibodies. Antibodies bind and activate TSH receptors, leading to unregulated production of thyroid hormones. A number of factors have been associated with the onset of autoimmune disease, including pregnancy, iodine excess, lithium therapy, viral or bacterial infection and glucocorticoid withdrawal.

Patients present with palpitations, nervousness, hyperkinesia, diarrhoea, sweating and heat intolerance and eye signs, ranging from little or no effect to loss of sight. Blood analysis reveals high circulating T3 and T4, low TSH and the presence of TSH-R antibodies. Treatment involves the management of the hyperthyroidism, rather than addressing the autoimmune mechanisms. Antithyroid drug therapy is used in younger patients with mild disease. The thioureylenes carbimazole, propylthiouracil or methimazole (not licensed in the UK) are given orally until the disease goes into remission, but this may take 15 years, and relapse is common (60–80%). Their mode of action is unclear, but they are thought to inhibit the iodination of tyrosyl residues in thyroglobulin. An alternative approach is to block thyroid activity with methimazole and then replace levothyroxine until the gland has returned to normal size. This results in long-term remission in up to 80% of cases. In patients with large glands, subtotal thyroidectomy may be used or radioactive iodine administered. ^{131}I emits β-particles and γ-rays, the former causing localized cytotoxicity when taken up into the thyroid gland, thereby selectively destroying thyroid cells and reducing gland mass. ◆

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Plasma Expanders

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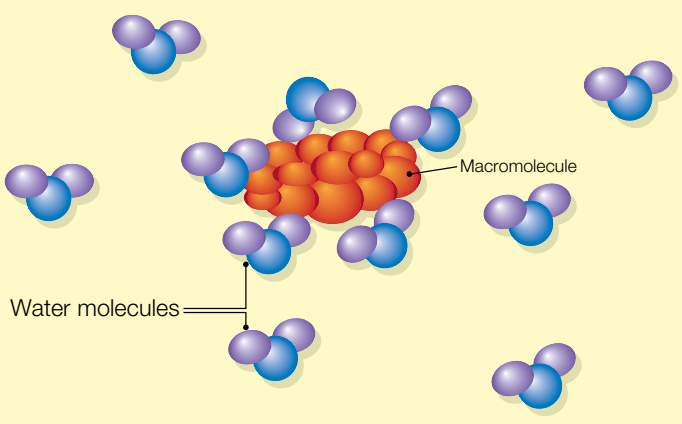
Provided capillary permeability is normal, colloidal solutions containing albumin, dextrans, gelatins or hydroxyethylated starch may be used as plasma expanders.

A colloid is defined as a solution containing large organic molecules dispersed in a solution. Organic molecules that contain polar covalent bonds attract a sphere of water molecules around them that hold them in solution (Figure 1). A colloid differs from a suspension in that the molecules remain in solution and do not settle out due to the force of gravity. A colloidal solution exerts a colloid osmotic pressure when in contact with a semipermeable membrane tending to draw fluid into the colloidal solution. When rehydration therapy is required, the advantages of using colloidal solutions over crystalloid (salts) solutions are that the volume infused is smaller, there is a prolonged increase in plasma volume and peripheral oedema is minimal. However, colloids are more expensive, have less effect in increasing urinary flow and are less effective in restoring interstitial volume. The relative merits of various fluid therapies during and after anaesthesia are more pertinent to clinical practice than to pharmacology.

Water associated with a macromolecule to form a colloidal solution



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Human albumin

Albumin is a protein (molecular weight 65 kDa), the main function of which in the blood is to maintain the colloid osmotic pressure of about 25 mm Hg. It is prepared from human plasma and is available as a concentrate containing 15–25% total protein or as an isotonic solution containing 4–5% protein. A stabilizer such as sodium caprylate may be included, but no antibacterial agent is present. It is sterilized by filtration and heated at 60°C for 10 hours. The latter reduces the risk of viral transmission. All commercially available solutions and those supplied by blood banks have been incubated and checked for microbial contamination before delivery. Human albumin is used to replace plasma volume and to restore colloid osmotic pressure in acute hypovolaemic shock, burns and other conditions associated with albumin loss. Side-effects are rare, but include allergic reaction such as anaphylactic shock. Human albumin is generally more expensive than other plasma expanders and recent evidence suggests that the use of albumin rather than other plasma expanders is not associated with better survival or change in morbidity.

Dextrans

Dextrans are polysaccharides produced by bacteria (usually *Leuconostoc mesenteroides*) growing on a sucrose substrate. All dextrans are composed of a-D-glucopyranosyl units and differ only in chain length or degree of branching. Hydrolysis and fractionation of the native dextrans produced by the bacteria result in dextrans containing different average molecular weights. The two used most commonly are dextran 40 (average molecular weight 40 kDa) and dextran 70 (average molecular weight 70 kDa). The former is infused as a 10% solution and the latter as a 5.5–6.5% solution.

The colloidal osmotic pressure of dextran 70 is similar to plasma, while dextran 40 exerts a greater osmotic pressure, thus drawing more extracellular fluid into the circulation. However, this effect is short lived and must be balanced against the greater incidence of renal complications. 70% of dextran 40 is rapidly excreted via the kidney and if urine flow is reduced the high urinary concentration of dextran can increase urinary viscosity inducing oliguria or renal failure. This problem is less with dextran 70, which is only 50% excreted unchanged. The remainder of both dextrans is metabolized to glucose.

Dextrans are used in the treatment of hypovolaemic shock and for improving circulatory flow to minimize thromboembolic disorders postoperatively. They have some antithrombotic effects that seldom cause a problem unless the patient has a clotting factor deficit. Hypersensitivity reactions to dextrans (e.g. fever, joint pain, urticaria, hypotension, bronchospasm) have been reported occasionally; severe hypersensitivity reactions are rare.

Gelatin solutions

Gelatin is a purified protein obtained from hydrolysis of animal collagen. The three groups commonly used as plasma expanders are oxypolygelatin, urea-linked gelatin (polygeline *Haemaccel*) and modified fluid (succinylated) gelatins. The average molecular weight is 30–35 kDa and thus gelatins remain in the circulation for a shorter time than dextrans. Gelatin solutions are used to treat hypovolaemic shock. In general, side-effects are few and there is little effect on platelet function, thus making gelatins safer than dextrans for patients with haematological deficits.

Intravenous preparations of polygeline contain calcium ions and are incompatible with citrated blood. They should be used with caution in patients being treated with cardiac glycosides. As with other plasma expanders, hypersensitivity reactions have been reported. At one time they were thought to be more common with polygeline solution, but the removal of excess hexa-methylene di-isocyanate remaining from the manufacturing process seems to have reduced this problem.

The possibility that such preparations may be contaminated with prion proteins from cattle suffering from bovine spongiform encephalopathy has caused some concern.

Hydroxyethylated starch

The branched component of starch, amylopectin, was originally studied as a potential plasma expander because its close structural relationship to glycogen should ensure its non-toxicity. Unfortunately, the rapid breakdown of amylopectin by plasma amylase to small easily excreted pieces meant that the persistence of the compound in the plasma was too short for a useful clinical effect. However, reducing the number of bonds available for hydrolysis by amylase allowed amylopectin derivatives to persist for a longer period of time in the plasma.

Hydroxyethyl starch is an example of such a product and it is prepared by treating starch with pyrimidine and ethylene chlorohydrin. The exact composition of this starch derivative has not been determined, but it contains 90% amylopectin in which 7–8 of the OH groups found in 10 glucopyranosyl units are esterified with CH_2CH_2OH. There are two preparations, hetastarch (molecular weight 450 kDa) and pentastarch (molecular weight 250 kDa) of which the former is more often used. Hetastarch is broken down relatively slowly by α-amylase in the blood and the kidney excretes the smaller molecules. Hypersensitivity reactions have been reported, but there is some evidence that the incidence is lower than with other plasma expanders. Hetastarch has little effect on blood coagulation though there is a reduction in factor VIII; an effect that is less likely with pentastarch. Figure 2 gives the intravascular half-lives of plasma expanders. ◆

Colloidal solutions used as plasma expanders

Colloid	Composition	Intravascular half-life (hours)
Albumin	Protein	> 24
Dextran 40	Polysaccharide	2–3
Dextran 70	Polysaccharide	6–12
Gelatin	Protein	< 4
Hetastarch	Amylopectin derivative	> 24
Pentastarch	Amylopectin derivative	10
Polygeline	Protein	< 4

2

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Premedication

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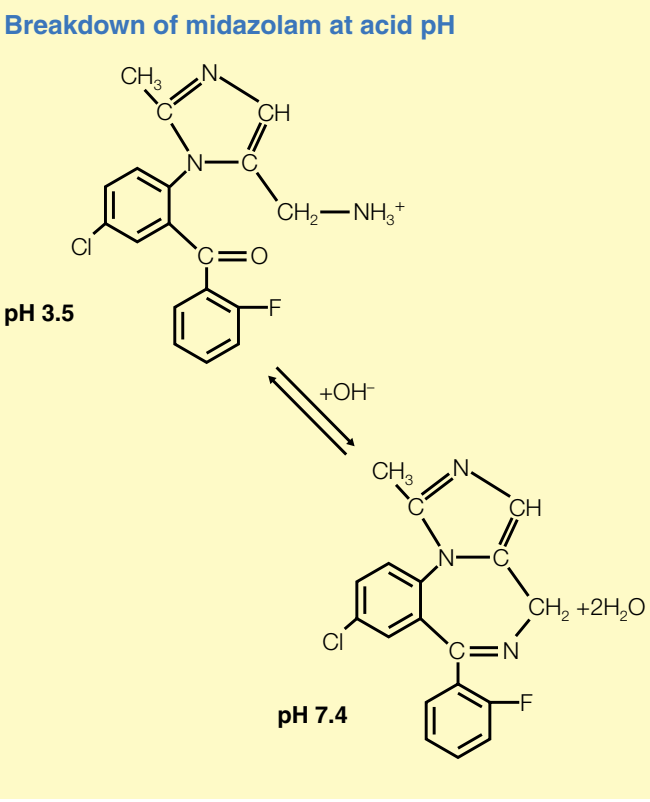
Clinical aspects of premedication are discussed in **CLINICAL ANAESTHESIA**. The present article concentrates on the pharmacology of the drugs used.

Anxiolytics and sedatives

The basic pharmacology of anxiolytics and sedatives is discussed on page 233. The agents selected from this group for use in premedication are the benzodiazepines with a relatively short duration of action such as temazepam and midazolam. Occasionally a longer acting drug (e.g. diazepam) is selected for procedures in which long duration of sedation is required. All these agents potentiate γ-aminobutyric acid (GABA) transmission through $GABA_A$ receptors by an action at a distinct binding site separate from that which binds GABA. The benzodiazepines used in premedication have no selectivity for the various subtypes of benzodiazepine receptors discussed elsewhere.

Midazolam is unusual in that it is soluble in acidified water because its lipid-soluble ring structure breaks down at acid pH (Figure 1). This simplifies intravenous administration, which does not require the solvents or emulsions needed with other parenteral benzodiazepines. In addition, it has a short half-life of less than 3 hours. Midazolam is metabolized to α-hydroxymidazolam, which has pharmacological activity. After intravenous administration this metabolite has a negligible role in the action of the drug but, after oral administration, the first-pass metabolism of the drug in the liver, may lead to a significant build-up of the active metabolite.

Breakdown of midazolam at acid pH



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Temazepam (half-life 4−10 hours) is available for administration only by mouth as either a tablet or an elixir. It is often listed as not having an active metabolite but it can be demethylated to oxazepam though this is a minor pathway and does not contribute greatly to the drug's activity.

Lorazepam (half-life 8−12 hours) can cause profound anterograde amnesia. It is not considered to have an active metabolite.

Anti-emetic drugs

The anatomy and physiology of vomiting has been relatively little studied. The vomiting reflex protects the body from ingested toxins that have not been detected by sight, taste or smell. Irritation or distention of the upper gastrointestinal tract (in particular distention of the duodenum) may also induce nausea and vomiting. Thus, vagal and, to a lesser extent, sympathetic afferent impulses travelling from the gastrointestinal tract to the vomiting or emetic centre can induce vomiting. These afferent impulses are initiated by mechanoreceptors that detect distention or mucosal chemoreceptors that detect acids, alkalis, irritants and probably bacterial toxins. Induction of vomiting, for example with cytotoxic drugs, is associated with mucosal damage and the liberation of 5-HT from the enterochromaffin cells. The released 5-HT probably stimulates the vagal afferent nerves by interaction with a $5\text{-}HT_3$ receptor. Substance P released from the gastric mucosa acts on tachykinin NK_1 receptors and may function cooperatively with 5-HT (acting on $5\text{-}HT_3$ receptors) in the upper gastrointestinal tract to induce vomiting.

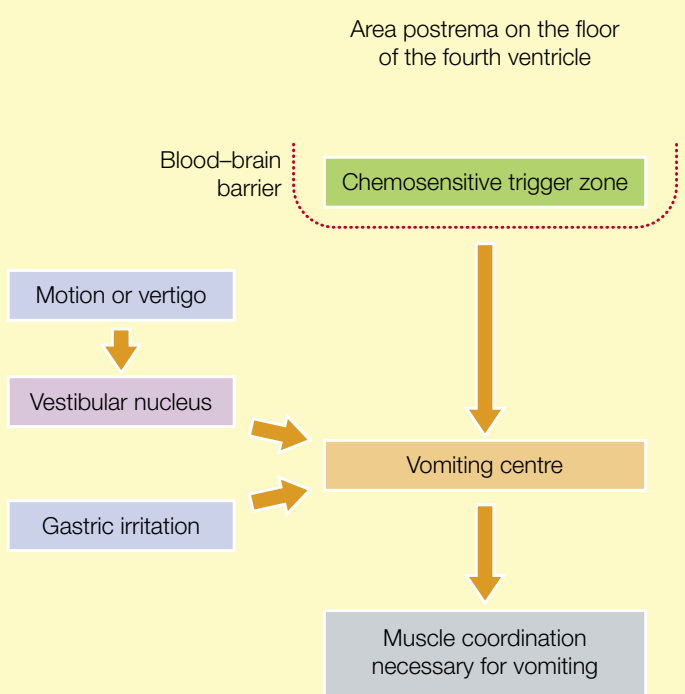
Vomiting can also be induced by chemicals carried in the blood, which are detected by the chemosensitive trigger zone in the area postrema on the caudal floor of the fourth ventricle (Figure 2). From a pharmacological point of view it is interesting and exploitable that the chemosensitive trigger zone is functionally outside the blood−brain barrier. Animal studies have shown that the area postrema contains high concentrations of $5\text{-}HT_3$, dopamine (D_2) and opioid receptors. In humans, drugs acting as agonists at these receptors cause nausea and vomiting. Antagonists at $5\text{-}HT_3$ and D_2 receptors are effective anti-emetic agents, but opioid antagonists are not.

Motion sickness involves the vestibular system and labyrinthine stimulation enhances the emetic effects of other vomiting triggers. Muscarinic cholinergic and histamine H_1 receptors are present in the vestibular nuclei.

Both the vestibular system and the chemosensitive trigger zone send impulses to the vomiting centre that initiate the sequence of smooth and skeletal muscle contraction associated with vomiting. The vomiting centre is a physiological rather than an anatomical structure but is found close to the area postrema. Both muscarinic cholinergic and histamine H_1-receptors are found in this area. Vomiting can also occur as a result of inputs from higher centres such as the limbic system though the mechanisms are uncertain.

The receptors involved in emesis and useful anti-emetic drugs are summarized in Figure 3.

Induction of vomiting



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Neurotransmitters involved in nausea and vomiting

Vomiting trigger	Neurotransmitter	Receptors involved	Anti-emetic drugs
Irritation and/or distention of the gastrointestinal tract	5-HT	$5\text{-}HT_3$	Ondansetron, granisetron
Toxins and chemicals acting on the chemosensitive trigger zone	Dopamine	D_2	Droperidol, domperidone, prochlorperazine, perphenazine, metoclopramide
	5-HT	$5\text{-}HT_3$	Ondansetron, granisetron
Motion on vestibular nuclei	Acetylcholine	Muscarinic	Hyoscine, atropine
	Histamine	H_1	Cyclizine, promethazine
Input directly to vomiting centre	Acetylcholine	Muscarinic	Hyoscine, atropine,
	Histamine	H_1	Cyclizine promethazine

3

Anti-emetic drugs in anaesthesia

The mechanism by which postoperative nausea and vomiting (PONV) occurs is unclear and almost certainly multifactorial. The risk factors for PONV are given in **PERIOPERATIVE CARE**. There are no animal models of PONV, therefore drug treatment has been restricted to trials of agents that are effective anti-emetics in other situations, rather than a rational design of drugs based on an understanding of the condition.

Dopamine receptor antagonists

Dopamine is involved in emesis and dopamine antagonists are effective anti-emetics. Most dopamine antagonists (e.g. droperidol) have no selectivity for the dopamine receptors in the chemosensitive trigger zone. By their action on dopaminergic systems in other part of the brain, dopamine antagonists also produce hyperprolactinaemia and extrapyramidal motor disturbances similar to Parkinson's disease. An exception is domperidone, which is less likely to cross the blood−brain barrier than other agents, and thus is less prone to, but not free from, extrapyramidal actions. There is some debate concerning the effectiveness of domperidone in PONV. There are also reports of severe cardiac arrhythmias after large doses, which resulted in the withdrawal of the parenteral preparation. These three factors have caused a loss of interest in domperidone from an anaesthetic point of view. Interestingly, despite its adverse effects, droperidol is still the standard anti-emetic with which others are compared.

Metoclopramide and domperidone have additional prokinetic activity (enhanced gastric and upper intestinal motility) that may contribute to their anti-emetic effects. The prokinetic action has been attributed to an agonist action of metoclopramide on $5\text{-}HT_4$ receptors. In addition, metoclopramide has some $5\text{-}HT_3$ antagonistic effects at higher doses.

Dopamine antagonists are not useful for motion sickness unless they have coincident muscarinic cholinoceptor antagonist properties.

Muscarinic cholinoceptor antagonists

In the treatment of PONV, the muscarinic receptors present in the vomiting centre are an important target. Two muscarinic antagonists (hyoscine, atropine) are used as anti-emetics in anaesthesia. Both are lipid soluble and penetrate the brain to reach the vomiting centre. Intramuscular hyoscine is more effective as an anti-emetic than intramuscular atropine but is associated with increased drowsiness and delayed recovery from anaesthesia. In order to increase its duration of action, hyoscine has also been used as a transdermal preparation. The patch needs to be applied several hours before the emetic stimulus to enable an adequate plasma concentration to be obtained. Several authors have demonstrated the efficacy of transdermal hyoscine in PONV, but others have failed to detect a significant difference from placebo. Negative results were more likely when the duration of patch application was short or additional premedication drug administration was uncontrolled. Muscarinic receptors are found in the periphery, associated with the effector organs of the parasympathetic nervous system. Thus, typical anti-muscarinic adverse effects such as dry mouth and blurred vision are common, though not usually serious.

Histamine H_1-receptor antagonists

Histamine H_1 and muscarinic receptors are present in both the vomiting centre and the vestibular nucleus. The antihistamine drugs used to treat nausea and vomiting also have additional anti-muscarinic activity, therefore it is unclear which property is more important regarding their anti-emetic action. Cyclizine has been used to treat PONV and most reports demonstrate efficacy with few side-effects such as sedation. Promethazine is a markedly sedative drug and has been used by anaesthetists to premedicate children, but whether this is for its sedative effect or anti-emetic effect is debatable. Oral dimenhydrinate given at least 1 hour before surgery has also been used to prevent PONV. Second-generation antihistamines (e.g. terfenadine, astemizole) are ineffective anti-emetics because they do not cross the blood−brain barrier. Neither muscarinic antagonist nor antihistaminic drugs are useful in treating emesis due to chemotherapy.

5-HT$_3$ receptor antagonists

5-HT is released by cytotoxic agents and contributes to nausea and vomiting by actions in the gastrointestinal tract and the brain. In addition, dopamine antagonists may be ineffective in the severe emesis induced by chemotherapy. These observations prompted the successful trial of 5-HT$_3$ antagonists (e.g. ondansetron) in chemotherapy-induced emesis. Subsequently, oral ondansetron was found to be effective in PONV, which has been confirmed, using the oral and intravenous route. Generally the adverse effects of ondansetron were mild with no signs of the extrapyramidal symptoms or dry mouth seen with alternative anti-emetics. Granisetron is also effective in PONV but other 5-HT$_3$ antagonists (e.g. dolasetron, tropisetron) have been used successfully only in the treatment of patients given emetogenic chemotherapy.

Comparative studies between individual 5-HT$_3$ antagonists in PONV have not been carried out, but there are some reports of comparisons with other anti-emetics; recent examples involving intravenous ondansetron are summarized in Figure 4.

Most clinical trials involving ondansetron used single doses and the equivalence of the dose of comparator may be questioned. However, in general, the 5-HT$_3$ antagonists appear to be more effective and to exhibit fewer adverse effects than alternative anti-emetics used for PONV. The cost of treating all patients at risk of PONV with these relatively new agents must be considered.

Comparisons between intravenous ondansetron and other anti-emetics for postoperative nausea and vomiting

Comparator (intravenous)	Surgery	Result
• Metoclopramide	Laparoscopic	Ondansetron superior to metoclopramide in cholecystectomy females (males showed little nausea or vomiting)
• Dimenhydrinate	Adenotonsillectomy	42% of children vomited with ondansetron compared with 79% with dimenhydrinate
• Droperidol	Laparoscopy	Both drugs equally effective in preventing nausea, though ondansetron slightly superior in preventing vomiting
• Droperidol	Strabismus surgery	Ondansetron and droperidol were equally effective and better than metoclopramide in decreasing pre-discharge vomiting but none were effective in decreasing post-discharge vomiting

4

Other anti-emetics

Although the glucocorticosteroids and the cannabinoid nabilone have been used as anti-emetics for cancer chemotherapy, they have not been used extensively in anaesthesia. The intravenous anaesthetic propofol has also been used to treat PONV in a patient-controlled trial. Although sedation could be a problem if the dose was too high, moderate doses were effective and, when compared with placebo, shortened the stay in the post-anaesthetic care unit.

Anti-muscarinic drugs

When anaesthetic drugs included diethyl ether (which produced copious bronchial and salivary secretions) and cyclopropane (which caused cardiac slowing) premedication with an antagonist at muscarinic cholinoceptors was considered essential. Now that these drugs are seldom administered, the rationale for routine anti-muscarinic premedication has gone. However, the drugs are still sometimes used for specific indications, such as procedures causing excessive parasympathetic stimulation (e.g. haemorrhoidectomy) and for patients with obstructive airway disease. Typical pharmacological effects of antagonists at the muscarinic receptors for acetylcholine are listed in Figure 5. The mechanism of the sedative effects of hyoscine with low doses is unknown as higher doses have similar excitatory effects as atropine. Glycopyrronium is a quaternary compound that does not penetrate the CNS and thus is devoid of CNS actions.

Effects of muscarinic antagonists

Inhibition of secretions:
- dry mouth and skin

Relaxation of:
- bronchial muscle
- biliary tract
- bladder and urinary tract (possibility of urinary retention)

Reduction of intestinal motility

Tachycardia (low doses of atropine can cause bradycardia by a central action)

Mydriasis

Cycloplegia

CNS actions:
- anti-emetic
- sedation (hyoscine)
- excitation (atropine)
- inhibition of the symptoms of Parkinson's disease

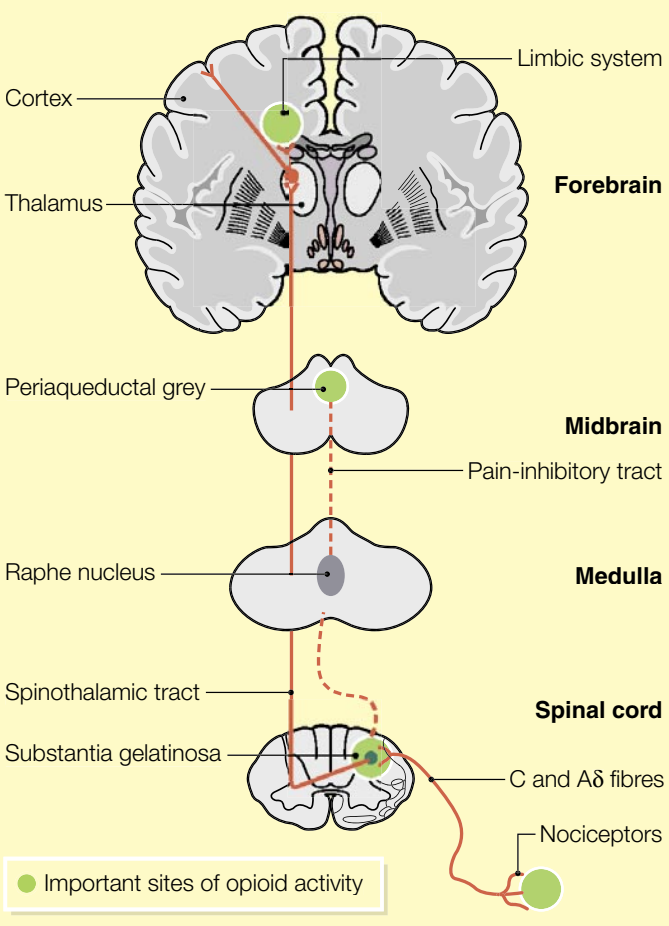
5

Analgesic drugs

The use of analgesic drugs as premedication in patients with preoperative pain is accepted, but their use as prophylactic (or pre-emptive) treatment for postoperative pain is more controversial. Opioids, non steroidal anti-inflammatory drugs (NSAIDs) and paracetamol have all been used for both purposes. Opioids mimic the actions of the endogenous opioid peptides acting on μ opioid receptors at various sites in the pain pathway (Figure 6) while NSAIDs and paracetamol inhibit the cyclo-oxygenase enzyme responsible for prostaglandin formation from arachidonic acid. In the periphery, prostaglandins sensitize nociceptors to pain mediators such as 5-HT and bradykinin. Within the spinal cord, prostaglandins enhance nociceptive processes and within the cerebral blood vessels they cause vasodilatation which leads to headache (Figure 7).

There is no evidence that the prophylactic use of NSAIDs or paracetamol has any beneficial effect though a reduction in subsequent postoperative opioid requirements has been reported. Pre-emptive opioid administration has been useful in some trials, but the trial designs were not perfect and more information is required before recommendations can be made.

Sites of opioid activity



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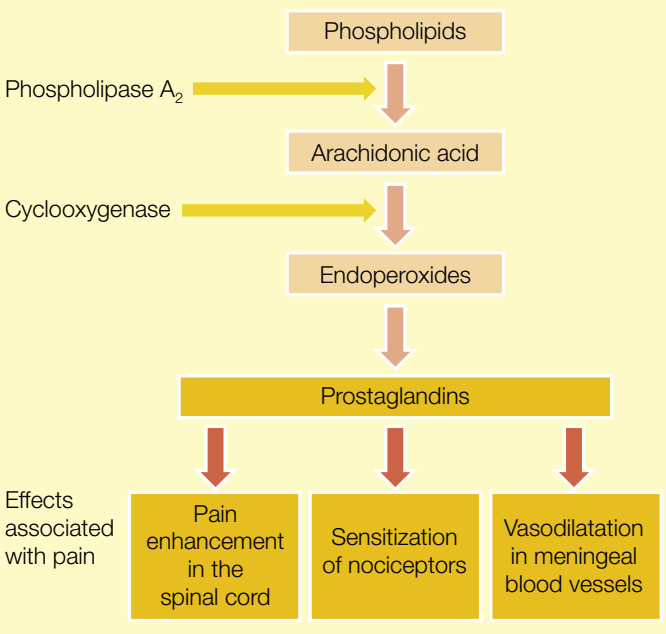
Action of prostaglandins



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Clonidine

Clonidine is a α_2-adrenoceptor agonist that has been used to lower blood pressure via inhibition of noradrenaline release (peripheral presynaptic action) and inhibition of sympathetic outflow (central action). Sedation has always been a consistent side-effect of the antihypertensive action of this class of drugs and anaesthetists needing to reduce anaesthetic requirements have exploited this property. Clonidine also has useful analgesic activity by mimicking the action of noradrenaline released in the dorsal horn of the spinal cord by the descending inhibitory pain pathways (Figure 6).

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Receptors, Agonists and Antagonists

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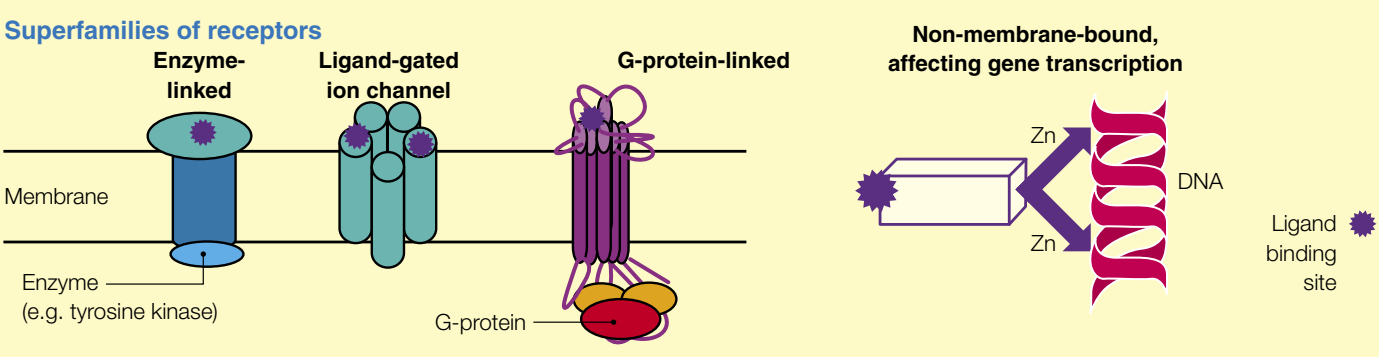
An understanding of the pharmacological basis of drug action can provide a scientific framework for therapeutic use. The molecular mechanism of a drug often explains its effect and the magnitude and timing of its action.

Drug receptors

Different types of drug receptors are shown in Figure 1.



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Ion channels

Cell plasma membranes contain ligand-gated and voltage-gated ion channels. At the neuromuscular junction, acetylcholine, and its structural analogue suxamethonium, bind to the nicotinic receptor, which is part of the sodium channel. Interaction of the drug with its receptor causes a conformational change, opening the channel, allowing influx of sodium ions into the skeletal muscle cells and triggering contraction. This explains why the onset of action of suxamethonium is rapid once it has reached its site of action.

Other drugs act on voltage-gated ion channels, examples are local anaesthetics acting on sodium channels in neurons and calcium channel blockers (e.g. nifedipine) acting on smooth and cardiac muscle. The pharmacology of drugs acting on both types of ion channels is described on page 324.

G-protein-linked receptors

Receptors linked by guanosine-binding proteins (G-proteins) to either ion channels or enzymes are also important for drug action. Salbutamol interacts with β-adrenoceptors to activate the enzyme adenylyl cyclase indirectly, thus increasing the conversion of adenosine triphosphate (ATP) to the second messenger cyclic adenosine monophosphate (cAMP), which in turn phosphorylates many key intracellular proteins resulting, for example, in bronchial relaxation. The muscarinic receptor for acetylcholine in the heart is linked via G-proteins to a potassium channel, opening of which causes bradycardia. This triggering of a biochemical cascade or indirect opening of an ion channel occurs within seconds so the onset of drug action by this type of mechanism is usually rapid. Many drugs have G-protein-coupled receptors as their site of action.

The existence of G-proteins was deduced when it was observed that stimulation of second messenger systems, such as adenylyl cyclase, required the receptor agonist and the presence of guanosine triphosphate (GTP). The G-protein was found to be three different proteins joined together, a heterotrimer, with subunits called α, β and γ, in order of decreasing molecular weight. An agonist–receptor complex causes a conformation change in the intracellular domain of the receptor to a form that has high affinity for the G-protein, which is freely diffusible in the plane of the cell membrane. The process of binding of the receptor to the G-protein catalyses the dissociation of guanosine diphosphate from the α subunit of the G-protein and it is exchanged for intracellular GTP, which causes dissociation of the α subunit from the β and γ subunits. The latter two proteins originally appeared to be involved in anchoring the protein to the plasma membrane but subsequent studies have suggested an independent signal transduction role. The
α subunit modulates the action of a given effector, which is not always adenylyl cyclase. The α subunit has GTPase activity and converts GTP to GDP followed by reassociation with the other two subunits and the cessation of the signal. In its resting state the G-protein complex is not associated with any particular receptor and can interact with several different receptors and effectors.

Many variants of the α, β and γ subunits have been described and the number is growing. Two bacterial toxins (pertussis and cholera) have been useful in distinguishing the type of G-protein involved in a particular situation. Cholera toxin causes persistent activation of the G-protein (Gs), which stimulates adenylyl cyclase causing the excessive secretion of fluid from the gastrointestinal epithelium characteristic of cholera. Pertussis toxin has no effect on Gs but prevents the actions of other G-proteins such as Gi, which inhibits adenylyl cyclase activity. Several other G-proteins are inhibited by pertussis toxin and thus its functional effects are less obviously explicable in terms of G-protein inhibition.

G-protein effectors

Adenylyl cyclase
Stimulated by Gs
Inhibited by Gi
Produces second messenger cAMP

Guanylyl cyclase
Produces second messenger cGMP

Phospholipase C
Activated by Gq
Produces second messengers inositol 1,4,5,-triphosphate (IP_3) and diacylglycerol (DAG)

Phospholipase A_2
Produces second messenger arachidonic acid

Ion channels
Particularly Ca^{2+}, Na^+ and K^+

2

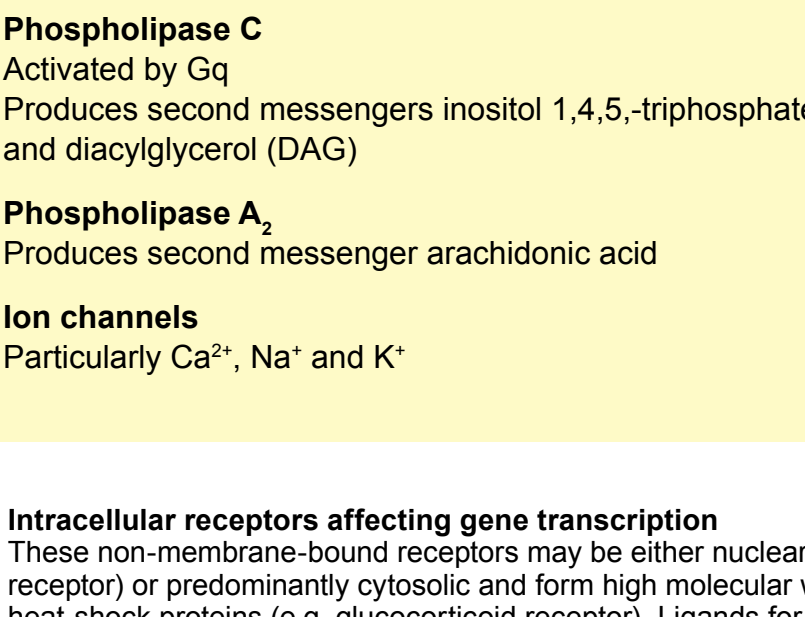
Intracellular receptors affecting gene transcription

These non-membrane-bound receptors may be either nuclear (e.g. thyroid hormone receptor) or predominantly cytosolic and form high molecular weight complexes with heat-shock proteins (e.g. glucocorticoid receptor). Ligands for these receptors must be lipid soluble and pass into the cell. The presence of a ligand leads to the dissociation of the receptor from the heat-shock proteins and the receptor−ligand complex moves into the nucleus. The binding of the ligand to the receptor results in an uncurling of the receptor protein to reveal the DNA binding domain. The DNA binding domain consists of two ‘zinc fingers’ which contain cysteine residues surrounding a zinc atom. These fingers are thought to wrap round the DNA helix at hormone-responsive elements in the strand. An increase in RNA polymerase activity and the production of a specific mRNA occurs and protein production is enhanced. A well-documented example is the increase in lipocortin production induced by glucocorticoid drugs. This sequence of events is relatively slow, thus the time to onset of action of drugs acting via this mechanism is measured in hours or days.

Agonists

An agonist is a drug that interacts with a receptor and induces changes in cellular activity, which may be excitatory (e.g. salbutamol inducing tachycardia) or inhibitory (e.g. salbutamol producing bronchial relaxation). The magnitude of response to an agonist is usually proportional to the fraction of receptors occupied and therefore the shape of the concentration–response curve commonly follows a hyperbola (Figure 3). If this relationship is expressed as response *versus* log of concentration a sigmoidal curve is usually seen (Figure 4). Agonists have the ability to bind to receptors (affinity) and once bound the ability to induce responses (intrinsic efficacy).

Hyperbolic concentration–response curve for a typical drug



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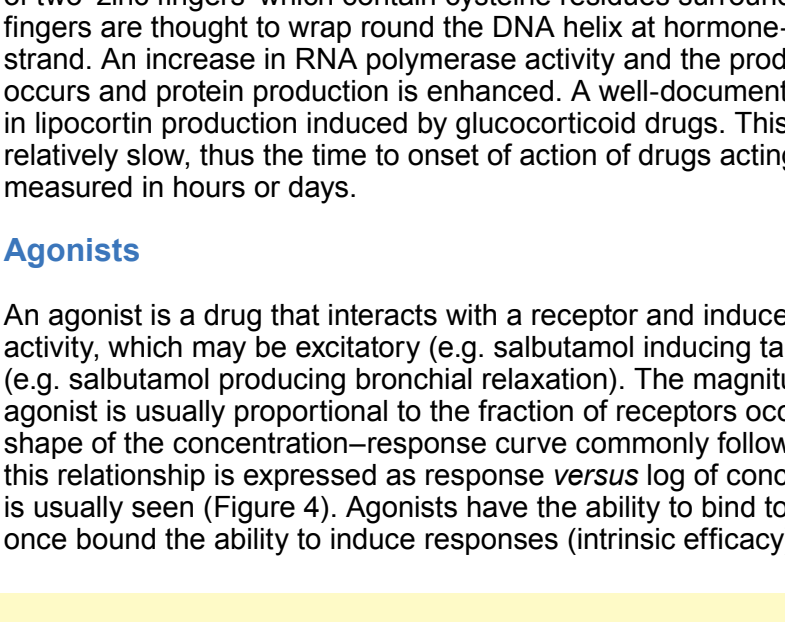
Sigmoidal log concentration–response curve for a typical drug



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Antagonism

Antagonism broadly describes the situation when the pharm-acological effect of two drugs is less than the sum of their individual effects. Some of the methods of drug antagonism are described below.

Chemical antagonism

This uncommon type of antagonism occurs when one drug chemically interacts with a second drug and reduces the effect of the second drug. An example is the ability of desferrioxamine to reduce the toxicity caused by the iron from ferrous sulphate tablets. Desferrioxamine, by chelating the iron, enhances its removal from the body and reduces toxicity.

Pharmacokinetic antagonism

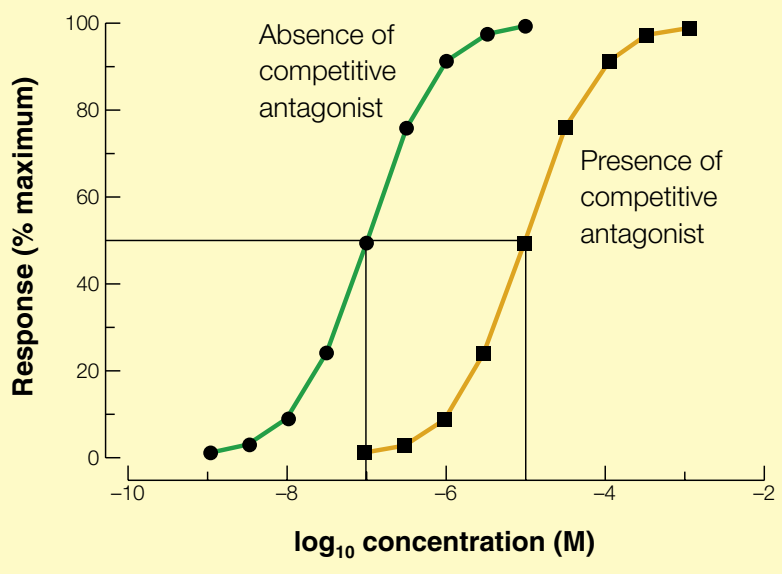
With pharmacokinetic antagonism, one drug alters the handling by the body of the second drug, reducing the effect of the latter. One example is the ability of rifampicin (used to treat tuberculosis) to enhance the liver metabolism of drugs such as ethinyloestradiol (a component of the oral contraceptive pill) reducing the steady-state concentration of ethinyloestradiol.

Pharmacodynamic antagonism

Pharmacodynamic antagonism can occur at a common receptor or at different receptors.

Common receptor: in practice, the most important type of antagonism is where an antagonist interacts with the same receptor as an agonist. Most of these drugs are competitive antagonists. When the antagonist binds to the receptor, it does not induce a response but prevents the binding, and hence action, of the agonist. The competitive antagonist has affinity but no intrinsic efficacy. Competitive antagonists do not form strong bonds with the receptor proteins and their effects are reversible on removal from the site of action. If the concentration of the agonist is sufficient a response is observed even in the presence of a competitive antagonist. The consequence of this interaction is that the log concentration–response curve is shifted to the right (Figure 5).

Log concentration–response curve for an agonist



5

The pharmaceutical industry has been successful in developing chemical analogues that are competitive antagonists of naturally occurring agonists. Examples are promethazine and ranitidine at histamine H_1- and H_2-receptors, respectively, propranolol at β-adrenoceptors, losartan at angiotensin receptors, naloxone at opioid receptors and atracurium at nicotinic acetylcholine receptors. Therapeutically competitive antagonists are used for their ability to reduce the effects of endogenously released agonists.

Some antagonists form strong, usually covalent, bonds with the receptor. They are known as non-equilibrium antagonists because the degree of antagonism increases with time and does not come to equilibrium, unlike competitive antagonists. Their effect is not readily reversible for the same reason. Often they are called non-competitive antagonists but that termin-ology is incorrect because they do compete with agonists for binding to receptors. An example of such an antagonist is phenoxybenzamine, which is a non-equilibrium antagonist at α-adrenoceptors.

Different receptor: antagonism can be produced even if the two drugs interact with different receptors. For example, high doses of nicotine act at peripheral ganglia to release noradrenaline from postsynaptic nerve endings and induce, say, tachycardia via β-adrenoceptors in the sino-atrial node. Propranolol would be able to reduce the effect of nicotine by acting as an antagonist at the β-adrenoceptors. This type of antagonism is indirect because the antagonist and agonist do not interact with the same site.

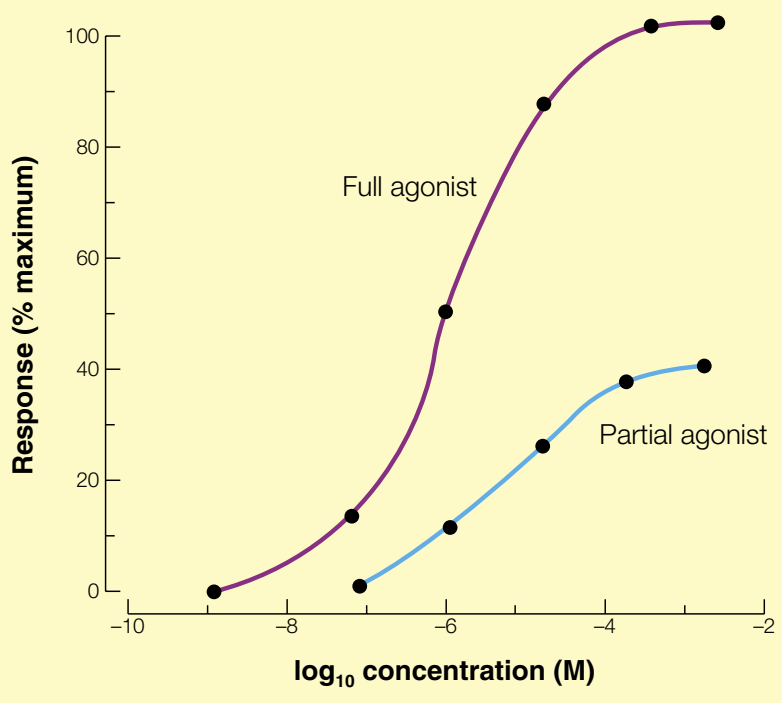
Antagonism can occur between two agonists and is called functional or physiological antagonism. For example, the agonist histamine will produce bronchoconstriction by acting as an agonist at histamine H_1-receptors while salbutamol will induce bronchodilatation as an agonist at β_2-adrenoceptors. If the two drugs are given in combination, the total effect they produce is less than the sum of their individual effects − the definition of antagonism.

Partial agonist and inverse agonists

A partial agonist has the properties of both agonists and competitive antagonists. When given alone, such compounds exhibit agonist properties but their maximal effect is less than that of a full agonist (Figure 6). When given with a full agonist, partial agonists reduce the effects of the full agonist. Partial agonists thus have affinity for receptors and some intrinsic efficacy but less than that of full agonists. Examples are buprenorphine at opioid receptors and alprenolol at β-adrenoceptors.

Recent years have seen the development of inverse agonists. In some artificial systems using G-protein-coupled receptors activity can be observed in the absence of agonist (constitutive activity). An inverse agonist is able to reduce the continuing activity in this system by interacting with the receptor and is described as having negative intrinsic efficacy. Some benzodiazepines are inverse agonists. Inverse agonists have therapeutic potential if there are pathophysiological situations where such constitutive activity occurs, but this awaits future research.

Log concentration–response curve for a full and a partial agonist



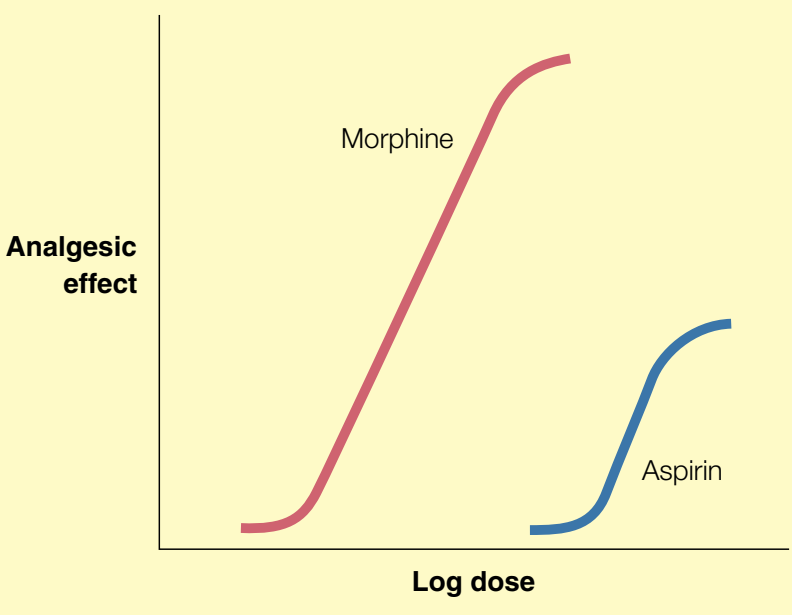
6

Potency, relative potency and maximum effect

The properties of many drugs are independent of their mechanism of action and there are useful descriptors to enable one drug to be compared with another. For most drugs, the relationship between response and concentration is hyperbolic (Figure 3). From such a curve the effective concentration producing 50% of maximal response (EC_{50}) can be determined. The potency of a drug is the reciprocal of the EC_{50} and therefore a drug that produces an effect at low concentrations is potent. If the effect is measured *in vivo* then dose substitutes for concentration. As explained above, such data are often expressed as response *versus* log concentration (or dose). It is then easy to compare the potencies of two drugs in terms of their log relative potencies, which can be antiloged to give their relative potencies.

Not all drugs have the same maximal effect on a system. Figure 7 illustrates the pain relief that might be induced by morphine and aspirin. Morphine is more potent (less drug is needed for a similar effect) and has a greater maximal effect than aspirin.

Log dose–response curves for two drugs illustrating the difference in their maximal effects



7

FURTHER READING

Foster R W. *Basic Pharmacology.* Oxford: Butterworth-Heinemann, 1996.

Rang H P, Dale M M, Ritter R M. *Pharmacology.* Edinburgh: Churchill Livingstone, 1999.

Computer-assisted learning packages:
Drug targets suite of programmes from the British Pharmacological Society, http://www.bps.ac.uk – deals with molecular mechanisms of action.
Experiments on the isolated guinea pig ileum from the Pharmacy Consortium http://www.coacs.com – deals with agonists, antagonism and antagonists.

Regulation of Drug Licensing

Rachel M Morten

Rachel M Morten is a Regulatory Affairs Consultant. She has worked in regulatory affairs for over 18 years and set up ChapelPharma in 1995. Typical projects have included licence maintenance, Marketing Authorizations and orphan drug applications for products in many therapeutic areas. Her principal interest is in new product development.

The drug licensing laws govern all aspects of pharmaceutical products. They cover not only the conduct of clinical trials, research and the approval of new Marketing Authorizations, but the control of a medicinal product throughout its marketed life. This includes the changes that may be made to the formulation, packaging or indications, and also the pharmacovigilance of the product. All of these activities aim to ensure the safety of the product to the patient and to those who administer it. This article introduces the legislation that affects product labelling, the conduct of clinical trials and pharmacovigilance.

The need for controls over pharmaceutical products was highlighted by the thalidomide tragedy in the 1960s. This prompted the introduction in the UK of the Medicines Act in 1968, which although now influenced by decisions made at a European level, is still in existence today.

At about the same time, the European Community was established to promote the economic and political integration of its Member States. The main objective of the now enlarged European Union is to establish a common market that allows free movement of goods, people, services and capital.

Pharmaceutical products are not exempt from this harmonization and are governed by many European laws that are incorporated into each Member State's national legislation.

European legislation

The two types of European legislation that have a legal basis are Regulations and Directives (Figure 1). They are supplemented by guidance documents and Points for Consideration.

Figure 2 lists the main legislation that governs the regulatory approval and sale of pharmaceutical products in Europe.

European legislation

Regulations
Cover European policy and procedural issues. European Member States must abide by every aspect of a Regulation

Directives
Cover issues such as the content of a Marketing Authorization Application (MAA), the procedure for MAAs, labelling, distribution, pharmacovigilance and manufacturing controls. The Member States must incorporate the laws into their own national legislation, but interpretation of the Directives depends on each Member State (which is why there still appear to be national differences)

Guidelines
Provide scientific guidance on, for example, the design and type of studies that are required to support an MAA. They have no legal basis. However, failure to follow a particular guideline would need to be justified in the MAA

Points for Consideration
Points that applicants should consider when conducting studies to support the MAA. They have no legal basis. They are often introduced when new issues arise that Regulatory Authorities feel should be addressed (e.g. Points to Consider for new Anti-Fungal Agents for Invasive Fungal Infections, which was released for consultation in July 2002)

As time goes on and more experience is gained, it is usual for the Points for Consideration document to be fleshed out into a more formal Guideline

1

Legislation governing the regulatory approval and sale of pharmaceutical products in Europe

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

- Council Regulation (EEC) No 2309/93, of 22 July 1993, laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. (Amended by Commission Regulation (EC) No 649/98 of 23 March 1998 amending the Annex to Council Regulation (EEC) No 2309/93)

These documents can be accessed electronically at http://pharmacos.eudra.org/F2/eudralex

2

Summary of product characteristics

It is a requirement of Directive 2001/83/EC that all Marketing Authorization Applications include a proposed Summary of Product Characteristics (SmPC).

The SmPC is the basis on which the Patient Information Leaflet and all labelling is based. Once approved, products must be used only for the indications and the patient population included on the label. Physicians using products outside the terms of their Marketing Authorization take full responsibility for the patient's safety.

At the start of any new product development, the first question that should be asked by the project team is 'What profile do we want the product to have?' Without answering this question, it is difficult to ensure that the development work is focused and that clinical trials will support the desired indication. The easiest way to begin thinking about this is to prepare a draft SmPC.

The statements in the SmPC must be supported by the clinical, preclinical and formulation studies that are undertaken during the product's development.

When the commercial need for a product is identified, it is the proposed indication on the SmPC that must drive the clinical development programme. For example, if a product is indicated for use in chronic pain, it is necessary to provide clinical data that show a statistically significant improvement in patients with chronic pain. Providing data on patients with acute pain may provide some supportive data but would not be sufficient to obtain approval of a Marketing Authorization.

Conducting clinical trials

Before 1992 there was no harmonization in Europe for the approval to conduct clinical trials. Each European country had its own legislation and *modus operandi*. The only harmonization was the need for all trials to be conducted to Good Clinical Practice as noted in Annex 1 of Directive 2001/83/EC and Guideline ICH E6 (CPMP/1CH/135/95). On 1 May 2001 the Clinical Trial Directive was published (Directive 2001/20/EC). This came into effect on 1 May 2003, when all Member States should have incorporated the terms of the Directive into their own national legislation. However, application will now be delayed until May 2004.

This Directive standardizes the rules for obtaining clinical trial authorizations in all Member States. This Directive has introduced several changes, including the following.

- The need for approval before all trials can begin (Phases I–IV). This has been a major change for the UK because previously trials in healthy subjects (most Phase I) were exempt from the need for a Clinical Trial Approval.
- A standardization of the documentation needed for submission to the regulatory authorities and ethics committees. In the UK, the simplified DDX (Doctors and Dentists Exemption) application process ceases to exist. All applications for investigational use must include the same documentation and follow the same procedure.
- A standard time to approval of 30 days, extendable to 60 days for a clinical trial application, with only a single clock stop permitted to ask questions (the approval time can be extended by 30 or 90 days for biotech products and there is no limit for gene and cell therapy products). In the UK, this could be longer than the CTX (Clinical Trial Exemption) approval time, which was
32 days. However, the MHRA (Medicines and Healthcare products Regulatory Agency) has indicated that it will review
Phase I trial applications in an average of 14 days and no later than 21 days.
- Clinical trial material must be manufactured to standards of Good Manufacturing Practice (GMP). However, there is unlikely to be a need for a Manufacturer's Licence or a Qualified Person to cover reconstitution and packaging of clinical trial material by a hospital pharmacist.
- The introduction of inspections to ensure compliance with Good Clinical Practice (GCP) and Good Manufacturing Practice.

In addition to the Clinical Trial Directive, there are (at the time of writing) 12 detailed guidelines covering all aspects of clinical trials. These guidelines are another step towards harmonizing the standard of many activities associated with conducting clinical trials. Copies of these can be found at http://pharmacos.eudra.org/F2/pharmacos/docs.html.

Pharmacovigilance

During the clinical trials of a new product, and post marketing, the need for monitoring the side-effects of the product are paramount. Pharmacovigilance is the term used to describe all of the activities surrounding the diagnosis, assessment and reporting of adverse events.

Physicians should be aware of the definition of an adverse event/reaction and serious adverse events/reactions. These are given in Annex 1 of Directive 2001/20/EC. The reporting times following occurrence of serious adverse reactions are also clearly defined in Article 17 of the Directive. These are 7 days for serious unexpected reactions that are fatal or life-threatening and 15 days for all other suspected serious unexpected adverse reactions. ◆

Supplementary Drugs in Anaesthesia

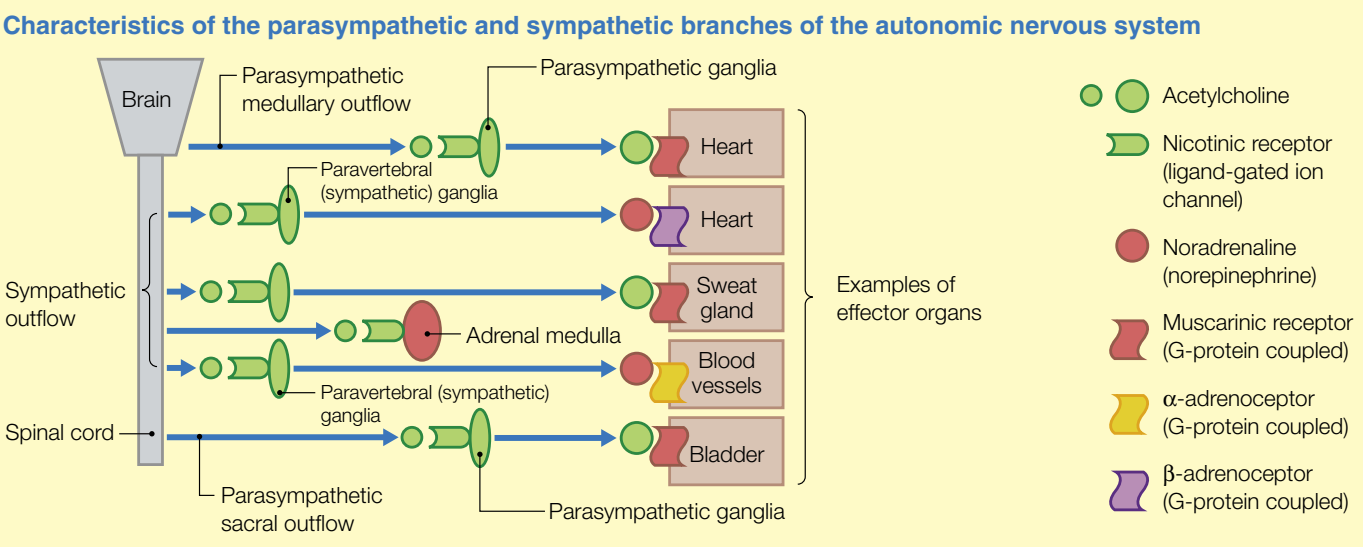
Barbara J Pleuvry

Barbara J Pleuvry is Senior Lecturer in Anaesthesia and Pharmacology at the University of Manchester, UK. Her research interests include pain, analgesia and anticonvulsant drugs.

Many supplementary drugs are given as part of a general anaes-thetic regimen. The hypnotics and sedatives are discussed in **PHARMACOLOGY**. This article deals with the drugs affecting the autonomic nervous system that are given before, during and after the anaesthetic agent.

The autonomic nervous system consists of the parasym-pathetic and sympathetic branches, and most pharmacological discussions concentrate on the efferent outflows of these two systems. The characteristics of these pathways are shown in Figure 1. In contrast to the somatic efferent pathways, in which a single motor neuron connects to the ventral horn of the spinal cord, the autonomic efferent pathway has two neurons that synapse at ganglia. In the case of the sympathetic nervous system, these ganglia lie close to the spinal cord in the paravertebral chain such that the pre-ganglionic fibre is short and the post-ganglionic fibre is long. The ganglia of the parasympathetic nervous system lie on or close to their effector organs so that the post-ganglionic neuron is short.

Characteristics of the parasympathetic and sympathetic branches of the autonomic nervous system



1

Cholinergic neurotransmission in the autonomic nervous system

Acetylcholine (ACh), interacting with nicotinic receptors (Figure 2), is the neurotransmitter at all autonomic ganglia. Thus drugs that stimulate or block these receptors do not differentiate between the sympathetic and parasympathetic ganglia. Nicotinic receptors are also found at the motor end-plate of skeletal muscle, but the molecular characteristics of the two receptors are different such that some nicotinic agonists and antagonists can have selectivity for the autonomic ganglia over the neuromuscular junction.

Actions of acetylcholine at nicotinic receptors

Stimulation of sympathetic and parasympathetic ganglia

- Increased blood pressure
- Tachycardia
- Variable effects on gastrointestinal motility
- Increased secretions
- Bladder contraction

Stimulation of skeletal muscle enabling movement

2

Trimetaphan
A number of fairly selective ganglion blockers have been developed, but only trimetaphan still has significant use in anaesthesia. Trimetaphan is used to induce controlled hypotension in surgery. Its mechanism of action involves ganglion blockade (inhibiting the sympathetic tone maintaining blood pressure), release of histamine to cause peripheral vasodilatation and a direct vasodilator effect. The principal advantage of trimetaphan over other ganglion-blocking agents is that it is short acting and can be given as an infusion to provide fine control of blood pressure. The effects of ganglion blockade on other effector systems depend on the dominant autonomic tone (sympathetic or parasympathetic; Figure 3).

Effect of ganglion blockade in a fit young adult

Effector	Predominant tone	Effect of ganglion blockade
Arteries	Sympathetic (noradrenaline; norepinephrine)	Vasodilatation
Veins	Sympathetic (noradrenaline; norepinephrine)	Vasodilation
Ciliary muscle	Parasympathetic (acetylcholine)	Cycloplegia
Iris		Parasympathetic
(acetylcholine)	Mydriasis	
Heart	Parasympathetic (acetylcholine)	Tachycardia
Gastrointestinal tract	Parasympathetic (acetylcholine)	Constipation
Salivary gland	Parasympathetic (acetylcholine)	Dry mouth (xerostomia)
Sweat glands	Sympathetic (acetylcholine)	Dry skin (anhidrosis)

3

ACh interacts with G-protein-coupled muscarinic receptors on parasympathetic effector systems and some sympathetic effector systems, such as the sweat glands (Figure 4). Five subtypes of muscarinic receptor (M_1–M_5) have been identified. Their physiological role is uncertain and they will be alluded to only when selective agonists or antagonists have a clinical efficacy. Pirenzepine, for example, is an antagonist with selectivity for M_1 receptors and is used to inhibit gastric secretion in the treatment or prevention of gastric ulcers. Agonists at muscarinic receptors have limited use in anaesthesia, but muscarinic antagonists are used in premedication (see Anaesthesia and Intensive Care Medicine 2:6: 245), during surgery to reverse bradycardia and in conjunction with neostigmine during reversal of neuromuscular blockade.

Actions mediated by acetylcholine acting on muscarinic receptors in the autonomic nervous system

- Bradycardia
- Decreased cardiac output
- Vasodilatation (via release of nitric oxide)
- Contraction of smooth muscle
  - Bronchi
  - Intestine
  - Bladder
- Stimulation of exocrine glands
  - Salivation
  - Lacrimation
  - Sweating
  - Bronchial secretion
- Miosis
- Contraction of ciliary muscle (accommodation of the eye)

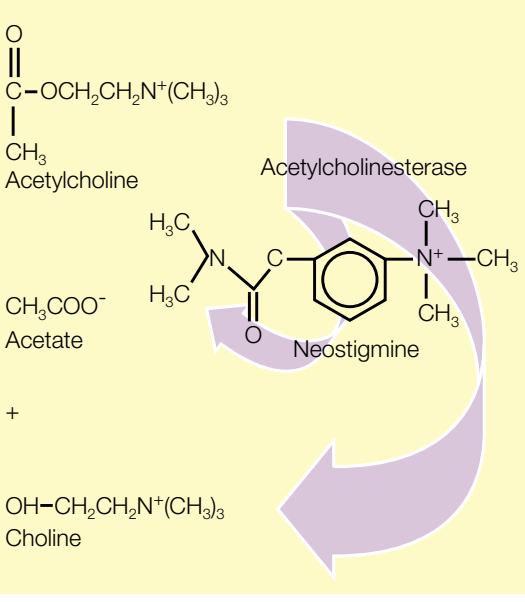
4

Anticholinesterase agents
The action of ACh is terminated by metabolism to choline and acetate by acetylcholinesterase (Figure 5). Acetylcholinesterase has two distinct active sites, an anionic site that attracts cationic groups and an esteratic site that produces catalytic hydrolyses of susceptible esters. In the case of ACh, acetate is removed from the molecule and temporarily transferred to a serine-OH group present on the enzyme. Choline is freed and the serine acetyl group is rapidly hydrolysed.

Neostigmine is an inhibitor of acetylcholinesterase. Like ACh it binds to both the anionic and esteratic sites on the acetyl-cholinesterase molecule but instead of an acetyl group it has a carbamyl group (Figure 5). The carbamyl group is transferred to the serine residues, but it only slowly hydrolyses from the enzyme, resulting in a relatively long inhibition of the enzyme.

Edrophonium is a very short-acting anticholinesterase agent. It is a quaternary ammonium compound that binds only to the anionic site of the enzyme and is thus readily reversible. Its major clinical use is for the diagnosis of myasthenia gravis, but it has been used in anaesthesia as an alternative to neostigmine. When reversing neuromuscular blockade, anticholinesterase agents preserve the action of ACh at the neuromuscular junction, thus antagonizing the competitive blockade of nicotinic receptors by neuromuscular blocking agents (see page 281). Unfortunately, ACh is also preserved at muscarinic sites and this could lead to excessive activation of the receptors with resultant bradycardia. This is prevented by the co-administration of a muscarinic antagonist, usually atropine. Atropine reverses all of the muscarinic effects of ACh listed in Figure 4. Glycopyrrolate is sometimes used as an alternative to atropine because it is devoid of CNS effects and its placental transfer is minimal. In addition, it has less effect on heart rate and pupil size.

Metabolism of acetylcholine



5

Adrenergic neurotransmission in the autonomic nervous system

Many drugs in this group are used to modulate myocardial function, vascular resistance and blood pressure, and some aspects of their pharmacology are discussed in **PHARMACOLOGY**. The neurotransmitter used at most sympathetic effector organs is noradrenaline (norepinephrine). Exceptions to this are ACh released at the sweat glands and possibly in skeletal muscle blood vessels and noradrenaline (norepinephrine) released from the adrenal medulla. The major subdivisions of the α- and β-adrenoceptors, and the principal pharmacological effects of their stimulation relevant to the autonomic nervous system are shown in Figure 6.

Sympathomimetic drugs
Both noradrenaline (norepinephrine) and adrenaline (epi-nephrine) act on all adrenoceptors, though noradrenaline (nor-epinephrine) has more activity on α-receptors than adrenaline (epinephrine). This means that intravenous administration of noradrenaline (norepinephrine) results in a decrease in heart rate. This is caused by the baroreceptor reflex response to the increase in blood pressure that occurs as a consequence of intense α-receptor-induced vasoconstriction increasing peripheral resistance. Adrenaline (epinephrine), in contrast, causes vasoconstriction, some vasodilation in skeletal muscle blood vessels and a moderate increase in heart rate.

Monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) (Figure 7) break down, both noradrenaline (norepi-nephrine) and adrenaline (epinephrine) so that their plasma elimination half-life ($t_{1/2}$) is a matter of minutes. More prolonged α-adrenoceptor stimulation can be achieved with a non-selective α-adrenoceptor agonist, such as methoxamine. Clonidine is usually used in anaesthesia for its sedative, general anaesthetic-sparing and analgesic effects that are mediated by α_2-adrenoceptor activation in the CNS. In the periphery, by reducing noradrenaline (norepinephrine) release via an action on presynaptic receptors, clonidine has been used as an antihypertensive agent, but is usually considered to be too long acting to be used for this purpose in anaesthesia.

Hypotensive complications in obstetric anaesthesia may be treated with ephedrine. This drug has direct effects on β- and β-adrenoceptors, and releases noradrenaline (norepinephrine) from sympathetic nerve endings. This combination of effects is less likely (than α-adrenoceptor agonists) to reduce placental perfusion and thus preserves fetal oxygenation. However, it does cross the placental barrier and the blood–brain barrier in the mother where it has an amphetamine-like effect.

Dopamine is another agent that combines β- and β-adrenoceptor stimulation. In addition, it causes renal and mesenteric vasodilatation by an action on dopamine (D_1) receptors in the vasculature. Its major use in anaesthesia is as an inotrope in low cardiac output states. Similarly, dobutamine (a β_1-selective agonist) and dopexamine (a β_2- and D_1-receptor agonist) are mainly used as inotropic agents.

Adrenoceptors

α_1-receptor

Principal responses to stimulation	**Selective agonist**
Contraction of smooth muscle in: • blood vessels • bronchi • gastrointestinal tract and bladder • sphincters • uterus • radial muscle of iris	Phenylephrine **Selective antagonist** Prazosin
Relaxation of smooth muscle in: • gastrointestinal tract	

α_2-receptor

Principal responses to stimulation	**Selective agonist**
Contraction of smooth muscle in blood vessels	Clonidine Dexmedetomidine
Decreased release of noradrenaline (norepinephrine) and acetylcholine	**Selective antagonist** Yohimbine[1]

β_1-receptor

Principal responses to stimulation	**Selective agonist**
Increase in: • heart rate • force of cardiac contraction	Dobutamine, Xamoterol **Selective antagonist** Atenolol
Increased release of noradrenaline (norepinephrine)	

β_2-receptor

Principal responses to stimulation	**Selective agonist**
• blood vessels • bronchi • gastrointestinal tract • bladder • radial muscles of iris	Salbutamol **Selective antagonist** Butoxamine[1]
Tremor and increased skeletal muscle mass Glycogenolysis	

β_3-receptor

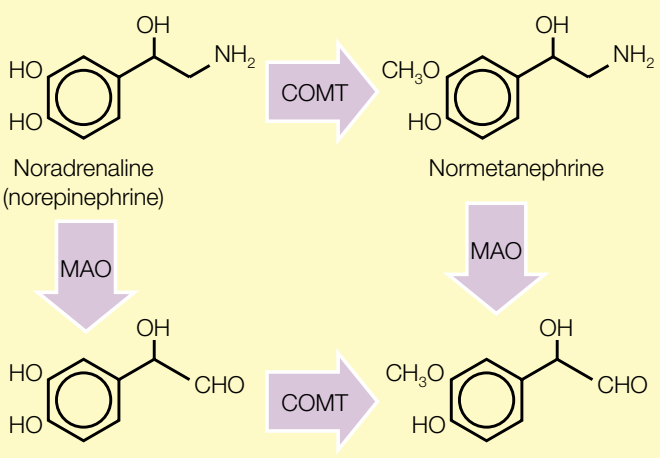
Principal responses to stimulation

Thermogenesis
Lipolysis

[1] Not clinically available.

6

Action of monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT)



7

Drugs that block adrenoceptors

The selective α_1-adrenoceptor antagonist prazosin, and the selective and non-selective β-adrenoceptor antagonists are mainly used for the treatment of chronic hypertension. As supplementary drugs used in anaesthesia, β-adrenoceptor antagonists are mainly used to treat cardiac dysrhythmias associated with dental extractions, cardiac or vascular procedures, thyroidectomy and the removal of phaeochromocytoma. The various agents are compared in Figure 8. Additional properties, such as sodium channel blockade (local anaesthetic actions) or potassium channel blockade, may contribute to the anti-dysrhythmic actions of some agents. Typical adverse effects of excessive dosage are bradyarrhythmias and hypotension.

Comparison of β-adrenoceptor antagonists

Drug	Receptor	Local selectivity	Partial anaesthetic action	Comments agonist action
Atenolol	β_1	No	No	Does not penetrate to the CNS
Esmolol	β_1	No	No	Rapidly metabolized by esterases in RBCs
Oxprenolol	β_1, β_2	Yes	Yes	CNS actions: euphoria and vivid dreams. Partial agonists should cause cardiac failure, but clinical evidence is equivocal
Propranolo	β_1, β_2	Yes	No	CNS actions: euphoria and vivid dreams
Sotalol	β_1, β_2	No	No	Racemic mixture that also blocks potassium channels

8

FURTHER READING

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Therapeutic Problems of Solid Organ Transplantation

Marc J Clancy

Marc J Clancy is a Specialist Registrar specializing in transplant surgery on the Northwest Regional Rotation. He graduated from Cambridge and Oxford Universities and trained at the Royal Free Hospital, London. He is a lecturer at the University of Manchester with research interests in chronic rejection and alternative forms of renal replacement therapy.

Solid organ transplantation provides an effective treatment for organ failure incompatible with life. This comes at the price of immunosuppression and a variety of potential complications, each presenting its own diagnostic and therapeutic problems.

Donor management: most transplant organs come from donors diagnosed with brainstem death. The autonomic, metabolic and endocrine changes induced by brainstem death produce a state of extreme cardiovascular instability. Up to 25% of potential organs are unusable owing to sudden hypotension or cardiac arrest. Meticulous donor care has benefits that are discernible many years after transplantation. The main components of organ maintenance therapy are:

- monitored fluid therapy
- inotropes
- vasopressors
- levothyroxine
- steroids
- insulin/dextrose infusion.

Problems common to all visceral transplants

Hyperacute rejection

Hyperacute rejection is a rapid reaction of pre-existing antibodies in the recipient plasma to antigens on the transplanted organ. It occurs within minutes to hours of surgery and leads to rapid thrombosis of supplying vessels with graft loss. This cross-reactivity can be identified by a transplant 'cross-match' in which donor cells and recipient serum are mixed and stimulation assayed. A positive cross-match indicates sensitization of the recipient to donor tissue, resulting from previous transfusion, transplant or pregnancy. In such cases, the risk of hyperacute rejection is sufficiently high that it is regarded as a contra-indication for kidney transplantation.

Acute rejection

Immediately the transplanted organ is perfused by recipient blood, the recipient immune system recognizes it as foreign. Within days of transplantation an acute inflammatory infiltrate, consisting predominantly of T cells, invades the allograft. This leads to tissue damage and graft hypofunction and without treatment would usually proceed to graft loss. Only if the graft is not recognized as foreign (e.g. a kidney from an identical twin) would this process not occur. In the early years of clinical transplantation, acute rejection was the major therapeutic barrier to a successful outcome. In the 1970s, up to 50% of transplanted kidneys were lost within 1 year largely through acute rejection. Most centres now report at least 85% 1-year survival rates.

Ciclosporin (cyclosporin) was developed in Cambridge in the late 1970s. Before then, the main agents used to treat rejection were glucocorticosteroids, azathioprine and antilymphocyte sera produced in animals. These agents still have a role, but the mainstay of immunosuppressive regimens is ciclosporin (cyclosporin). This cyclical fungal peptide is thought to act by inhibition of calcineurin, leading to decreased transcription of the cytokine genes mediating acute rejection. In the mid-1990s, tacrolimus (FK506/prograf) was introduced as an alternative to ciclosporin (cyclosporin). It is thought to work via a similar mechanism and has similar side-effects. Some units have adopted it as a baseline immunosuppressive. Recently, mycophenolate mofetil (MMF) and rapamycin (sirolimus) have been used but any advantage they have is unproven.

Most transplants are between non-identical people, therefore acute rejection is assumed and a baseline immunosuppressive protocol is used. Typically this involves monotherapy (with ciclosporin (cyclosporin) or FK506) or 'triple therapy' with a lower dose of one of the former plus a daily dose of glucocorticosteroid and azathioprine. The incidence of histological (subclinical) acute rejection in the first 3 months after kidney transplantation is about 30% with ciclosporin (cyclosporin) and less than 5% with FK506.

Immunosuppressive treatment reduces the frequency of clinically significant rejection episodes. However, the powerful immunological rejection process breaks through regularly and further treatment is required to restore or maintain graft function. In kidney transplantation, a rise in serum creatinine can indicate acute rejection. After the exclusion of other causes, which often requires a biopsy, a 'pulse' of glucocorticosteroids, 0.5 or 1 g/day i.v. for 3 days, is normally given. In acute cellular rejection of a liver transplant for example, a glucocorticosteroid pulse resolves about 75% of acute rejection episodes. In severe glucocorticosteroid-resistant rejection, a further therapeutic option is the use of an antilymphocyte globulin. This treatment requires careful monitoring of T cell levels and produces severe immunosuppression. Patients are usually nursed in isolation. Changing the baseline immunosuppressive from ciclosporin (cyclosporin) to FK506 is also effective in some cases of refractory rejection.

Infections

Immunosuppressive treatment leads to an increased incidence of most common infections. Patients also become susceptible to opportunist infections including cytomegalovirus (CMV) and *Pneumocystis carinii*.

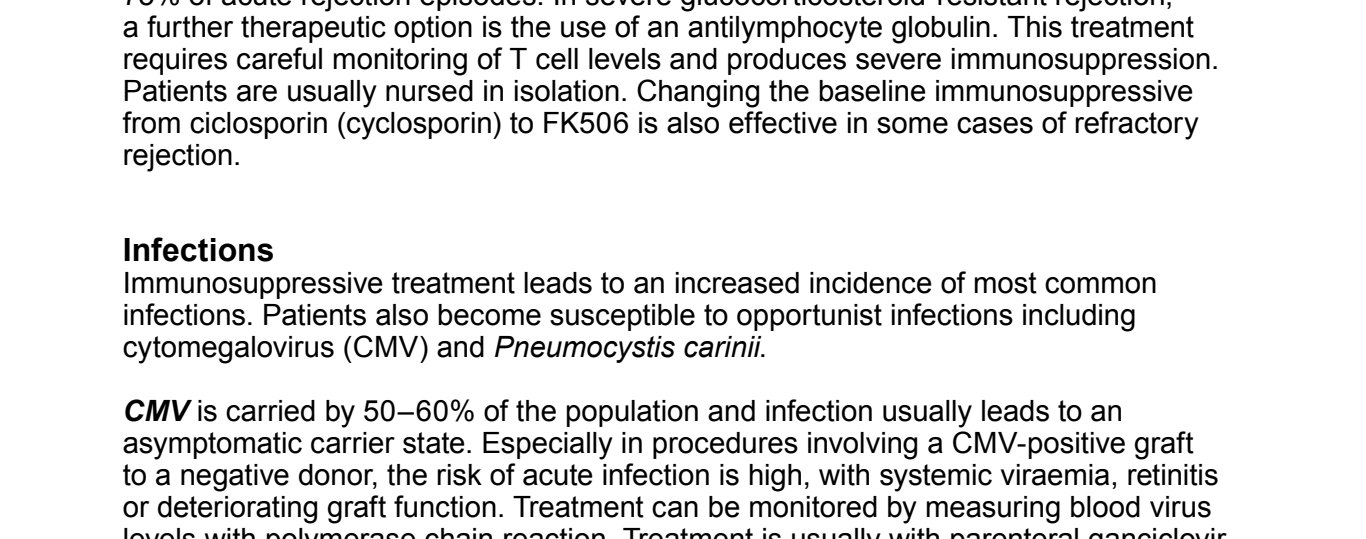
CMV is carried by 50–60% of the population and infection usually leads to an asymptomatic carrier state. Especially in procedures involving a CMV-positive graft to a negative donor, the risk of acute infection is high, with systemic viraemia, retinitis or deteriorating graft function. Treatment can be monitored by measuring blood virus levels with polymerase chain reaction. Treatment is usually with parenteral ganciclovir (gancyclovir) but oral antiviral preparations and prophylaxis have a role.

P. carinii pneumonia is an infrequent cause of respiratory infection in transplant patients. If prophylaxis is not given, there is a 5% incidence of pneumonia due to *P. carinii*. Acute pneumonia usually responds to a combination of trimethoprim (sulfamethoxazole (sulphamethoxazole) and cotrimoxazole). Many patients receive this as prophylaxis and in kidney transplants it is also prophylaxis against most urinary pathogens. Sensitivity to the sulphonamide component is common and aerosolized pentamidine is the second-line therapy.

Papilloma virus – cutaneous warts are a common complication of the long-term immunosuppression needed for a successful graft. Standard topical treatment or cryotherapy may not be sufficient and extensive areas of infection often require surgery.

Chronic rejection

Most episodes of acute rejection are rapidly resolved, but there is a steady loss of transplants with time. The most significant cause in all organs is a chronic fibrotic process affecting the graft and its vasculature (Figure 1). This is commonly called chronic rejection but is better termed chronic transplant vasculopathy in the heart or chronic allograft nephropathy in the kidney. This chronic, progressive and currently untreatable condition is incompletely understood. Epidemiological analysis suggests it is caused by chronic alloimmune damage, chronic immunosuppressive toxicity and the effects of the period of ischaemia followed by reperfusion at the time of grafting. Ciclosporin (cyclosporin) and FK506 are profibrotic so regimens without these agents are being evaluated in clinical trials. Antifibrotic agents (e.g. antibody raised against transforming growth-factor β) may also be beneficial but none has reached clinical practice.



Microscopic appearance of acute and chronic vascular rejection in the kidney. **a** Acute vascular rejection showing an intimal arteritis and a lymphocytic infiltrate in the surrounding interstitium. **b** Chronic vascular rejection shows intimal fibrosis and atrophy of adjacent tubules. The chronic damage created by **a** is strongly implicated in the development of the fibrosis that characterizes **b**.

Immunosuppressive side-effects

The side-effects of steroids and azathioprine are long established (Figure 2). The calcineurin inhibitors (ciclosporin (cyclosporin), FK506) are erratically absorbed and metabolized. Therapeutic monitoring with trough or D-2 levels (blood sample is taken 2 hours after the oral dose) is required to maintain immunosuppressive levels while avoiding the acute toxic effects that include tremor, nausea and vomiting as well as acute renal impairment.

Side-effects of immunosuppressive treatment (excluding infections)

Steroids (prednisolone)
- Mineralocorticoid effects (e.g. fluid retention, hypertension)
- Cushing's syndrome
- Diabetes
- Osteoporosis

Ciclosporin (cyclosporin)
- Nephrotoxic (high creatinine, implicated in chronic rejection)
- Neurotoxic (tremor, fits)
- Gum hypertrophy
- Hirsutism
- Hypertension
- Hyperlipidaemia
- ?Accelerated atherosclerosis

FK506
- Gastrointestinal disturbances
- Anxiety/depression
- Cardiomyopathy in children reported

Azathioprine
- Hypersensitivity
- Bone marrow suppression
- Hair loss

Mycophenolate mofetil (MMF)
- Gastrointestinal disturbances
- Pancreatitis
- Cough
- Rhinitis

Rapamycin (sirolimus)
- Lymphocele
- Gastrointestinal disturbances
- Anaemia
- Thrombocytopenia

Vascular complications

All visceral transplants entail anastomosis between the recipient vascular system and the corresponding vessels in the donor. Haemorrhage is rare and usually due to technical failure. Acute arterial and venous thrombosis is a significant cause of graft loss (2–4% of kidneys) and revascularization is seldom possible. Vascular stenosis commonly develops at anastomoses or within transplant vessels. These may be treated conservatively, by surgery, angioplasty, stenting, coumarin anticoagulation or antiplatelet therapy.

Kidney

Recipient care: most patients on the waiting list are in a reasonable state of health and many are maintained by dialysis. Most require dialysis before surgery to optimize their blood biochemistry. Preoperative blood transfusion is occasionally required but is to be avoided because of its sensitizing effect.

Tissue matching for major histocompatibility (MHC) antigens is routine and forms a major part of the UK scoring system for the allocation of cadaveric kidneys. A highly matched donor, differing by none or only one allele at the 6 MHC loci has an excellent expected graft survival time. This is termed a beneficial match and accorded priority in organ allocation.

Problems specific to kidney transplantation

Primary non-function – organs are scarce, necessitating the use of borderline organs, which may have donor pathology or long ischaemic periods. Often such organs exhibit acute tubular necrosis and do not function for days or weeks following implantation. In these cases, patients need continuing support with dialysis and erythropoietin therapy.

Urinary tract complications – an acute urinary leak, slowly presenting ureteric stenosis or acute obstruction are common. Irritant urine is painful and leaks usually require surgical repair. If hydronephrosis or subfunction results from ureteric narrowing or external compression, the renal tract may be decompressed by a ureteric stent or a percutaneous nephrostomy. Compressive lymphatic collections (lymphoceles) sometimes require long-term drainage because they often recur after aspiration.

Recurrence of original pathology is a significant cause of renal transplant dysfunction and loss, particularly the more aggressive of the glomerulonephritides. These conditions are treated with similar agents to the original conditions. Steroids are the mainstay of treatment but chemotherapy or plasmapheresis is sometimes indicated.

Liver

Recipient care*:* liver recipients vary from entirely stable to very ill, encephalopathic ITU patients. This is reflected in the stringency with which the transplant team assesses the donor liver suitability. Tissue matching is not performed but compatibility of ABO blood group antigens and size is routinely sought.

Problems specific to liver transplantation

Reperfusion syndrome – on reconnection with the recipient circulation, inflammatory mediators and cold perfusion solution are washed out of the extensive hepatic vascular bed and enter the systemic circulation. This can produce hypotension and cardiac irregularities. Awareness, prophylactic optimization of vascular filling and venting of initial portal blood can help to avoid difficulties, but further treatment with vasoactive drugs is often necessary.

Bleeding/coagulopathy is a major sequel to loss of hepatic synthetic function. A liver transplant is a huge procedure; extensive dissection is needed to remove the native organ and significant blood loss is unavoidable. Transfusion requirements are often high with large quantities of clotting factors needed. The use of aprotinin has led to a reduced mean transfusion requirement but the possibility of increased thrombotic complications remains.

Mechanical/biological assist devices – there is no hepatic equivalent of dialysis but bioartificial livers (which connect the circulation to external human or animal hepatocytes) and molecular adsorbent recirculating systems (which provide a modified form of dialysis capable of removing some toxins and waste products) are potential therapeutic tools to maintain recipients preoperatively and in the early phase following transplantation.

Neurological problems – fitting is common in encephalo-pathic, urgent recipients and prophylactic anticonvulsants are normally used. This tendency can be exacerbated by neuro-toxic immunosuppressives such as FK506 and ciclosporin (cyclosporin).

Biliary complications – fine biliary anastomoses with their tenuous blood supplies often cause complications.

Nutrition – in contrast to a kidney transplant, in which a retroperitoneal approach is used, or a heart transplant, in which sternotomy is required, a liver transplant is an extensive intraperitoneal procedure. Much handling and retraction of the viscera is needed and paralytic ileus results, therefore it may be some time before oral feeding can commence. Coupled with the high incidence of cachexia/malnutrition preoperatively this indicates the importance of nutritional support. Total parenteral nutrition is often required, but some surgeons prefer enteral feeding via jejunostomy or a nasojejunal tube. Dietitian input and oral supplementation are required long after oral feeding is re-established.

Heart

Recipient care: unlike kidney transplantation, which might be termed semi-elective, most heart transplants involve critically ill patients who already require intensive levels of management. Inotropic support or even mechanical assist devices may be required to maintain the recipient before grafting. In the USA, the use of long-term mechanical assist devices is common. In less urgent recipients, heart failure must be optimized with standard medical therapy to give the best chance of success.

Problems specific to heart transplantation

Bypass – cardiac transplantation requires cardiopulmonary bypass with its attendant complications.

Rhythm – the usual surgical technique entails anastomosing the donor heart to the remnants of the two recipient atria. This disrupts conduction and can produce atrial arrhythmias and dysfunction. Anastomosis of an intact donor heart to the two cavae, preserving the donor atrium, is an alternative.

Rate/output control – a newly transplanted heart is de-innervated and rate/output control is reliant on circulating factors only. Temporary cardiac pacing is usually necessary to ensure adequate ventricular function.

Bleeding – the anticoagulation needed for a heart bypass means blood loss is a significant problem. Support with blood products and the use of aprotinin are the main therapies. ◆

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Physics

Anaesthesia
and intensive care medicine
on CD-ROM

Amplifiers and Biological Signals

John Chapman

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Medical monitoring equipment is now so convenient, reliable and compact that almost any physiological variable can be measured, displayed and recorded in real time and in difficult electrically 'noisy' environments such as operating theatres and MRI scanners. The technical advances and miniaturization of electronic devices that have made this possible have come mainly from the needs of space exploration and computing.

Biological signals
Biological voltages (Figure 1) are small, measured in thousandths or millionths of a volt, and except when needle electrodes are used, are detected through the resistance of the skin. Sometimes two signals are present at once, for example muscle action potentials can overlay the ECG and filtering may be necessary to separate them. The interfering signal may be larger than the desired signal and special separation techniques are available.

Biological signals

Frequency	Voltage
EEG	
0.5–100 Hz routine	0.5–100 μV
0.05–150 Hz diagnostic	Up to 1 mV recorded directly from brain surface
ECG	
0.5–30 Hz theatre monitor	100 μV–3 mV
0.05–100 Hz diagnostic	
EMG	
1–20,000 Hz	About 1 mV

1

Signal-to-noise ratio
The signal-to-noise ratio compares the power in the signal with the power of the interference and is measured on a logarithmic scale in decibels. Familiar examples of interference degrading the signal-to-noise ratio are hiss on a radio, 'snow' on a television picture, and the loss of quality on a video tape that has been copied several times.

The signal to be amplified has travelled along a wire to the amplifier, and can pick up small voltages from nearby interference sources such as mains wiring, fluctuating magnetic fields, radio signals and surgical diathermy. Therefore, the signal may be contaminated with a variety of voltages over a wide range of frequencies.

The passage of an electrical current through any conductor inevitably generates small random voltages and therefore noise is generated in the amplifier itself and combines with the signal. Useful information can be swamped by unwanted electrical noise and the smaller the original signal the bigger the problem.

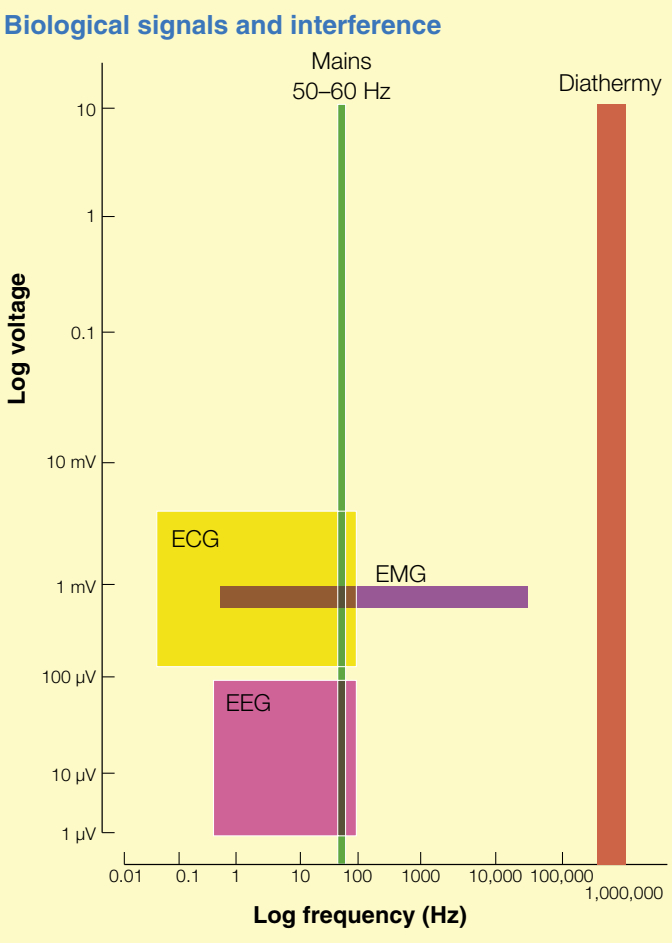
Amplifiers
An amplifier is a device that allows a small electrical signal, containing very little power, to control an external power source to reproduce the signal at a higher level. An example is a public address system that takes a signal of a few millivolts from a microphone and uses it to control the electrical power fed to hundreds of loudspeakers in a stadium, totalling thousands of watts.

The bandwidth of an amplifier is the range of frequencies it reproduces accurately. An amplifier must be designed to suit the signal it has to process; for example a good audio amplifier deals with audible frequencies of 15–20,000 Hz, and a radio frequency amplifier must be able to handle the frequencies the radio is to receive, from hundreds of thousands to tens of millions of Hz.

Biological amplifiers: an ECG amplifier is designed to reproduce the frequencies present in the ECG, from less than 0.5 Hz if the pulse rate were 30 beats/minute, to 100 Hz to reproduce detail in the QRS complex, and higher again if it is to be able to show very brief pacing artefacts.

Any stray signal at the mains frequency (which is 50 Hz in Europe and 60 Hz in the USA) falls within the bandwidth of the amplifier and distorts the display unless filtered out (Figure 2). Biological amplifiers are normally fitted with a notch filter, which in the UK blocks frequencies of 48–52 Hz.

Biological signals and interference



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DC amplifiers: a very slowly changing signal (e.g. daily variation in body temperature) can be treated as if it were a steady voltage and requires a special type of direct current amplifier. Historically, these were difficult to make free of 'drift'. This is a spurious slow change in the output signal when the input is steady. Drift was usually caused by changes in the temperatures of components within the amplifier causing changes in their resistance, and very long warm-up times were necessary before measurement could begin. With modern integrated circuits, the whole amplifier is formed on a tiny silicon chip which is too small to permit significant temperature differences to occur between closely spaced components.

Differential amplifiers: one type of amplifier widely used for biological signals has two input terminals and amplifies the voltage difference between them, while ignoring a much larger voltage between both terminals and earth. In this way, if two ECG wires run side by side from the patient to the amplifier, the same amount of mains interference is picked up by each wire but is ignored when it reaches the amplifier that is sensitive only to the voltage difference between the ECG patches. The quality of such a device is expressed on a log scale as the common mode rejection ratio, that is the ratio by which the difference signal is amplified more than the common mode.

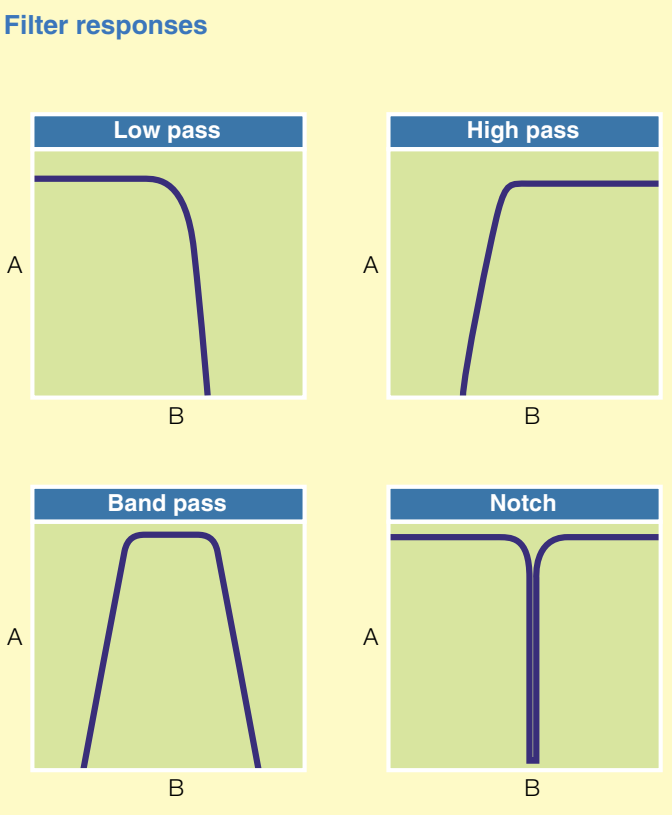
Fourier analysis
Any repetitive waveform can be dissected mathematically and described in terms of various proportions of a set of related frequencies that are multiples (harmonics) of one another. The original waveform can be reassembled from this mathematical recipe. Knowledge of the range of frequencies present in a signal is necessary to design an amplifier that reproduces it faithfully. Among biological signals, the ECG and arterial pulse are repetitive, but random signals such as the EMG and EEG can be analysed in much the same way.

Spectral analysis
It is possible to perform spectral analysis in real time on an EEG signal, and to display the amount of neural activity present in each of several groups of frequencies. The dominant frequencies change and slow with the depth of anaesthesia and this is the basis of the cerebral function monitor.

Processed signals
Additional information can be extracted from signals by computer processing. For example, if the P wave of the ECG is identified, and then the time between it and the corresponding R wave measured for each heartbeat, a beat-to-beat variation in P–R interval emerges, and may give information on the state of autonomic tone and the health of the conducting system.

Filters
Filter circuits pass or block a signal according to its frequency (Figure 3). They can be used to separate interference from a wanted signal provided their frequencies are sufficiently different. Filters are commonly built into amplifiers to suit them to a particular use.

Filter responses



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A low pass filter allows a low frequency signal to pass through, but obstructs the passage of high frequencies, and a high pass filter does the reverse.

A band pass filter blocks high and low frequencies, but passes a group of frequencies in between.

A notch filter blocks a narrow band of frequencies centred on an interfering signal, for example a 48–52 Hz filter removes mains 50 Hertz interference from an ECG signal, but makes little difference to the fidelity of the recording.

Special techniques
A very small signal can be extracted from large amounts of random electrical 'noise' if the signal can be made to recur regularly. The basis of the evoked auditory response test of cochlear function is to feed precisely regular clicks into the ear through headphones, and then search for equally regular, but small, responses within the EEG. If the EEG is summed for each of a large number of successive short time periods after each click, then random signals will average towards zero, but a constant response will build up in size and become visible through the noise.

Electrical interference
Sources: in electrical terms, the world is a noisy place. In industrial countries most buildings have an electricity supply, are close to roads carrying traffic that emits interference from ignition systems, while radio, television, radar and mobile phone signals are ubiquitous.

In the operating theatre
Mains frequency – so much equipment in theatre is mains powered that wires carrying mains voltage snake everywhere. Each wire emits an electric field fluctuating at 50 Hz (60 Hz in the USA) and a magnetic field the strength of which varies with the current. Any conductor in an electric field has a voltage induced on it, and any conductor exposed to a fluctuating magnetic field also has a voltage induced in it.

High frequency sources – surgical diathermy (Bovie) apparatus is a radio transmitter. The high frequency current has a heating, charring or explosive effect on tissue depending on the power setting, the waveform selected and the current density. A high frequency of 0.5–1 MHz is chosen because, other than heating, it has little or no effect on excitable tissue such as muscle and nerve. In use, surgical diathermy operates at a power level of tens of watts, the wire to the surgeon's handpiece is a transmitting aerial and the current is picked up by any wire nearby. Because the frequency is high compared with any biological signal, it is easily filtered.

MRI: monitoring a patient in an MRI scanner introduces additional problems. The scanner uses a powerful magnet, a radio transmitter and a receiver all aimed at the part of the patient being scanned. The radio frequency is swept rapidly over a range centred on the resonant frequency of water or other molecules of interest in the magnetic field. So the patient and the monitoring leads are at the focus of intense energy fields. One solution is to use a small radio transmitter operating at a non-interfering frequency to take the ECG signal to a monitor outside in the control room. Another is to use fibre-optic leads to bring light to and from the patient's finger for pulse oximetry. The common feature is that metal wires carrying small signals through an intense energy field are avoided.

The MRI scanner is subject to interference from external radio signals, and the whole room is enclosed in a Faraday cage. The walls, floor, ceiling, and doors all contain a conductive copper mesh, and the windows are of special conductive glass. The edges of the doors have a copper strip to complete the cage when they close. Any wires or other metallic parts implanted in a patient can have significant voltages, temperatures or mechanical forces induced in them during scanning. A useful website that gives advice on MRI safety is www.MRIsafety.com. ◆

Anaesthesia Monitoring Techniques

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Depth of anaesthesia

Most anaesthetics are given without monitoring the effect of the anaesthetic on the target organ. Depending on the stimulus, there is a depth of anaesthesia at which the patient becomes aware. The incidence of awareness or recall during general anaesthesia is about 1/500.

Historical methods

Clinical assessment uses autonomic signs such as pulse, blood pressure, sweating and lacrimation to predict anaesthetic depth. However, autonomic functions are not affected by depth of anaesthesia only, and patients with autonomic neuropathy will not react as predicted.

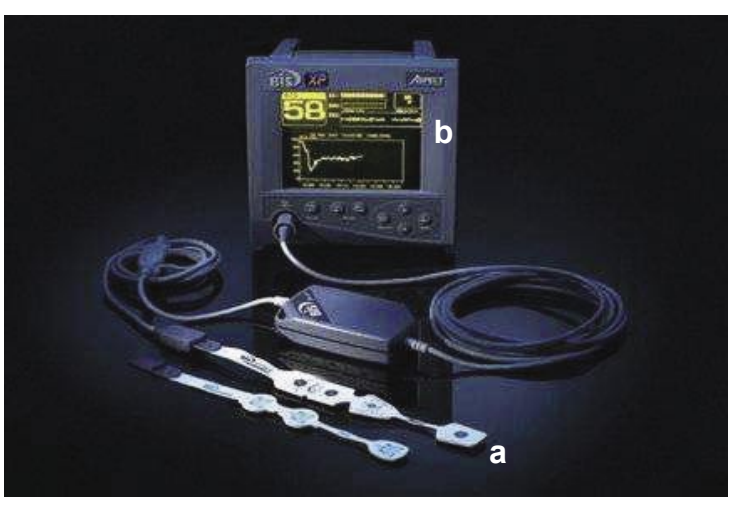
Tourniquet – Tunstall described inflating a tourniquet to the upper arm above systolic pressure before induction of anaesthesia. This prevents neuromuscular agents reaching the forearm muscles, and the patient's arm moves if anaesthesia is too light. This method is unsuitable for routine use because it indicates awareness once it has occurred, and the time for which the tourniquet can be inflated is limited by neuronal ischaemia from compression.

Electroencephalogram (EEG)

Recording the electrical activity of the brain provides information on depth of anaesthesia. However, the equipment is expensive and skilled operators are required to obtain useful information. Different drugs have varying effects on the EEG. Hypotension, hypoxia, metabolic encephalopathy and cerebral oedema can all depress EEG signal output.

The EEG detects voltages of 1–500 μv. It comprises α, β, θ and δ waves. With increasing depth of anaesthesia there is a progressive increase in signal amplitude and a reduced frequency (burst suppression). The EEG is non-invasive and presents cortical electrical activity derived from summated excitatory and inhibitory postsynaptic activity that is paced by subthalamic nuclei. Fourier analysis is used to separate the raw EEG into a number of component sine waves. The derived parameters, spectral edge frequency and median frequency describe the entire EEG as a single value. Spectral edge frequency is a single value representing the frequency below which 95% of the total power is present. The median frequency is the point at which 50% of the power lies above and below this value. Median frequency has been shown to control closed loop feedback of intravenous drug administration, but no studies have demonstrated the usefulness of spectral edge frequency.

Bispectral index (BIS) is a derived variable that uses information on EEG power and frequency, and includes information derived from the mathematical technique of bispectral analysis (Figure 1). BIS records a state of the brain and not the effect of a particular drug. BIS gives a numerical value and the data are generated over 30 EEG recordings, with the average updated every 2–5 s. A low BIS value indicates hypnosis. BIS decreases during natural sleep, though not to the level produced by anaesthetic drugs.



1 Bispectral index (BIS) monitor. **a** Electrodes. **b** Display screen showing digital and analogue recording of BIS. Photograph courtesy of Aspect Medical System Inc.

Evoked potentials

Cortical evoked potentials to auditory, visual or somatosensory stimuli are suppressed in a dose-dependent manner by anaesthetic agents, and correlate well with peroperative wakefulness, awareness and explicit and implicit memory. Voltage potentials are small (1–2 μv) compared with background electrical activity (> 100 μv). Evoked potentials are generated using repeated stimuli, and the electrical responses pre- and post-stimuli are averaged so that only the electrical activity corresponding to the generated stimulus is analysed.

The evoked response is divided into early, mid-latency and late cortical waves. Early waves originate in the brainstem and are unchanged by anaesthesia. Mid-latency waves (40–60 ms post-stimulus) are highly influenced by increasing depth of anaesthesia, particularly the Pa and Nb waves. Anaesthetic agents increase latency and decrease amplitude in a dose-dependent manner. The correlation of mid-latency auditory evoked potentials to depth of anaesthesia approaches that of BIS.

The late cortical response (50–100 ms post-stimuli) reflects activation of the frontal cortex but is heavily influenced by attention, sleep and sedation.

Neuromuscular blockade

Neuromuscular blockade is monitored during surgery to guide repeated doses of muscle relaxants and to differentiate between the types of block. All techniques for assessing neuromuscular blockade use a peripheral nerve stimulator (PNS) to stimulate a motor nerve electrically. The PNS generates a standard electrical pulse, which should be:

- supramaximal to ensure recruitment of all available muscle units
- a square wave of short duration (0.1–0.2 ms) with uniform amplitude (10–40 mA).

The muscle response can be assessed by visual and tactile methods, electromyography, acceleromyography and mechanomyography. Visual observation and palpation of the contracting muscle group are the easiest but least accurate methods of assessing neuromuscular block from PNS stimulation.

Electromyography uses electrodes to record the compound muscle potential stimulated by the PNS. Typically, the ulnar nerve is used and the electrodes are placed over the motor point of adductor pollicis. A drawback is that small movements of the hand can change the response by altering the electrode geometry.

Acceleromyography – acceleration of a distal digit is directly proportional to the force of muscle contraction (because force equals mass times acceleration), and therefore inversely proportional to the degree of neuromuscular block. The transducer uses a piezoelectric crystal secured to the distal part of the digit measured and the PNS provides the electrical stimulus. Accurate and stable positioning of the digit is important for accurate results.

Mechanomyography uses a strain gauge to measure the tension generated in a muscle. A small weight is suspended from the muscle to maintain isometric contraction. The tension produced on PNS stimulation is converted into an electrical signal. Mechanomyography requires splinting of the hand and is generally used for research.

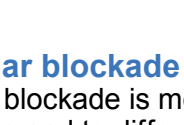
Different modes of PNS stimulation

Single twitch – an electrical pulse is delivered at 1 Hz, and the ratio of the evoked twitch compared with that before muscle relaxation gives a crude indication of neuromuscular blockade (Figure 2). When 75% of the acetylcholine (ACh) receptors on the postsynaptic membrane of the neuromuscular junction are occupied by a neuromuscular blocking agent (NMBA), twitch magnitude starts to decrease. When there is 100% drug occupation, no twitch is elicited.

Pulse patterns

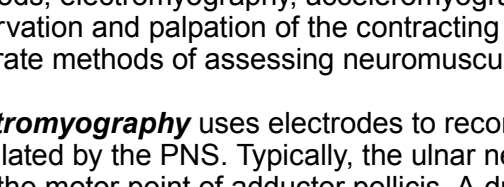
Twitch

- Single twitch
- Used with depolarizing blockade
- Degree of twitch depression used to calculate level of blockade



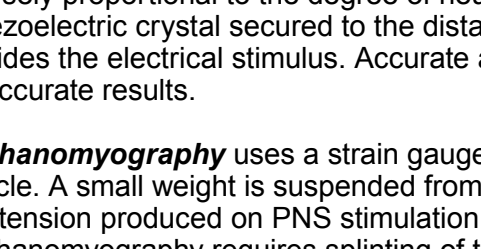
Train of four

- Four single pulses at 2 Hz
- Shows fade
- Ratio of first to fourth twitch used to calculate level of blockade



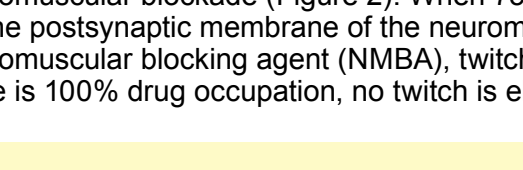
Tetanus

- Sustained burst of pulses at 50 or 100 Hz
- Usually held for around 5 s
- Used to 'kick start' the nerve under deep paralysis



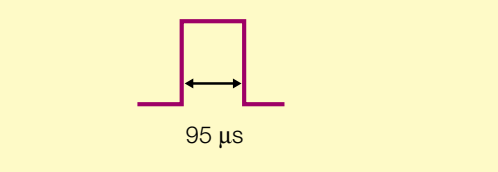
Double burst stimulation

- Two bursts 0.5 s apart
- Either 3 pulses followed by 2 pulses (3:2) or 3 followed by 3 (3:3)
- Used under light paralysis where train of four ratio is difficult to distinguish



Post-tetanic count

- 5 s tetanus followed by 20 pulses at 2 Hz
- Shows fade response earlier than train of four
- Used under deep paralysis to estimate time to recovery



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Train of four (TOF) – four stimuli are given at a frequency of 2 Hz, potentially eliciting 4 twitches (T1–T4). The ratio T4:T1 indicates the degree of neuromuscular block. Non-depolarizing NMBAs produce a decrease in magnitude of the first twitch compared with a pre-relaxant stimulus, and a progressive reduction in magnitude of T1–T4. The number of elicited twitches indicates the degree of receptor occupancy. Disappearance of T4, T3, T2, T1 corresponds to 75%, 80%, 90% and 100% occupancy. With recovery of neuromuscular function the twitches appear in the reverse order. Accepted values for TOF count are:

- 1 twitch for tracheal intubation
- 1–2 twitches during established anaesthesia
- 3–4 twitches before reversal of neuromuscular blockade is attempted.

Double burst stimulation consists of two bursts of three stimuli at 50 Hz with each triple burst separated by 750 ms. These manifest visually as two separate stimuli (T1 and T2). The ratio is related to the TOF ratio and is easier for the operator to interpret reliably.

Tetanic stimulation at 50 Hz for 5 s produces detectable fade in muscle contraction, the extent of which is related to neuromuscular block. No fade indicates no neuromuscular block. In intense neuromuscular block, TOF stimulation elicits no twitches. Post-tetanic facilitation (PTP) uses tetanic stimulation for 5 s to mobilize presynaptic ACh. Subsequent 1 Hz twitch stimulation can overcome the high concentrations of NMBAs. The number of twitches generated (i.e. the post-tetanic count) reflects the degree of neuromuscular blockade.

Depolarizing NMBAs react differently to the PNS modes of stimulation. They produce equal but reduced twitches in response to single twitch and TOF stimulation (the T4: T1 ratio is 1), reduced but sustained contraction with tetanic stimulation, but do not demonstrate either tetanic fade or PTP.

Temperature

In health, body temperature is maintained at 37 ± 0.2°C. Intraoperative monitoring can be via electrical or non-electrical techniques.

Non-electrical techniques

An aneroid gauge uses the expansion of air with increasing temperature to change the size of a bellows connected to a needle. The needle moves across a calibrated scale to display the temperature.

Liquid thermometers typically rely on the thermal expansion of alcohol or mercury. The liquid is forced into a fine transparent glass tube with an appended scale. An angulation and constriction below the fine-bore tube prevents the liquid retracting into the bulb reservoir until the thermometer is shaken. A short time (2–3 minutes for mercury) is required for complete thermal equilibration between the liquid and the surrounding environment. There is a risk of poisoning if the thermometer breaks and mercury leaks.

Bimetallic strip thermometers comprise two metals with different coefficients of thermal expansion. With a change in temperature one metal changes size more than the other causing the strip to bend; this is displayed via a mechanical linkage on a temperature scale.

Chemical thermometers use liquid crystals composed of chemicals such as cholesterol esters, that change colour with temperature. Typically these scales can be accurate only to 0.5°C. They are used for monitoring skin temperature which may be markedly different from core temperature.

Infrared thermometers use the principle of black body radiation. Only the temperature of that object determines the maximal amount of radiation emitted by a body. The amount of radiation emitted by a surface (e.g. the tympanic membrane) is less than that emitted by a black body at the same temperature. The emissivity of the surface is the ratio of these radiation levels. Thus, measurement of a surface's emitted radiation combined with a pre-existing knowledge of that surface's emissivity can determine the temperature of that surface. Infrared tympanic membrane thermometers are in common clinical use.

Electrical techniques

Thermocouples use the Seebeck effect, whereby a small voltage is produced at a junction between two dissimilar metals, commonly either platinum/rhodium or copper/constantan. The temperature at the junction determines the voltage produced. There is a second junction to complete the electrical circuit. This is either maintained at a constant temperature, to provide a reference level, or has built-in compensation for the reference junction temperature, enabling the first junction to act as a thermometer.

A thermistor is a semiconductor made from tiny beads of heavy metal oxides, which can be incorporated into the tips of fine temperature probes. Electrical resistance of semiconductors decreases exponentially with increasing temperature. Thermistors require signal conditioning and calibration because resistance may alter with time. Thermistors exhibit hysteresis in that their electrical resistance is different at the same temperature depending on whether the temperature is increasing or decreasing.

Platinum wire thermometers – electrical resistance of platinum increases with increasing temperature. The increase is linear in the range 0–100°C. They are accurate to within 0.0001°C, but are fragile.

Respiration

In anaesthesia, ventilatory pattern, gas flow, airway pressure and tidal and minute volumes are measured. Only methods of measuring gas flows and volumes are mentioned here.

Gas flow can be used to derive volume. Flow is laminar or turbulent, and Reynolds number is used to predict the type of flow. Laminar flow is described in the Hagen–Poiseuille equation. Pneumotachographs measure flow by inducing laminar flow through a gauze screen. The screen produces a resistance to flow and thus generates a small pressure difference on either side. This pressure difference is measured with two transducers. These convert pressure into an electrical signal, which is processed to produce a display of flow. The screen is manufactured to provide minimal resistance to respiration, and is heated to maintain a constant temperature. If the screen was allowed to cool in the gas flow this would affect the gas viscosity, altering flow characteristics of the gas and thus affecting accuracy. Warming also prevents condensation developing on the screen, which would increase resistance to flow.

Respirometers can be used to monitor expiratory gas volumes. The most common is Wright's anemometer (Figure 3). Expired gas passes through oblique slits, which creates circular gas flow in a chamber, causing rotation of a double-vaned rotor. The rotor is coupled via a set of linkage gears to a display indicator dial and needle. The respirometer measures gas volume in one direction only. Flow can be calculated by averaging recorded volumes over time. Its advantages are that no power supply is necessary, and the device is lightweight and portable. Owing to the inertia in the system it tends to overestimate higher volumes and underestimate lower volumes. ◆

3 Wright's respirometer. **a** Small pointer shows accumulated volume; **b** large pointer indicates tidal volume (it can be reset each breath); **c** to the breathing sytem.

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Basic Measurement Concepts

John Curnow

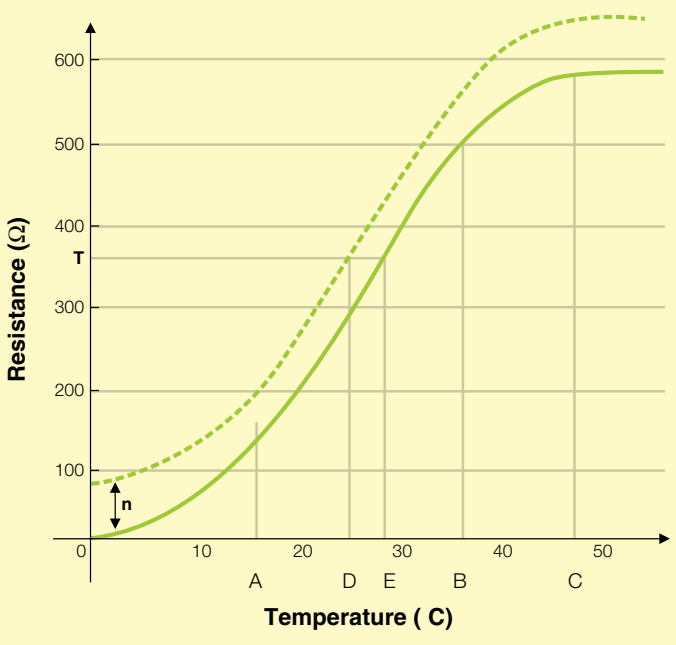
John Curnow is Biomedical Engineer at Derriford Hospital, Plymouth, Devon, UK. His specialist interest is in patient monitoring and the application of computing techniques in medicine.

Anaesthetists commonly record data from patients, intermittently or continuously. Data collection can be as simple as measuring the heart rate by feeling the pulse and counting it over a period of time, through regular intermittent monitoring of blood pressure and heart rate to continuous monitoring of variables using electronic data collection, analysis and storage systems. The general concepts discussed here are mainly related to continuous mon-itoring though some of them also apply to intermittent methods.

Measurement is the interpretation of a feature or function in a way that is repeatable and calibrated so that it can be understood and compared with other measurements taken at different times or by different people and on different patients. In many basic measurement techniques such as measuring length, the device used to make the measurement is calibrated to a national or international standard. This use of a standard to calibrate a measurement is the basis of making it repeatable and accurate so that measurements made by anyone with a calibrated instrument can be compared with other measurements.

For medical monitoring, data are collected directly from the patient using two different systems. If the feature to be monitored is an electrical activity in the body, electrodes are used to collect the data directly. If the feature to be monitored does not produce electrical activity then a transducer is used to collect the data. A transducer measures the feature required and produces an electrical signal proportional to it. For example, a standard method of temperature measurement is to use a thermistor as the sensor. A thermistor is an electronic device that has been specifically designed so that its electrical resistance changes with temperature in a regular and defined way (Figure 1).

Characteristic thermistor curve



See text for explanation

1

This characteristic curve shows several important features. Within the temperature range A to B the change in temperature is directly related to change in resistance and therefore the curve for this part can be represented by a straight line. This is called a linear relationship because it can be represented by the straight line characteristic and therefore the changes in resistance mirror the changes in temperature. Many systems are said to be linear and the linearity of a measurement system is a measure of how well the measured variable and the measurement variable can be represented by a straight line.

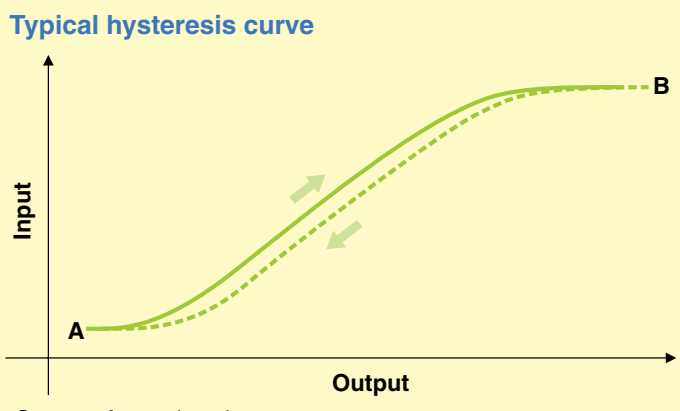
In the temperature ranges zero to A and B to C the characteristic is a curve that follows a fixed mathematical function. In this case, the relationship can be modelled within the electronics of the measurement system to produce a linear relationship and allow monitoring. In the range above C, the curve approximates to a straight horizontal line because there is no change of resistance with change of temperature. The measuring system is said to have reached saturation at point C and no readings can be made above this temperature. Saturation can be a problem to the unwary because the measurement system is apparently giving an acceptable reading although it is wrong. It is always important to identify the maximum value a system should read before using it.

Offset is a change within the transducer that can happen in real systems; it is shown by the dotted curve in Figure 1. In the case shown it represents a vertical shift equivalent to a resistance change of n ohms at each temperature. The effect in this case is to underestimate the temperature as shown by points D and E for a temperature T. It is difficult to identify offset unless a known source at a standard value is available to check the system.

Drift – most transducers used with monitoring equipment have active electronic devices such as a thermistor. These devices are designed to work accurately over a known environmental temperature range. If they are used at environmental temperatures outside this range the results may be incorrect because of drift. Drift can be seen as a change of the characteristic curve and can consist of offsets and/or changes in slope of the characteristic curve. The later will reproduce as an overestimate or under-estimate of temperature that changes across the measurement range of the system. If one or the other of these occurs the final result will be an error in the reading of the measurement that will be difficult to identify. One method of identifying drift is to monitor the expected baseline continuously. If it shows a consistent rise or fall, which is not expected then drift may be the cause.

Hysteresis – some transducers (e.g. pressure measurement transducers) use the mechanical properties of a material as the basic measurement technique. In the case of some pressure transducers a thin metal or plastic membrane is fitted over the end of a small chamber connected to the fluid having its pressure measured. The membrane flexes out as the pressure increases and goes back towards its original position as the pressure falls. The flexing of the membrane is measured using an electrical method. Many solid materials demonstrate a feature called hysteresis when stretched and relaxed repeatedly. A typical hysteresis curve is shown in Figure 2. If the system starts at point A and the input rises, the characteristic will follow the full line to point B where saturation occurs. If the input is then reduced the characteristic will follow the dotted line back to the lower saturation level at A. Therefore, the output value for any input value depends on the direction the input is changing in at the time and means accurate calibration of the output values is impossible. If the input signal is continuously changing, the output will also be a continuously changing value but will appear to read above the expected value during increasing input and below the expected value during reducing input. This will produce a distorted signal shape.

Typical hysteresis curve



See text for explanation

2

Measurement equipment electronics

Most medical measurement equipment depends on electronic systems to process and display the data collected. These electronic systems therefore become part of the overall measurement system. The electronics is often intended to make correction for known consistent errors in the signal produced by the transducer or to make non-linear responses linear.

The bulk of the electronics of a measurement system usually means that electrodes and transducers need long cables to connect them. These cables lie in the general environment and act as an aerial to airborne electrical signals. These signals consist mainly of power line frequency signals and radiofrequency signals. The signal is added to the signal from the electrode or transducer and both signals are presented to the electronics for processing. The unwanted signals are called noise. Other sources of noise are unwanted body potentials such as the muscle activity added to an ECG signal. The level of noise is important when considering the quality of a signal. The signal-to-noise ratio (SNR) is a ratio of the amplitude of the required signal to the amplitude of the noise signal and is used to define the quality of the signal. SNR is equal to 20 $\log_{10}$ (ratio of signal amplitude to noise amplitude measured in volts). A value of 6 dB means the signal is twice the size of the noise, and 60 dB means the signal is 1000 times larger than the noise.

The electronic system can also affect the signals, for example saturation occurs if the signal requires a voltage higher than that available from the electronics. Also the electronics can have thermal drift which can produce the same results as transducer drift. The usual cause is the electronics becoming too hot and it is essential that all vents are kept clear to minimize this effect. ◆

Basic Principles of Lasers

R John Parsons

R John Parsons was appointed Head of Medical Physics and Biomedical Engineering in Plymouth in 1992. He first worked with medical lasers in the 1970s and has taken a great interest in laser safety. He represents the British Medical Laser Association on the BSI committee dealing with Optical Radiation Safety.

The acronym LASER stands for **L**ight **A**mplification by the **S**timulated **E**mission of **R**adiation. Stimulated emission is an atomic process predicted by Einstein in 1917, but it was not until 1960 that the first laser was demonstrated. Lasers produce light of varying frequencies and power depending on their construction. They heat tissue, causing eventual destruction and are used in a variety of medical situations. They pose risks to all present, but by observing local rules they can be used safely with low risk to staff and patients. The three elements needed to make a laser are a medium, a power supply and positive feedback.

A medium that can exhibit stimulated emission implying amplification is required. This process takes place at the atomic level and involves inverting the normal steady-state thermal equilibrium of the medium – 'the population inversion'. Many substances exhibit this phenomenon though usually additional materials are required to make the system work. The laser is normally referred to by the name of the medium used (Figure 1).

Examples of media used in common medical lasers

- Gas – carbon dioxide (mixed with helium and nitrogen), argon, krypton
- Solid – Nd:YAG (neodymium doped yttrium aluminium garnet) crystal, holmium YAG, erbium YAG
- Metal vapour – copper, gold
- Liquid – organic dye
- Semi-conductor

A power supply drives the process. Many types are used including high voltage power supplies, radiofrequency power supplies, flashlight systems and small batteries driving devices like lecture theatre pointers.

Positive feedback: stimulated emission within the optical cavity is seldom sustainable without positive feedback. As the output is in the form of optical radiation this can be achieved by two mirrors placed one at each end of the cavity. One of these is made to have a very high reflectivity whereas the other allows some radiation to be transmitted through it, thus forming the laser output.

Properties
Laser light output has three main properties. It is collimated, coherent and monochromatic.

Collimated refers to the parallel nature of the output. In contrast to the light emanating from a light bulb, that from a laser is almost parallel showing very low divergence. This means that it can be focused using a lens to a very small spot size, greatly increasing the power per unit area. This is exploited in most medical lasers because the energy can be concentrated to affect tissues, up to destruction, with high positional precision. It also means that the light can be 'bundled' into a fibre-optic cable for transmission to otherwise inaccessible places in the body.

Coherent means that all light waves are in step with one another. This is responsible for the proliferation of holograms. They are little used in medicine though they have been extensively researched.

Monochromatic means output of one colour or frequency. This is not strictly true because most lasers emit more than one frequency with each one occupying a narrow band in the spectrum. This output depends on the active medium and can be in the ultraviolet, visible or infrared part of the spectrum (Figure 2).

Output of different media

- Carbon dioxide emits in the far infrared spectrum – invisible
- Neodymium YAG emits in the near infrared spectrum – invisible
- Copper vapour and argon emit in the visible spectrum
- Excimer (excited dimer) lasers emit in the ultraviolet spectrum – invisible

Light–tissue interaction

Light energy impacting on tissue has wide potential for changing tissue components and structures, depending on several factors. The most important of which are the intensity and frequency of the light.

Intensity
As the light intensity increases, different effects dominate, roughly following an order of magnitude scale. Below about 4 J/cm^2 biostimulation at a cellular level occurs. This effect is exploited in physiotherapy applications of low power lasers. If the power level is increased above this figure biosuppression starts to occur.

By about 40 J/cm^2 any sensitizing agents become activated. Ultraviolet therapy using psoralens and sunscreen creams are two examples of this phenomenon. By 400 J/cm^2, with tissue temperatures approaching 60°C, protein denaturization and photocoagulation dominate. Another order of magnitude increase sees the temperature rise to 100°C and vaporization and ablation occur. These descriptions are general and there are variations within an organ and between organs. However, the sequence of events leads from gentle heating to complete destruction.

Most continuous lasers can be 'pulsed' singly or in a repetitive way under user control. The effect of pulsing is to lower the average power delivered and consequently the temperature. During the 'off' phase the tissue has a chance to dissipate the heat and therefore thermal damage to surrounding tissue is reduced.

Lasers described as Q-switched have an internal shutter in the optical cavity which controls the release of the radiation. The energy is stored and then released as a high energy, short duration pulse. The population inversion then collapses briefly (i.e. stimulated emmission ceases) before recovering as the shutter closes. This burst of energy causes non-thermal tissue damage by electromechanical effects. These lasers are widely used in ophthalmology. UV lasers (Excimer) work in a similar way, by a photoablative action in which tissue can be removed in a controlled way with minimal thermal damage.

Frequency (wavelength)
The penetration of light energy into the body depends on its wavelength. At both far infrared and ultraviolet wavelengths light does not penetrate easily because of absorption by water. Absorption is rapid and surface effects dominate. In the visible part of the spectrum the two components mainly responsible for absorption are haemoglobin and melanin. Greater penetration therefore occurs before full absorption takes place. The deepest penetration into tissue takes place towards the red end of the spectrum and into the near infrared. The laser wavelength therefore controls the depth of effect and the type of tissue affected.

A carbon dioxide laser, emitting in the far infrared, is absorbed by water in 1 mm or less and is, therefore, a cutting and vaporising tool. A Nd:YAG laser is absorbed by haemoglobin and melanin about equally with water. It cuts and coagulates to a depth of about 3–5 mm and has the deepest penetration. An argon laser does not penetrate as far but coagulates to a depth of about 2 mm with maximum effect on haemoglobin.

Safety

Lasers are used in many specialties but the most important from an anaesthetic point of view is ENT. The only reported deaths from laser therapies have been associated with ENT and resulted from ignition of tracheal tubes. It is important to be aware of safety considerations with lasers as with all clinical treatments. However, their use is strictly controlled.

All installations using lasers, both public and private, have to have local rules drawn up to define:

- the hazards of the particular laser
- the control of those hazards
- where it can be used
- who can use it
- how it should be used.

The reader is referred to the MDA Guidance Notes for full information on laser use (see Further Reading). It is also important to ascertain the identity of the Laser Protection Adviser. This person has to be appointed by employers wherever a laser that poses a risk to personnel is in use. Their job is to assess the installation for risk, advise on safety measures, oversee the writing of the local rules and investigate all accidents and incidents. In addition, a Laser Protection Supervisor should be appointed in each area, who is responsible for the day-to-day activities of laser use.

Not all lasers are as potentially dangerous as others. There is a complex relationship between frequency, power and time of exposure. Lasers are classified into four main classes (these are further subdivided) from Class 1 (inherently safe) to Class 4 (hazardous). Most medical lasers are Class 4 and thus present the highest level of risk.

The other major risk is to the eyes of all present (including the patient). Stray beams can impinge on the eye and cause permanent damage. Skin exposure can also occur but is not usually so damaging. The Laser Protection Adviser will have specified the type of safety goggles to be worn and the local rules will say that they must be worn. Absorption by goggles is wavelength dependent. Goggles are specific to a laser and should not be moved from one laser to another.

Lasers should be operated by trained personnel only. The training should include safety and clinical training. Everyone present should have had basic safety training. This particularly applies to anaesthetists because they are often 'at the wrong end' of the laser, which means that the beam could easily point in their direction thereby exposing them to a high risk.

The room in which a laser is to be used is designated a 'laser controlled area' and is clearly delineated. Only authorized people should be in the room and other activities minimized. Windows and doors are often blacked out to avoid inadvertent exposure to passers-by. Although the likelihood of this happening is low the potential damage to the eye could be high.

All Class 4 lasers have the potential to ignite suitable materials. Paper drapes and spirit solutions should not be used near lasers but there is an even greater danger in ENT laser surgery. The combination of a tracheal tube, oxygen and the ignition potential of the laser has been responsible for lethal fires in the trachea. Strategies to overcome this have evolved (e.g. Venturi anaesthesia) but strict adherence to the rules is necessary to avoid such problems. ◆

FURTHER READING

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Common Errors in Clinical Measurement

Sarah Ford

Sarah Ford is Consultant Anaesthetist at Derriford Hospital, Plymouth, Devon, UK. She qualified from Otago University, New Zealand, and trained in anaesthesia in south west London. Her current interests are anaesthesia for major spinal surgery and general surgery.

Increasingly sophisticated instruments are being used for monitoring and guiding patient care but the onus is on the observer to be aware of the limitations of measurements and the causes of error.

Confounding errors in clinical measurements are readings that are not true reflections of the underlying signal. They may be caused by instrumental, sampling and patient factors.

The measuring system must be accurate and precise to produce reliable clinical measurements. Accuracy is the difference between the measurement and a 'gold standard' measurement of the underlying signal. Precision is the reproducibility of repeated measurements of the same biological signal. A repeated consistent measurement may be precise but inaccurate, for example an erroneous arterial pressure in an un-zeroed system. A continuous measuring system needs:

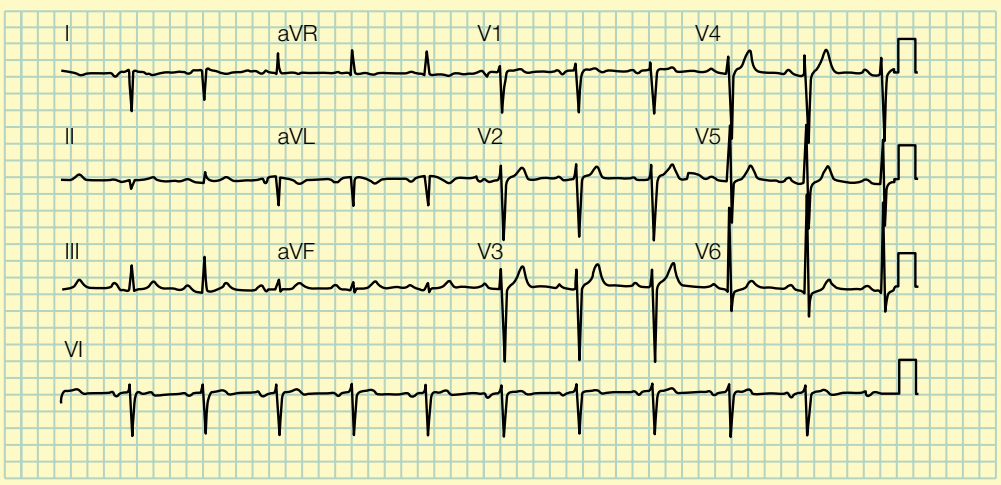
- high signal-to-noise ratio
- good zero stability and constant gain to prevent slow drift
- linearity of amplification over a range of signal
- no amplitude or phase distortion of fundamental frequencies up to the 10th harmonic
- correct calibration by the user.

ECG

The ECG measures potentials of 0.5–2 mV at the skin surface. Noise and interference that obscure these tiny signals are the main cause of a poor ECG trace. The most obvious error is incorrect electrode placement relative to the heart because QRS complexes vary with position of the electrodes (Figure 1). The ECG signal must be isolated from noise and interference before amplification and display (Figure 2).

Incorrect attachment of the arm leads

Incorrect attachment of the arm leads is recognized because of reversal of the axis with Q waves in I and positive QRS in aVR



Speed: 25 mm/s
Limb: 10 mm/mV
Chest: 10 mm/mV
Electrode Off
0.05–150 Hz

1

Interference to ECG signals

Type of interference	Sources	Means of reducing ECG distortion
Electromagnetic induction	Any power leads or lights	Long ECG leads twisted together therefore induced signal rejected as common mode Selective filters in amplifiers
Electrostatic induction and capacitative coupling	Stray capacitances between table, lights, monitors, patients and power leads	Copper screens round ECG leads
Radio interference (> 100 Hz)	Diathermy enters system by: • entering mains supply • direct application by probe • radio transmission via probe and wire	High-frequency filters clean up signal before entering input Filtering power supply of amplifiers Double screen electronic components of amplifiers and earth outer screen Newer machines operate at higher frequencies

2

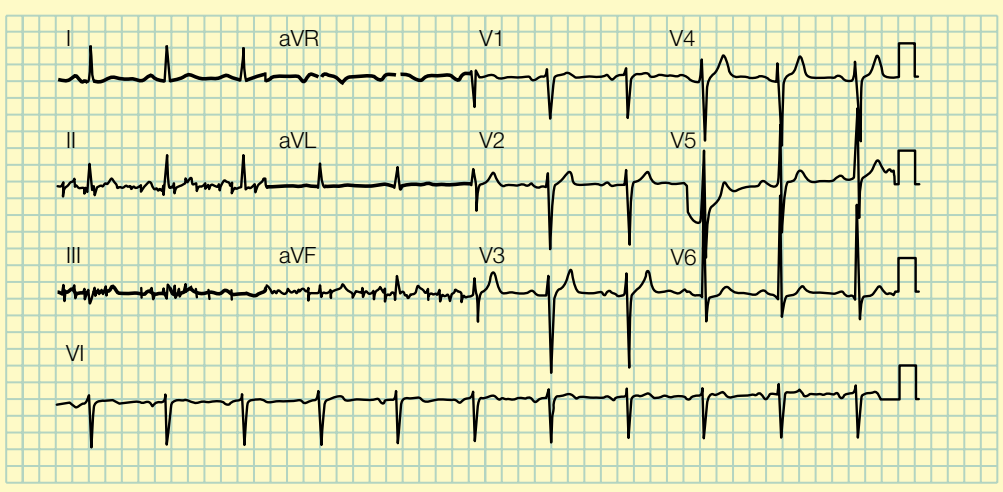
Noise originating from the patient – high frequency electromagnetic activity caused by shivering or movement is filtered by low-pass filters.

Noise originating from the patient–electrode interface – high skin impedance is the most common reason for a poor ECG signal and can be reduced by de-greasing the skin with alcohol. Modern disposable electrodes are made of silver coated with silver chloride with stable impedances reducing slow drift. Gel-impregnated foam pads decrease movement artefact and lower skin impedance.

Noise originating from the environment – the operating theatre is cluttered with sources of AC current that may distort ECG recordings (Figure 3).

Mains frequency interference

Characteristic mains frequency 50 Hz electrical interference visible in all leads



Speed: 25 mm/s
Limb: 10 mm/mV
Chest: 10 mm/mV
Electrode Off
0.05–150 Hz

3

The very small currents caused by capacitative and inductive coupling are exaggerated if electrode impedance is high, causing severe 50 Hz interference. Radiofrequency signals may saturate the input stages of the amplifier and block any output. Newer diathermy machines with higher frequency output may produce less interference.

Modern ECG monitors often allow selection of a diagnostic filtering band up to 100 Hz while the monitoring mode is a narrower band up to 50 Hz, which reduces motion artefact and mains interference. These high pass filters attenuate slow drift and maintain a stable baseline, but low-frequency elements of the ECG, such as the T wave, may appear biphasic or distorted.

Invasive blood pressure measurement

Intra-arterial cannulation with electromechanical transduction provides continuous monitoring of arterial blood pressure with greater accuracy in patients with unstable blood pressures or hypotension. The arterial pressure wave narrows and increases in amplitude in peripheral vessels, so the systolic pressure is higher in the dorsalis pedis than in the radial artery. Improper damping and calibration account for a large percentage of the errors in direct arterial pressure monitoring.

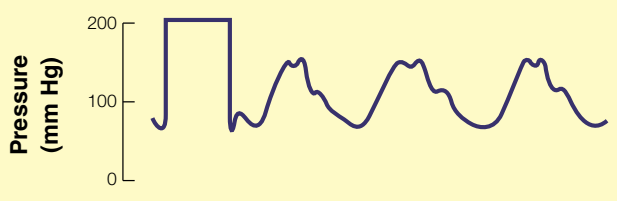
The fluid and diaphragm of the pressure transducer constitute a mechanical system that oscillates at the natural resonant frequency (F_n). This determines the frequency response of the measuring system. Factors that decrease F_n to within the range of frequencies of the arterial waveform result in sine wave oscillations being superimposed on the blood pressure trace. Depending on the shape of the arterial pressure wave, this distortion can introduce a 20–40% overshoot error in systolic blood pressure readings; it is worse with tachycardia. The most common reason for an under-damped spiked arterial trace is soft tubing inserted to extend the arterial line.

Damping results from friction of the fluid moving within the tubing which tends to extinguish any oscillations and decrease the frequency response of the transducer system. Excessive damping causes loss of detail in the waveform and under-estimation of pressures. Air bubbles in the system, clotting or kinking in the cannula and arterial spasm increase damping. The use of relatively wide-bore cannulae and minimizing stopcocks improves the frequency response of the system.

The amount of distortion in a system is assessed by snapping the flush valve and observing the response (Figure 4). Commercial damping devices (Accudynamic) are available to avoid the risks of air embolism. It is essential to calibrate and zero the transducer system correctly to the right atrium. Baseline drift of the transducer's electrical circuits may occur requiring periodic checks and re-zeroing.

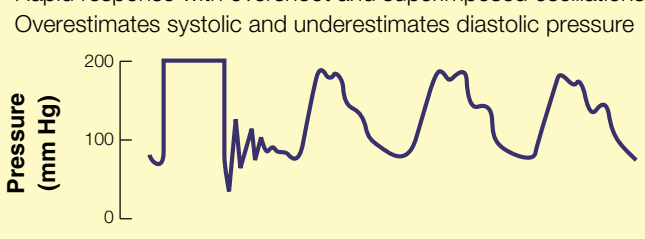
An optimally damped arterial trace

Small overshoot of 7% of the step change with no oscillations then follows arterial trace



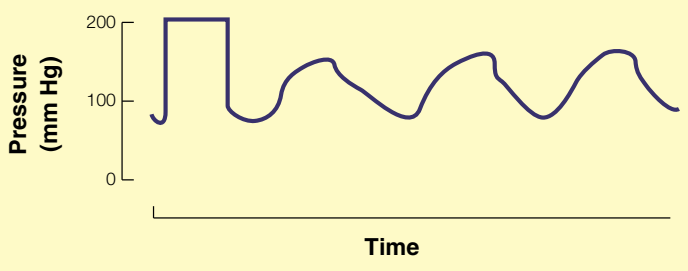
An under-damped arterial trace

Rapid response with overshoot and superimposed oscillations
Overestimates systolic and underestimates diastolic pressure



An over-damped arterial trace

Slow response with no overshoot
Phase shift as response gets slower



4

Non-invasive blood pressure measurement

Indirect methods of blood pressure measurement provide intermittent readings that tend to overestimate at low pressures and underestimate at high pressures. Readings vary according to the site of measurement owing to hydrostatic effects and increased arterial pulse wave velocities in the peripheries.

Manual methods – errors in the auscultatory method occur because of deficiencies in the transmission of sound energy owing to overlong or loose stethoscope tubing. Korotkoff sounds may be difficult to hear in hypotension and arteriosclerosis, resulting in underestimation of blood pressure. Readings in shivering patients require an excessively high occluding pressure and produce pseudohypertension. Further measurement errors may occur due to the auscultatory gap and confusion over whether phase IV or V is to be taken as the diastolic point. Phase V is closer to directly measured diastolic pressure with better inter-observer agreement, but may be absent in high output conditions (e.g. aortic regurgitation, pregnancy or after exercise).

Common sources of error are wrong cuff size, zero and calibration errors in aneroid manometers, and leaks from the pneumatic system that prevent a slow and controlled deflation of the cuff. The width of the cuff should be 20–30% of the circumference of the limb, of which the pneumatic bladder should span at least half and should be centred over the artery. Narrow cuffs yield erroneously high readings while wide cuffs underestimate the pressure.

Automatic methods based on the oscillometric principle rely on a regular cardiac cycle, and inconsistent readings may occur in patients with atrial fibrillation. Over-frequent readings may cause impeded blood flow and can produce inaccurate results. The appropriate cuff size must be used. The apparatus fails to record at pressures below 50 mm Hg.

Systolic pressure correlates well with a bias towards overestimation at low pressures and underestimation at high pressures. Mean arterial pressure shows a less satisfactory correlation with a similar systemic bias as does diastolic pressure. Newer devices deflate the cuff continuously rather than in steps, thus achieving a shorter measurement cycle.

Cardiac output measurement
Thermal indicator dilution with saline at room temperature is used to measure cardiac output. Sources of error relate to incorrect pulmonary artery catheter placement and incomplete mixing of the bolus with venous blood. The thermistor probe must be matched to the cardiac output processor and errors related to data input are reduced due to automated computer control that rejects any artefacts or non-exponential curves. Errors may arise when there is tricuspid incompetence or cardiac arrhythmias, and measurements should be averaged over several beats. Injections during the inspiratory or expiratory phases of mechanical ventilation may vary by up to 50% in calculated cardiac output. To minimize this error, injections are made at end-expiration.

Central venous pressure (CVP)
Low-pressure CVP measurements require that the saline manometer or tip of the stopcock in a transducer system are accurately referenced to the right atrium. If the manubriosternal junction is used the measured pressure is 0.5–1.0 kPa (5–10 cm H_2O) lower. Errors are also caused by the catheter being inserted too far or being blocked.

Pulse oximetry
Oximeters determine the oxygen saturation of haemoglobin by measuring the absorbance of light by arterial blood. The pulse oximeter is accurate to within ± 2% but is less accurate below saturations of 85% (Figure 5). Algorithms in commercial devices are based on studies in volunteers breathing low concentrations of oxygen, and calibration points are in the range 80–100%. Values below 70% are extrapolated from higher readings and may be grossly inaccurate. The absolute measurement of oxygen saturation in arterial blood (SaO_2) may vary between probes due to variability in the centre wavelength of light-emitting diodes (LEDs). This produces probe-to-probe variability in the absolute measurement of SaO_2 but trends are accurate. Sophisticated devices have a mechanism for identifying the sensor LED wavelengths allowing internal correction for different wavelengths.

Erroneous readings during pulse oximetry

Source of error	SpO_2 reading	Note
HbCO	Increase	50% HbCO content SpO_2 reads 95%
MetHb	Approaches 85%	Independent of arterial saturation
Fetal Hb	No effect	Identical to HbA
Sickle Hb	No effect	Right shift of HbO_2 so for given PaO_2, SpO_2 lower than expected
Anaemia	Decrease	Ht < 10% SpO_2 under-reads by 5%
Polycythaemia	No effect	
Methylene blue	Decrease	
Iodocyanate green	Lesser decrease	
Fluorescein	No effect	
Nail polish	Decrease	Especially blue colours

Hb, haemoglobin; HbA, haemoglobin A; HbCO, carboxyhaemoglobin; HbO_2, oxyhaemoglobin; Ht, haematocrit; MetHb, methaemoglobin; PaO_2, partial pressure of oxygen in arterial blood; SpO_2, oxygen saturation

The most common causes of errors are signal artefacts, which produce a poor signal-to-noise ratio. Artefacts have three major sources: ambient light, low perfusion and especially movement. The light detectors cannot differentiate the red light LED wavelength from other sources of light such as infrared heaters and room lights. Manufacturers have incorporated minimum values for signal-to-noise ratios below which the device displays no value for oxygen saturation (SpO_2) and modern oximeters display a low signal strength error message. Patient motion may be the most difficult artefact to eliminate. The device can average its measurements over a longer period to reduce the effect of an intermittent artefact but this slows the response time to an acute change in SaO_2. Increasingly sophisticated algorithms are being incorporated to identify and reject spurious signals.

Pulse oximetry is a global measure of functional oxygen saturation; it reveals nothing about adequacy of ventilation (e.g. patients with supplementary oxygen with a rising $PaCO_2$), or oxygen content (e.g. a grossly anaemic patient with severely deficient oxygen content and delivery to the tissues with normal saturations). Another source of error is a delay in response caused by instrumental and circulatory delay. The delay in response to step reduction in alveolar gas concentration is longer with a finger probe than with a ear probe. Cold-induced vasoconstriction, hypovolaemia and venous engorgement increase the response time. Atrial fibrillation may also cause measurement errors. Signals may be inadequate in the elderly with arterial disease.

Capnography
Modern CO_2 analysers are based on the absorption of infrared light by CO_2 in a gas sample based on the Beer–Lambert law. There are many sources of error. There must be no leaks in the breathing system, the non-rebreathing valve should be functioning perfectly and the inspired gas well mixed and of constant composition.

Errors related to the machine include the overlap of absorption wavebands of different gases so that the nitrous oxide (N_2O) absorbs some of the infrared energy within the CO_2 bandwidth and the CO_2 measurement is falsely high. A second error arises from 'collision broadening' in which the absorption spectrum for CO_2 is widened by the presence of other gases such as N_2O and N_2. The simplest method of eliminating these errors is to calibrate the instrument with gas mixtures containing the same background gas concentration as that to be analysed. Modern infrared analysers provide a simultaneous breath-by-breath analysis of CO_2, O_2, N_2O and the volatile agents. Microprocessor technology can automatically identify and correct for the presence of other gases. Exhaled alcohol can confound vapour concentration in these machines.

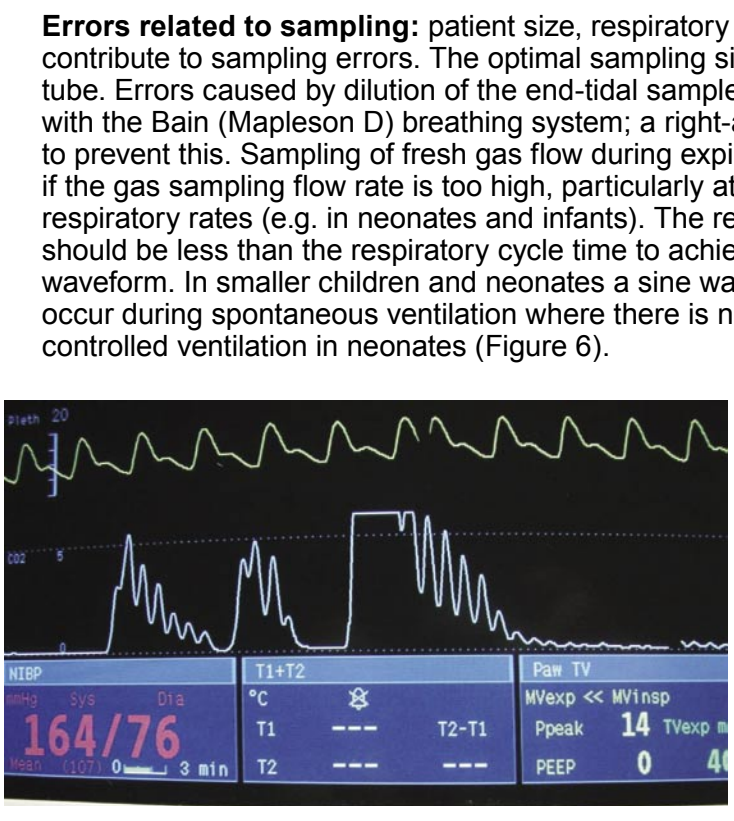
Response time – a capnograph needs a rapid response time because a slow response may result in failure to reach the true maximum values at normal breathing frequencies. This alters the capnogram profile with prolongation of phase II with a steeper phase III (similar to asthma), decreases in peak end-tidal CO_2 measurements and elevation of the baseline during rebreathing.

Water vapour – a slow response time is caused by long tubing and blockage in the sampling line by secretions or condensation of water vapour, hence the water trap. Liquids and particulate matter entering the measuring chamber cause erroneous readings of CO_2 owing to their high infrared absorbance.

Calibration – it is essential to calibrate the machine with the background gas and intended sampling system in place. Modern CO_2 analysers should have a three-point calibration with known concentrations of CO_2 at regular intervals. Frequent calibration checks are necessary to minimize errors from changes in atmospheric pressure.

Ram-gas effect – because infrared analysers act as partial pressure detectors of the number of molecules of absorbent gas in the sample chamber, changes in atmospheric pressure affect output. A pressure drop across the sampling line (e.g. inadequate suction along an extended sampling tube) causes under-estimation of end-tidal CO_2.

Errors related to sampling: patient size, respiratory rate and site of sampling may contribute to sampling errors. The optimal sampling site is at the top of the tracheal tube. Errors caused by dilution of the end-tidal sample by fresh gas flow can occur with the Bain (Mapleson D) breathing system; a right-angled connector should be used to prevent this. Sampling of fresh gas flow during expiration may occur inadvertently if the gas sampling flow rate is too high, particularly at lower tidal volumes and faster respiratory rates (e.g. in neonates and infants). The response time of the analyser should be less than the respiratory cycle time to achieve predictable CO_2 values and waveform. In smaller children and neonates a sine wave type of capnogram can occur during spontaneous ventilation where there is no clear alveolar plateau or with controlled ventilation in neonates (Figure 6).



6 Cardiogenic oscillations in a patient requiring assisted ventilation after opioid administration.

Errors related to the patient: during a prolonged expiration or end-expiratory pause, when the gas flow exiting the trachea approaches zero, the sampling of the monitor may aspirate gas alternately from the trachea and the inspiratory limb causing ripples on the expired CO_2 trace. These are called cardiogenic oscillations and appear during the alveolar plateau in synchrony with the heartbeat and are thought to be due to mechanical agitation of deep lung regions that expel CO_2-rich gas. Such fluctuations are smoothed over when the lung volume is increased by application of positive end-expiratory pressure. In patients with asthma or chronic obstructive airway disease, the end-tidal CO_2 may under-read, especially if the response time is slow.

Gas volumes
Dry spirometers require patient cooperation and depend on voluntary effort. Gas meters such as the Wright respirometer over-read at high tidal volumes and under-read at low tidal volumes because of inertia of the moving parts. ◆

Electricity and Magnetism

Adrian K Dashfield

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Most clinical measuring devices and anaesthetic equipment can be used with no knowledge of electronics. However, an understanding of this subject is necessary to use equipment to its full potential.

Electric charge
Early observations on the effect of electricity involved the production of 'static electricity' by friction when two materials such as glass and silk were rubbed together. These two materials become oppositely charged, the two forms of charge being positive and negative. It was subsequently discovered that the electron was responsible for the negative charge, while the atomic nuclei were found to be positive. The quantity of electricity associated with a body is measured in coulombs (C). 1 C is the charge associated with the electrolytic deposition of 0.001118 g of silver from silver nitrate solution.

Electric current
Electric current is the rate of passage of electric charge. Current is measured in C/s and this unit is called the ampere (1 A = 1 C/s). The ampere is the SI unit, thus 1 C is the charge deposited when 1 ampere flows for 1 second.

Resistance to flow of electricity
When a potential difference between two points on a conductor exists, current flows. The relationship between the current and the potential difference is expressed as Ohm's law. This quantifies the concept of resistance when electrons or ions move through a material under the action of an electric potential difference. This resistance is due to collisions of electrons resulting in heat as energy being imparted to surrounding molecules. Thus, a resistance of R units restricts the current from a source of E volts to I amperes, where:

$$I = E/R$$

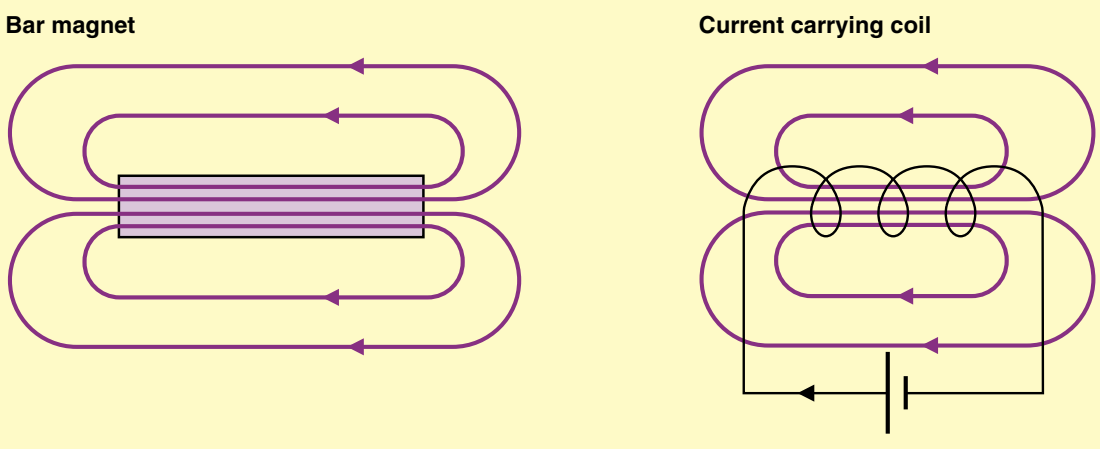
The unit of R is the V/A, which is abbreviated to the ohm (Ω), (1 Ω = 1 V/A).

If two resistors are connected in series the total resistance is the sum of the two. If the resistors are connected in parallel, the combined resistance is:

$$1/R = 1/R^1 + 1/R^2$$

Magnetism
Magnetic fields are regions in which there is attraction and repulsion of magnets and magnetizable pieces of metal. There is interaction with current-carrying conductors in electrical generators and transformers. There is a magnetic field within and around a permanent magnet and a conductor (in the form of turns of wire) carrying current. Imaginary lines indicating the presence of these phenomena, known as magnetic 'flux' (Figure 1) often represent the magnetic field.

Magnetic flux



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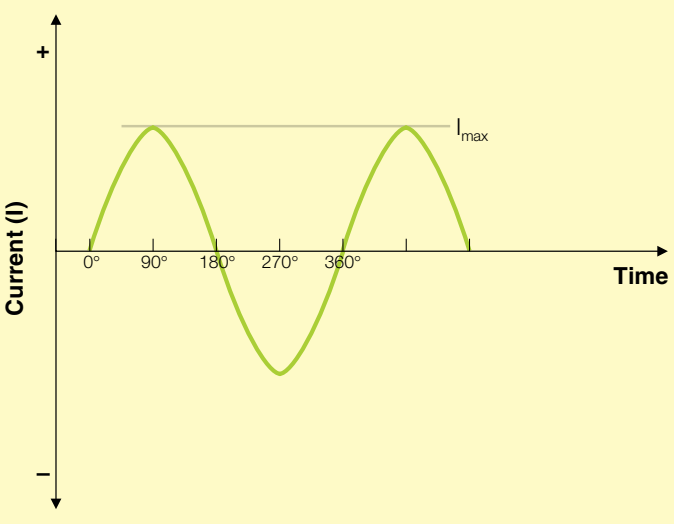
Electromagnetic induction and generation of electricity
Faraday's law of electromagnetic induction states that when flux linkage between a coil and a magnetic field is varying, an electromotive force (emf) proportional to the rate of change of flux linkage is induced in the coil. When a loop of wire is rotated between the poles of a permanent magnet the flux linkages change continuously. This induces an emf that reverses polarity every 180° of rotation. The flux linkage alternates from maximum when the plane of the coil is at right angles to the flux, through zero when they are coplanar, to a maximum in the reverse direction after 180° of rotation. The easiest way of doing this is to produce the flux by passing current through some other conductor and varying this magnetizing current. The more rapid the change using either method of induction, the larger the emf. This gives rise to a sinusoidally varying emf such as is encountered with alternating current (AC) mains electricity supply (Figure 2). The frequency of the AC is the number of complete cycles per second, expressed in hertz (Hz). Mains electricity is supplied at 50 Hz in the UK and at 60 Hz in the USA. The number of cycles per second is known as the frequency (f). The time T for a complete cycle of alteration is the period or periodic time. Thus f = 1–T. The unit of magnetic flux is the weber (Wb) and is defined so that flux linkage changing at the rate of 1 weber per second (in one turn) causes an emf of 1 volt to appear. Transformers can increase or decrease the size of an alternating emf as required. For transmission of power it is easier to work at high voltages with low currents in the cables. The voltages are brought down to safer values before reaching the consumer.

Alternating current produced by the rotation of a coil in a magnetic field



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Power
Sources of electrical current such as generators or electric cells are capable of creating excess positive or negative charge at their terminals. They cause separation of charges in otherwise neutral material. The attraction between opposite charges causes the flow of current. The work done by an electrical generator when it drives unit quantity of electric charge around a circuit is known as the emf force. 1 J of work done in driving 1 C of electricity is known as 1 V (1 V = 1 JC).

Power calculations are applied to even the simplest circuit design. Thus, if a 10 Ω resistor rated at 0.5 W passes 1 A through it:

$$W = EI$$

where: W = work in joules; E = potential difference in volts.

From Ohm's law:

$$E = IR$$

where: I = current in coulombs, R = resistance in ohms.

Substituting:

$$W = I^2R = 0.5^2 \times 10 = 2.5 \text{ W}$$

Capacitance
If two conductors of electricity are separated by an insulator, a capacitor is formed. The insulator is known as the dielectric. This simplest form of capacitor consists of two metal plates separated by a thin layer of air. If an emf is applied across the two conductors, the two plates are left in a 'charged' state.

A potential difference is associated with the separated charges that rise to be equal to the emf, at which point the process stops. An 'electric field' is set up in the dielectric in which attraction in a specific direction is experienced by any charged body. Capacitance is the charge stored (in coulombs) per volt of potential difference and is abbreviated to the farad (1 F = 1 C/V).

Three factors determine the capacitance between two bodies. Capacitance increases if the area of the bodies is increased. Decreasing the distance between the bodies intensifies the field and permits more electrons to arrive at one plate and repel from the other. Finally the introduction of an insulating material in place of a vacuum or air can increase capacitance depending on the material used. Capacitance in an electrical circuit is defined as volume taken up per unit change of pressure difference set up.

Impedance
The two electrical energy-storing devices (inductors and capacitors) behave differently from one another as frequency is changed. Electrical circuits may have mixtures of components, resistive and reactive, which are not simply proportional to the current. For mixed circuits the term impedance is used to suggest opposition. ◆

$$\text{Impedance (Z)} = \frac{\text{Size of potential difference across circuit}}{\text{Size of current through it}}$$

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Force, Mass and Acceleration

Jeremy A Langton
Richard Struthers

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In 1665, Isaac Newton developed the laws of motion that link the movement of a body with the force applied to it – allegedly after noting an apple falling from a tree. These built on the work of Galileo a century earlier and the advances in mathematics at that time. In 1687, in his book *Philosophiae Naturalis Principa Mathematica* Newton published three laws of motion along with laws of fluid dynamics, calculus, gravity and planetary motion. Newton's laws still hold true – and were used to place man on the moon – but Einstein's theories have surpassed them when dealing with forces in astronomy. Advances in quantum physics may provide a theory to link Newtonian physics with theories in particle physics and astronomy.

Newton's first law

An object will continue moving with a constant velocity, or remain at rest, unless acted upon by a resultant force.

This law deals with inertia. A resultant force is the sum of all forces acting on an object. If the forces are balanced there will be no resultant force and no change in velocity. Therefore a change in the velocity of an object needs an unbalanced force.

Newton's second law

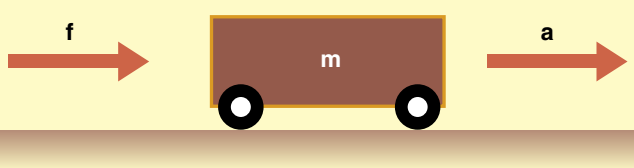
The resultant force acting on a body is proportional to its rate of change of momentum.

This quantifies the change in velocity by looking at changes in momentum. The momentum of an object depends on both its mass and velocity. If the mass is constant then the rate of change in velocity (or acceleration) is proportional to the resultant force (Figure 1). The second law can therefore be reworded as 'An unbalanced force acting on an object causes it to accelerate in the direction of the force at a rate proportional to the force applied and inversely proportional to the mass of the object.' This gives the equation:

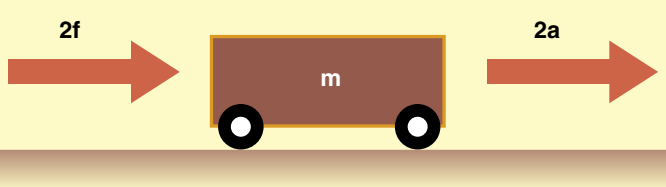
Force = Mass x Acceleration

The SI unit of force, the Newton, is defined as the force needed to accelerate a mass of 1 kilogram by 1 metre per second per second.

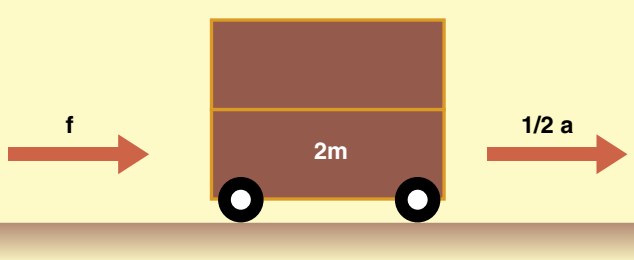
Force = mass x acceleration



a If an unbalanced force f is applied to an object with mass m then it will accelerate in the direction of the force at a rate a



b If twice the force (2f) is applied to the object then it will accerelate at twice the rate (2a)



c If the force f is applied to an object of twice the mass (2m) then it will accelerate at half the rate

Newton's third law

To each action there is an equal and opposite reaction.

This relates to the nature of forces. An action is taken to be a force or a change in momentum. Hence the apple falling from the tree towards the earth exerts an equal force pulling the earth towards it. However, because the mass of the apple is insignificant relative to the mass of the earth we do not see the resultant acceleration of the earth.

The third law also leads to the idea of the conservation of momentum – that after a collision between two bodies the sum of their momentums will be the same as before the collision. ◆

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Heat and Thermodynamics

David Birt

David Birt is Consultant Anaesthetist at Derriford Hospital, Plymouth, Devon, UK, and a Surgeon Commander in the Royal Navy. He qualified from St Mary's Hospital, London, and trained in anaesthesia in the South West of England and Glasgow. His special interests include paediatric anaesthesia and regional blockade.

The concepts of heat energy and temperature are easy to confuse. Heat is a measure of the vibrational movement of molecular or atomic particles; it is determined by the kinetic energy in each particle and the number of particles involved. Temperature is a measure of the ability of one object or area to transfer heat to another and is independent of the quantity of matter. Consequently, a small object may be at a higher temperature than a large one, but it does not necessarily possess more heat energy. Like all energy, the derived SI unit for quantifying heat is the joule (J). Temperature is measured by various linear scales but the SI unit is the degree kelvin (K), named after Lord Kelvin, one of James Joule's close associates.

Calorimetry and the laws of thermodynamics

Organic compounds contain chemical potential energy derived originally from photosynthesis. The amount of stored energy can be determined by calorimetry. This process involves the combustion of the compound to carbon dioxide and water in an oxygen-containing chamber surrounded by a known quantity of water or ice. By measuring the rise in the temperature of the water or the quantity of ice that melts, the amount of energy released may be calculated.

In biological systems, the chemical potential energy in certain organic compounds is converted from one form to another. This process is governed by the laws of thermodynamics. There are four laws, including the improbably named zeroth law, but two of them are important in biological systems.

The first law of thermodynamics states that, in a closed system, the total quantity of energy in that system must remain constant. If glucose undergoes combustion to carbon dioxide and water, it produces the same amount of energy whether that occurs with oxygen in a calorimeter or by complex metabolic pathways such as glycolysis and oxidation. Alternatively, if amino acids are metabolized by human metabolic pathways, the end product, urea, possesses chemical potential energy and the amount of energy produced is less than that from complete combustion in a calorimeter. The energy deficit is stored in the urea, however, and the total amount of energy in the system remains constant.

The second law of thermodynamics relates to the entropy, or disorder, of a system. It states that a system's entropy increases if energy is exchanged. Therefore, when two objects exchange heat, the heat flows from the object with the higher temperature to that with the lower, until equilibrium is reached at the highest level of entropy. The transfer of this heat is achieved by the mechanisms described in Figure 1. In anaesthetic practice, heat loss occurs through a combination of these mechanisms. Conduction occurs between a patient and his surroundings, convection then assists heat transfer to the wider environment, while radiation heat loss occurs from skin and visceral surfaces.

Some physical mechanisms of heat transfer

Mechanism	Description	Comments
Conduction	The flow of heat energy through solid matter from places of high temperature to those of lower temperature without movement of the matter itself	• The rate and magnitude of conductive heat transfer across an object is determined by its shape, the temperature gradient across it and the thermal conductance of the substance from which it is made
Convection	The flow of heat energy through a liquid or gaseous fluid from places of higher temperature to places of lower temperature by movement of the fluid itself	• In contrast to conductive heat transfer, convection involves the higher energy molecules retaining their heat energy, moving within the medium, and carrying heat energy with them • The two basic forms are natural convection, when the fluid movement is maintained by its tendency to move as it warms, and forced convection, when the fluid movement is assisted
Radiation	The flow of heat from places of higher temperature to places of lower temperature by means of electromagnetic waves	• Radiation is independent of fluid movement and is the only means of transferring heat across a vacuum • All visible objects emit radiation in the form of light waves but as temperature increases, both the range of frequencies and the quantity of emitted radiation increase

Deriving mechanical work from heat

Mechanical work can be derived from heat energy. As heat energy is applied, individual particles of matter vibrate with greater amplitude and the distance between them increases. This results in expansion. Inevitably, heat is lost from such a system but, in obedience to the first law of thermodynamics, the total energy in the system remains constant. Therefore, the heat input equals the heat output plus the amount of work done. Complete conversion of heat to mechanical work without the loss of some energy to the surroundings is impossible. This principle is applied to thermostats and vaporizers that use bimetallic strips or in heat engines, the most familiar of which is the internal combustion engine. ◆

Mathematical Concepts

John Curnow

John Curnow is Biomedical Engineer at Derriford Hospital, Plymouth, UK. His specialist interest is in patient monitoring and the application of computing techniques in medicine.

Science uses mathematics to model theories and to provide methods that allow theories to be applied to solve practical problems. Anaesthetists as members of a science-based profession can gain insight into their subject and produce better forecasts of the probable outcomes using mathematics and mathematical modelling.

Mathematics describes processes using algebraic equations and solves the problems using numeric methods. The general form of a mathematical algebraic equation is written as y = fn(x) where fn(x) is called the function of x. A function is a basic mathematical method used to describe how the value of a variable y is controlled by the value of another variable x. In general, the variable x is the variable the researcher has control over, and it can be given values that can be used to calculate the value of y. If a graphical representation of the function is being drawn it is usual practice for the controlled variable x to be represented by the horizontal axis and the variable y by the vertical axis.

Indices

The use of indices is one of the shorthand methods used in mathematics. If a mathematical equation requires a number of multiplications of the same variable (i.e. n.n.n) this is written as n^3 where the 3 is called the index of n. The general form is written n^x. If the value of x is less than 1 it represents a root of the number n, which is the basic number that if multiplied by itself 1/x times, gives n as the answer. Thus $n^{1/2}$ indicates the square root of n and $n^{1/3}$ the cube root of n. If the index is negative it implies it is the reciprocal of the result that is needed (i.e. $x^{-n} = 1/x^n$).

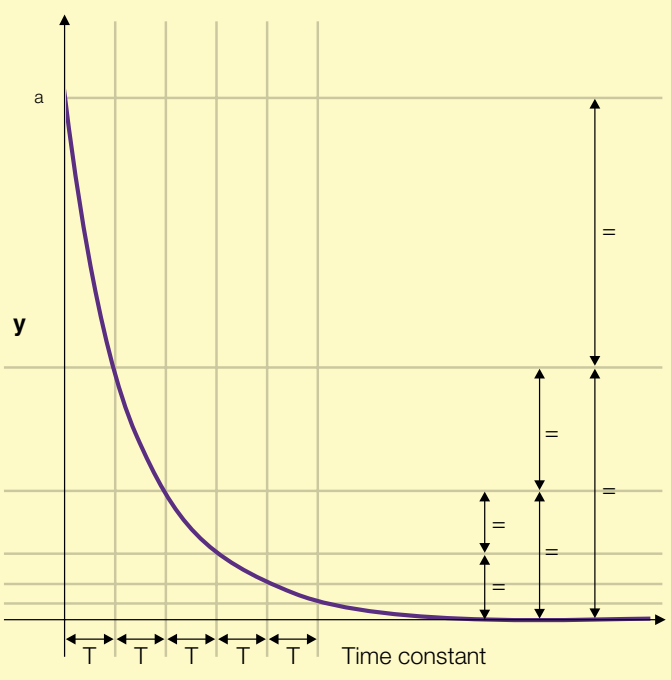
Any value of x can be used and the value of the function for simple values of x such as 2 or 3 can be found in tables. Computers and calculators have inbuilt methods for calculating n^x for any real value of n and x.

Exponential

Exponential functions are common in medicine and anaesthesia; examples include the growth of a bacterial colony and the charging and discharging of a capacitor in a defibrillator. A specific form of the index method, briefly described above, is the exponential where n is replaced by e (Euler's number) more commonly called the natural number which has a value of 2.718. The general, mathematical equation for an exponential is $y = a.e^x$. The main properties of the function are a which represents the initial value of y, and x which is the power or index. Values for the function e^x can be found in mathematical tables and are available on calculators and computers.

The index of e, in many applications of this equation will be a time period and the equation can then be written as $y = a.e^{\lambda.t}$. Where a is the initial value of y and λ is a constant for the particular exponential function which is called the time constant. The time constant is related to an important value of an exponential curve, the half-life T by the equation $T = 0.693/\lambda$ making the above equation $y = a.e^{t/T}$. At any point on an exponential curve, a point T seconds later will have a y value half of that at the initial point as shown in Figure 1. In general the value of y halves every T seconds along the curve and thus is a useful way to plot an exponential curve (Figure 1). One application of the exponential function in medicine is in modelling radioactive decay of radioisotopes. In this case the time constant is called the half-life of the isotope and it represents the time taken for the isotope activity to reach half its value.

Exponential curve $y = a.e^{-t/T}$



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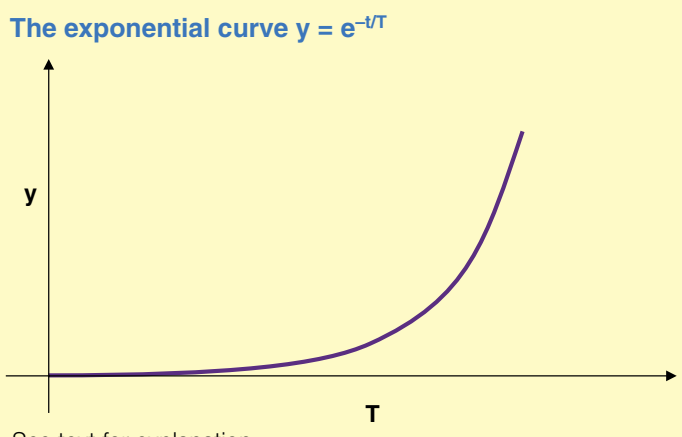
As an application of the exponential function consider the discharge of a capacitor through a resistor. This follows an exponential function where the initial amplitude of the potential across the capacitor is V volts and it follows an exponential curve towards zero. The time constant of this circuit is C.R seconds, where C is the capacitance of the capacitor in farads and R is the resistance of the resistor in ohms. An application of this in equipment used by anaesthetists is the simple capacitor discharge defibrillator. In this case, the discharge resistor is usually considered to be the patient circuit resistance consisting of electrode and patient resistance between the two paddles and the charge time is set by an internal resistor.

Logarithms

The logarithm is a mathematical method used to make calculations of index representations easier. If $y = a^x$ then the logarithm is defined such that $x = \mathrm{Log}_a(y)$ where a is called the base of the logarithm. The most common base used for logarithms is 10. Logarithms are used extensively in the modelling of data and to transform data when producing graphs. A graph of a function that follows an exponential function for instance can be plotted as a straight line if the natural logarithm of the function is drawn. This is easier to use and allows certain features such as the time constant to be identified simply. Figure 2 displays the graph of $e^{t/T}$, it would be difficult to identify the time constant of the process from this. Figure 3 displays the graph of $\mathrm{Ln}\ (e^{t/T})$, which is a straight line. The time constant is the slope of this line and is easy to measure.

The exponential curve $y = e^{-t/T}$



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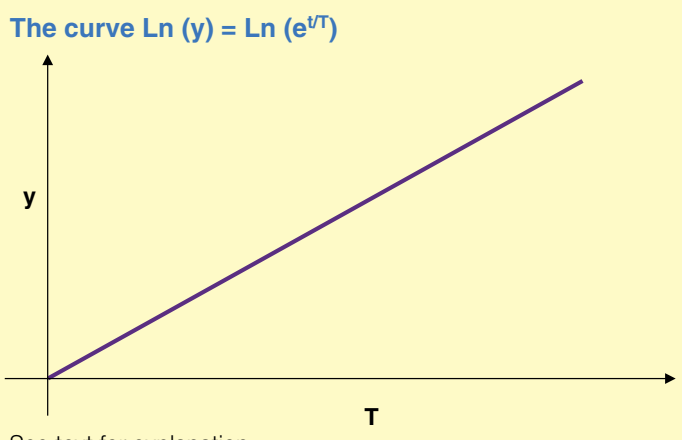
The curve $\mathrm{Ln}\ (y) = \mathrm{Ln}\ (e^{t/T})$



See text for explanation

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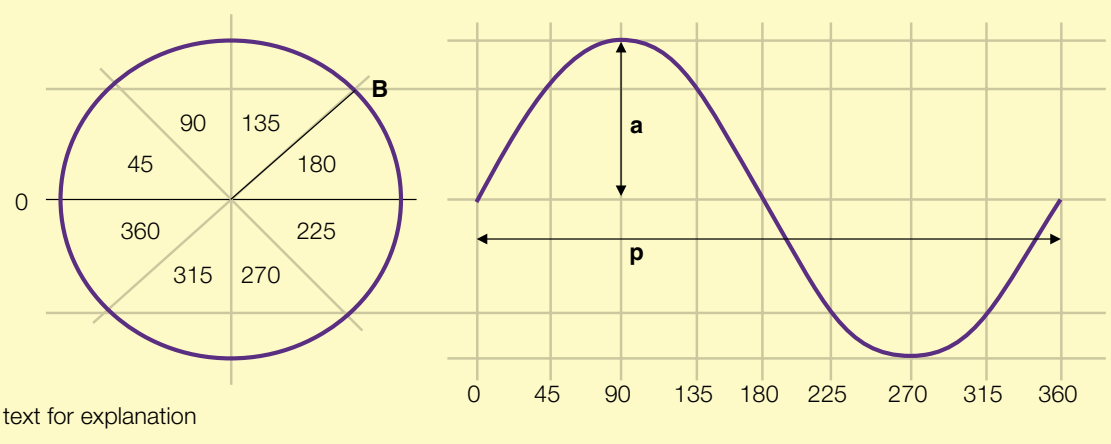
An example of the use of a natural logarithm plot to display an exponential function and allow easier understanding and data calculation is in the modelling of pharmacokinetics and pharmacodynamics. Each compartment of the model is plotted as a logarithm of the plasma concentration against time. The model can be fitted to real data collected from patients to show the interaction of each compartment to the whole model.

Sinusoid

Some functions are regularly thought of by their graphical representation and can also be described by a specific mathemat-ical function. A sinusoidal waveform is shown in Figure 4 with the two main features of the sinusoid, a the amplitude which is the maximum positive and negative excursion of the waveform and p the cycle length of the waveform. The horizontal axis of the graph can be a time scale with the waveform showing the amplitude change with time. In this case the cycle length is called the period of the waveform. The frequency, or number of cycles per second f of the waveform is defined by f = 1/p where p is measured in seconds, the unit of frequency is the hertz where 1 hertz is the frequency of a waveform with a period of 1 second.

A sinusoid can be plotted from circular motion. If you view a rotating object from one side as shown in Figure 4, the position of a point on the circumference 'B' plotted against angle of rotation or time assuming the point is moving at constant speed around the circumference, will follow a sinusoidal waveform as shown. If the horizontal axis represents the angle of rotation of the point from its start point then one cycle or one period is represented by one rotation or an angle of 360°.

Sine wave



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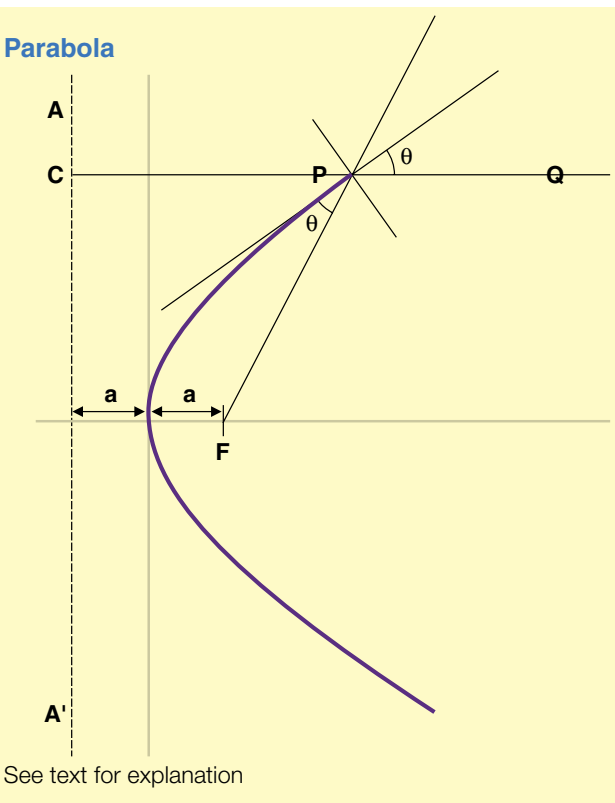
The sine wave is most commonly found as the wave shape of the mains electricity supply. In the UK, the frequency is 50 Hz, which gives a period for each complete wave of 1/50 s or 100 ms. The potential is usually quoted as 230 V, which is the root mean square value. For a sine wave this is calculated as peak value divided by 1.414 ($2^{½}$). Therefore, the peak value of each cycle of the mains supply is 230 x 1.414 or 325 V.

Parabola

The conic sections (circle, ellipse, hyperbola, parabola) are standard curves that are the boundary shapes of cutting a circular cone at different angles to its axis. Each conic section has a set of features that describe it. For the parabola (Figure 5), the point F is called the focus of the parabola, the line AA' is called the diretrix of the parabola and these form the basis for its construction. The distance from the directrix to the y axis and the focus to the y axis are equal and represented by 'a'. The parabolic shape is defined such that the distance from any point on the curve is equal distance from the line AA' the directrix represented by PC and F the focus, represented by PF which gives PC = PF.

Parabola



See text for explanation

5

The parabola has a unique feature demonstrated at point P. The line from F the focus to P the point of interest has an angle θ to the tangent to the curve at the point. A line drawn at the equal angle away from the point in the opposite direction PQ will always be parallel to the axis of the parabola. This means that if a reflector for any radiation is designed to have a parabolic cross-section any radiation coming from the focus will be 'focused' into a parallel beam and any radiation that enters such a reflector parallel with the axis will be 'focused' to a point at the focus of the parabolic cross-section.

A parabola is the shape of a reflector used for many different radiations from light through radiowaves to microwaves. A specific application is in spotlights used to intensify light in one area such as in theatre lamps where each light source has its own parabolic reflector. Because the lamp is not a point source the beam will diverge a little, but the main beam will be focused. ◆

Measurement of Gas Concentrations

Chris Seavell

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Accurate, fast, continuous measurement of inspired and expired gases and volatile agents is vital to the safe practice of modern anaesthesia. The technology required is readily available in compact form. The user should check the manufacturer's handbook to determine which method is utilized in the equipment being used.

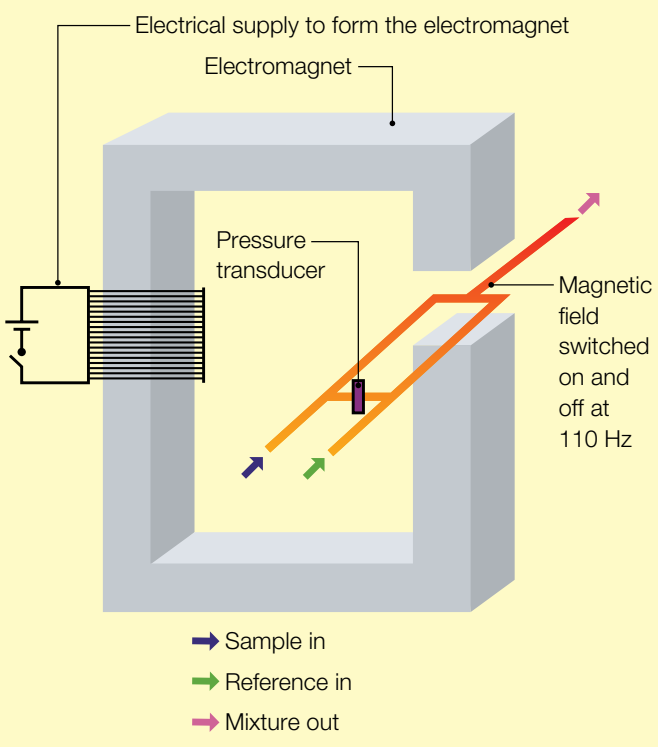
Oxygen concentration measurement

The three methods commonly used are the paramagnetic technique, the fuel cell (galvanic cell) and the polarographic cell (Clark's electrode).

Paramagnetic technique

Oxygen is unique among anaesthetic gases because it has unpaired electrons in its outer shell. This makes it paramagnetic – attracted into a magnetic field. Most other gases, including nitrogen, are diamagnetic and are repelled from a magnetic field. The Pauling apparatus was the first to use the paramagnetic technique. A sample of gas is drawn into a chamber containing a sealed, glass, nitrogen-filled dumb-bell arrangement, suspended in a powerful permanent non-homogeneous magnetic field by a small wire. Oxygen in the sample is attracted to the magnetic field, thus displacing the spheres. To improve accuracy, the displacement of the spheres can be prevented by an electric current applied to the dumb-bell arrangement such that the current required is proportional to the oxygen concentration. This is the principle of null deflection. Datex has refined this technique (Figure 1) so that the gas sample is drawn into a pneumatic bridge at the same rate as a sample of air (i.e. reference value of 21% O_2). An electromagnet is placed over the junction of these two tubes and switched on and off at 110 Hz. If the two samples contain a different oxygen concentration, a pressure difference is produced because of the paramagnetic properties of oxygen. This pressure difference is detected by a transducer and is proportional to the difference in oxygen concentration between the two samples. From this, the oxygen concentration of the sample can be calculated and displayed.

Datex paramagnetic analyser



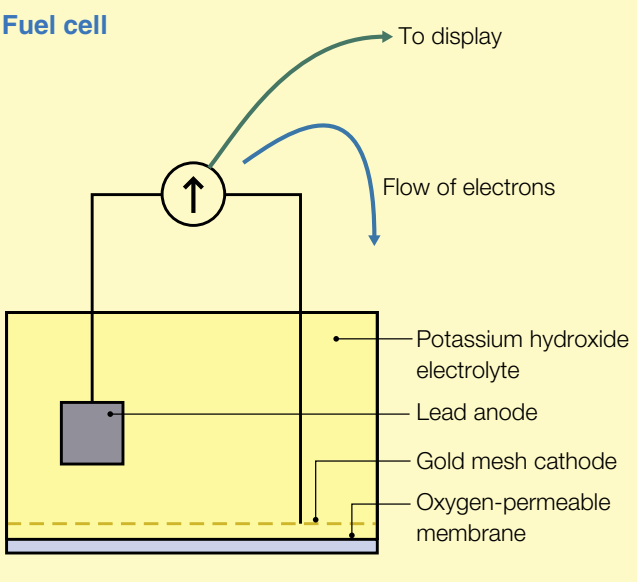
1

Fuel cell (galvanic cell)

The fuel cell is effectively a battery requiring oxygen for a current to flow (Figure 2). Oxygen from the sample being analysed diffuses through the base membrane and is consumed at the gold mesh cathode:

$$O_2 + 4e^- + 2H_2O \rightarrow 4(OH)^-$$

Fuel cell



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The electrons are supplied from the reaction at the anode:

$$Pb + 2(OH)^- \rightarrow PbO + H_2O + 2e^-$$

The voltage produced is thus proportional to the concentration of oxygen. This device has to be temperature compensated and eventually wears out. If the gas sample is supplied under pressure the fuel cell reads erroneously high (the Ram-gas effect).

Polarographic cell (Clark's electrode)

Oxygen diffuses through a membrane and combines with elec-trons supplied by a voltage of about 0.6 v. The small current produced is amplified and displayed as oxygen concentration. Temperature compensation is required. This device is seldom used for analysis of gas concentrations though it is still used for the estimation of the concentration of oxygen in blood.

Measurement of N_2O, CO_2 and volatile agents

Infrared absorption spectroscopy

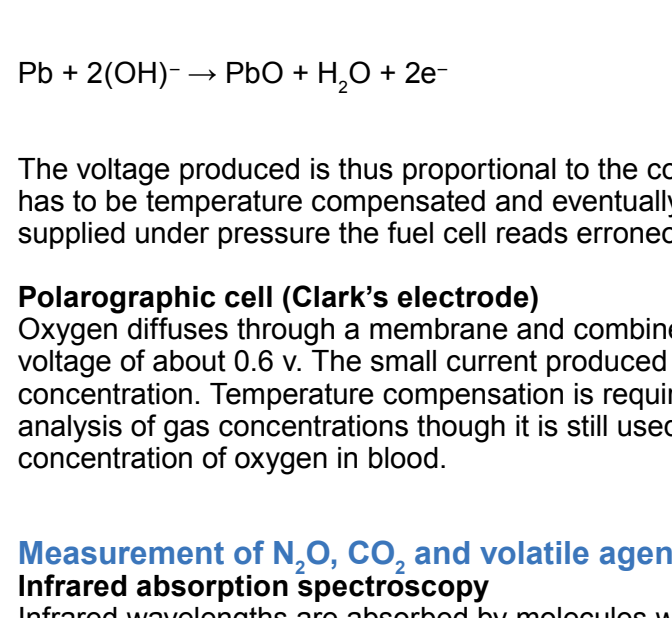
Infrared wavelengths are absorbed by molecules with two or more different atoms such as carbon dioxide (CO_2), nitrous oxide (N_2O) and volatile agents. Each molecule has a unique 'fingerprint' wavelength absorption pattern. Absorption is proportional to the concentration present and follows the Beer–Lambert law:

$$A = \varepsilon dC = \log \frac{I_0}{I_I}$$

where A is absorption, ε is molar extraction coefficient, d is path length through which radiation passes, C is concentration of sample, I_0 is incoming intensity and I_I is exit intensity.

The basic components of infrared spectroscopy are described in Figure 3. A unit consists of an infrared source, measuring chamber, a filter and a detector/amplifier. In an infrared analyser measuring only one gas, a single filter is used, but to allow measurement of several different gases and vapours simultaneously the filter is made up of several different rotating windows, each of which allows only infrared radiation at the peak absorption wavelength of the gases under test. For example, 4.3 μm for CO_2, 3.9 μm for N_2O and 3.3 μm for volatile agents (monitors capable of differentiating between different volatile agents use several different wavelengths between 3.24 and 3.39 μm). Rotating filters also cause a changing signal to strike the detector, which makes it easier to amplify. When CO_2 absorbs infrared wavelengths its vibrational energy increases. This can be passed on to N_2O allowing CO_2 to absorb more infrared wavelengths. This appears as if the spectrum is broadened and is called 'collision broadening'. It is compensated for automatically in new monitors.

Principles of infrared spectroscopy



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The absorption of each of the wavelengths is measured by the detector and compared with reference data to allow display of the concentrations of gases and volatile agents. The system allows rapid detection of CO_2, N_2O and volatile agents though larger molecules such as the volatile agents have a slightly slower response time of about 750 ms compared with 250 ms for CO_2 and N_2O. Alcohol has a similar absorption spectrum to the volatile agents and high expired concentrations of alcohol can cause interference.

Piezoelectric effect

Quartz crystals can be set to oscillate at high frequency when placed in an electric field. They can be coated with an oil that absorbs volatile agents. Through the absorption process, the set frequency of the crystals changes, allowing rapid measurement of volatile concentration. Neither CO_2 nor N_2O can be measured in this way and the method is unable to distinguish between different volatile agents.

Photoacoustic spectroscopy

If N_2O, CO_2 and volatile agents are irradiated with pulsatile infrared radiation they absorb energy (see above) and expand causing a pressure increase. This can be detected by a microphone and the concentration displayed. As with infrared spectroscopy, a rotating filter is used to produce the desired frequency. Photoacoustic spectroscopy seldom requires recalibration and can produce fast response times.

Raman scattering

When N_2O, CO_2 and volatile agents are irradiated with an argon laser (488 nm) they each give off a characteristic set of different wavelength energies. These 'new' wavelengths are filtered out from the argon laser and passed through another series of filters, specific to each gas being tested, to identify each agent.

Interferometry

Two parallel beams of light pass through sample chambers, one containing air and the other the anaesthetic mixture. There is a difference in velocity of light through the two chambers so that when the beams are brought back together an interference pattern is seen. The amount of shift of the pattern is proportional to the concentration of anaesthetic gas. The interferometer can only provide a one-off measurement of a known gas; however it is cheap, portable and accurate and can be used to calibrate vaporizers.

Mass spectrometry

A sample is continuously drawn into a chamber from where a few molecules are allowed to diffuse into a near vacuum ionization chamber. Here, the sample is hit by a stream of electrons, which causes some of the molecules to become charged. These charged particles are accelerated by a negatively charged plate and are separated out by molecular weight in one of two ways. In a magnetic mass spectrometer a powerful magnet bends the line of trajectory, the lightest particle being bent the most. The particles are detected by a series of up to six plates each sampling different molecular weights. In a quadruple mass spectrometer, four charged rods are arranged in parallel around the line of accelerated particles. By varying the charge on the rods, only particles of a certain mass pass through to a detector plate. In both methods, the ionization process breaks some molecules down into smaller components (cracking pattern) thus allowing differentiation of molecules with the same molecular weight (e.g. CO_2 and N_2O with a molecular weight of 44). Mass spectrometry can rapidly (less than 0.1 s) measure several different gases simultaneously and requires only small samples. However, spectrometers are bulky and costly and seldom used in theatre.

Clinical aspects

Sampling

Clinical uses of capnography are given in Figure 4. The gas to be analysed can be sampled by sidestream or mainstream analysis (Figure 5).

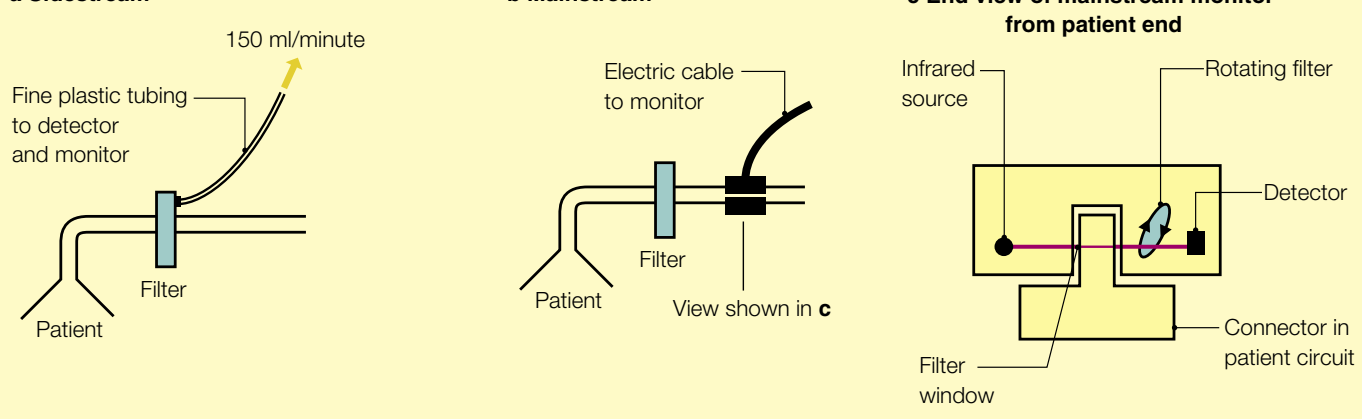
Sidestream analysis: gas is drawn off continuously usually at about 100–150 ml/minute from the breathing circuit, into the detectors inside the monitor. For accuracy, only the tubing provided by the manufacturer should be used. Depending on the technique used for detection, the sample gas may be returned to the breathing circuit, thus preventing a leak. This allows low flows to be used in a circle system.

Clinical uses of a constant carbon dioxide trace

- Respiratory rate
- End-tidal CO_2 estimates hypo- or hyperventilation (increased (alveolar–arterial) difference with significant lung disease)
- Indication of ventilation to perfusion mismatch (sloping up slope)
- Detection of oesophageal intubation
- Can act as a disconnect alarm if correctly set
- Detection of rebreathing (sloping down slope and eventually raised baseline – pattern depends on circuit)
- Reveals wear off of paralysis – regular pattern of CO_2 is interrupted and dips may appear in the expired trace
- Sudden loss of trace
  - Disconnection
  - Cardiac arrest
  - Gas/fluid emboli
- Rising CO_2 – part of diagnosis of malignant hyperthermia

4

Sidestream and mainstream gas analysis



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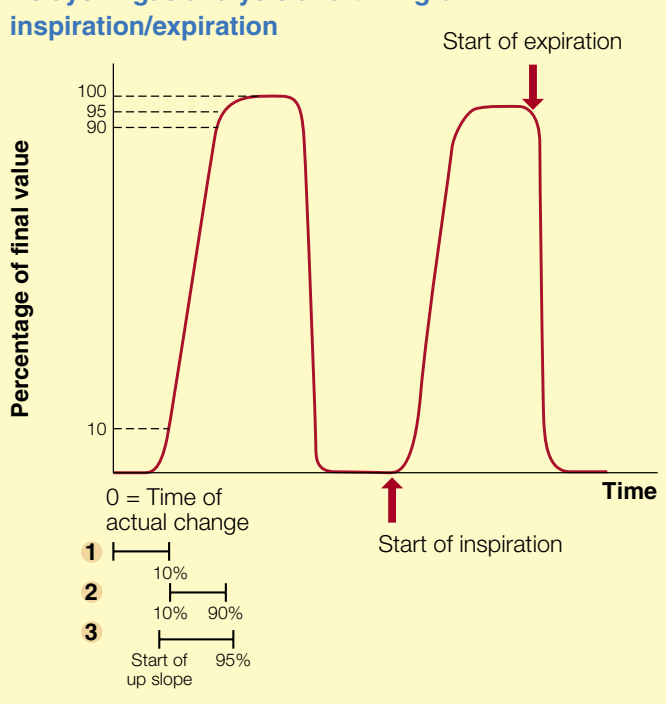
Advantages

- There is a lightweight connector to the breathing circuit and no bulky detector in the circuit (major factor).
- Multi-analysis is possible via the same circuit tube (e.g. N_2O, CO_2 and volatiles).

Disadvantages

- The lag time (Figure 6) from the sample leaving the breathing circuit to the monitor is long.
- Water vapour contamination occurs if the take-off point is placed in the circuit between the patient and a filter or if no filter is used.
- Mixing of fresh gas flow and expired gas can occur in the sample tubing, especially at small tidal volumes and in spontaneous ventilation, producing erroneously low end-tidal readings; to prevent this, the sample tubing take-off point should be as close to the patient's trachea as possible.

Delays in gas analysis and timing of inspiration/expiration



1 Delay time – time of actual change to 10% rise (increased with sidestream analysis)
2 Rise time – from 10% to 90% value (prolonged with V/Q mismatch)
3 Response time – first upward movement to 95% value

6

Mainstream analysis: the gas to be analysed does not leave the patient circuit, but a detector is placed into the sample. This technique can be used with a fuel cell attached to the common gas outlet or with infrared radiation detection for CO_2.

Advantages

- immediate readings
- no water vapour contamination possible
- no gas lost from circuit.

Disadvantages

- bulky attachment at patient end of circuit (major factor)
- only one gas can be measured at a time
- needs a clean window to prevent erroneous readings.

Sources of error

Potential sources of errors linked to the instrument are calibration error, electrical error, alcohol contamination or collision broadening. Errors related to the sampling technique include incorrect sampling tubing, water or secretion contamination, mixing of fresh and expired gas and the Ram-gas effect. If the patient has a high alveolar–arterial (A–a) difference the equipment may under-read end-tidal values. ◆

FURTHER READING

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Parbrook G D, Kenny G N C, Davis P D. *Basic Physics and Measurement in Anaesthesia*. Oxford: Butterworth-Heinemann, 1998.

Measurement of pO_2, pCO_2, pH, Pulse Oximetry and Capnography

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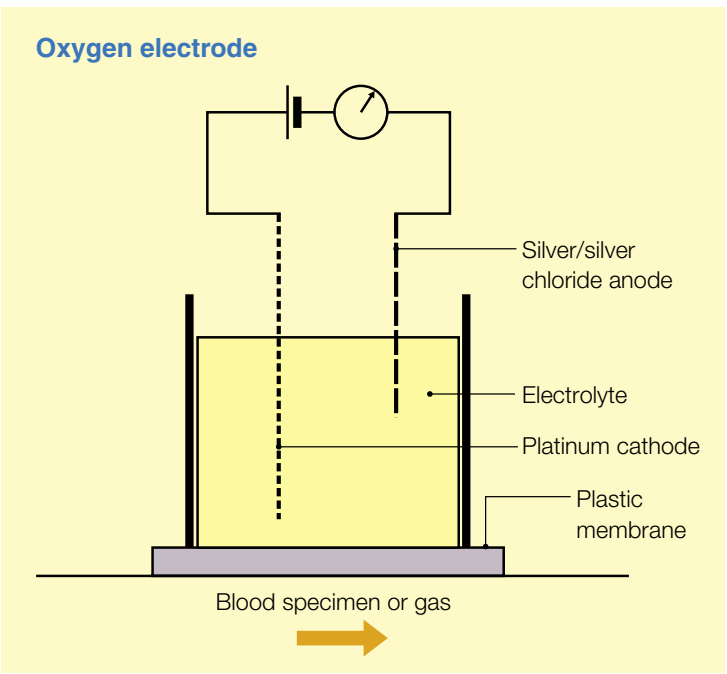
The assessment of respiratory function and metabolic state with blood gas analysis, combined with continuous monitoring from pulse oximetry and capnography is routinely performed in patients during anaesthesia, in resuscitation and in the critically ill.

Blood gas measurement
Blood gas analysers report a wide range of results, but the only parameters directly measured are the partial pressures of oxygen (pO_2) and carbon dioxide (pCO_2) and blood pH. The haemoglobin saturation (HbO_2%) is calculated from the pO_2 using the oxygen-dissociation curve and assumes a normal P50 and that there are no abnormal forms of haemoglobin. Some blood gas analysers incorporate a co-oximeter that directly measures the various forms of haemoglobin including oxyhaemoglobin, total haemoglobin, carboxyhaemoglobin and methaemoglobin. The actual bicarbonate, standard bicarbonate, and base excess are calculated from the pH and pCO_2 using the Siggard-Anderson nomogram derived from a series of *in vitro* experiments relating pH, pCO_2 and bicarbonate.

Practical precautions: a heparinized, freshly drawn, bubble-free, arterial blood sample is required. Heparin is acidic and if too much is present, the measured pCO_2 and calculated bicarbonate are spuriously reduced. Delay in measurement allows continued metabolism by the erythrocytes and reduces pH and pO_2 and increases pCO_2. Keeping the specimen on ice allows accurate measurement to be delayed for up to 1 hour. Air bubbles introduce error and cause a fall in pCO_2 and an increase in pO_2.

The polarographic (Clark) oxygen electrode measures the oxygen partial pressure in a blood or gas sample. A platinum cathode and a silver/silver chloride anode are placed in a sodium chloride electrolyte solution, and a voltage of 700 mv is applied (Figure 1). The following reactions occur.

- At the cathode: $O_2 + 2H_2O + 4e^- = 4OH^-$.
- In the electrolyte: $NaCl + OH^- = NaOH + Cl^-$.
- At the anode: $Ag + Cl^- = AgCl + e^-$.

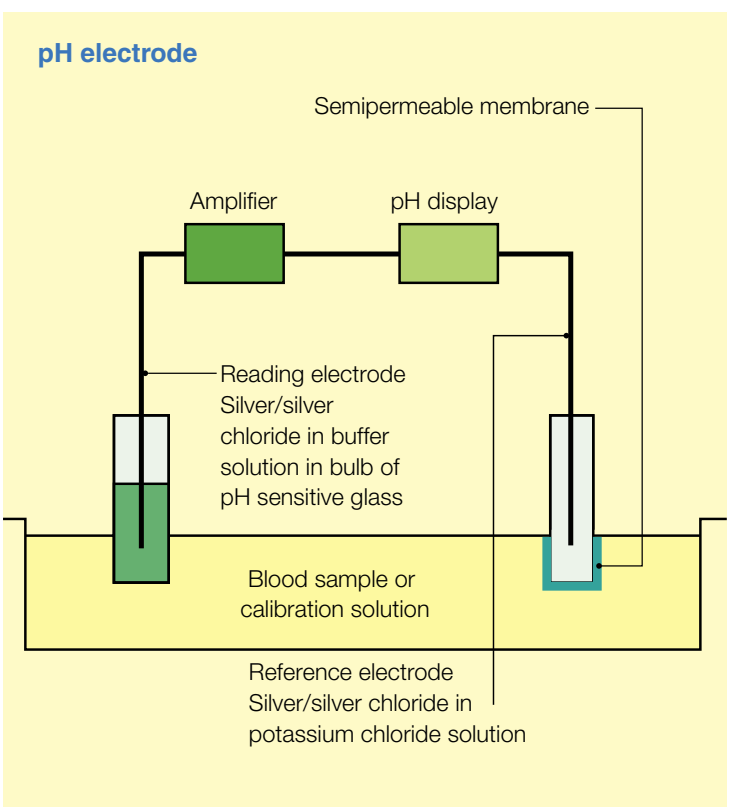


1

Electrons are taken up at the cathode and the current generated is proportional to oxygen tension. A membrane separates the electrode from blood, preventing deposition of protein but allowing the oxygen tension in the blood to equilibrate with the electrolyte solution. The electrode is kept at a constant temperature of 37°C and regular checks of the membrane are required to ensure it is not perforated or coated in proteins. Sampling two gas mixtures of known oxygen tension allows calibration.

pH electrode: if a glass membrane separates two solutions of different hydrogen ion concentration a potential difference develops that is proportional to the hydrogen ion gradient between the two. A potentiometric electrode is designed to measure the potential between the sample and a buffer solution.

A measuring silver/silver chloride electrode is encased in a bulb of special pH-sensitive glass and contains a buffer solution that maintains a constant pH (Figure 2). This glass electrode is placed in the blood sample and a potential difference is generated across the glass, which is proportional to the difference in hydrogen ion concentration. The potential is measured between a reference electrode (in contact with the blood via a semi-permeable membrane) and the measuring electrode. Both electrodes must be kept at 37°C, clean and calibrated with buffer solutions of known pH.



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The Severinghaus or carbon dioxide electrode is a modified pH electrode in contact with sodium bicarbonate solution and separated from the blood specimen by a rubber or Teflon semi-permeable membrane. Carbon dioxide, but not hydrogen ions, diffuses from the blood sample across the membrane into the sodium bicarbonate solution, producing hydrogen ions and a change in pH.

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

Hydrogen ions are produced in proportion to the pCO_2 and are measured by the pH-sensitive glass electrode. As with the pH electrode, the Severinghaus electrode must be maintained at 37°C, be calibrated with gases of known pCO_2 and the integrity of the membrane is essential. Because diffusion of the CO_2 into the electrolyte solution is required the response time is slow at 2–3 minutes.

Hypothermia, pH-stat, and alpha-stat: the solubility of all gases, including CO_2 and O_2, in blood increases with a fall in temperature. Thus, hypothermia causes the pO_2 and pCO_2 to fall and the pH to rise. As analysis of a sample taken from a hypothermic patient occurs at 37°C, the pO_2 and pCO_2 results are artificially high. The result can be corrected to represent the pH, pO_2 and pCO_2 at the patient's temperature. In practice such correction is unnecessary. When cardiopulmonary bypass was developed it was thought that the reduction in $PaCO_2$ during hypothermia would result in cerebral vasoconstriction. In pH-stat management, CO_2 was added to the oxygenator to maintain a temperature-corrected $PaCO_2$ of 5.3 kPa and a pH of 7.4. The alternative and now standard strategy is that of alpha-stat in which a non-temperature corrected $PaCO_2$ of 5.3 kPa and a pH of 7.4 is maintained. The true value of $PaCO_2$ is lower than this but the associated alkalosis is thought to aid enzyme function during hypothermia.

Pulse oximetry
Pulse oximeters provide a safe, reliable and non-invasive method of continuous arterial oxygen saturation monitoring. They are standard monitors during anaesthesia and in the ICU. Haemoglobin saturation is measured from the absorption of light emitted from a probe placed on a digit or ear lobe.

The probe contains two high intensity, monochromatic, light- emitting diodes, one emitting red light (660 nm) and the second infrared (940 nm) on one side and a photodetector on the other to measure the amount of light transmitted through the finger. The saturation of haemoglobin is calculated from the absorption at the two different wavelengths. The diodes are switched on in sequence with a pause with both diodes off. This pause allows the photocell and microprocessor to compensate for any ambient light. By analysing the pulsatile changes in light absorption, the absorption by venous blood and tissue is deducted and arterial saturation measured. The measurements are plotted against a standard calibration curve, determined by direct measurements of the arterial oxygen saturation of normal resting healthy volunteers.

Limitations and errors: pulse oximetry is accurate above 90% oxyhaemoglobin saturation, but much less so below 70%, and inaccurate below 50%. Pulse oximeters estimate arterial haemoglobin oxygen saturation (SaO_2) and not arterial oxygen tension (PaO_2). Because of the shape of the oxygen-dissociation curve, large changes in PaO_2 may occur at the extremes of the curve with minimal change in SaO_2. They have a response time of 10–30 s, depending on the signal averaging time, circulation time and the site of the probe.

Increase in the non-pulsatile component of light absorption through nail varnish or dirt increases error. Skin colour does not influence accuracy. Excess ambient light, infrared heaters and diathermy also interfere with accuracy. Hyperbilirubinaemia does not affect accuracy, nor anaemia unless the haematocrit is below 10%. Low peripheral perfusion due to low cardiac output or vasoconstriction interfere with accurate detection of arterial pulsations, as do atrial fibrillation or other arrhythmias.

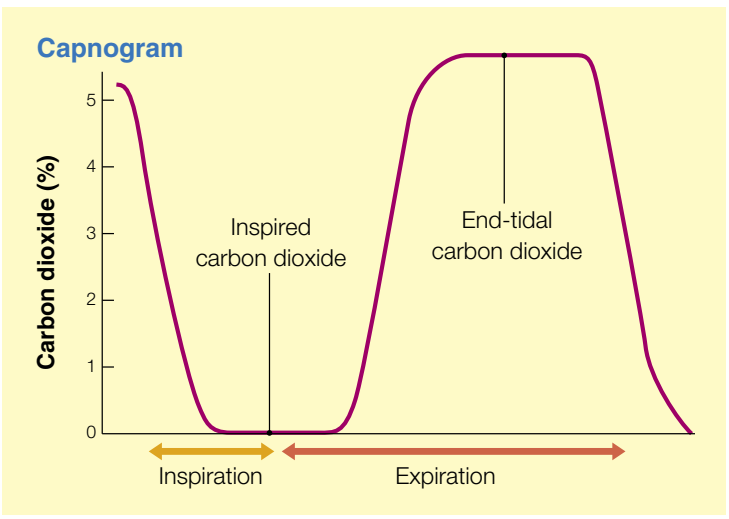
Carboxyhaemoglobin has a similar absorbance to oxyhaemoglobin and gives a falsely high reading for SaO_2. Methaemoglobin has an absorption that is similar at 660 and 940 nm and produces a SaO_2 towards 85%. The intravenous dyes methylene blue and indocyanine green also lead to falsely low values. Fetal haemoglobins do not cause error. A co-oximeter can measure carboxyhaemoglobin and methaemoglobin by analysing the absorption of at least three different wavelengths of light by blood *in vitro*.

Capnography
Capnography is a standard method of monitoring during anaesthesia and is increasingly used in the ICU. It describes the continuous measurement of expired carbon dioxide tension at the airway to allow the monitoring of the end-tidal CO_2 tension. An analyser with a rapid response time is required and most devices measure CO_2 tension from the absorption of infrared light, though other techniques such as mass spectrometry can be used.

Sidestream sampling is most common and describes the technique of continually aspirating a sample of gas from the respiratory circuit which is then fed through the analyser. The gas is either returned to the respiratory circuit or scavenged. Sidestream capnography is favoured during anaesthesia owing to the convenience of a lightweight attachment to the airway but may be troublesome due to sampling line blockage by water vapour following protracted use.

Mainstream sampling – the analyser head is attached directly to the airway and the gas is analysed within the respiratory circuit through a clear window or cuvette. In the ICU where inspired gases are often humidified actively, mainstream may be more reliable than sidestream capnography.

Capnogram: a typical capnogram is shown in Figure 3. During inspiration the CO_2 tension should be neligible unless there is rebreathing. Dead space gas is exhaled first, it contains no CO_2, and is followed by alveolar gas and a rapid rise in CO_2 which reaches a clear plateau in normal lungs and is termed the end-tidal CO_2 tension. However, if there is significant inhomogeneity of ventilation within the lungs no clear plateau is discernible and an accurate end-tidal CO_2 cannot be measured (Figure 4). This occurs in obstructive airway disease and asthma. If tidal volumes are very small there is inadequate distinction between dead space and alveolar gas resulting in an indistinct expiratory plateau and the end-tidal CO_2 tension is inaccurate.



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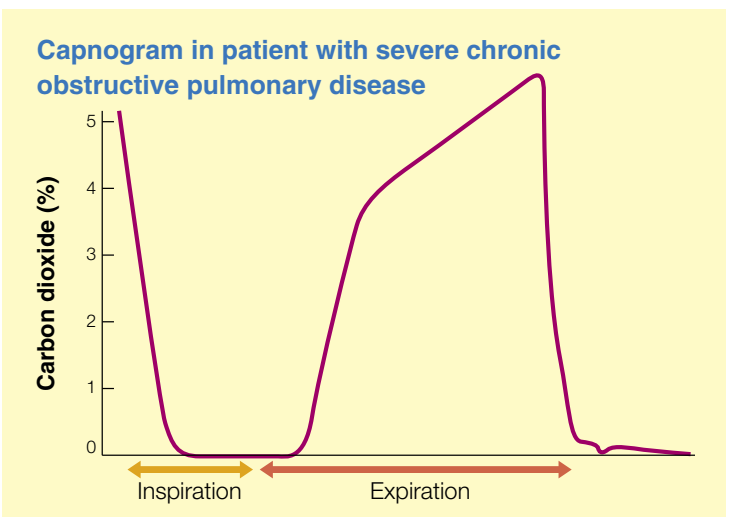

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End-tidal CO_2: in normal lungs the end-tidal CO_2 tension is 0.5–0.8 kPa less than the arterial CO_2 tension and is a useful non-invasive estimate of arterial CO_2. The difference between end-tidal and arterial CO_2 is increased if there is mismatch of ventilation and perfusion within the lung, as occurs in lung disease. In these circumstances, the end-tidal CO_2 may markedly underestimate arterial CO_2 tension. A reduction in lung perfusion increases alveolar dead space and results in an end-tidal CO_2 tension considerably lower than the arterial CO_2 tension. This may occur in pulmonary emboli, low cardiac output states, hypotension and following the application of high levels of positive end-expiratory pressure during mechanical ventilation. A sudden drop in end-tidal CO_2 during anaesthesia may reflect a decrease in cardiac output or pulmonary embolism (e.g. thrombus, gas, fat). Monitoring end-tidal CO_2 is useful during cardiopulmonary resuscitation for assessing adequacy. The causes of changes in end-tidal CO_2 are summarized in Figure 5. ◆

Changes in end-tidal carbon dioxide ($ETCO_2$)

Increased $ETCO_2$

Decreased alveolar ventilation
- Reduced respiratory rate
- Reduced tidal volume
- Increased equipment dead space

Increased CO_2 production
- Fever
- Hypercatabolic state

Increased inspired pCO_2
- Rebreathing
- CO_2 absorber exhausted
- External source of CO_2

Reduced $ETCO_2$

Increased alveolar ventilation
- Increased respiratory rate
- Increased tidal volume

Reduced CO_2 production
- Hypothermia
- Hypocatabolic state

Increased alveolar dead space
- Reduced cardiac output
- Pulmonary embolism
- High positive end-expiratory pressure during intermittent positive-pressure ventilation

Sampling error
- Inadequate tidal volume
- Water blocking sampling line
- Air entrainment into sampling line

5

FURTHER READING

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Measurement of Temperature and Humidity

John Bernard Carlisle

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The temperature of matter is equal to the mean translational kinetic energy of its particles.

Thermodynamic principles
Energy (E) can perform work. It exists in discrete quantities as the photons of electromagnetic radiation ($E = h\nu$; where h is Planck's constant and ν is the electromagnetic frequency) or the mass of quarks and leptons ($E = mc^2$; where m is mass and c is the velocity of light).

A mass in motion has more energy than a mass at rest (kinetic energy = $\frac{1}{2}mv^2$; where m is mass and v is velocity). Atomic or molecular internal energy can displace the centre of the mass (translation) or not (vibration or rotation around interatomic bonds).

Kinetic temperature is the translational component of internal energy. The atoms or molecules of two substances with the same temperature have the same mean translational kinetic energy. For an ideal monatomic gas all the internal energy is translational kinetic energy, the mean value of which determines the temperature. The kinetic energies of atoms at thermal equilibrium follow a statistical distribution defined by the Maxwell–Boltzmann equation. The mean atomic kinetic energy is $\frac{1}{2}kT$ in one dimension and kT in three dimensions (where T is temperature in Kelvin, k is Boltzmann's constant 1.4×10^{-23} J/K). The speed of gas particles depends on their mass and temperature ($kT = \frac{1}{2}mv^2$). For air (average molecular mass 29) the mean molecular speed at room temperature is 466 m/s (1679 km/hour). At atmospheric pressure a gas molecule in air would be expected to collide with another every 2×10^{-10} s.

Heat is the transfer of energy quanta that change internal molecular energy. Heat quanta increase all three kinetic modes (vibration, rotation, translation), while temperature measures only the translational component of internal energy. Heat and temperature are not usually simply related, particularly for phase changes; for instance, five times as much heat energy (2260 kJ) is required to vaporize 1 kg of water at 100°C (no temperature change) as to increase the temperature of the same water from 0°C to 100°C (419 kJ).

Energy quanta are transferred by particle collision or electromagnetic radiation (emr). The absorption of emr that increases temperature is efficient at wavelengths between 1000 nm and 1×10^6 nm (infrared).

The international standard measurement scale for temperature is the Kelvin (K). The reference point for this scale is the triple point of water at 273.16K. Pure water freezes at 273.15K (0.00°C) and boils at 373.125K (99.975°C) at standard pressure (International Temperature Scale 1990 or ITS-90).

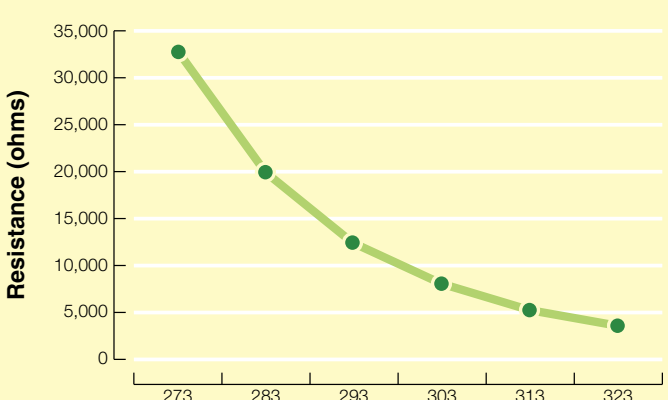
Thermometers
Thermometers measure their own temperature resulting from the net gain or loss of heat (radiation and molecular collision). Thermometer temperature is signalled in one of two ways.

- Physical thermometers signal the density change of a gas, liquid or solid with temperature (e.g. bulb thermometers, Galileo thermometers, gas expansion gauge sensors, acoustic sensors) or a phase change, usually solid to liquid, as in 'dot matrix' thermometers.
- Electrical thermometers signal changes in the energy of electrons. There are a variety of methods for measuring electron energy, including changes in potential difference (thermocouple, thermopile, transistor), conductivity (thermistors, resistance temperature detectors, electrical noise thermometers), capacitance (pyroelectric crystals in emr sensors), inductance and colour.

Thermistors are temperature-dependent semiconductors. Negative thermal conductivity thermistors (Figure 1) are made from metal oxides (cobalt, copper, manganese, nickel), positive thermal conductivity thermistors from barium titanate.

Thermocouples generate a temperature-dependent electromagnetic force at the junction of two different metals (Seebeck effect) (Figure 2).

Negative temperature coefficient thermistor



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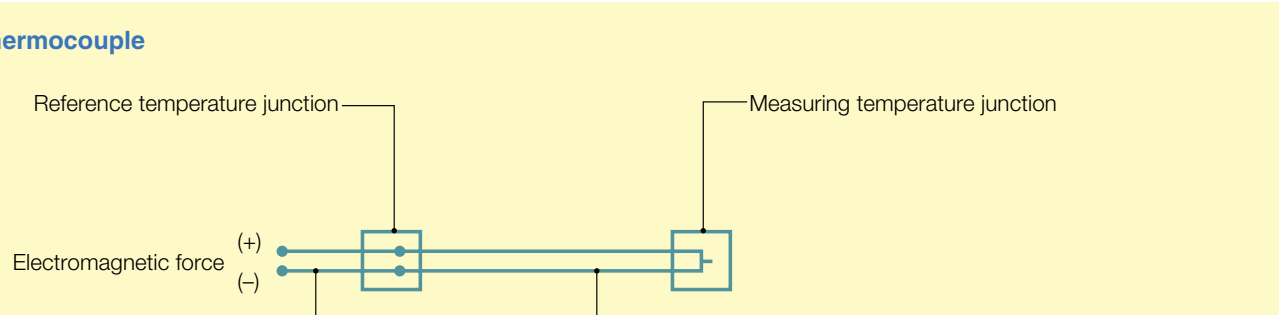
Thermocouple



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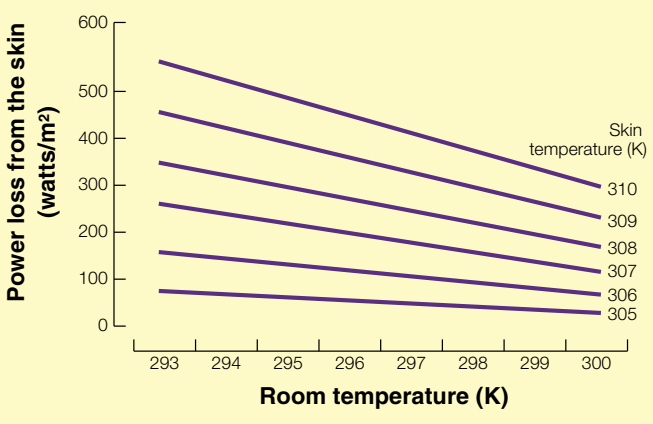
Infrared sensors detect the electromagnetic energy radiated from the body (whole body thermography) or from parts of the body (e.g. tympanic membrane thermometers). Skin absorbs and emits almost all of its thermal energy (emissivity 0.97). The radiated energy flux (power per unit area) depends on the temperature obeying the Stefan–Boltzmann law = $e \times \sigma \times (T^4_{hot} - T^4_{cold})$ (Figure 3) where e is emissivity (perfect black body = 1), σ is the Stefan–Boltzmann constant 5.7×10^{-8} W/m^2/K^4, T is the temperature (K).

Effects of room and skin temperature on radiative heat loss



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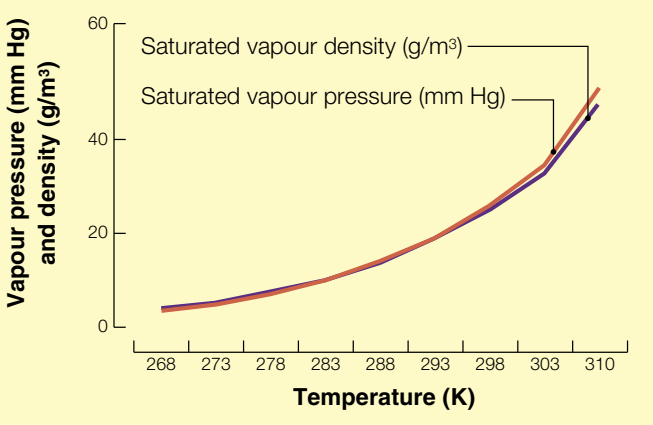
Technical specifications should detail range, precision, time constant to reach thermal equilibrium, sensitivity to emr interference (1 m long leads are subject to radiofrequency interference and heating), applications and requirement for recalibration. Thermometers are subject to damage and inaccuracy over time. Calibration laboratories should fulfil national (National Measurement Accreditation Scheme) and international (ISO/IEC 17025) standards, using Standard Platinum Resistance Thermometers (SPRTs) and fixed-point isothermal cells.

Humidity
Humidity is the vapour density of water in air (g H_2O/m^3 air). The water molecules in a closed container of air and fluid water have a spectrum of translational kinetic energies determined by the Maxwell–Boltzmann equation. At thermal equilibrium the saturated vapour density (SVD) has a corresponding saturated vapour pressure (SVP); both increase non-linearly with temperature. VP (mm Hg) = $7.5 \times 10^{-6} \times$ VD (g/m^3) $\times$ R $\times$ T where R is the specific gas constant for water (462 J/kg/K) and T is the temperature (K) (Figure 4).

Variation of saturated vapour pressure and saturated vapour density of water with temperature



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Relative humidity (RH) is the measured vapour density of water divided by the SVD, expressed as a percentage. Compression or cooling of gas increases RH. Excess water vapour condenses when the RH of cooled gas exceeds 100% (dew point).

Measuring water vapour density in air
Primary hygrometers use fundamental thermodynamic principles. They include gravimetric hygrometers, electrolytic hygrometers (the electrolytic current is proportional to the humidity), chilled mirror hygrometers (dew point detected by cooling the air) and psychrometers.

Psychrometers compare the temperatures of two thermometers; one has a dry bulb, a wet wick encloses the second. The wet bulb is cooled by water evaporation (latent heat of vaporization) until the SVD is reached. The difference in thermometer temperatures depends on the RH of the sampled air. Absolute humidity (for mirror hygrometers and psychrometers) is calculated using the temperature of the dry bulb. Psychrometers calculate the water vapour pressure from:

$$VP = SVP_{Tw} - [\gamma \times (T_d - T_w)]$$

Rearranged this shows that wet bulb temperature increases with increasing humidity:

$$T_w = T_d - [(SVP - VP)/\gamma]$$

When the sample air is saturated (SVP–VP = 0) wet and dry bulb temperatures are equal. Where: VP is actual vapour pressure, SVP_{Tw} is saturated vapour pressure (kPa) at wet bulb temperature, T_W and T_d are wet and dry bulb temperatures (K). γ is the psychometric variable that relates the heat energy lost from the wet bulb by water vaporization to the temperature measured. $\gamma = P \times C_p / (0.622 \times L)$ where P is atmospheric pressure (kPa), C_P is the heat capacity of the thermometer (J/kg/K) and L is the latent heat of vaporization for water at T_W (J/kg).

Secondary hygrometers depend on observed changes in the properties of materials with humidity. They include physical properties (oscillating crystal frequency, fibre tension, weight) or electrical properties (capacitance, resistance, impedance). A gravimetric hygrometer measures the difference in weight between an untreated and a desiccated sample of gas (using P_2O_5).

Permeable capacitive hygrometers measure the variation in capacitive charge by the effects of water vapour on the dielectric constant of the material between the capacitor plates. The charge, $C = \varepsilon A/d$. Area (A) and plate separation (d) are fixed, so the charge is proportional to the dielectric constant (ε).

Water molecules can also be measured using mass spectrometry, absorption spectrophotometry or Raman spectroscopy. Absorption spectrophotometers measure the absorption of photons by water molecules in the gas sample between the emitter and detector. Wavelengths used to detect water vapour are either in the ultraviolet (λ 121.56 nm) or infrared (λ 2.5 μm) parts of the spectrum. The electrical current (I) generated by the photodetector = $I_0 \exp^{[-k\ d\ VD]}$ where VD is the vapour density, d is the path length, I_0 is the current produced in the absence of water and k is the absorption coefficient of the photons by water vapour.

Calibration: the National Physical Laboratory (NPL) holds the UK's international standard, calibrating hygrometers between –60°C and 60°C in dew point at standard pressure (error ± 0.003 to 0.84°C in dew point depending on conditions). Commercial calibration laboratories use a transfer standard (usually a chilled mirror hygrometer) that has been calibrated against an NPL standard.

Hygrometers also need to be recalibrated at regular intervals (traceable to the NPL standard). Most hygrometers are calibrated at 25°C. Sensor precision decreases away from the calibration temperature; the efficacy of any electronic compensation for this imprecision is likely to decrease with time. Contamination of the analysed gas (particulates, inorganic salts, organic compounds) reduces hygrometer precision, particularly as they accumulate on or in the sensor. ◆

Measurement of Volume and Flow in Gases

Fred Roberts

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The ability to measure gas flows and volumes accurately is essential to the anaesthetist, both for precise delivery of gas mixtures and for monitoring respiratory volumes in the ventilated or spontaneously breathing patient. Gases are fluid, compressible and usually invisible, which makes them difficult to measure. Gas volumes (and associated flows) can be measured directly using a system with a calibrated chamber, but in clinical practice, measurement is usually made indirectly, using a property of the gas that changes in parallel to flow or volume and which can be more easily determined.

Scientific principles

To understand the working principles of the various devices used for measurement, a few aspects of the relevant basic science must be considered. Gas flow conventionally refers to volume flow per unit time (Q) rather than linear velocity (v) of the flowing gas.

Relationship between flow and volume: for gas delivery systems (e.g. oxygen flowmeters), flow is generally constant and the relationship between flow and volume is expressed by $V = Q\,t$, where V is volume, Q is flow and t is time.

In a physiological setting (e.g. tidal volume) flow is seldom constant and thus volume must be calculated by integrating the measured flow rate with respect to time. In a graph plotting flow against time, this represents the area under the curve; if the data are recorded electronically it is usually computed.

Types of flow: the influence of many of the variables that determine flow depends on whether flow is laminar or turbulent. Several factors determine which type of flow predominates, and these are amalgamated into Reynolds' number (Re), a dimensionless value that can be calculated for a smooth parallel-sided tube by:

$$Re = \frac{v\,\rho\,d}{\eta}$$

where v is linear velocity, ρ is density, d is diameter and η is viscosity. At an Re less than 2000 flow will probably be laminar; an Re over 2000 indicates flow is likely to be turbulent.

Laminar flow is efficient, with layers passing smoothly over each other producing a parabolic (bullet-shaped) flow profile, with the greatest velocity centrally. It is determined by the Poiseuille–Hagen formula:

$$Q = \frac{P\,\pi\,r^4}{8\,\eta\,l}$$

where: P is pressure drop, r is the radius of the tube and l is the length of the tube. Important features are that flow is:

- directly proportional to the pressure drop
- proportional to the fourth power of the radius
- related to the viscosity but not the density of the gas.

Turbulent flow is less efficient, with multiple eddy currents occurring in the overall direction of flow. Because of the variable nature of turbulence, there is no precise and comprehensive equation to calculate flow, but turbulent flow is related to the:

- square root of the pressure drop
- density of the gas rather than its viscosity.

If flow is being calculated by measuring one of the above variables, unforeseen changes in any of the others will compromise accuracy. Changes could occur directly, such as by alteration in gas composition, or indirectly, such as temperature variation causing a change in viscosity.

Working principles

Direct measurement: gas volumes (and associated flows) can be measured directly using bulk filling of an enclosed space of known volume. Instruments using direct measurement include the gas meter, vitalograph and water-displacement spirometer. Because of the logistical problems of such devices, their use in clinical practice is limited.

Indirect measurement: for clinical use, measurement is usually made indirectly, using a property of the gas that changes in parallel to flow or volume and which can be more easily determined.

Pressure drop across a resistance – as flow occurs through a resistance, a pressure drop occurs. This effect can be used to calculate flow by:

- keeping the resistance constant and measuring the pressure change as the flow varies, as in a pneumotachograph
- having a constant pressure drop and varying the resistance in a measurable way (e.g. bobbin rotameter).

Mechanical movement – flowing gas has kinetic energy related to its velocity, which can be converted into a measurable value by:

- rotation of a vane (e.g. a spirometer)
- bending a flexible obstruction, transducing this to produce an electrical signal.

Heat transfer – gas flowing past a heated element acts to cool it, as in a hot-wire anemometer.

Ultrasound interference – the velocity of an ultrasound signal is increased by a gas flowing alongside it in the same direction, and decreased if the gas is flowing against it.

Ideal features of a device used for gas flow or volume measurement in clinical practice include:

- accurate across a wide range of flows
- unaffected by changes in gas temperature or composition
- low resistance so that it can be used in a spontaneously breathing patient
- minimal impairment of performance with prolonged use.

Measurement site: for measuring tidal volume, it is important that the characteristics of the breathing system are taken into consideration when deciding where to measure. For a semi-closed rebreathing system (any of the Mapleson A–F classification), measurement must be made at the distal end of the system, adjacent to the mask or tracheal tube, or the fresh gas flow may produce an addition to the tidal volume.

With some older designs of circle system, circulating fresh gas flow could erroneously increase the tidal volume when measured within the circle and the only reliable site was distal to the Y-piece. With improved circle design, appropriate placement of flow sensors adjacent to the unidirectional valves enables the tidal volume to be measured accurately within the circle in the inspiratory or expiratory limb.

Intensive care ventilators are non-rebreathing systems, and measurements can be made accurately in the inspiratory or expiratory parts of the system. In practice, both inspiratory and expiratory tidal volumes are usually measured, because clinically important discrepancies between them can occur, for example a leak caused by lung pathology or the use of an uncuffed tube.

Specific devices

Most devices for measuring gas flow and volume measure the whole gas flow, though some incorporate a mechanism for splitting the flow and then measure only a part of it, extrapolating from this sample to calculate the whole flow. Devices may be designed to measure primarily flow or volume, though the two are closely related and information about both may be readily obtained. Some devices also give other clinical data, such as inspiratory pressure and information about the pattern of flow.

Gas meter

A gas meter acts as a volumetric turnstile, with sequential filling of internal chambers of known volume and recording the number of times each has been filled. They are classified as dry or wet, depending on whether an underwater seal is used in the mechanism. They have a substantial resistance and are cumbersome, thus largely restricting use to industrial applications.

Vitalograph

The vitalograph is used specifically to record a single vital capacity breath. Its design uses an expanding bellows with a recording pen attached and a motor to move the paper at constant speed. Volume is displayed on the y-axis and time on the x-axis, so that the pattern of expiration is shown as well as the volume.

Water-displacement spirometer

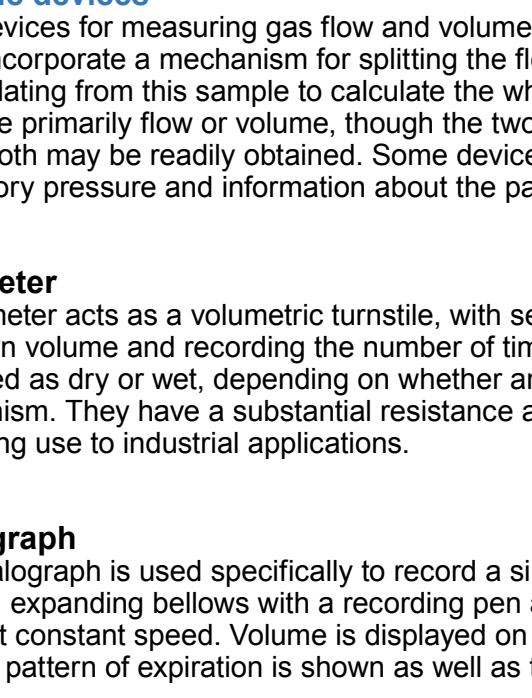
A water-displacement spirometer involves directing gas (usually respiratory gas) into an inverted bell chamber that is immersed in water but free to move up and down via a pulley as the volume of gas in the chamber varies. This movement is linked to a recording system calibrated to display the volume change. It is accurate, but is impractical for everyday clinical use because of its size and it is used mainly as a research instrument.

Pneumotachograph

In a pneumotachograph, a resistance is put in the gas pathway and the resulting pressure drop across it measured rapidly and accurately using a differential pressure transducer, from which flow rate and volume are calculated.

For improved accuracy, the resistance is usually designed to produce laminar flow, so that the flow rate is directly proportional to the measured pressure drop. This is achieved using a series of small-bore tubes arranged in parallel (Figure 1), through which the gas flow must pass. A heating element is sometimes incorporated to prevent the build-up of condensation that could compromise accuracy. The total resistance added by the pneumotachograph should be small so that it can be used in a spontaneously breathing patient.

Pneumotachograph



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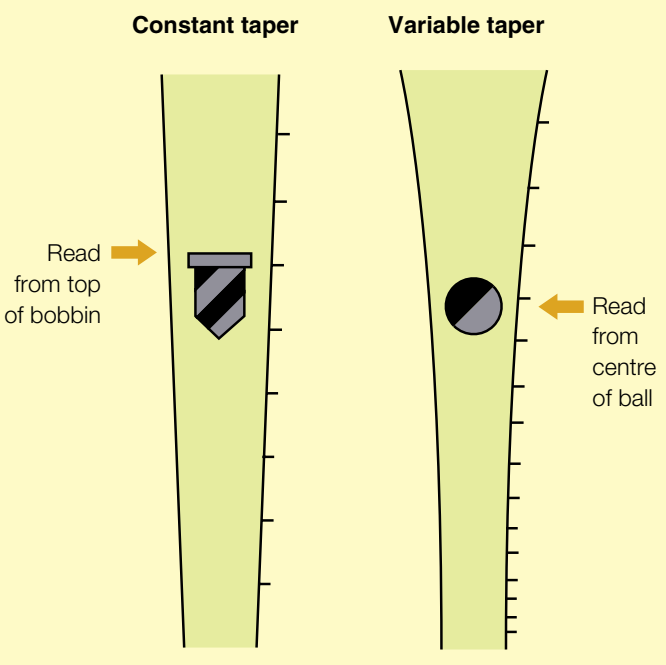
Measurement can be made at various points in the breathing system or ventilator, and a pair of sensors is often used so that inspired and expired tidal volumes can be measured independently. Alternatively a single sensor may be used at the Y-piece, when a sampling port is usually included for gas analysis. In addition to the differential pressure across the chamber, the absolute pressure in the airway can be easily measured. When linked to the recorded tidal volume, compliance can be calculated and displayed in real time.

Rotameters

Rotameters are widely used in gas delivery systems for continuous flow measurement. Several designs have been used, though now almost all use a vertical tapered tube containing a bobbin or ball (Figure 2) which is supported by the gas flow as it passes upwards through the tube. The weight of the bobbin (and thus the pressure drop required to support it) is constant, but as the flow increases its position in the tube rises, lowering the resistance as a larger pathway is created alongside the bobbin.

Amalgamation of the space for gas flow around the bobbin to equate to a simple pathway reveals that at the bottom of the flowmeter the resulting dimensions lead to laminar flow but at the top of the tube produce turbulent flow. The physical characteristics of the gas that determine the resulting flow are therefore viscosity at the bottom and density at the top of the tube. The main implication of this is that calibration of rotameters is gas-specific and for accuracy its use must be restricted to that gas. Calibration is usually done to read the flow rate from the top of a bobbin but the centre of a ball.

Rotameters



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The range of gas flow measurements can be increased by using two tubes (one for low and one for high flow rates), or by varying the taper so that a greatly increased diameter results at the top of the tube.

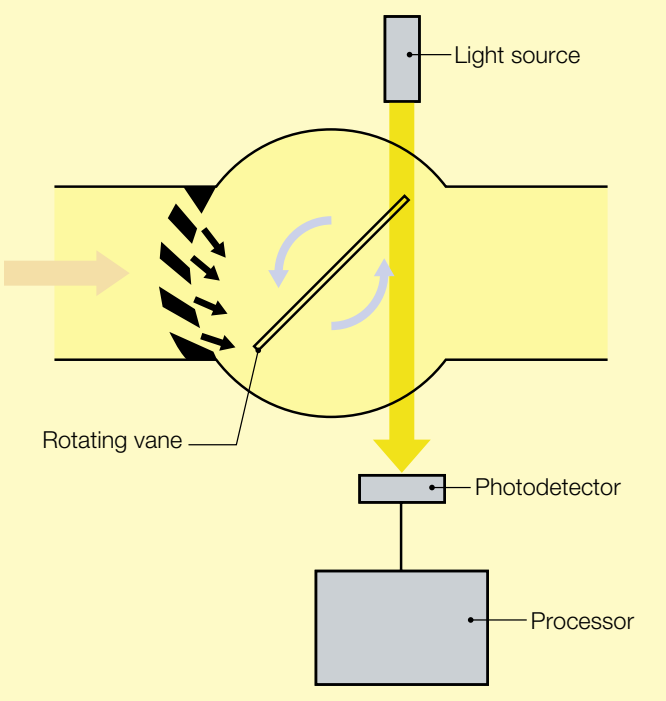
Inaccuracy results from anything that causes the bobbin to stick in the tube, including dirt or static electricity. To prevent build-up of static, the inside walls of a rotameter and its mounting points are made of conductive material. To demonstrate that the bobbin is not stuck, it has angled flutes to produce rotation, which is made easier to see by appropriate colouring.

Back pressure caused by downstream resistance also leads to an inaccurately low reading on a rotameter, though the actual flow is the same as that shown before the resistance was applied.

Vane meters

The most common vane meter is the Wright's spirometer, in which the gas flow is directed tangentially to strike a rotating vane in the gas pathway (Figure 3). Originally this rotation was linked mechanically to a needle and the volume read from the adjacent dial, but modern versions use a light source and photodetector positioned across the vane to count its rotation. The Wright's spirometer tends to under-read at low flows (because of friction) and to over-read at high flows (because of momentum).

Wright's spirometer (electronic)



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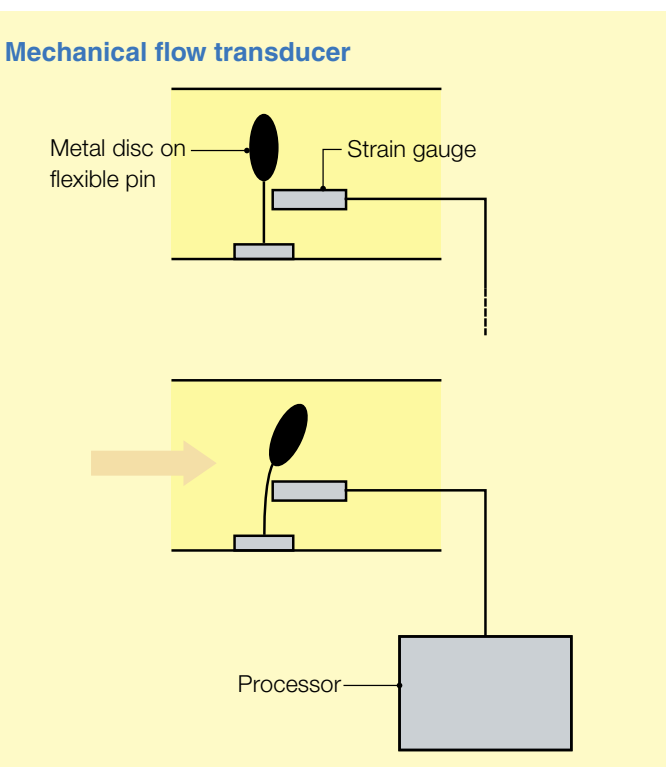
The peak flow meter is a specialized vane meter that measures the maximum flow rate only, without calculation of the associated volume. It is modified so that movement of the vane by expiratory gas results in a steadily enlarging pathway for gas escape. The final position to which the bar has moved corresponds to the peak expiratory flow rate.

Its clinical use is to assess conditions such as asthma, where the problem is largely confined to airway resistance, which limits the expiratory flow rate. Although its use is limited in this respect, it is a very simple and reliable bedside test.

Mechanical flow transducers

Another device using mechanical movement is the flow transducer used in the Siemens Servo™ 300 and 900 series intensive care ventilators. The gas flow is split so that measurement is made in a small side channel using a thin metal disc supported on a flexible pin, resembling a lollipop (Figure 4). The disc is placed in the measuring channel at right angles to the direction of gas flow, which results in it being bent backwards by the flow. A strain gauge situated immediately behind the pin is compressed as it is bent, with a force dependent on the flow. The resulting electrical signal is processed to calculate the flow rate with a high degree of accuracy.

Mechanical flow transducer



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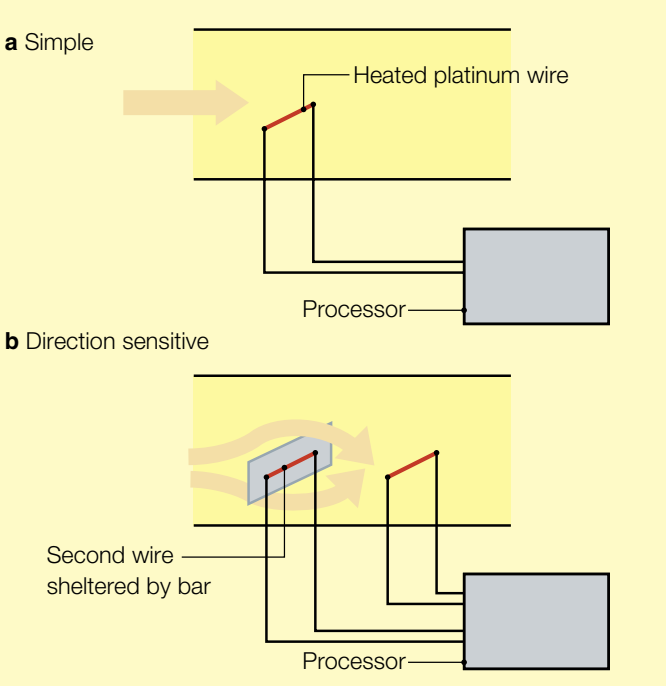
Hot wire anemometer

In this device an electrically heated wire is placed in the gas pathway, which is cooled by the gas flow (Figure 5). The degree of cooling depends on the gas flow rate, which can thus be calculated. A modification of this device uses a heated screen or film instead of a wire.

Hot wire anemometer



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The hot wire (usually platinum) has an operating temperature as high as 400°C, and is incorporated into a balanced Wheatstone bridge circuit. Cooling the wire changes its resistance and unbalances the bridge. Most designs work on the constant-temperature system, whereby a correcting current is applied through the hot wire to compensate for the cooling effect of the gas, maintaining a constant wire temperature and thus restoring the balance in the Wheatstone bridge. This current is measured and from it the gas flow rate is determined. To compensate for changes in the gas temperature, a second wire is usually incorporated, which is maintained at ambient temperature. Minor corrections are also made according to the gas composition, to accommodate the variation in specific heat capacity, but hot wire anemometry is generally extremely accurate.

This cooling effect occurs with flow in either direction, and so to measure exhaled tidal volume the hot wire anemometer is placed in the expiratory limb of the circuit. It can be modified to provide information about the direction of flow by using an additional heated wire placed just downstream from a small bar, as shown in Figure 5b. This bar shelters the wire from the full cooling effects of flow in one direction but not the other, and thus inspiratory and expiratory flows can be calculated separately. For this purpose the sensor must be placed in the Y-piece of the circuit. This technique is particularly useful for neonatal ventilation.

Ultrasonic flowmeter

6

Ultrasonic flowmeters

Ultrasonic flowmeters work on the principle that when an ultrasound signal is being transmitted within a flowing gas, its velocity changes in proportion to that of the gas flow. When the gas flow and ultrasound signal are in the same direction, an increase in signal velocity occurs. Conversely, when the signal is against the direction of gas flow, its velocity decreases. The usual design is to incorporate a pair of ultrasound beams aimed in opposite directions, each with a sensor. The beams can be situated either directly along the line of flow (within the lumen of the tubing) or tangentially across it (Figure 6). When no flow is present the velocity of the two beams is equal, and pulses of ultrasound arrive at the sensors simultaneously. When flow occurs there is a time difference between signal detection at the sensors, from which the gas velocity and flow rate can be calculated. ◆

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Monitoring Arterial Pressure

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In 1733, Stephen Hales first measured arterial blood pressure in animals by the direct cannulation of an artery. In 1828, Poiseuille used a mercury manometer to measure blood pressure. Subsequently non-invasive measurement of arterial blood pressure developed. However, direct monitoring of the arterial blood pressure using cannulation of an artery provides the most information on a continuous beat-to-beat basis. Arterial blood pressure monitoring is performed in critical care areas and operating theatres to monitor patients with actual or potential haemodynamic instability.

The preferred site of insertion of the intra-arterial cannula is the radial artery, because it is not an end-artery, it is readily observed for complications and it is in a relatively clean location. Alternative sites include the femoral, brachial and dorsalis pedis arteries. Arterial pressure monitoring can be complicated by haemorrhage, air embolism, thrombosis, infection and inadvertent intra-arterial drug administration.

Indications for arterial pressure monitoring

Direct arterial blood pressure monitoring provides a continuous record of arterial pressure, but also facilitates repeated blood sampling for blood gas and acid–base analysis as well as standard laboratory investigations. Relative indications for its use include:

- patients with organ failure or impairment in a critical care area
- major surgery with a significant risk of major blood loss or haemodynamic instability
- patients with significant cardiac disease undergoing non-cardiac surgery for which close monitoring of their haemodynamic status is required
- manipulation of intracranial pressure and/or cerebral perfusion pressure
- induced systemic hypotension or hypothermia
- severe morbid obesity or burns of the extremities (or other tissue damage) if non-invasive blood pressure cuffs cannot be used
- high risk of significant cardiac dysrhythmia
- inter- and intra-hospital transfer of intubated and ventilated patients.

Equipment used for arterial pressure monitoring

A purpose-built pressure transducer system is required to provide a continuous and accurate arterial waveform. The lumen of the artery is cannulated with a Teflon or polyurethane cannula which is connected to an electronic pressure trans-ducer by non-compliant fluid-filled tubing. A continuous flush system prevents occlusion of the cannula with clots by flushing saline (with or without low-dose heparin) at a constant rate of 1–3 ml/hour. This constant flow is generated by a syringe driver or more commonly with a pressurized bag of fluid (usually 300 mm Hg). The transducer should be placed at the level of the right atrium and the transducer zeroed to atmospheric pressure. This provides the reference point for measuring blood pressure. For monitoring cerebral perfusion pressure, the reference point is altered to a fixed point relating to the intracranial contents, traditionally the external auditory meatus.

Damping or resonance of the monitoring system can cause a decrease or an increase of the pulse pressure around an unaltered mean arterial pressure. This can result in erroneous analysis of the information provided. Clots, air bubbles or a kinked cannula can cause damping. Hyper-resonance is the result of long connecting lines, small tubing or an oversized cannula for the size of vessel. It occurs when the rapidity of the pressure change approaches the natural resonant frequency of the system, producing a distorted and falsely amplified signal.

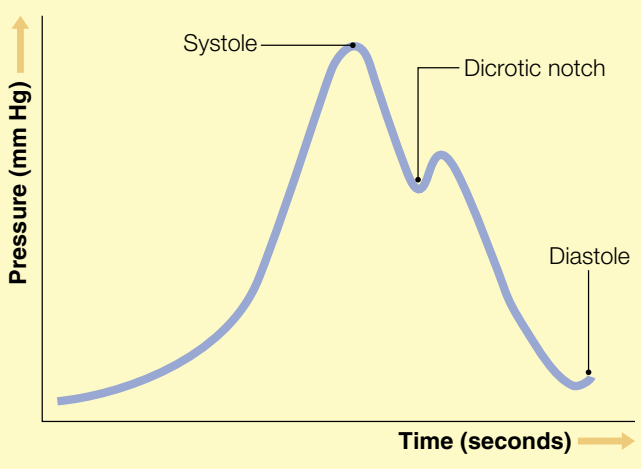
Transducer physics

Left ventricular systole produces a pressure wave within the bloodstream that is propagated along the aorta to the peripheral arteries. The transmission velocity of the wave is considerably faster than that of the actual forward flow of the blood. This pressure wave is transmitted through the cannula in the artery via the fluid-filled tubing to the transducer interface. The mechanical motion of the fluid in the tubing is converted into electrical signals by a mechanoelectrical transducer. The transducer contains a chamber with a diaphragm in its base providing the interface with the fluid. Mechanical motion of the fluid moves the diaphragm in the chamber. Sensing elements attached to the diaphragm measure small changes in resistance and convert this movement into an electrical signal. The small electrical signals that are generated by the pressure transducer are amplified and processed before being displayed on the monitor screen. Individual monitors can display the arterial pressure values on a beat-to-beat basis or averaged over time.

Interpretation of arterial waveform

The waveform of normal individuals has a higher peak pres-sure in large peripheral arteries than in the aorta, but the mean and diastolic pressures are unchanged (Figure 1). The dicrotic notch and pulse pressure also become more prominent peripherally.

Arterial pressure waveform



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The pressure waveform not only gives systolic and diastolic pressures but also allows indirect assessment of myocardial performance, vascular resistance and intravascular volume. The upstroke of the arterial waveform (dP/dT) gives an indication of myocardial contractility except in patients with aortic stenosis. The area under the arterial pressure waveform from the beginning of the upstroke to the dicrotic notch (closure of the aortic valve) reflects the left ventricular stroke volume. This is also an indication of blood volume. The systolic blood pressure can vary considerably during the respiratory cycle if the patient is hypovolaemic. A reduction of systemic vascular resistance results in a lowering of the position of the dicrotic notch within the waveform. It is important to realize that factors within the monitoring system can impair the accurate assessment of the shape of the waveform. A horizontal line drawn dividing the waveform such that the area above and under the line is equal gives the mean arterial pressure. This is continuously calculated and displayed by all modern monitors. The mean arterial pressure is commonly used for setting a target for an individual patient, such as cerebral perfusion pressure following brain injury or a systemic mean arterial pressure for a critically ill patient with organ failure. The mean arterial pressure can also be calculated by adding one-third of the pulse pressure to the diastolic pressure.

Additional information: analysis of the arterial waveform using standard patient monitors or more advanced dedicated monitoring devices can provide additional information:

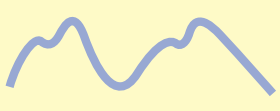
- heart rate (useful during electrical interference and patient shivering)
- limited analysis of heart rhythm
- cardiac output.

The cardiac output can be calculated using software that measures the appropriate area under the curve to determine stroke volume and multiply this by the heart rate. Two current commercial monitors that perform arterial waveform analysis and generate continuous cardiac output values both use a calibration of the calculated output. One system uses lithium chloride dilution (LiDCO, LiDCO Ltd, UK) and the other uses transpulmonary thermodilution (PiCCO, PULSION Medical UK Ltd).

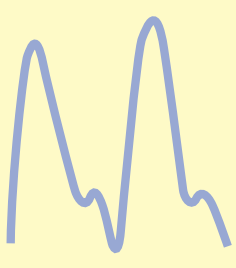
Abnormal waveforms are characteristic of some disease states (Figure 2). ◆

Abnormal arterial waveforms

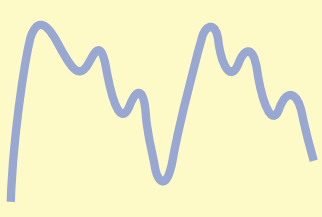
Anacrotic: aortic stenosis



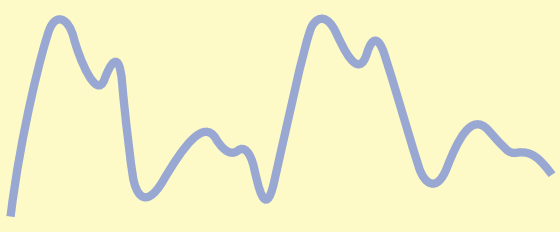
Collapsing: hyperdynamic circulation (e.g. sepsis, anaemia, aortic regurgitation, hyperthyroidism, arteriovenous fistula, pregnancy)



Bisferiens: aortic stenosis with aortic regurgitation



Alternans: left ventricular failure



2

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Monitoring Central Venous Pressure

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Central venous pressure (CVP) was first measured by Stephen Hales in 1733 in a mare. It was first measured in man by Frey in 1902 but it was not until 1910 that the technique was used clinically. The development of the first plastic (polythene) intravenous catheter in 1945 led to a surge in the use of CVP monitoring. In 1952, Aubaniac described using central venous catheters for cannulation of the subclavian vein to resuscitate wounded soldiers on the battlefield.

Monitoring CVP as a reflection of the right atrial pressure is now commonly used in the management of patients on the wards, those undergoing major surgery, during resuscitation and in the critical care environment. The triad of cardiac contractility, preload and afterload maintain the circulatory dynamics of a patient. These factors determine blood pressure, cardiac output and therefore tissue perfusion. The CVP is commonly used to evaluate preload and thus the volume status of the patient.

Indications for CVP monitoring

Cannulation of a central vein is indicated for transvenous pacemaker insertion, drug or parenteral nutrition admin-istration, poor peripheral venous access, renal support and CVP monitoring.

Assessment of circulatory volume – monitoring CVP is indicated in patients in whom large fluid shifts are occurring or are anticipated. However, it is only one component of haemodynamic monitoring that enables assessment of the circulatory volume; the patient's clinical condition and underlying disease process should also be considered.

Venous air embolism – maintaining a positive venous pressure at the level of the surgery helps to prevent venous air embolism by ensuring that there is no negative pressure gradient. Monitoring CVP facilitates this, but care must be taken that the patient's cardiac status permits the maintenance of a relatively high CVP. Monitoring CVP may then facilitate aspiration of the air embolus via the central venous cannula. Venous air embolism is associated with intracranial surgery, spinal procedures, caesarean section and other operations in which large veins may demonstrate a negative pressure gradient.

Clinical use of CVP monitoring

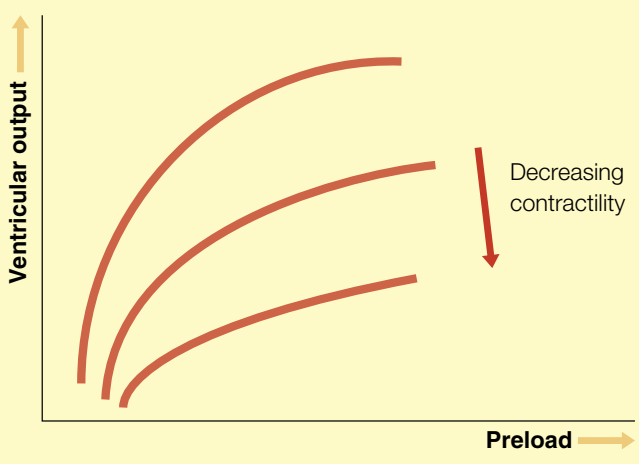
Monitoring CVP is useful for assessing the haemodynamic status of a patient. Absolute values are of little use, it is more important to study CVP trends with fluid challenges and not to use individual values in isolation. The CVP should be used in conjunction with clinical observation of peripheral perfusion; the rate, volume and pressure of the arterial pulse; and the state of hydration.

The underlying principle of using CVP monitoring to determine circulatory volume status is the use of repeated fluid challenges. The CVP is a dynamic measurement and is measured before, during and after administration of a fluid challenge. The fluid is given as aliquots of 100–250 ml of crystalloid or colloid given rapidly via a large-bore intravenous cannula. If the CVP does not increase with a bolus of fluid, it implies that the patient is hypovolaemic. If there is a sustained increase in the CVP, it is likely that the patient is approaching relative fluid overload. This may be isolated hypervolaemia, but may indicate poor myocardial contractility. If the increase is temporary, and the CVP falls back to the previous level, the patient is isovolaemic.

The Starling relationship

Frank Starling, and later others, described the relationship of preload as right atrial pressure to ventricular output (Figure 1). Muscle fibre length and tension are closely related. In the heart, myocardial fibre length and tension determine ventricular volume and ventricular pressure, respectively. The resting tension of cardiac muscle corresponds to the end-diastolic pressure and is dependent on the degree of filling (preload). The end-diastolic volume determines the stroke volume of the heart. Thus the CVP, being almost equal to right atrial pressure (which in turn approximates to right ventricular end-diastolic pressure) becomes the monitor of right heart preload in the absence of tricuspid outflow obstruction.

Starling relationship



Preload determines ventricular output with decreasing contractility. As the preload increases in a poorly contracting heart, the ventricular output decreases

1

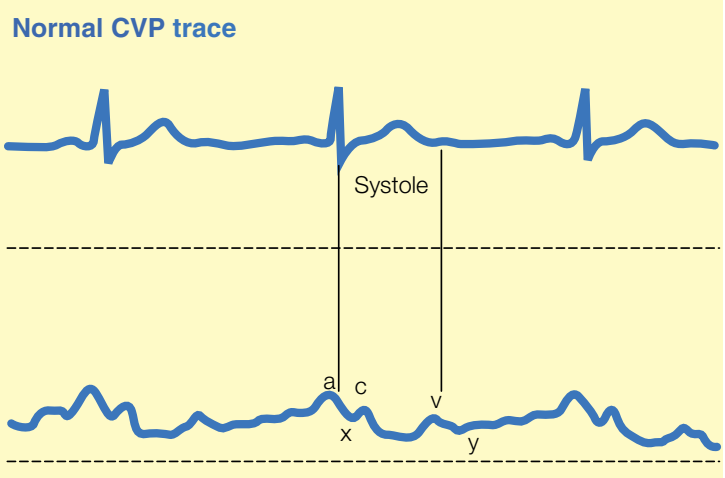
CVP measurement

The patient should lie flat with the reference level being a point level with the right atrium. This is traditionally taken to be the mid-axillary line. The mean CVP should then be measured with the patient in expiration. A wide range of normal values is quoted (usually 0–10 cm H_2O). In spontaneously breathing, isovolaemic, healthy individuals negative values can be seen during inspiration. In the past, CVP monitoring was performed with a water manometer, but this technique is now generally limited to ward use. In theatres and critical care areas this method has been superseded by the use of electronic transducers measuring the CVP in mm Hg (1 mm Hg = 1.3 cm H_2O).

The CVP trace

The normal CVP trace has three positive waves (a, c and v) and two negative deflections (x and y) (Figure 2). Each wave and descent represents distinct elements of the cardiac cycle and may be altered in cardiac disease (Figure 3).

Normal CVP trace



See text for explanation

2

Features of the CVP trace

a wave
- Represents right atrial contraction
- Begins before the first heart sound
- Absent in atrial fibrillation
- Inconsistent in various heart blocks
- Large a waves are seen in tricuspid stenosis, right ventricular hypertrophy, pulmonary stenosis and pulmonary hypertension
- Cannon (giant) a waves occur when the right atrium contracts against a closed tricuspid valve as in complete heart block

c wave
- Caused by bulging of the tricuspid valve into the right atrium during the onset of ventricular contraction
- Occurs after the first heart sound and the QRS complex

x descent
- Produced by atrial relaxation and a downward displacement of the tricuspid valve during ventricular systole
- Absent in tricuspid regurgitation

v wave
- Occurs during right atrial filling with a closed tricuspid valve
- Large v wave seen with tricuspid regurgitation

y descent
- Produced by opening of the tricuspid valve and flow into the right ventricle

3

Factors that increase CVP – causes of an increased right-sided preload produce a rise in CVP. This can occur acutely with any cause of raised intrathoracic pressure (e.g. tension pneumothorax, Valsalva manoeuvre), impaired cardiac function, venoconstriction, relative volume overload or significant intra-abdominal hypertension. Chronic elevation of the CVP is associated with right ventricular dysfunction, obstruction of the superior vena cava (as occurs with intrathoracic malignancy), pulmonary hypertension and chronic respiratory disease.

Factors that decrease CVP include right-sided preload reduction. This occurs when venous return is reduced during hypovolaemia or venodilatation and as a normal variation during the inspiratory phase of spontaneous ventilation.

Factors that cause a false CVP reading – before any monitoring variable is acted on, spurious values must be excluded. During CVP monitoring of a correctly located cannula, spurious volumes can result from inaccurate positioning of the transducer and kinking or occlusion of the central venous cannula. In the presence of hypovolaemia, the vessel wall can be sucked against the monitoring port of the cannula resulting in falsely elevated readings. Rapid infusion of fluids during CVP monitoring can also result in spurious elevation of the CVP. ◆

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Physical Principles of Defibrillators

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Defibrillation is the application of a preset electrical current across the myocardium to cause synchronous depolarization of the cardiac muscle with the aim of converting a dysrhythmia into normal sinus rhythm. Over 135,000 people die annually following acute myocardial infarction. The main cause of sudden death is ventricular fibrillation; the only effective treatment for which is early defibrillation. The defibrillator was invented in 1932 by Dr William Bennett Kouwenhoven.

Capacitors

The most important component of a defibrillator is a capacitor that stores a large amount of energy in the form of electrical charge, then releases it over a short period of time. A capacitor consists of a pair of conductors (e.g. metal plates) separated by an insulator (called a dielectric). Conductors lose and gain electrons easily, and therefore allow current to flow; whereas insulators do not lose their electrons, and hardly allow any current to flow. The maximum working voltage is the voltage that when exceeded causes the dielectric to break down and conduct, often with catastrophic results.

The unit of electric charge (Q) is the coulomb (C). 1 coulomb is the quantity of electricity transported in 1 s by a current of 1 ampere (A) and is equivalent to 6.24 x 10^{18} electrons (Figure 1).

Key formulae and definitions

Current is charge per second	A = Q/s
Power is energy (or work) per second	W = J/s
Power is current x potential difference	W = AV
Stored charge	Q = CV
Stored energy	J = CV
Delivered energy	J = QV/2

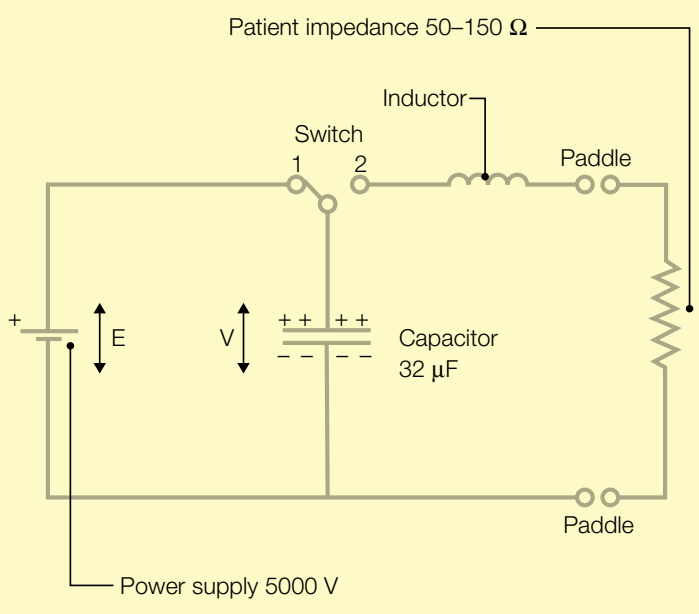
C, capacitance in farads; Q, charge in coulombs; V, potential difference in volts; J, energy (or work) in joules; W, power in watts; A, current in amperes

1

Capacitance (C) is the ability to store charge. A capacitor has 1 farad of capacitance if a potential difference of 1 volt is present across its plates, when a charge of 1 coulomb is held by them (i.e. C = Q/V). Capacitors typically have values of microfarads ($\mu F = 10^{-6} F$), nanofarads ($nF = 10^{-9} F$) or picofarads ($pF = 10^{-12} F$). For a simple capacitor, the capacitance is proportional to the area over which the plates overlap (A), inversely proportional to their distance apart (D), and related to the di-electric constant (E_o). Thus $C \alpha A/D. E_o$

Figure 2 shows a defibrillator. When the switch is in position 1, direct current (DC) from the power supply is applied to the capacitor. Electrons flow from the upper plate to the positive terminal of the power supply and from the negative terminal of the power supply to the lower plate. Therefore current flows and a charge begins to build up on each electrode of the capacitor, with the lower plate becoming increasingly negatively charged, and the upper plate increasingly positively charged. As the charge builds up on the plates, it creates a potential difference across the plates (V), which opposes the electromagnetic force of the power supply (E). Initially when there is no charge on the plates, V is zero and it is easy to move electrons onto the plates. As V increases, however, it opposes further movement of electrons, and increasing work must be done to move more electrons onto the plates. The work done (W) to move charge (Q) through a potential difference V is: W = VQ. Charging a capacitor is therefore an exponential process, with a time constant determined by the capacitance and the resistance of the circuit through which the current flows (Figure 3). When V equals E, the current ceases to flow and the capacitor is fully charged. In this example, the amount of charge stored (Q = CV) is 32 μF x 5000 V = 160 mC.

Mechanism of action of a defibrillator



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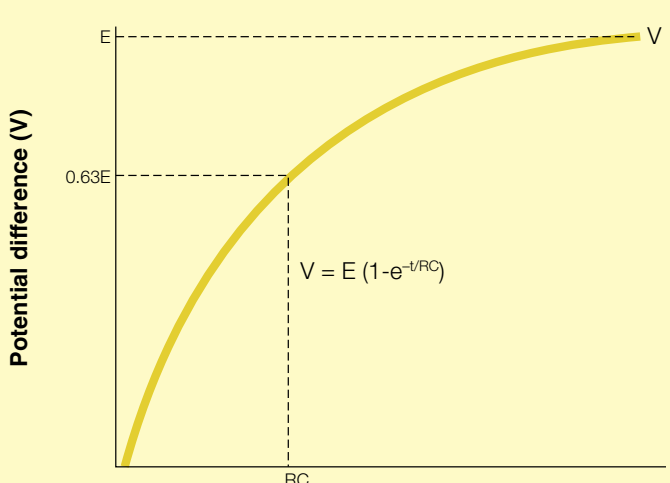
Charging a capacitor



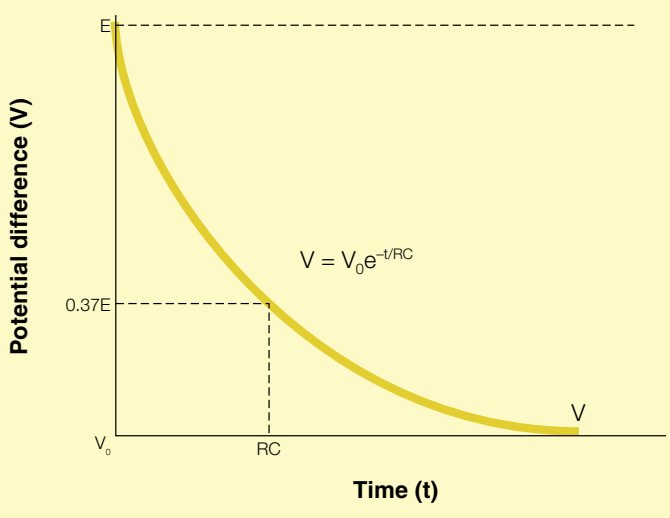
RC is the time constant, and is the time taken for the potential difference across the plates (V) to reach 63% ($1^{-1/e}$) of the value of the electromotive force of the power source (E)

3

Work must be done against the field to store charge in the capacitor. The charged capacitor is therefore a store of potential energy, which may be released on discharge. Theoretically, the amount of energy stored in a capacitor is CV.

When the paddles are applied to the patient's chest and the switch is moved to position 2, a circuit is completed. Electrons stored on the lower (negative) plate of the capacitor are able to pass through the patient and back to the upper plate. Thus, curent flows, stored electrical energy is released, and the potential difference across the plates (V) falls to zero (i.e. the capacitor is discharged). The rate of discharge declines as the potential difference across the plates falls; it is an exponential process (Figure 4) with a time constant determined by the capacitance and the resistance of the circuit through which the current flows.

Discharging a capacitor



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The energy delivered may be calculated from: Energy (J) = ½ x stored charge (Q) x Potential (V) (i.e. Energy = QV/2). Thus, 400 J = ½ x 160 mC x 5000 V. The apparent loss of half of the stored charge on discharge is due to circuit resistance, radiation and arcing of switch contacts.

Inductors

For successful defibrillation, the current delivered must be maintained for several milliseconds. However, the current and charge delivered by a discharging capacitor decay rapidly and exponentially. Inductors are therefore used to prolong the duration of current flow. They are coils of wire that produce a magnetic field when current flows through them. When current passes through an inductor, it generates a flow of electricity in the opposite direction which opposes current flow as predicted by Faraday's law of electromagnetic induction. This opposition to current flow is called inductance (L) and is measured in henries (H). Inductors typically have values of microhenries (μH).

Power supply

Step-up transformers are used to convert the mains voltage of 240 V AC to 5000 V AC. This is then converted to 5000 V DC by a rectifier. In practice, a variable voltage step-up transformer is used so that different amounts of charge may be selected by the clinician. The control switch is calibrated in energy delivered to the patient (J), because this determines the clinical effect. If a mains supply is unavailable, most defibrillators have internal rechargeable batteries. These supply DC, which is then converted to AC by means of an inverter, and then amplified to 5000 V DC by a step-up transformer and rectifier as above.

Patient factors

Successful defibrillation depends on delivery of the electrical charge to the myocardium. Only part of the total current delivered (about 35 A) flows through the heart. The rest is dissipated through the resistance of the skin and the rest of the body. The impedance of skin and thoracic wall act as resistances in series, and the impedance of other intrathoracic structures act as resistances in parallel with the myocardium. The total impedance is about 50–150 Ω, however, repeated administration of shocks in quick succession reduces impedance.

Safety

Patient: before administering the charge, it is essential to make the correct diagnosis to avoid defibrillating a patient who is already in sinus rhythm. If a defibrillator monitor is being used, check that the leads are correctly connected, and whether the device is monitoring from the paddles or from chest electrodes.

The paddles should be placed across the long axis of the heart to facilitate effective defibrillation. The paddles should not be placed over transdermal patches, because they may block current delivery or if they contain an inflammable substance (e.g. glyceryl trinitrate) may result in burns or explosion. The paddles should not be placed near metal objects, either on the surface of the skin (e.g. ECG leads or electrodes, skin clips, jewellery), or subcutaneously (e.g. implanted pacemakers), because the current follows the path of least resistance through the metal, resulting in arcing, heating or burns. The paddle size should be appropriate for the patient (typically 13 cm diameter for adults): large enough to prevent burns but small enough to deliver an adequate current density.

Conductive gel pads and firm pressure (about 10 kg force) are used to improve electrical contact between the paddles and the patient's chest. Liquid electrode gel should not be used, because excess may cause arcing across the surface of the chest wall or the operator's hands.

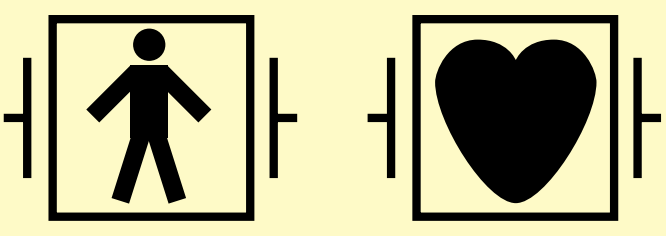
All sources of oxygen must be removed from the patient during defibrillation, because it supports combustion if arcing occurs.

Staff should not touch the bed, patient or any equipment connected to the patient during defibrillation. Fluids may conduct electricity, therefore it is important to ensure that the immediate area is clean and dry. The defibrillator should not be charged until the paddles are applied to the patient's chest, because accidental discharge from open paddles may cause injury or death. The operator must not touch any part of the paddle electrodes. Before administering the charge, the operator must shout "Stand clear!" and check that all staff have done so.

If the defibrillator is charged but a shock is no longer indicated, it should be discharged through the defibrillator internally by turning the control knob to zero before removing the paddles from the patient's chest: charged paddles should never be returned to the defibrillator.

International Electrotechnical Committee (IEC) symbols for 'defibrillator safe' equipment

The two symbols outside each square indicate that equipment is protected from damage if the patient to whom it is connected receives cardiac defibrillation



a Equipment meeting IEC type BF leakage current requirements

b Equipment meeting IEC type CF leakage current requirements

5

Equipment that does not have the 'defibrillator protected' symbol (Figure 5) should be disconnected from the patient before de-fibrillation to prevent damage, heating or arcing effects. The de-fibrillator should never be discharged with the paddles shorted together, as this may cause burning and damage to the electrical contacts. ◆

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Physics of Gases

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In whichever state a substance exists, it is made up of the same atoms or molecules. The difference between a solid and liquid, and a liquid and gas is the strength of the forces attracting the molecules and atoms to each other. These interparticular forces in a solid hold the molecules together in a lattice. When a solid is heated the kinetic energy of the individual molecules increases, leading to an increase in their vibrational energy, causing them to move apart and the substance to melt. When the molecules in a liquid acquire further kinetic energy, they break away from the interparticular forces and the substance becomes a gas. The kinetic theory accounts for all three states of matter by assuming that above absolute zero, molecules are in continual motion – they have kinetic energy. The molecules exert forces of attraction on each other and so possess potential energy. At small separations the forces must be repulsive, because if the attractive force were to exist down to zero separations, matter would collapse in on itself.

When a liquid and gas coexist, as occurs in a cylinder of *Entonox* (a 50:50 mixture of oxygen and nitrous oxide), molecules enter the liquid as well as leaving it. When the rate at which molecules are leaving and entering the liquid phase becomes equal, the vapour above the liquid is said to be saturated. When a liquid reaches its boiling point all the molecules are transferring into vapour. The terms gas and vapour are synonymous but vapour relates to the gaseous phase at a temperature and pressure close to that at which the gas would condense into a liquid.

In a gas, the atoms collide with each other and their surroundings, and thus a force is exerted. The force exerted over an area equals pressure.

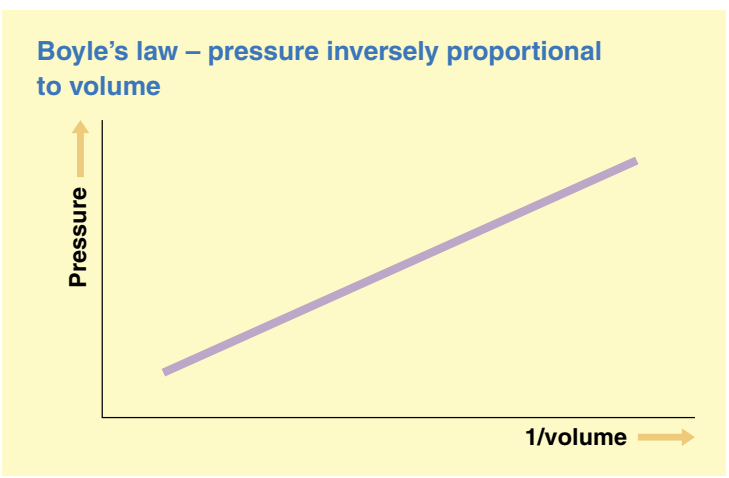
Absolute and relative pressure

Atmospheric pressure at the surface of the earth is due to the gravitational force exerted on air molecules. The pressure depends on air density, which depends on altitude and weather conditions. (Absolute pressure = gauge pressure + atmospheric pressure.)

Zero gauge pressure is equal to atmospheric pressure. If this were not so, empty cylinders would collapse in on themselves. Anaesthetists tend to ignore absolute pressure and record gauge pressures such as ventilator and gas-cylinder pressures, arterial blood pressure and venous pressures.

The gas laws

Boyle's law (Figure 1) – at a constant temperature, the volume of a mass of gas is inversely proportional to the pressure (PV = Constant).



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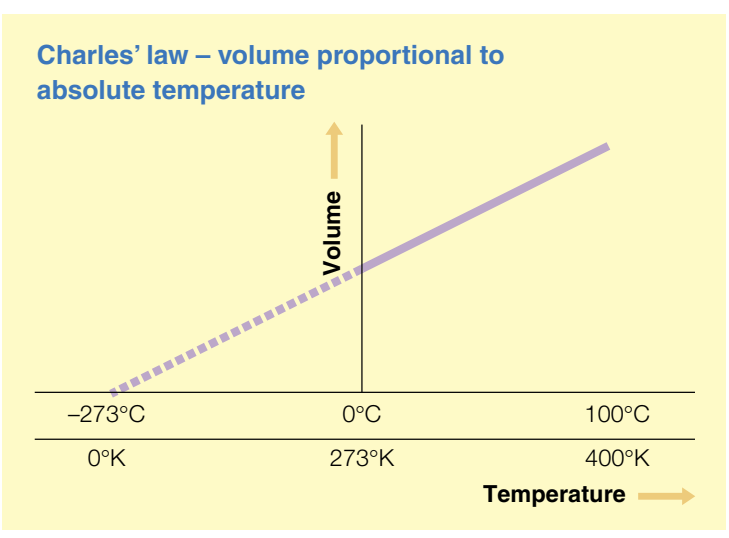
Charles' law (Figure 2) – at a constant pressure the volume of a gas is directly proportional to its absolute temperature (V/T = Constant). Volume is proportional to temperature. Gases expand when they are heated and become less dense, thus hot air rises.



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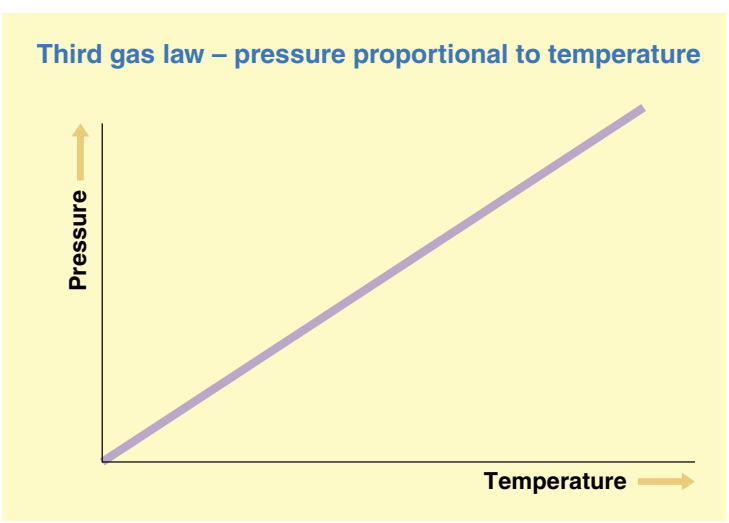
The third perfect gas law (Figure 3) – at constant volume the absolute pressure varies directly with absolute temperature (P/T = Constant). Pressure is proportional to temperature. An example is the hydrogen thermometer. A constant volume of hydrogen when heated produces a change in pressure.



3

Standard temperature and pressure (STP) – it is important to specify the temperature and pressure at which the measurement of a volume is made. Standard temperature and pressure is defined as 273.15°K (0°C) and 101.325 kPa (760 mm Hg).

The practical effects of temperature change include:

- change in vaporization rates of volatile agents
- increased temperature reduces the density of fluids
- increased temperature reduces the viscosity of liquids
- increased temperature increases the viscosity of gases (increased molecular activity).

Adiabatic changes in a gas

Applying the three gas laws, for a change to occur in the state of a gas, heat energy is either added or taken away from the gas. If the state of a gas is altered without a change in heat energy it is said to undergo adiabatic change. If a compressed gas expands adiabatically, cooling occurs as seen in the cryoprobe. Energy is required as the gas expands to overcome van der Waal's forces. No heat exchange occurs between the gas and its surroundings because the source of energy is from the molecule's own kinetic energy, thus the gas cools as it expands. Conversely, if a gas is rapidly compressed its temperature rises (the Joule–Kelvin principle). When a cylinder connected to an anaesthetic machine is turned on too quickly the temperature rises in gauges and pipelines and in the presence of oil or grease may lead to a fire or explosion.

Dalton's law of partial pressures

In a mixture of gases, the pressure each gas exerts is the same as that which it would exert if it alone occupied the container.

Avogadro's hypothesis

Equal volumes of gases at the same temperature and pressure contain equal numbers of molecules. As the mass of molecules present in a fixed volume varies depending on the individual gas, the number of molecules present is expressed as a mole. A mole is the quantity of a substance containing the same number of particles as there are atoms in 0.012 kg of carbon 12. The number of particles is 6.022×10^{23}. One mole of gas at standard temperature and pressure is contained in a volume of 22.4 litres.

A clinical application would be to calculate the volume of nitrous oxide in a cylinder. A nitrous oxide cylinder contains 2.2 kg of nitrous oxide. The molecular weight of nitrous oxide is 44. One mole is 44 g. At STP we know that 44 g occupies 22.4 litres, therefore 2200 g occupies 22.4 x 2200/44 = 1120 litres.

The universal gas equation (the ideal gas law)

If the perfect gas laws and Avogadro's hypothesis are combined PV/T = Constant. For one mole of gas, PV/T equals the universal gas constant R. The equation can be rearranged to PV = nRT (the universal gas equation) where n equals the number of moles present. The practical application of this law is the use of pressure gauges to assess the contents of a cylinder. The volume, temperature and gas constant remain the same and pressure is therefore proportional to n, the number of moles.

Temperature scales – the triple point of water

Different thermometers use particular thermometric properties. For example, a mercury-in-glass thermometer uses the change in length of a column of mercury confined to a capillary tube of uniform bore; a platinum thermometer uses the increase in resistance with increasing temperature.

To establish a temperature scale it is necessary to make use of fixed points: a fixed point is the single temperature at which it can be confidently expected that a particular physical event always takes place.

The ice point is the temperature at which pure ice can exist in equilibrium with water at standard atmospheric pressure.

The steam point is the temperature at which pure water is in equilibrium with its vapour at standard atmospheric pressure.

The triple point of water is that unique temperature at which pure ice, pure water and pure water vapour can exist together at equilibrium. The triple point is particularly useful, because there is only one pressure at which all three phases (solid, liquid and gas) can be in equilibrium with each other.

Critical temperature

The critical temperature is the temperature above which a gas cannot be liquefied however much pressure is applied (for CO_2 Tc = 31.1°C).

Critical pressure is the minimum pressure that causes liquefaction of a gas at its critical temperature (for CO_2 pc = 73 atm).

Specific critical volume is the volume occupied by 1 kg of a gas at its critical temperature and pressure.

Therefore one can define a gas as a substance in the gaseous phase above its critical temperature. Vapour is the term applied to a substance in the gaseous phase below its critical temperature. Thus, simply increasing the pressure can liquefy a vapour, but not a gas. The relationship between pressure, volume and temperature is displayed as a family of isotherms (Figure 4).

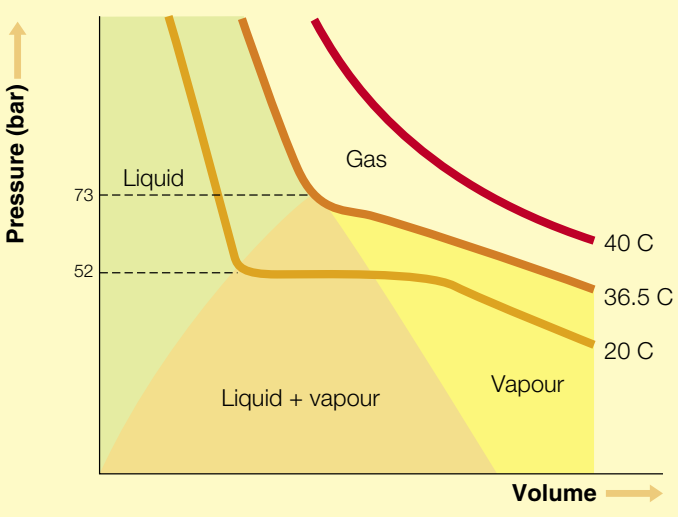
Oxygen, nitrogen and hydrogen are traditionally called permanent gases, because it was thought they could not be liquefied. This is because each of these gases has a critical temperature below room temperature (oxygen –118°C, nitrogen –146°C, hydrogen – 240°C).

Poynting effect (overpressure effect) – the critical temperature and pressure of a gas may be affected when it is mixed with another gas. For example, in a cylinder of *Entonox*, the new critical temperature of nitrous oxide (known as the pseudo-critical temperature) changes to –6°C. Therefore, precautions regarding the cooling of cylinders should be taken into account.

Density and viscosity of gases – fluid flow

Liquids and gases are fluids. The density of a substance is the mass per unit volume ($kg/m^3 = \rho$) (silver, 10500; water, 1000; oxygen, 1.43; air, 1.29; helium, 0.18; hydrogen, 0.09).

Isotherms of nitrous oxide



The isotherm at 40 C is above the critical temperature of nitrous oxide (36.5 C) and threfore obeys Boyle's law. As the volume decreases the pressure rises. At the critical temperature 36.5 C there is a critical pressure at which nitrous oxide becomes a liquid. Liquids are relatively incompressible and therefore a decrease in volume leads to a dramatic rise in pressure. At 20 C as the nitrous oxide is compressed some of it liquefies at a pressure of 52 bar (saturated vapour pressure of nitrous oxide). Further reduction in volume causes more vapour to condense with no change in pressure. When all the vapour is condensed to liquid a rapid rise in pressure is seen with further decrease in volume.

4

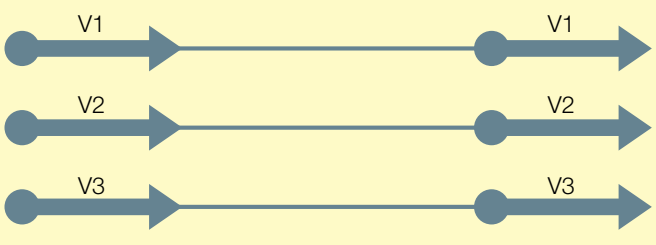
If a fluid is viscous it offers resistance to the motion of any solid through it or to its own motion past a solid body. In both these circumstances (except where the fluid is a gas of very low density) the layer of fluid in immediate contact with the solid is stationary. The motion causes adjacent layers of fluid to move past each other. An internal friction offers resistance to the motion of one layer of fluid past another, and this is the origin of viscous force. In liquids, the internal friction is due to intermolecular forces of attraction. In gases, the friction is due to the interchange of molecules between different layers. This results in the average speed of molecules in adjacent layers changing.

If the flow of a fluid is steady (also known as streamline flow, orderly flow and uniform flow) all the fluid particles that pass any given point, follow the same path at the same speed – they have the same velocity. The path followed by a particle of the fluid is called the line of flow of the particle.

In steady flow, streamlines coincide with the lines of flow. A streamline is a curve whose tangent at any point is along the direction of the velocity of the fluid particle at that point. Streamlines never cross.

Laminar flow is a special case of steady flow in which the velocities of all the particles on any given streamline are the same, though the particles of different streamlines may move at different speeds (Figure 5).

Streamlines of a liquid in laminar flow



Velocities V1, V2 and V3 are not necessarily equal

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Poiseuille's formula – when considering a viscous liquid undergoing steady flow through a pipe of circular cross-section, the velocity varies from a maximum at the centre of the tube to zero at the walls. Poiseuille originally described the relationship between flow and the properties of the fluid as:

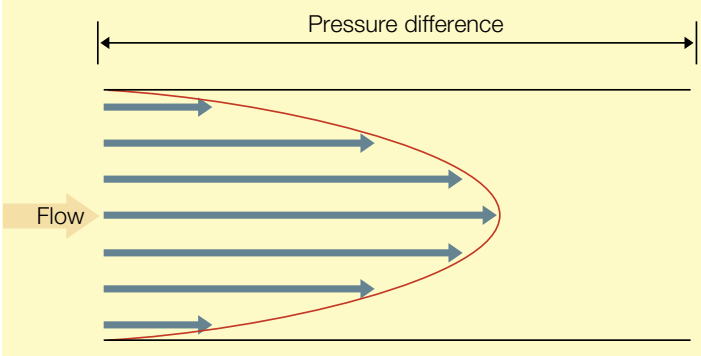
$$Q = \frac{kr^4p}{\eta l} \qquad \text{mathematical analysis shows that } k = \frac{\pi}{8} \text{ therefore}$$

$$Q = \frac{\pi r^4 p}{8\eta l}$$

where: Q is flow; η is viscosity; p/l is the pressure gradient; r is the radius of the tube. The formula applies only to Newtonian fluids (in which viscosity is constant) undergoing steady flow. This applies to all gases and some fluids. Water is a Newtonian fluid; blood is non-Newtonian.

The flow profile of a viscous fluid flowing in a pipe of circular diameter is conical (Figure 6). The fluid flows in a series of concentric cylinders. All the particles within an individual cylinder flow at the same speed. The speed of the cylinder adjacent to the wall of the pipe is zero, and the speeds increase towards the centre.

Velocity profile at laminar flow



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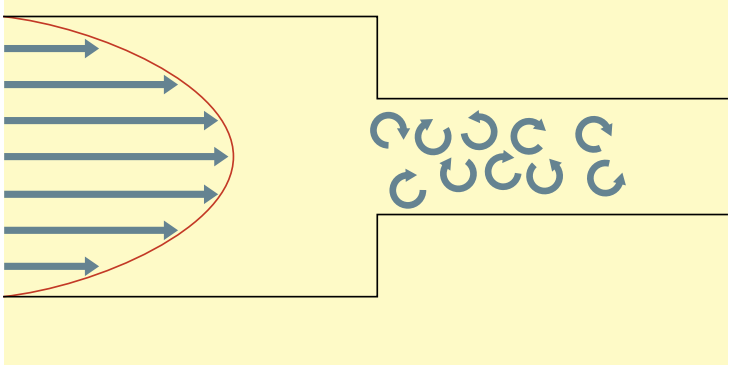
Turbulent flow is also known as disorderly flow. In this type of flow the speed and direction of the fluid particles passing any point varies with time. When laminar flow encounters a constriction, fluid velocity increases and turbulent flow occurs (Figure 7). At turbulent flows the resistance is higher than for a similar laminar flow. The variation in fluid velocity is different in turbulent flow and flow is no longer directly proportional to pressure. The property of a fluid that dictates the degree of turbulent flow is density.

Transition from laminar to turbulent flow



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The ability to predict the onset of turbulent flow is aided by calculating the Reynolds number (Re). If the Reynolds number exceeds 2000, then turbulent flow is likely to occur. When flow is turbulent there is a change in viscous forces and an increased pressure change along a tube:

$$Re = \frac{v\,\rho\,d}{\eta}$$

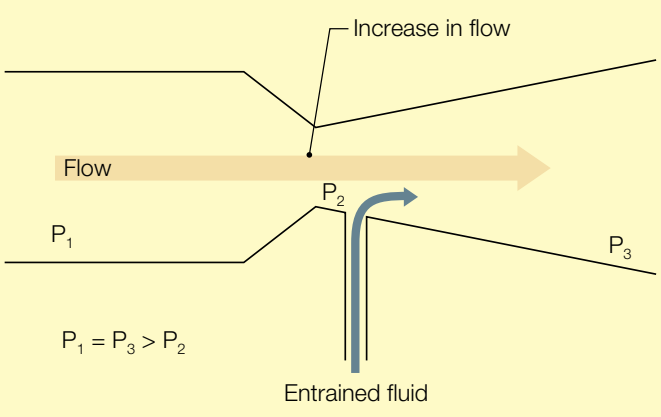
where: v is linear velocity of fluid; ρ is density; d is the diameter of the tube; η is viscosity. The effect of density (mass/volume) on flow is evident in the use of helium and oxygen to promote flow in patients with upper airway obstruction. The density of air is 1.29, of oxygen 1.43 and helium 0.18 at STP.

The Bernoulli equation states that for an incompressible, non-viscous fluid undergoing steady flow, the pressure plus the kinetic energy per unit volume plus the potential energy per unit volume is constant at all points on a streamline:

$$P + \tfrac{1}{2}v^2 + \rho gh = \text{Constant}$$

where: P is the pressure within the fluid; v is the velocity of the fluid; ρ is the density of the fluid; g is acceleration due to gravity; h is the height of the fluid above some arbitrary reference line. It follows from Bernoulli's equation that whenever a flowing fluid speeds up, there is a corresponding decrease in the pressure and/or the potential energy of the fluid and an increase in kinetic energy. If the flow is horizontal the whole of the velocity increase is accounted for by a decrease in pressure as the total energy must remain constant.

Principle of Venturi



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A Venturi tube has a constriction in which the bore gradually decreases and then increases (Figure 8). At the narrowest point the pressure drops as the flow of a fluid through the constriction increases. In medicine, applications include oxygen masks and nebulizers. Everyday applications include an aerofoil, spinning ball, filter pumps, Bunsen burners and carburettors. ◆

Processing, Storage and Display of Physiological Measurements

John Curnow

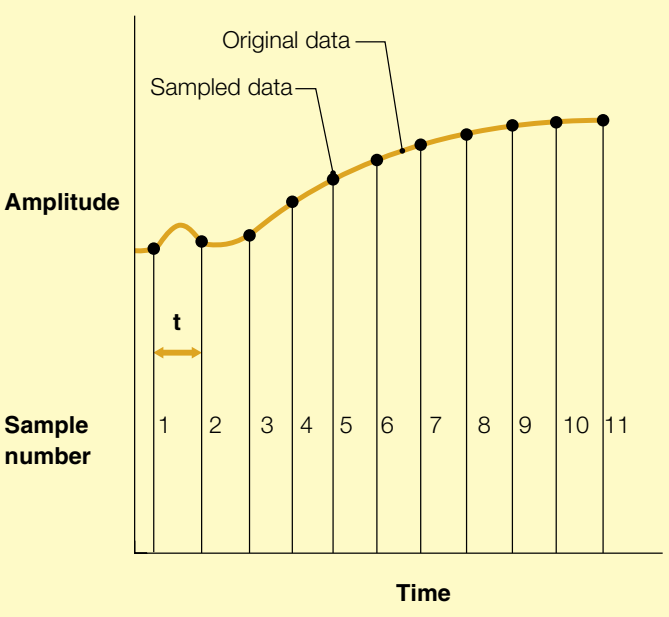
John Curnow is Head of the Biomedical Engineering Group at Derriford Hospital, Plymouth, UK. He gained a degree in electrical engineering from Bath University. He has worked in biomedical engineering for over 30 years. His special area of interest is in developing novel methods for clinical measurements.

The collection, display, analysis and storage of physiological data from patients are important functions for all anaesthetists. Modern electronic patient-monitoring equipment provides these functions, but to understand the final data it is important to have an understanding of the underlying functions involved in each process. Methods of collecting data from patients have changed little in recent years. Analogue electronic data proportional to the physiological variable being measured are the source of most of the signals collected.

Data collection and analysis

The use of micro-computing technology in monitors makes it easier to analyse data, but the data have to be digitized. Digitization consists of taking the instantaneous value, or sample, of the signal at fixed time points and storing these numbers as representation of the signal as shown in Figure 1. The time between each sample is the sample period (t seconds) and its inverse is the sampling frequency or sampling rate (f = 1/t Hz). The shorter the time between each sample or the faster the sampling frequency the closer the series of numbers can replicate the original data. However, there is always a limit on the storage space for the data and, partly for this reason, the sampling rate is kept as low as possible. There is an optimum minimum sampling frequency that allows mathematical reconstruction of the original signal defined by the sampling theorem, called the Nyquist frequency, which is twice the maximum frequency present in the signal. In Figure 1, the data from sample 1 to sample 3 are sampled too slowly and it can be seen that some information is lost, such as the peak between samples 1 and 2, while the data from sample 3 to sample 11 could be sampled at a slower rate without loss of information.

Comparison of sampled data and continuous analogue data



t, time between each sample

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Digitization is achieved using an analogue to digital converter (ADC) that reads the instantaneous value of a signal when triggered and represents it as a fixed accuracy number. There are two limitations to using digital data. The accuracy of the value is set by the smallest change in signal the ADC can detect, which is often about 1/4096 of the maximum signal size including signal noise and offset. The accuracy of the amplitude data is ± 0.5 v where v is the minimum amplitude change that the ADC can measure. The timing accuracy is set by the sample period and any times must be defined as ± 0.5 t, where t is the sample period.

The raw sampled data collected from the patient can be analysed to extract more useful information in the form of features extracted from the data. Analysis often identifies individual waveform groups in the continuous trace such as an ECG complex within a whole ECG trace. Features are then extracted, such as peak values, mean values and time intervals between known landmarks on the trace. Also, more complex features and interrelationships of multivariate signal features can be calculated. This is usually achieved using signal processing techniques such as digital filters, neural networks and fuzzy logic. Modern signal processing techniques have improved the quality of feature identification and thus improved the quality of the data. Also, the newer methods combined with fast processor speeds have allowed the real time extraction of features such as heart rate variability and EEG frequency spectrum analysis, which require more complex calculations to be performed for their identification.

Data storage

The sampled data that represent the signal and the values of extracted features are usually stored in the short term, and sometimes in the long term, in the monitor. Short-term storage is usually on electronic memory chips. This type of storage is usually used to hold the sampled data long enough for its analysis and display. However, memory chips require power to continue to store data. Therefore, data can be stored only while the system is switched on. In some cases, a battery supply is used to keep the memory active when the rest of the system is switched off. However, long-term storage is not feasible in this way. If the data collection is a single operation such as intermittent collection of blood pressure, the data are held in the memory at least until the next sample period. With many systems, raw digitized data are collected and the features immediately extracted and represented by new numeric values, and it is only these feature values that need to be stored longer term, so the sampled data are erased immediately.

If data have to be stored for months or years, the usual method is to store the information on a disk storage system as used on a PC. The drive may have a removable floppy disk that can store a small amount of data or it may have a hard disk on which large amounts of data can be stored. The floppy disk has the advantage that it can be removed and more disks inserted. Thus, for the storage of relatively small amounts of data, specific to one condition or patient, a floppy disk could be ideal. However, to store large amounts of data and data on multiple patients a hard disk is more suitable. The hard disk may be on a network such as a central station or even a network server rather than within the monitor itself.

The disk system uses magnetic methods of data storage, therefore over years the data quality reduces until it can no longer be read. For long-term data storage it is better to use optical data storage such as CD or, for large amounts of data, a DVD disk.

Data display

The raw data collected and the results of analysis by a monitoring system can be displayed in several different ways. The method of display depends partly on the use to be made of the data and on the type of data.

A basic system may display a set of numeric values for predefined features of the data. The display is often made up of a series of seven segment displays which allows easily identifiable numerals to be displayed. Many bedside blood pressure and oxygen saturation monitors use this type of display where a single set of values is needed for ward observations.

When a similar type of instrument is being used with an anaesthetized patient and regular updates of the values are being taken, then a small screen using liquid crystal display (LCD) may be used to provide a time series chart of the values to allow trends to be detected easily. This type of display allows a number of predefined displays to be used with graphical and alphanumeric displays combined. An example is a pulse oximeter with a numeric display of the most recent value and a trend chart of values over the past hour.

Multivariate monitoring systems, which are typically used during surgery and in the ICU, have a display monitor screen. These screens provide a larger display area and allow a variety of layouts of data with combinations of graphical displays for real time, trend and numeric values. The displays can usually be modified by the user to provide a preferred layout that can be stored and recalled whenever the specific user uses the monitor. The monitor may use a cathode ray tube as the screen or modern systems use colour LCD screens where each dot of the screen is made of three diodes of red, green and blue which are controlled to produce the required colour at each picture cell or pixel.

Modern trends to networked patient management systems are providing entry for patient monitoring data directly to the patient record. This type of system can provide a complex display of monitored data, laboratory results and diagnostic images. ◆

SI Units: Fundamental and Derived

Jeremy A Langton
Richard Struthers

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The decimal metric system originates from the creation of the prototype metre and kilogram during the French Revolution at the end of the 18th century. The Systéme International d'Unités (SI) was adopted in 1960 after a meeting of the Conférences Générales des Poids et Mesures (CGPM) – an international convention of 50 member states including all the major industrialized nations.

The system defines seven fundamental units (Figure 1) that are dimensionally independent. The fundamental units can be algebraically combined to create derived units (Figure 2). These derived units can be named and given symbols and can then be used to derive further units. The SI also defines prefixes (Figure 3) for multiples and submultiples of SI units to avoid very large or small numbers and defines the correct usage of SI notation. The prefix attaches directly to the name or symbol of a unit.

Fundamental units

Dimension	SI unit	Symbol
Time	Second	s
Length	Metre	m
Mass	Kilogram	kg
Electrical current	Ampere	A
Thermodynamic temperature	Kelvin	K
Amount of substance	Mole	mol
Luminous intensity	Candela	cd

1

Derived SI units

Derived unit	Name	Symbol	Derivation	
Frequency	Hertz	Hz	/s	
Force	Newton	N	m/kg/s	
Pressure; stress	Pascal	Pa	N/m^2	$/m/kg/s^2$
Energy; work	Joule	J	N/m	$m^2/kg/s^2$
Power	Watt	W	J/s	$m^2/kg/s^3$
Quantity of electricity	Coulomb	C	s/A	
Electric potential difference	Volt	V	W/A	$m^2/kg/s^3/A$
Capacitance	Farad	F	C/V	$/m^2/kg/s/A^2$
Electric resistance	Ohm	Ω	V/A	$m/kg/s^3/A^2$
Celsius	Degree celsius	°C	K	

2

SI prefixes

Factor	Prefix	Symbol
10^{24}	yotta	Y
10^{21}	zetta	Z
10^{18}	exa	E
10^{15}	peta	P
10^{12}	tera	T
10^{9}	giga	G
10^{6}	mega	M
10^{3}	kilo	k
10^{2}	hecto	h
10^{1}	deca	da
10^{-1}	deci	d
10^{-2}	centi	c
10^{-3}	milli	m
10^{-6}	micro	μ
10^{-9}	nano	n
10^{-12}	pico	p
10^{-15}	femto	f
10^{-18}	atto	a
10^{-21}	zepto	z
10^{-24}	yocto	y

3

In the UK, the National Physical Laboratory (NPL) is responsible for national standards in measurement and is a member of the conference maintaining the SI units.

Fundamental SI units

Six of the fundamental SI units are based on physical properties of defined systems and therefore are reproducible to a high degree of certainty in any suitably equipped laboratory. The unit of mass (the kilogram) is still dependent on comparison with the original kilogram, which is theoretically at risk of changing over time.

Time (second s)
The second corresponds to the duration of 9 192 631 770 periods of the radiation corresponding to the transition between the two hyperfine levels of the ground state of the caesium-133 atom. Caesium atoms can flip between two energy states by microwave stimulation. In an atomic clock, an oven boils off caesium atoms, which are then magnetically gated to isolate those in one energy state. These are subjected to microwaves to energize them further and a second magnetic gate is used to send those that have flipped energy states to a detector.

The second measured by this technique is accurate to about 2 parts in 10^{15} – equivalent to 1 second in 15 million years. These atomic clocks calibrate Coordinated Universal Time (UTC) which is broadcast globally by radio and navigation satellites.

Length (metre, m)
The metre is the length of the path travelled by light in a vacuum during a time interval of 1/299 792 458 of a second. At NPL the metre is measured through the wavelength of the 633 nm radiation from an iodine-stabilized helium-neon laser, with an accuracy of about 3 parts in 10^{11}. This is equivalent to measuring the earth's mean circumference to an accuracy of about 1 mm.

Mass (kilogram, kg)
The kilogram is defined by the international prototype of the kilogram. The kilogram was originally the mass of 1 litre of water at its freezing point. In 1799 a platinum ingot was cast as the prototype and in 1879 Johnson Matthey and Co. of London successfully cast an ingot of a more stable alloy of platinum and iridium which was then regarded as the standard.

In 1889, 40 copies of the kilogram were made and distributed to national standards laboratories worldwide to be their primary standard. The UK received Kilogram 18, which is now kept at NPL.

Masses can be compared at NPL on a precision balance to an accuracy of 1 microgram. Because mass still requires comparison to a standard it might be regarded as less satisfactory than the other fundamental units.

Electric current (ampere, A)
The ampere is that constant current which, if maintained in two straight parallel conductors of infinite length, of negligible circular cross-section, and placed 1 metre apart in a vacuum, would produce between these conductors a force equal to 2×10^{-7} newton per metre of length.

The ampere is measured at NPL using a current-weighing and induced electromagnetic potential (EMP) method. It is accurate to 0.08 μA.

Thermodynamic temperature (kelvin, K)
The kelvin is the fraction 1/273.16 of the thermodynamic temperature of the triple point of water. The triple point of water is the unique temperature and pressure in a special water cell at which all three phases of water coexist (about 0.01 K above water's freezing point). This can be measured accurately to about 1 mK. From this point, gas and radiation thermometers can be calibrated.

As well as thermodynamic temperature (T) measured in kelvin the SI also recognizes celsius temperature (t) defined by $t = T – 273.15$.

Amount of substance (mole, mol)
The mole is the amount of substance of a system that contains as many elementary entities as there are atoms in 0.012 kilogram of carbon 12. Measurements of the amount of a substance are often made without referring to this definition. Methods are used that give results in moles using measurements made with other SI units.

Luminous intensity (candela, cd)
The candela is the luminous intensity, in a given direction, of a source that emits monochromatic radiation of frequency 540×10^{12} Hz and that has a radiant intensity in that direction of 1/683 Watt per steradian.

NPL uses a cryogenic radiometer that equates the heating effect of optical radiation with that of electric power. It has an uncertainty of 0.02%.

Derived SI units

Derived units are those which may be expressed in terms of multiplication or division of fundamental units. Certain derived units have been named and given special symbols and may be further combined to express other derived units.

As an example, the SI unit of force, the Newton (N), is defined as the force needed to accelerate a mass of one kilogram by one metre per second per second. Thus one Newton equals one kilogram metre per second squared.

Pressure is defined as the force applied per unit area. The SI unit of pressure, the Pascal (Pa), is therefore derived from Newtons per square metre. Thus one Pascal equals one Newton per square metre or one kilogram per metre per second squared. The use of derived units reduces the number of such longwinded units. ◆

Websites

National Physical Laboratory: www.npl.co.uk
Bureau International des Poids et Mesures: www.bipm.fr

Thermal Energy and States of Matter

David Birt

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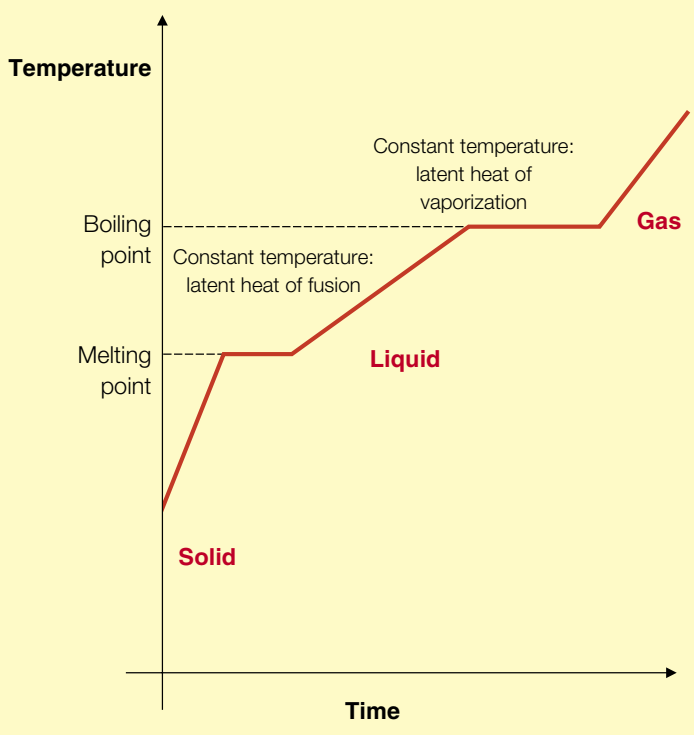
Molecular and atomic particles in close proximity exert attractive and repulsive electrical forces on each other. The particles oscillate around a fixed position but, as long as the attractive and repulsive forces are in equilibrium, the matter retains its shape and volume and exists as a solid. Thermal energy is a measure of the vibrational kinetic energy possessed by such particles. If the thermal energy level increases, the particles oscillate with greater amplitude and become able to move freely over short distances. The substance becomes liquid because the particles are in company with each other for such a short time that the attractive forces fail to gain a grip. The distance between the particles, however, remains small and although liquid matter has no shape it retains its volume. If more thermal energy is given to the particles, some of them will oscillate with such vigour that they will escape from the influence of the attractive electrical forces. Once clear, they move freely in the space available above the liquid and the matter exists as a gas.

Melting point and latent heat

If a liquid is to solidify, it must lose energy. When this occurs, the temperature of the liquid falls to a level at which an additional quantity of energy must be lost by the particles as they form a coherent structure. At this stage the substance is at its freezing point and, instead of causing a fall in temperature, further loss of energy causes fusion. Likewise, when a solid is supplied with thermal energy, it reaches its melting point and the temperature stops rising as the supplied energy is required to enable particles to break away from the fused structure. These events all occur at the same temperature and the quantity of energy released or required is known as the latent heat of fusion. When matter changes from liquid to gas, a similar phenomenon occurs at the boiling point, and the energy required is the latent heat of vaporization (Figure 1).

Variation in temperature of a substance as it is heated at a constant rate through its states of matter



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Vapour pressure

When evaporation occurs from the surface of a liquid in a closed vessel, the particles that have left the liquid collide with the wall of the vessel and create pressure. This is known as the vapour pressure and it occurs in addition to any existing atmospheric pressure.

The particles evaporate from the liquid until a stage is reached when they leave and enter the liquid at the same rate. A state of dynamic equilibrium then exists and the number of particles in the space above the liquid has reached a maximum. The vapour is therefore saturated and the vapour pressure exerted at this point is the saturated vapour pressure.

Colligative properties

If the substance in question is a solution, the response to changes in thermal energy is influenced by the number of solute particles present. These altered responses are known as colligative properties and are independent of the chemical properties of the solute. Melting point, osmotic pressure and vapour pressure are all influenced in this way and by comparing them with the corresponding properties of the pure solvent, it is possible to determine the number of solute particles present.

Since osmotic pressure also depends on the number of particles present in solution, colligative properties may be used to determine the osmolality of a solution. An osmometer applies colligative principles by using the depression of a solution's freezing point to calculate its osmolality. The resulting 'real' measurement takes account of the incomplete electrolyte dissociation that occurs in organic solutions such as plasma. ◆

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Acid–Base Balance: Maintenance of Plasma pH

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Maintenance of plasma pH ($-\log_{10}[H^+]$) within the range 7.38–7.42 is an essential requirement for life, because many metabolic processes (e.g. enzymatic reactions) are exquisitely sensitive to changes in H^+ concentration. The range compatible with life is 7.00–7.70 (i.e. a 5-fold change in H^+ concentration). The intracellular H^+ concentration is higher (about pH 7.00) than that in extracellular fluid (ECF), but it is sensitive to changes in extracellular H^+ concentration. ECF is normally alkaline. This narrow pH range must be maintained in the face of the production of large quantities of volatile acid from cellular metabolism (mainly CO_2) and non-volatile acid from the metabolism of fats and certain proteins. The main problem encountered in the homeostatic control of plasma pH is the defence of the alkaline environment in the face of this massive, daily acid load.

Volatile acid: in terms of the total acid production, CO_2 provides the largest contribution at 15–20 mols/day. This can occur either by hydration of CO_2 to form the weak, volatile carbonic acid (equation 1) or by hydroxylation of CO_2 following the splitting of water (equation 2). The products of both reactions are H^+ and HCO_3^-.

$$CO_2 + H_2O = H_2CO_3 = H^+ + HCO_3^- \quad (1)$$
$$H_2O = OH^- + H^+$$
$$OH^- + CO_2 = HCO_3^- \quad (2)$$

Production of this amount of acid would certainly change the plasma pH if it were not for the fact that most of the CO_2 is excreted from the lungs.

Non-volatile acids contribute much less to daily acid production. Such acids include sulphuric acid from sulphur-containing amino acids (e.g. cysteine, methionine), hydrochloric acid from cationic amino acids (e.g. lysine, arginine) and phosphoric acid from the metabolism of phospholipids and phosphorylated amino acids (e.g. phosphoserine). In addition, faecal loss of HCO_3^- from gastrointestinal secretions can be regarded as a significant (and variable) contribution to non-volatile acid production. Metabolism of anionic amino acids (e.g. aspartic, glutamic) and some organic anions (e.g. citrate) yield HCO_3^-, which will partially offset some of the non-volatile acid production. The contribution of non-volatile acids to total acid production depends on dietary composition. If meat is a major component of the diet, non-volatile acids are significant (about 50 mmol/day), whereas this value is lower if vegetables and fruit are the major components.

Buffer systems in body fluids

A buffer system consists of an undissociated weak acid (HA) and its base (A^-), and can be represented by:

$$HA = H^+ + A^- \quad (3)$$

Following the addition of a strong acid, some of the H^+ is mopped up through the formation of more HA and thus the change in free H^+ is limited. Conversely, the decrease in H^+ caused by the addition of strong alkali is limited by freeing H^+ from the weak acid. The main buffer systems in body fluids are given in Figure 1. The main buffer system in plasma is bicarbonate/carbonic acid, therefore pH can be represented using the Henderson–Hasselbalch equation:

$$pH = pK' + \log_{10}\frac{\text{buffer salt}}{\text{weak acid}} = \log_{10}\frac{[HCO_3^-]}{[H_2CO_3]} \quad (4)$$

where pK' is the apparent dissociation constant.

Since there is little H_2CO_3, the acid moiety of the system is primarily CO_2 which is proportional to the partial pressure of CO_2 (pCO_2 mm Hg). Thus:

$$pH = 6.1 + \log_{10}\frac{[HCO_3^-]}{0.03 \times pCO_2} \quad (5)$$

where 0.03 is the solubility coefficient of CO_2 in plasma

$$= 6.1 + \log_{10}\frac{24 \text{ mmol/litre}}{(0.03 \times 40 \text{ mm Hg}) \text{ mmol/litre}} = 7.4$$

Defence mechanisms

Defence of the alkaline environment is achieved through the operation of three basic mechanisms.

- Physicochemical buffering (i.e. removal of the H^+ by the various reactions listed in Figure 1) is instantaneous but only limits the fall in pH.
- Respiratory compensation is rapid (in minutes) and operates via the control of plasma pCO_2 through changes in alveolar ventilation and subsequent evolution of CO_2; plasma pH is returned towards the normal values, but acid–base status cannot be corrected completely.
- Renal compensation is slower (measured in hours or days) and operates via the control of plasma bicarbonate through changes in the renal secretion of H^+, reabsorption and production of bicarbonate; acid–base status can be corrected.

Main buffer systems in body fluids

Blood

• Plasma proteins	HPr	=	Pr^-	+	H^+
• Haemoglobin	HHb	=	Hb	+	H^+
• Bicarbonate	H_2CO_3	=	HCO_3	+	H^+

Interstitial fluid

• Bicarbonate	H_2CO_3	=	HCO_3	+	H^+

Intracellular fluid

• Proteins	HPr	=	Pr	+	H^+
• Phosphate	H_2PO_4	=	HPO_4	+	H^+

Disturbances in acid–base balance

It is evident from equations 4 and 5 that disturbances in acid–base balance can occur via changes in either the numerator (plasma HCO_3^- concentration) or the denominator (plasma pCO_2). Respiratory disturbance occurs if the primary change is altered pCO_2 whereas metabolic (non-respiratory) disturbance occurs if the primary change is altered plasma HCO_3^-. Thus, if pCO_2 is either increased (e.g. asphyxia, chronic pulmonary disease, voluntary hypoventilation) or decreased (e.g. anxiety attacks, rapid ascent to high altitude, voluntary hyperventilation), these disturbances are referred to as respiratory acidosis and respiratory alkalosis, respectively. If plasma HCO_3^- is decreased by addition of non-volatile acids (e.g. uncontrolled diabetes mellitus, renal failure, severe diarrhoea, ammonium chloride ingestion) or increased (e.g. excessive vomiting, sodium bicarbonate ingestion for chronic dyspepsia), these disturbances are referred to as metabolic acidosis and metabolic alkalosis, respectively.

Compensatory responses to these changes can also be predicted from equations 4 and 5. Thus, increasing or decreasing pCO_2 can be compensated for by decreasing or increasing plasma HCO_3^-, whereas acid-induced changes in plasma HCO_3^- can be compensated for by opposite changes in pCO_2. In other words, primary respiratory disturbances are compensated for by metabolic responses, and primary metabolic disturbances by respiratory responses.

Respiratory acidosis

Increasing pCO_2 will lead to a reduction in pH (i.e. the equilibrium in equation 1 is shifted to the right with an increase in H^+ concentration). The plasma bicarbonate buffer system cannot be used to compensate for this change because to do so would need the equilibrium simultaneously moving to the left (i.e. in a direction opposite to that which is causing the change). However, some H^+ will be taken up by non-bicarbonate buffers (plasma proteins and phosphates) with a subsequent small elevation in plasma HCO_3^-. CO_2 readily diffuses across all cell membranes, including capillary and RBC membranes. Thus, interstitial fluid H^+ will increase and thereby lower pH to a large extent because the concentration of non-bicarbonate buffers is low. However, the haemoglobin buffer system will make a significant contribution. Thus, the increasing intracellular CO_2 will be hydrated or hydroxylated in the presence of the catalytic enzyme, carbonic anhydrase, with the end products being H^+ and HCO_3^-. The former will be buffered by the haemoglobin system and the latter will be exchanged for Cl^- across the cell membrane (known as the chloride shift). Thus the first line of defence (physicochemical buffering) will limit but not restore plasma pH.

It should be evident that the second line of defence, respiratory compensation, cannot contribute since the primary cause of the change in pH is respiratory.

The third line of defence, renal compensation, will be important; H^+ will be excreted and plasma HCO_3^- will be increased by the renal tubular cells reclaiming virtually all the filtered HCO_3^- and producing HCO_3^-. As stated above, it can take days to compensate fully for the increase in CO_2. Hence, primary respiratory disturbances are followed by a few days of lowered plasma pH before compensation occurs.

Respiratory alkalosis

Decreasing pCO_2 will lower the denominator of equation 4, hence pH will become more alkaline. Again the plasma bicarbonate buffer system cannot contribute H^+ since this would require a simultaneous shift in the equilibrium (equation 1) to the right. Non-bicarbonate buffers will contribute by releasing H^+ and produce a small reduction in plasma HCO_3^- which will restrict, but not prevent, the rise in pH. Respiratory compensation cannot contribute since the primary disturbance is respiratory. Renal compensation will be important in lowering plasma HCO_3^- by reducing HCO_3^- reabsorption and production by the renal tubular cells.

Metabolic acidosis

Increased production or addition of non-volatile acid to plasma will lower pH. However, the change in pH will be limited by both HCO_3^- and the non-bicarbonate buffer systems:

$$H_2SO_4 + 2NaHCO_3 = Na_2SO_4 + 2H_2CO_3 \quad (6)$$
$$2H_2CO_3 = 2H_2O + 2CO_2$$

Thus, the added H^+ will be buffered so the concentrations of Hb^-, plasma proteins and HCO_3^- will be reduced. The H_2CO_3 so formed will dissociate into CO_2 and H_2O; the CO_2 will be rapidly excreted by alveolar ventilation. In addition, the increase in plasma H^+ will stimulate alveolar ventilation so that a further reduction in pCO_2 occurs. Although these compensatory changes minimize any change in pH, full compensation to return acid–base status to normal requires renal excretion of H^+, and tubular reabsorption and production of HCO_3^-.

Metabolic alkalosis

Following the addition of $NaHCO_3$ or the removal of H^+ through excessive vomiting, the sequence of change is the reverse of that described for the addition of acid. Non-bicarbonate buffers will contribute as will alveolar hypoventilation to minimize the change in pH. Renal compensation will occur through the excretion of HCO_3^-.

Role of the kidneys in regulation of plasma pH

The involvement of the kidneys in acid–base balance is primarily through the reabsorption of filtered HCO_3^- and the excretion of H^+ leading to production of HCO_3^- to replenish buffer stores depleted during buffering of non-volatile acids (i.e. the reverse of the reaction represented in equation 6).

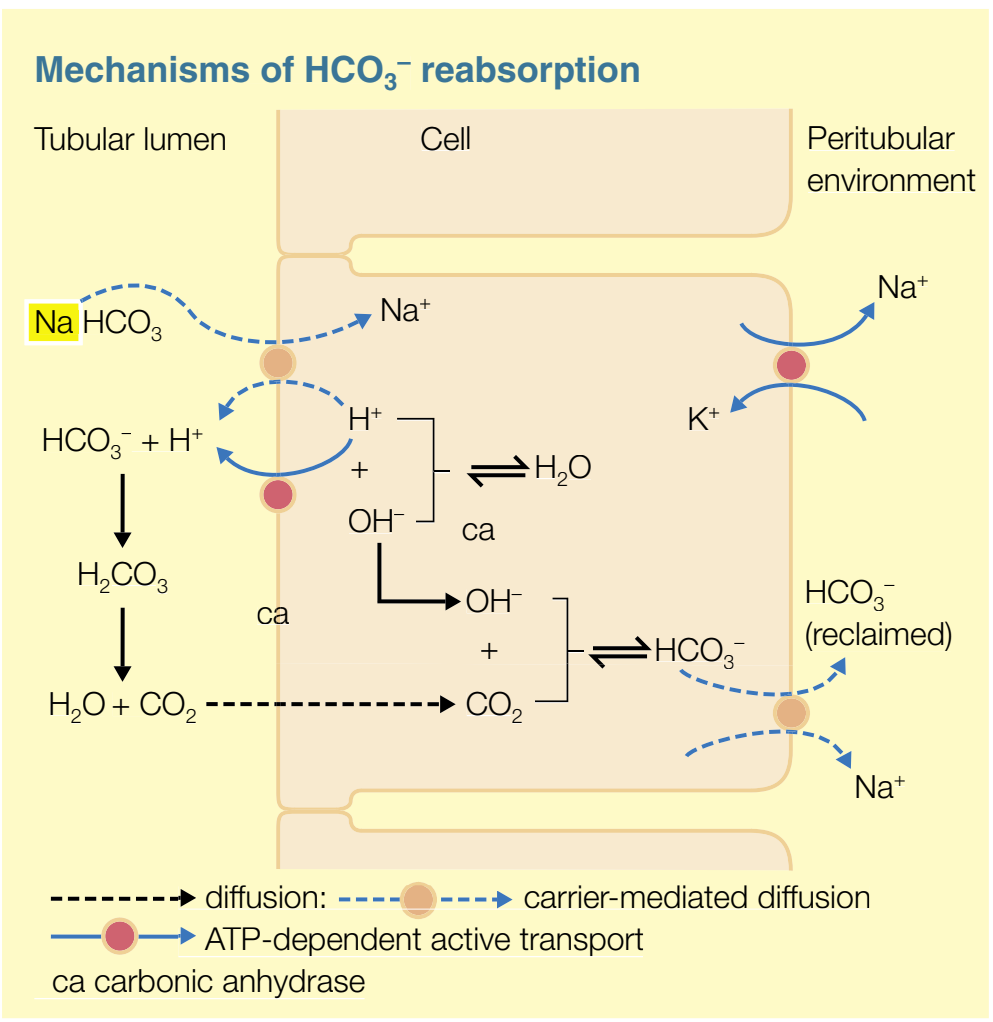
Reabsorption of filtered HCO_3^-: daily filtered HCO_3^- (calculated as glomerular filtration rate x plasma HCO_3^- concentration) approximates 4–5 moles. Renal reabsorption of this ion is in excess of 99.9% of the filtered load. If this high percentage reabsorption did not occur, bicarbonate stores in the body would soon be depleted.

In terms of the contributions of the different nephron segments, 70–85% of the filtered load is reabsorbed in the early part of the proximal tubule. The contributions of the loop of Henle, distal tubule and collecting duct are 15–20%, 3–5% and 1–2% of the filtered load, respectively.

The mechanisms for the reclamation of the filtered HCO_3^- are shown in Figure 2. Intracellular H^+, formed from the splitting of H_2O, is secreted into the tubular lumen by either passive Na^+/H^+ exchange using a protein carrier, or active transport via the energy-requiring proton pump (H^+-ATPase). A third mechanism (H^+/K^+-ATPase) operates in the α intercalated cells in the collecting duct but, quantitatively, this is far less important than the other two mechanisms.

Secreted H^+ combines with filtered HCO_3^- in the tubular lumen to form H_2CO_3 which dissociates to CO_2 and H_2O. The presence of carbonic anhydrase in the luminal cell membrane (proximal tubule and thick ascending limb of the loop of Henle) ensures that this dissociation occurs rapidly. The CO_2 formed diffuses into the cell where it is hydroxylated by OH^- (catalysed by carbonic anhydrase) to form HCO_3^-, which moves across the basolateral cell membrane into the peritubular environment on either Na^+-HCO_3^- co-transporters or Cl^--HCO_3^- ion exchangers.

The rate of HCO_3^- reabsorption appears to be influenced by a number of factors including the amount filtered, ECF volume and arterial pCO_2. Thus, if the amount filtered is increased by increasing the filtered load, total reabsorption is increased. Following ECF volume expansion, reabsorption is reduced. The mechanisms by which these changes occur are uncertain, but the fact that Na^+ reabsorption is similarly affected suggests that HCO_3^- and Na^+ might be linked. The influence of arterial pCO_2 on HCO_3^- reabsorption is thought to be by changes in the filtered load and by a direct effect on the active pumps for H^+ secretion.



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Production of HCO_3^-: the secretion of H^+ as described above does not lead to net excretion because the CO_2 formed within the tubular lumen is returned to the cell where more H^+ is formed and then secreted. However, H^+ can be excreted either as neutral ammonium salts (e.g. $(NH_4)_2SO_4$) or as acid buffer salts (NaH_2PO_4). The latter is also referred to in some texts as the excretion of titratable acid. Both these routes for H^+ excretion lead to the formation of one new HCO_3^- for every H^+ secreted.

Excretion of NaH_2PO_4: the mechanisms involved in the formation and excretion of NaH_2PO_4 are shown in Figure 3. H^+ secreted into the lumen, combines with the filtered neutral buffer salt (NaH_2PO_4) to form the acid buffer salt. Intracellular splitting of water to form the H^+ for secretion provides OH^- which combines with CO_2 to form HCO_3^- which moves into the peritubular environment with Na^+ released from the neutral salt. Formation of HCO_3^- by this mechanism occurs in the proximal tubule, distal tubule and collecting duct. Note that unlike the reclamation of filtered HCO_3^- (Figure 2), HCO_3^- is newly formed and thus will replenish some of the HCO_3^- utilized in buffering non-volatile acid (equation 6).

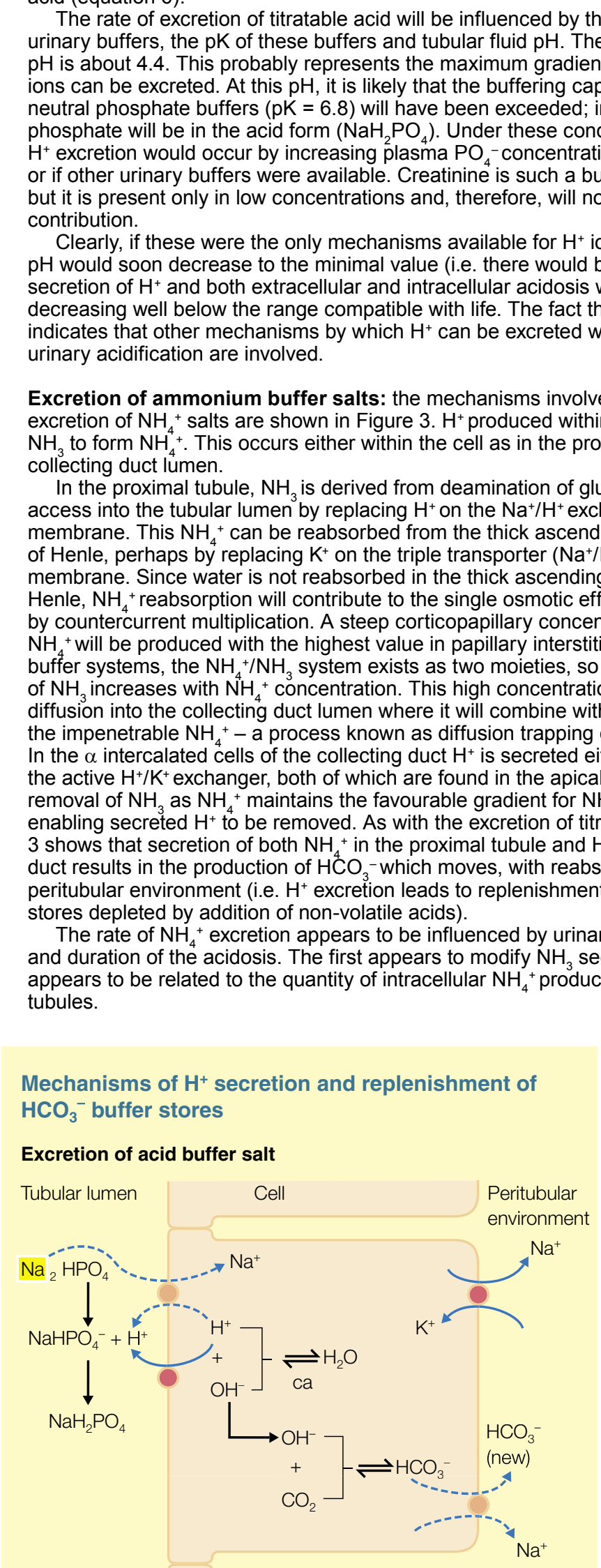
The rate of excretion of titratable acid will be influenced by the availability of the urinary buffers, the pK of these buffers and tubular fluid pH. The minimal tubular fluid pH is about 4.4. This probably represents the maximum gradient against which H^+ ions can be excreted. At this pH, it is likely that the buffering capacity afforded by the neutral phosphate buffers (pK = 6.8) will have been exceeded; in other words, all the phosphate will be in the acid form (NaH_2PO_4). Under these conditions, increases in H^+ excretion would occur by increasing plasma PO_4^- concentration (thus filtered load) or if other urinary buffers were available. Creatinine is such a buffer (pK about 5), but it is present only in low concentrations and, therefore, will not make a significant contribution.

Clearly, if these were the only mechanisms available for H^+ ion excretion, urinary pH would soon decrease to the minimal value (i.e. there would be little further net secretion of H^+ and both extracellular and intracellular acidosis would occur) with the pH decreasing well below the range compatible with life. The fact that this does not occur indicates that other mechanisms by which H^+ can be excreted with minimal changes in urinary acidification are involved.

Excretion of ammonium buffer salts: the mechanisms involved in the formation and excretion of NH_4^+ salts are shown in Figure 3. H^+ produced within the cell combines with NH_3 to form NH_4^+. This occurs either within the cell as in the proximal tubule, or in the collecting duct lumen.

In the proximal tubule, NH_3 is derived from deamination of glutamine and NH_4^+ gains access into the tubular lumen by replacing H^+ on the Na^+/H^+ exchanger in the apical membrane. This NH_4^+ can be reabsorbed from the thick ascending limb of the loop of Henle, perhaps by replacing K^+ on the triple transporter ($Na^+/K^+/2Cl^-$) in the apical membrane. Since water is not reabsorbed in the thick ascending limb of the loop of Henle, NH_4^+ reabsorption will contribute to the single osmotic effect which is multiplied by countercurrent multiplication. A steep corticopapillary concentration gradient for NH_4^+ will be produced with the highest value in papillary interstitial fluid. As with all buffer systems, the NH_4^+/NH_3 system exists as two moieties, so the concentration of NH_3 increases with NH_4^+ concentration. This high concentration will promote NH_3 diffusion into the collecting duct lumen where it will combine with secreted H^+ to form the impenetrable NH_4^+ – a process known as diffusion trapping or non-ionic diffusion. In the α intercalated cells of the collecting duct H^+ is secreted either by H^+-ATPase or the active H^+/K^+ exchanger, both of which are found in the apical membrane. The rapid removal of NH_3 as NH_4^+ maintains the favourable gradient for NH_3 diffusion, thereby enabling secreted H^+ to be removed. As with the excretion of titratable acid, Figure 3 shows that secretion of both NH_4^+ in the proximal tubule and H^+ in the collecting duct results in the production of HCO_3^- which moves, with reabsorbed Na^+, into the peritubular environment (i.e. H^+ excretion leads to replenishment of the HCO_3^- buffer stores depleted by addition of non-volatile acids).

The rate of NH_4^+ excretion appears to be influenced by urinary pH, and the severity and duration of the acidosis. The first appears to modify NH_3 secretion and the second appears to be related to the quantity of intracellular NH_4^+ produced in the proximal tubules.



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Action Potential: Generation and Propagation

Anthony C Wareham

Anthony C Wareham was Senior Lecturer in Physiological Sciences at the University of Manchester until taking early retirement in April 2001. He obtained his BSc in Zoology and his PhD from Durham University. His research interests focus on the electrophysical properties of skeletal muscle during development, denervation and disease, particularly muscular dystrophy.

Nerve and muscle cells have a highly developed ability to generate and propagate electrical impulses. An impulse, the action potential, is a reversal of the potential developed across the cell membrane at rest.

Resting membrane potential

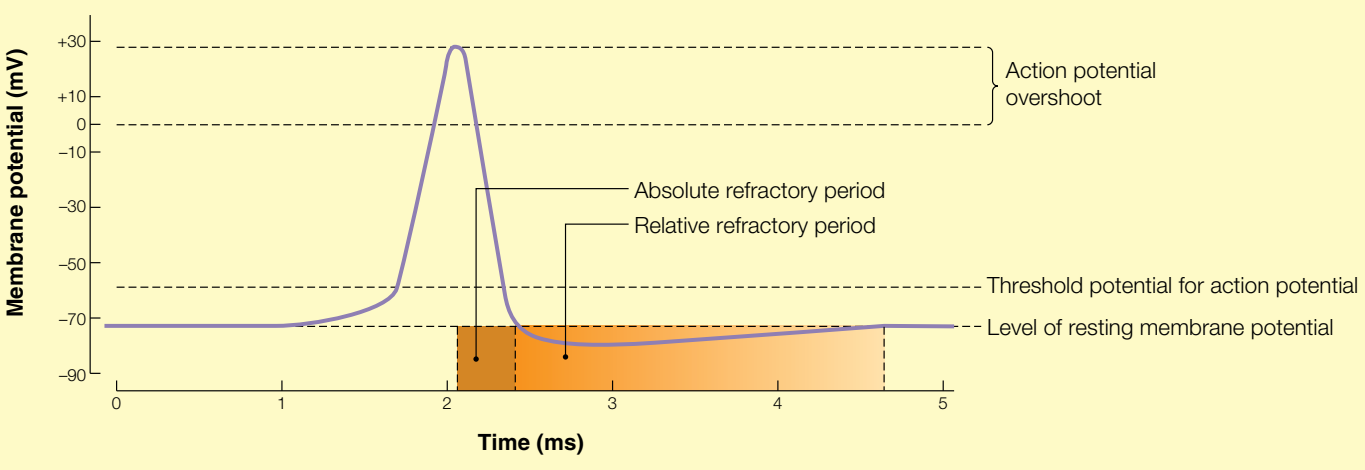
Electrically excitable cells normally have a potential of 70–90 mV across their cell membranes, with the inside negative. The K^+ concentration inside the cell is 28–30 times greater than that outside, whereas the Na^+ concentration is about 14 times greater outside. These differences are generated and maintained by the Na^+/K^+ pump. However, it is the presence in the membrane of Na^+ and K^+ leak channels, which are passive and always open, that allows the generation of the membrane potential. Because the membrane is 100 times more permeable to K^+ than to Na^+ there is a greater tendency for K^+ to diffuse out of the cell than for Na^+ to diffuse in. Such a net movement of positive charge out of the cell sets up a potential difference across the membrane with the inside negatively charged. When the difference is great enough (–70–90 mV), the negativity inside is sufficient to prevent any further net outward movement of K^+. At this point an electrochemical equilibrium is established. Thus, the resting membrane potential is sensitive to change in the extracellular K^+ concentration because this upsets the established equilibrium and leads to an adjustment of K^+ distribution, reflected in a change in resting membrane potential. Therefore, hyperkalaemia results in membrane depolarization and hypokalaemia in hyperpolarization. Since there are also Na^+ leak channels, there is a small resting Na^+ permeability and consequent slight depolarization at rest that modifies the K^+ electrochemical equilibrium and reduces the magnitude of the resting membrane potential by a few millivolts. A major value of the resting membrane potential is that it can be changed transiently, simply by altering the membrane ion permeability, and thus can generate electrical signals. Usually these are not propagated but serve to transduce sensory stimuli and to generate synaptic potentials such as the end-plate potential at the neuromuscular junction. The main exception is the action potential, which is bigger than any synaptic potential and is propagated.

Generation of the action potential

An important property of the cell membrane of electrically excitable cells is the possession of two types of voltage-gated ion channels. These are the voltage-gated Na^+ and voltage-gated K^+ channels that respond to depolarization by opening and allowing either Na^+ or K^+ to diffuse down their chemical gradients. Thus, when the Na^+ channel opens there is a net diffusion of Na^+ into the cell and when the K^+ channel opens there is a net diffusion of K^+ out of the cell. At the resting membrane potential most voltage-gated channels are closed. Other types of ion channels are opened, or gated, by chemical transmitters (e.g. by acetylcholine at the neuromuscular junction).

When an excitatory stimulus of adequate strength, a threshold stimulus (one that takes the membrane potential to –60–55 mV), is applied to a resting nerve or muscle cell, it results in the activation or opening of all the voltage-gated Na^+ channels at the point of stimulation. This results in an inward rush of Na^+ down its concentration gradient. Such inward movement of positive charge depolarizes the membrane and typically generates a positive potential of about 30–40 mV. This is the depolarizing phase of the action potential which, because it takes the membrane from its negative resting value across zero potential to a positive value, is said to ‘overshoot’. Generation of this overshoot is fast, typically taking less than 1 ms (Figure 1). To act as an effective signalling system it is essential that the membrane potential is returned to its resting value quickly. To understand how this is achieved requires a knowledge of some of the properties of voltage-gated Na^+ and K^+ protein channels.

Changes in membrane potential during a neuronal action potential



A skeletal muscle action potential is similar except that the resting membrane potential is 10–15 mV more negative and it may last for 5 ms

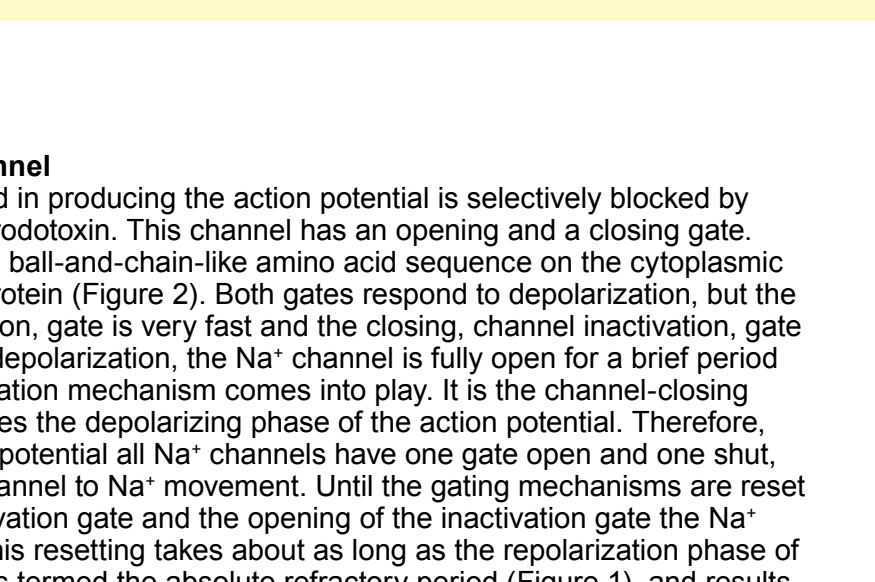
Voltage-gated Na^+ channel

The Na^+ channel involved in producing the action potential is selectively blocked by the puffer fish poison tetrodotoxin. This channel has an opening and a closing gate. The inactivation gate is a ball-and-chain-like amino acid sequence on the cytoplasmic surface of the channel protein (Figure 2). Both gates respond to depolarization, but the opening, channel activation, gate is very fast and the closing, channel inactivation, gate is slower. Therefore, on depolarization, the Na^+ channel is fully open for a brief period of time before the inactivation mechanism comes into play. It is the channel-closing mechanism that terminates the depolarizing phase of the action potential. Therefore, at the peak of the action potential all Na^+ channels have one gate open and one shut, effectively closing the channel to Na^+ movement. Until the gating mechanisms are reset by the closing of the activation gate and the opening of the inactivation gate the Na^+ channel is inexcitable. This resetting takes about as long as the repolarization phase of the action potential and is termed the absolute refractory period (Figure 1), and results in action potentials being unitary events, with no possibility of summation.

Voltage-gated K^+ channel

The K^+ channel involved in excitation is different from the Na^+ channel because it is not blocked by tetrodotoxin but by tetraethyl ammonium ions and it does not have an inactivating mechanism but only an activation or opening mechanism, initiated by depolarization (Figure 2). However, its activation mechanism is delayed so, although it is activated at the same time as the Na^+ channels, it takes longer to open. It is fully open at the peak of the action potential just as the Na^+ channel is inactivated. At this stage, the inside of the cell is positive and, with the high internal K^+ concentration, there is both an electrical and chemical force driving K^+ out of the cell. Such outward movement of positive ions drives the membrane potential in a negative direction, leading to repolarization of the resting membrane. The K^+ channel also closes quite slowly and there is thus an extended period of high K^+ permeability after an action potential that may last for several milliseconds and is termed the relative refractory period (Figure 1). During this period, owing to the high resting K^+ permeability, the membrane is electrically stable and requires a larger stimulus to reach threshold for a further action potential to be generated.

Ion movements during an action potential



Changes in membrane permeabilities to Na^+ (green) and K^+ (red) during an action potential, shown in black. Associated figures indicate the states of Na^+ and K^+ voltage-gated channels at different stages of the action potential. The Na^+ channel is always shown on the left of the K^+ channel.
ECF, extracellular fluid; ICF, intracellular fluid

Membrane currents

There is a high density of voltage-gated Na^+ and K^+ channels in the excitable cell membrane. The sum of their individual activities is measured as membrane currents and it is these currents flowing across the resistance of the cell membrane that can be recorded as depolarizations. A threshold stimulus activates sufficient Na^+ channels to lead to a strong inward Na^+ current. This inward current activates further Na^+ channels in the area in a positive feedback manner until all are activated and the peak inward Na^+ current is flowing. The action potential is a single all-or-none event. Suddenly the inactivating mechanism of Na^+ channels stops the inward Na^+ current. This is the point where the K^+ channels are fully open and there is a strong outward K^+ current flowing. This current stops quite slowly, after which the resting permeabilities of the membrane are re-established. The action potential is brief, lasting 0.5–1 ms in large axons and up to 5 ms in skeletal muscle fibre. Because action potentials are unitary all-or-nothing events, stimulus intensity in the nervous system is coded by the frequency of action potentials transmitted and not by the magnitude of the signal. Thus, the nervous system is a frequency-modulated signalling system.

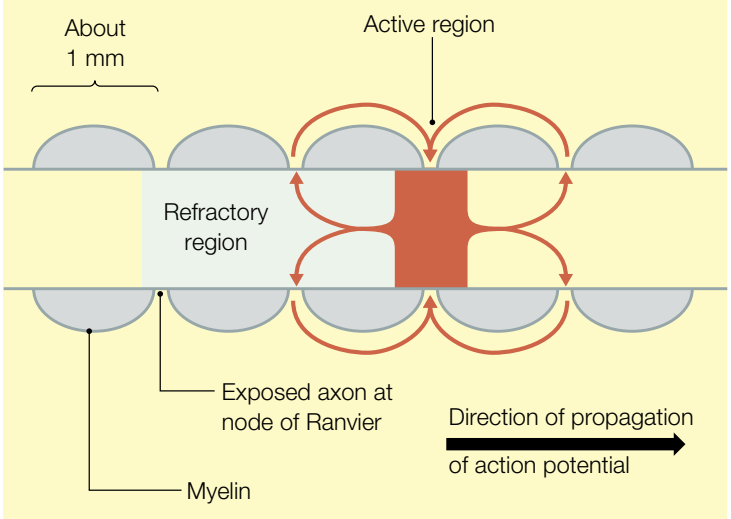
Membrane ion movements

These membrane currents result from the movement of ions into or out of the cell. However, it is important to realize that the cell does not fill up with Na^+ during the action potential. It is best to consider that the events of the action potential concern only the membrane and the ions on its surfaces. Thus, while there is a massive, but brief, increase in Na^+ permeability to generate the action potential, the number of ions that move into the cell during this increase is small in comparison to the volume of the cell. It is the movement of these positive ions that generates the inward current and not their total concentration in the cell. It can be calculated that such Na^+ influx results in a minute increase in the whole cell Na^+ concentration. Because of this, the Na^+/K^+ exchange mechanism in the membrane is not directly involved in the generation of the action potential. It is not necessary to remove all the influxing Na^+ before another action potential can occur. In fact, tens of thousands of normal action potentials may be generated in a cell whose Na^+/K^+ pump has been blocked. The role of the pump is to maintain ion gradients across the membrane and it will eventually remove the Na^+ that enters during excitation. However, its rate of pumping is relatively slow and it plays no part in the repolarization phase of the action potential.

Propagation of the action potential

At the site of action potential generation, the inside of the cell is positive. The area of membrane around this is at rest and inside is negative. Such a difference in polarity results in the movement of positive ions away from and negative ions towards the activated area. Similar but opposite effects occur outside the cell membrane. This leads to the generation of electrotonic potentials flowing through regions of the membrane adjacent to the active areas driving the resting membrane potential towards the threshold for activation. Where this electrotonic current is intense enough, voltage-gated Na^+ channels are activated and another action potential is generated. In this way, the action potential appears to move along the cell membrane (Figure 3). In fact, it is being generated wherever there are voltage-gated Na^+ channels. In the case of muscle cells and unmyelinated neurons this is all over the surface membrane. In myelinated axons, Na^+ channels occur only at the nodes of Ranvier and therefore this is where the subsequent action potential is generated. The electrotonic potentials flowing around an activated node are sufficiently intense to reach, with the help of the insulating properties of myelin, the next node of Ranvier (about 1–2 mm apart) at a sufficient intensity to cross the threshold. The action potential thus appears to ‘skip’ down the myelinated axon and results in saltatory conduction (from the Latin *saltare* to leap or dance). An action potential proceeds away from the site of initial generation and cannot reverse direction because of the absolute refractory period of the membrane previously activated (Figure 3). In electrical terms, the generation of an action potential is relatively slow and therefore propagation down a muscle fibre or unmyelinated axon is slow (about 1 m/s). However, in a myelinated axon, because the electrotonic potentials spread very rapidly, and because an action potential is generated only at discrete portions of the axon, conduction velocity is relatively quick; in large type A fibres it is up to 140 m/s. ◆

Propagation of an action potential in a myelinated axon



The active region where an action potential is occurring, shown in red, is associated with electrotonic potentials that are strong enough to activate the membrane 1 mm away at the next node of Ranvier. The direction of propagation is ensured by the refractory nature of the activated membrane. Electrotonic potentials travel much faster than an action potential, therefore myelination significantly increases conduction velocity

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Adrenocortical Hormones

Adrian Heald

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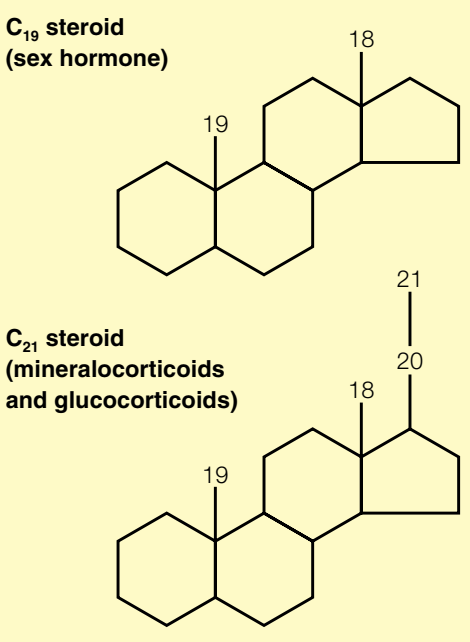
If adrenocortical disorders are untreated they are associated with significant morbidity and mortality, however, effective treatments are available that can dramatically alter the course of the disorder. Thus, a high index of clinical suspicion coupled with use of established algorithms for investigation is an appropriate clinical strategy.

Adrenal cortex

Mineralocorticoids (aldosterone) and glucocorticoids (cortisol)

Synthesis and release: all the hormones of the adrenal cortex are derived from cholesterol. This can be synthesized in the gland or taken up from the circulation. The mineralocorticoids and glucocorticoids have 21 carbon atoms in their chemical structure and may be called C_{21} steroids (Figure 1). The sex hormones, which are normally synthesized in small amounts relative to gonadal production, are mainly androgens, contain 19 carbon atoms and may be called C_{19} steroids.

Basic structures of the steroid hormones

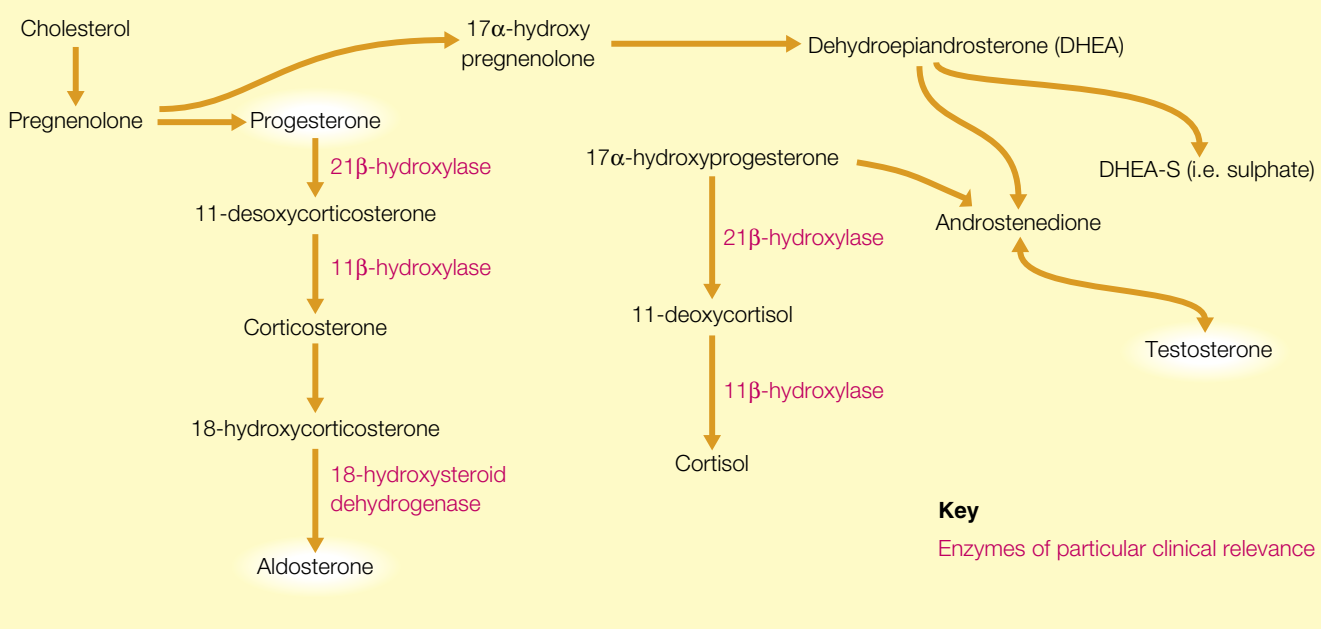


1

The most important mineralocorticoid in humans is aldo-sterone. It is synthesized from cholesterol which is converted to pregnenolone and then to progesterone (Figure 2). The enzyme 18-hydroxysteroid dehydrogenase is present only in the zona glomerulosa therefore aldosterone can be synthesized only in this part of the adrenal cortex. Cortisol synthesis is also via hydroxylation of progesterone with 17α-hydroxylase. This enzyme is present only in the zona fasciculata and reticularis of the adrenal cortex (Figure 2). Of the androgens secreted by the adrenal cortex, dehydroepiandrosterone (DHEA) is the most important. Significant quantities of adrenal androgens are produced only if the adrenal cortex is hyperactive in disease or when there is deficiency of specific enzymes leading to diversion of substrate down alternative pathways, for example in 21-hydroxylase deficiency, the most common form of congenital adrenal hyperplasia.

In the healthy individual, the secretion of cortisol follows a diurnal rhythm following that of cortisol release from the anterior pituitary. Adrenocorticotrophic hormone (ACTH) and cortisol levels rise during the hours of sleep and reach their highest levels in the morning soon after waking.

Principal metabolites produced in the synthesis of corticosteroids in adrenal glands



2

Actions

Aldosterone – the principal effect of aldosterone is to stimulate sodium absorption from the distal convoluted tubule of the kidney. Its release is stimulated by several factors including:

- a direct effect of plasma sodium (decrease) and potassium (increase)
- either a generalized fall in systemic blood pressure or a decrease in blood volume (secondary to haemorrhage or salt and water loss). This causes a decrease in renal arteriolar blood pressure which stimulates renin release and causes angio-tensin II levels to rise via the renin–angiotensin system. This in turn stimulates aldosterone production in the zona glomerulosa
- ACTH release from the anterior pituitary.

Cortisol – the effects of cortisol are:

- stimulation of hepatic gluconeogenesis and antagonism of peripheral action of insulin and glucose uptake
- stimulation of protein catabolism
- some mineralocorticoid activity on salt and water balance, an effect that is particularly important when the hormones are produced in excess.

Other effects of cortisol may be observed when the hormone is produced in excess:

- decreased growth hormone secretion by the anterior pituitary
- inhibition of the healing process in tissues
- immunosuppression.

Hyperaldosteronism

In primary hyperaldosteronism there is autonomous secretion of excess aldosterone by the adrenal cortex (unilateral adenoma) or bilateral adrenal hyperplasia. In secondary hyperaldosteron-ism, the high aldosterone production is induced by elevated levels of angiotensin II resulting from high plasma renin activity.

Primary hyperaldosteronism – patients present with hypertension caused by salt and water retention. There is often hypokalaemia and sometimes alkalosis. Confirmation of the diagnosis is by measurement of supine renin and aldosterone levels. Typically there is increased plasma concentration of aldosterone with low or suppressed plasma renin activity. Differentiating between an aldosterone-secreting adenoma (Conn's syndrome) and idiopathic adrenal hyperplasia is crucial and requires MRI scanning of the adrenals, bilateral adrenal vein catheterization or adrenal scintigraphy with ^{131}I- or ^{75}Se-labelled precursors of aldosterone.

Treatment of bilateral hyperplasia is with spironolactone, an aldosterone antagonist often combined with an ACE inhibitor. Treatment of Conn's adenoma is initially with spironolactone to normalize blood pressure and potassium levels, followed by surgical removal.

Secondary hyperaldosteronism – patients have high levels of aldosteronism and renin. Common causes are diuretic therapy, congestive cardiac failure, cirrhosis of the liver and ascites and nephrotic syndrome.

Adrenocortical insufficiency

Primary insufficiency is caused by disease of the adrenal gland (Addison's disease) which presents with glucocorticoid and mineralocorticoid deficiency. The causes of primary adrenal insufficiency are given in Figure 3. Secondary insufficiency follows absent or low levels of ACTH. It presents principally with glucocorticoid deficiency. This may result from disease of the anterior pituitary or suppression of the hypothalamo-pituitary system during long-term administration of exogenous steroids.

Causes of primary adrenal insufficiency

Chronic primary adrenal insufficiency

- Autoimmune adrenalitis, associated with circulating adrenal autoantibodies and other autoimmune disorders (e.g. pernicious anaemia, hypothyroidism and premature ovarian failure (autoimmune spectrum disorder))
- Tuberculosis of the adrenal gland
- Infiltration of the adrenal glands with metastatic tumour or amyloid
- Haemochromatosis

Acute primary adrenal insufficiency

- Any case of chronic primary adrenal insufficiency when subject to significant physiological stress
- Septicaemia with adrenal haemorrhage usually caused by meningococcal septicaemia (Waterhouse-Friderichsen syndrome)

3

Patients with the acute condition present with vomiting, abdominal pain, hypotension, dehydration and prostration (Addisonian crisis). The chronic condition has an insidious onset with fatigue, anorexia, weight loss, postural hypotension, hypoglycaemia and increased pigmentation in exposed areas and in the palmar creases and buccal mucosa.

Diagnosis is by the demonstration of impaired output of cortisol in the presence of a high circulating ACTH concentration. In the chronic situation, impaired cortisol may become apparent only on stimulation with exogenous ACTH (synacthen test) in which failure of basal cortisol levels to rise significantly is a reliable marker for insufficiency of cortisol production.

The treatment of an acute Addisonian crisis is with high-dose intravenous hydrocortisone, 100 mg q.d.s., together with intra-venous normal saline. As soon as the patient improves they may be given oral therapy with hydrocortisone, 20–30 mg/day, often supplemented with fludrocortisone, 50–100 μg/day). This is also the treatment in the non-critical case.

The diagnosis of adrenal insufficiency in the context of a pituitary tumour is by a short synacthen test or an insulin tolerance test (with induction of hypoglycaemia to act as a stimulus to adrenal cortisol production). Treatment of the condition is with glucocorticoid (hydrocortisone) replacement alone. In order to avoid secondary adrenal insufficiency in patients maintained on corticosteroid therapy for other reasons, any reduction in steroid dose must be made over a period of months with close monitoring of the patient's condition.

All patients on maintenance steroid therapy are at risk in physiologically stressful situations such as infection, operation or trauma, because they are unable to mount an adequate adrenal steroid response. At such times the dose of hydrocortisone should be increased. For simple surgical procedures or routine labour, hydrocortisone, 100 mg, should be given at induction or at the start of labour. In major operations, hydrocortisone, 100 mg every 6 hours, should be given perioperatively and postoperatively with dose reduction by 50% every 1–2 days thereafter.

Cortisol excess (Cushing's syndrome)

Cushing's syndrome is caused by excessive levels of gluco-corticoids. These may be secreted by the adrenal cortex or be derived from administered corticosteroids. Excessive secretion of cortisol may be caused by increased ACTH production by the anterior pituitary (Cushing's disease) or ectopic production of ACTH most commonly by an oat cell carcinoma of the lung. It may also result from independent hypersecretion of cortisol by the adrenal gland caused by adenoma or carcinoma.

Typical features are a red 'moon face,' purple striae on the lower abdomen and upper thighs, thin skin that bruises easily, hypertension, centripetal obesity with proximal muscle wasting giving a 'lemon on a stick' appearance, a fat pad between the shoulders (buffalo hump) and in women hirsutism and acne due to excess androgen production. There is sodium retention and potassium loss, the latter leading to hypokalaemia, impaired glucose tolerance or frank diabetes mellitus (type II), because of the counter-regulatory effects of cortisol on insulin action, and with osteoporosis.

Confirmation of the diagnosis of Cushing's disease is by 24-hour urine collection which shows a raised level of free cortisol and by the overnight dexamethasone suppression test in which a midnight dose of dexamethasone, 1 mg, fails to suppress the 9 a.m. cortisol level. Differentiation between pituitary- dependent Cushing's syndrome and adrenal Cushing's syndrome or ectopic ACTH production is by the 48 hour high-dose dexamethasone test which involves 6 hourly administration of dexamethasone, 2 mg. In pituitary Cushing's syndrome the cortisol level is suppressed after 48 hours but not in Cushing's syndrome of adrenal or ectopic origin. MRI scanning of the pituitary is the primary radiological investigation for suspected ACTH-secreting pituitary tumours. The most definitive test for the differential diagnosis is the measurement of ACTH levels in the inferior petrosal venous sinuses after corticotrophin-releasing hormone stimulation (given peripherally).

CT/MRI scanning of the adrenal glands is used to localize an adrenal tumour. Isotope scanning with ^{131}I-labelled cholesterol is sometimes used to confirm that an identified adrenal adenoma is a functioning cortisol-producing tumour.

Pituitary dependent Cushing's syndrome is treated by transphenoidal surgery often followed by external beam radiotherapy. Previously, bilateral adrenalectomy was the treatment of choice but this may result in increased growth of the pituitary tumour with very high levels of ACTH and hyperpigmentation (Nelson's syndrome). Benign tumours of the adrenal should be treated by surgical removal of the affected gland. Treatment of adrenal carcinoma is by surgical removal and administration of the adrenolytic agent o,p′-DDD. Most patients die within 2 years of diagnosis.

Congenital adrenal hyperplasia
Congenital adrenal hyperplasia comprises a set of inherited disorders of adrenal steroidogenesis. Most arise from congenital enzyme defects that impair the synthesis of cortisol and aldosterone. Depending on the precise enzyme defect there may be production of excess androgens and/or excessive secretion of mineralocorticoids other than aldosterone. Plasma levels of ACTH are raised with resulting hyperplasia of the adrenal glands.

21-hydroxylase deficiency is the most common defect and is an autosomal recessive disorder. In the absence of this enzyme there is failure of conversion of progesterone to the precursor of aldosterone and of 17-hydroxyprogesterone to the precursor of cortisol (Figure 2). The excess substrate allows enhanced synthesis and secretion of androgens in response to increased ACTH drive.

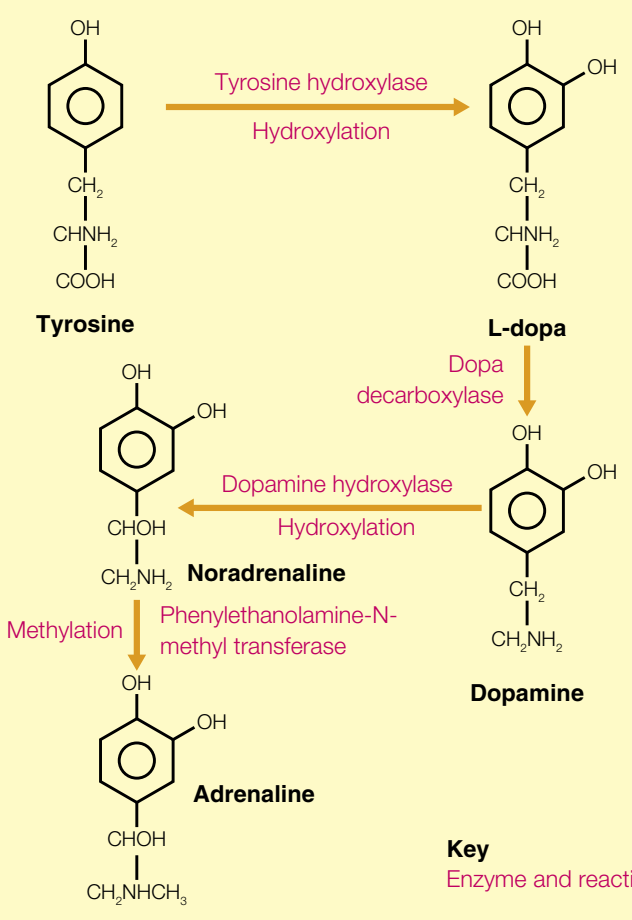
Boys present with pseudo-precocious puberty and girls with masculinization (fusion of the labia and clitoromegaly) if the disorder manifests *in utero* or virilization (hirsutism, muscle hypertrophy, clitoral enlargement and coarseness of the voice) if the disorder presents later.

Diagnosis is by demonstration of a raised plasma level of 17-hydroxyprogesterone. Treatment is with the glucocorticoids dexamethasone or prednisolone given as a morning dose and then a late evening dose to suppress the overnight release of ACTH.

Adrenal medulla
The adrenal medulla is embryologically derived from the neural crest and secretes catecholamines of which adrenaline is predominant, the remainder being noradrenaline. The adrenal medullae are not essential for life because their function is compensated for by increased sympathetic activity.

Catecholamines
The catecholamines, dopamine, noradrenaline and adrenaline, are synthesized within the adrenal medulla in addition to sympathetic postganglionic nerve endings and the brain. The synthetic pathway is shown in Figure 4 and originates with the amino acid tyrosine (mainly derived from the diet). This is hydroxylated to L-dopa which is decarboxylated to dopamine. This can be converted to noradrenaline by hydroxylation and on to adrenaline by methylation.

Principal features of the synthesis of noradrenaline and adrenaline



4

The catecholamines are stored in granules within the chromaffin cells of the adrenal medulla. Their release is stimulated by acetylcholine from preganglionic sympathetic nerve endings.

Phaeochromocytoma
Phaeochromocytoma is potentially lethal if untreated but eminently curable once identified. 90% of phaeochromocytomas arise in the adrenal and 10% are malignant. There is an association with multiple endocrine neoplasia type 2 (MEN 2), the other features being medullary thyroid carcinoma and parathyroid hyperplasia.

Most tumours secrete noradrenaline and adrenaline. Large tumours secrete almost entirely noradrenaline. Diagnosis is by the measurement of metadrenaline and normetadrenaline in a 24-hour urine sample collected with acid preservative. Localization is by CT/MRI scanning or by isotope scanning with ^{131}I metaiodobenzylguanidine (MIBG), an analogue of noradrenaline. This is particularly useful in the localization of extra-adrenal phaeochromocytomas. Treatment is initially medical, with combined α- and β-adrenoreceptor blockade (e.g. phenoxybenz-amine plus propranolol) followed by surgical removal in a specialist unit. Recently, this has been successfully carried out laparoscopically. Careful preoperative preparation is vital. During the operation any marked elevation of blood pressure caused by sudden release of catecholamines can be overcome by the intravenous administration of the α-blocker phentolamine.◆

Applied Cardiovascular Physiology

Roger Hainsworth

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Exercise

Physical exercise involves complex coordinated responses involving the locomotor, respiratory and cardiovascular systems. The first cardiovascular changes are initiated by a central drive, which starts either in anticipation of, or at the start of, exercise and leads to a decrease in cardiac vagal activity and an increase in sympathetic activity. Though an increase in heart rate may be the first observable change, the main factor causing the cardiovascular responses is the increase in muscle work. The increased metabolic activity by the working muscle results in the local build-up of the various metabolic products, including adenosine and phosphates, potassium, carbon dioxide and lactate. The consequent vasodilatation results in a large increase in blood flow in the working muscle with a greatly enhanced filling of veins. The rhythmically contracting muscle alternately compresses and relaxes compression of veins, and venous valves ensure that blood return to the heart is enhanced. Cardiac filling is also enhanced by the 'thoraco-abdominal' pump mechanism whereby alternating pressure gradients between the thorax and abdomen effectively pump blood into the right atrium.

The role of the heart is essentially to respond to the increased inflow. A reduction in vagal activity and increased activity in the sympathetic nerves increase both rate and force of ventricular contractions. The increase in cardiac output is achieved mainly through the increase in heart rate (Figure 1) though, particularly for endurance athletes, the increased stroke volume is also important. It should be noted that an increase in heart rate *per se* does not necessarily increase cardiac output. It is the enhanced venous inflow and the shortening of systolic time by sympathetic drive that allows the heart to fill adequately so that the increase in rate is not offset by a decrease in stroke volume.

The generalized increase in sympathetic drive results in vasoconstriction in regions of the body not involved in the exercise and has the effect of diverting the blood to exercising regions. Sympathetic vasoconstrictor nerves have little effect on flow to exercising muscle and there is no evidence for the existence of vasodilator nerves to human muscle. Blood pressure, particularly systolic, increases in proportion to the exercise intensity and systolic pressure may reach 200 mm Hg in maximal exercise.

Training causes widespread changes to improve exercise performance (Figure 1). In trained muscle, there are increases in mitochondrial oxidative enzymes and in capillary density, which together with increased muscle mass, increase oxygen extraction. The resting heart rate is reduced and stroke volume increases. During exercise, the maximal heart rate is mainly age-dependent, but the relative increase is greater in athletes. Other effects of endurance training are increases in red cell count and plasma volumes, and in cardiac mass and volume. Inactivity, particularly bed rest and weightlessness in space, results in opposite changes (see below).

Responses to exercise in a healthy young subject and a trained endurance athlete

	Healthy subject at rest	Athlete at rest	Maximum exercise	
			Healthy subject	Athlete
Heart rate (beats/minute)	70	50	200	200
Stroke volume (ml)	70	100	100	200
Cardiac output (litre/minute)	5.0	5.5	20	40
Total muscle blood flow (litre/minute)	1.0	1.2	15	35
Volume of oxygen utilization (litre/minute)	0.25	0.30	3.0	6.0

Haemorrhage

The cardiovascular effects of haemorrhage are dependent on the volume of blood lost and the rate at which the loss occurred. A slow gastrointestinal bleed or heavy menstrual loss results in anaemia and the main effect of this on the cardiovascular system is to cause an increase in cardiac output to maintain a normal oxygen delivery. A rapid loss of up to 0.5 litre may be unnoticed though the effects of posturally related blood shifts may be enhanced. Larger and rapid bleeds invoke reflex responses and, if sufficiently severe, result in shock.

Because most of the blood volume (about 70%) is contained in veins, and veins are readily able to reduce their volume by passive recoil and by active constriction in some veins, it is venous volume that is mainly reduced following blood loss. The reduced venous volume leads to a decrease in cardiac filling and consequently (Starling's law) a reduced stroke volume and cardiac output. Blood pressure is well maintained, and mean pressure may even increase. In moderate haemorrhage, the smaller stroke volume results in a reduction in arterial pulse pressure and it is this that alters the pattern of baroreceptor discharge, and leads to increases in vascular resistance and heart rate. The small rapid pulse and the cutaneous vasoconstriction are observable clinically. More severe, hypotensive haemorrhage affects chemoreceptors and results in further vasoconstriction and hyperventilation. Severe systemic hypotensive haemorrhage may result in cerebral ischaemia and a very intense vasoconstriction. Other responses to haemorrhage involve the endocrine system and increased secretion of cortisol, adrenal catecholamines, renin–angiotensin–aldosterone and vasopressin.

Following an acute haemorrhage, the blood volume is largely restored within a few hours by absorption of fluid from the tissues into the capillaries. This occurs because precapillary arteriolar vasoconstriction reduces capillary hydrostatic pressure, leaving the protein oncotic pressure relatively unopposed. Regeneration of protein by the liver and increased formation of RBCs by the bone marrow have a longer time course.

Severe, untreated hypotensive haemorrhage may lead to irreversible changes and death. Tissue hypoperfusion results in hypoxia and acidosis, and a point may be reached when replacement of the lost blood fails to restore blood pressure. Hypoperfusion of the intestine may lead to bacteria and toxins entering the circulation, with disastrous consequences. Nitric oxide is synthesized and this causes relaxation of vascular smooth muscle and severe hypotension. Myocardial function may be depressed, causing cardiac failure. Blood clotting is abnormal, with both disseminated intravascular thromboses and widespread haemorrhages occurring. Renal failure also occurs. Irreversible shock is fatal, and the aim of treatment of haemorrhage must be to prevent this from occurring.

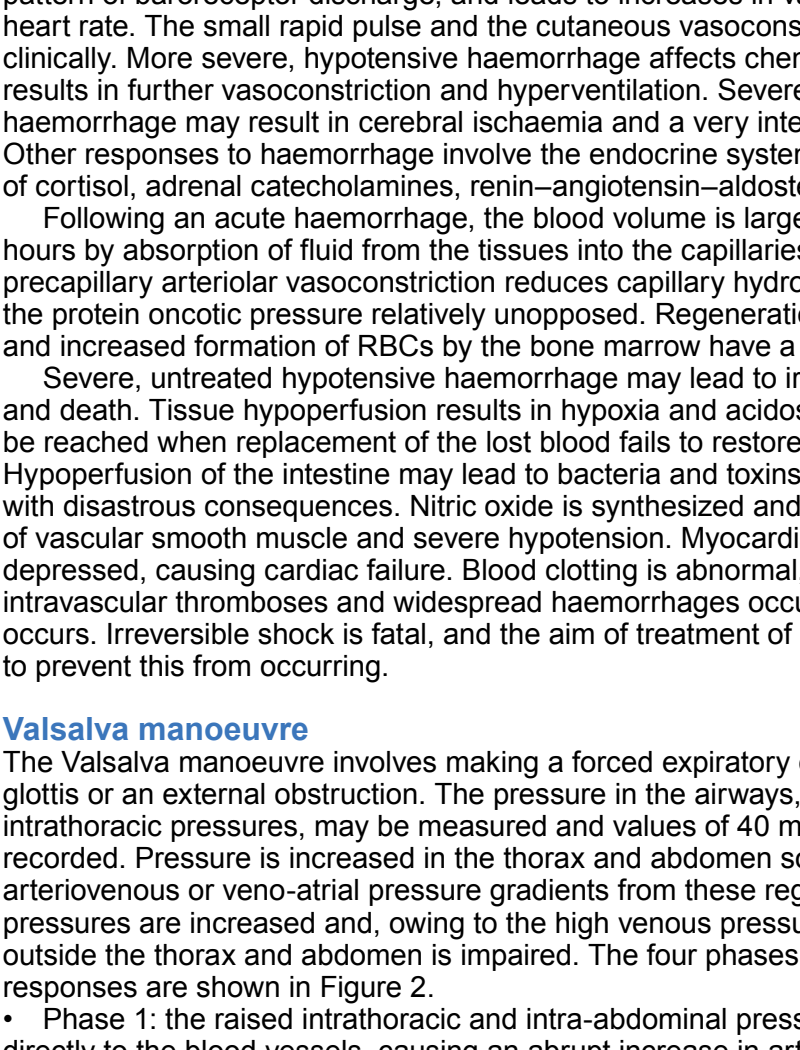
Valsalva manoeuvre

The Valsalva manoeuvre involves making a forced expiratory effort against a closed glottis or an external obstruction. The pressure in the airways, and therefore intrathoracic pressures, may be measured and values of 40 mm Hg or more are recorded. Pressure is increased in the thorax and abdomen so that it has little effect on arteriovenous or veno-atrial pressure gradients from these regions. Absolute vascular pressures are increased and, owing to the high venous pressure, inflow of blood from outside the thorax and abdomen is impaired. The four phases of the blood pressure responses are shown in Figure 2.

- Phase 1: the raised intrathoracic and intra-abdominal pressures are transmitted directly to the blood vessels, causing an abrupt increase in arterial pressure.
- Phase 2: pressure (particularly pulse pressure) decreases due to decreased stoke volume resulting from the reduced inflow from veins draining limbs and head. This partly recovers owing to venous pressures increasing and to baroreceptor-mediated vasoconstriction.
- Phase 3: a fall in pressure occurs as the arterial compression is released.
- Phase 4: an overshoot occurs owing to the increased venous return following relief of the obstruction being pumped by the heart into a constricted circulation. There is usually reflex bradycardia in phase 4.

The Valsalva manoeuvre can be used as a test for normal autonomic control and baroreceptor reflexes. In autonomic disorders, the recovery of pressure in phase 2 and the overshoot in phase 4 are absent.

Valsalva manoeuvre



There are four phases. **1** Compression of intrathoracic and intra-abdominal arteries causes blood pressure to increase.
2 Decreased inflow from outside the thorax and abdomen results in decreased venous inflow and there are decreases in stroke volume, pulse pressure and mean pressure, followed by partial recovery due to reflexes and high venous pressures.
3 Pressure falls as compression of arteries is removed.
4 Overshoot as high venous inflow is pumped into constricted circulation. There may be a reflex bradycardia.

Source: Hainsworth R. Autonomic Nervous System. In: McClaughley W, Clarke R S J, Fee J P H, Wallace W F M, eds. *Anaesthetic Physiology and Pharmacology.* Edinburgh: Churchill Livingstone, 1997: 305–22.

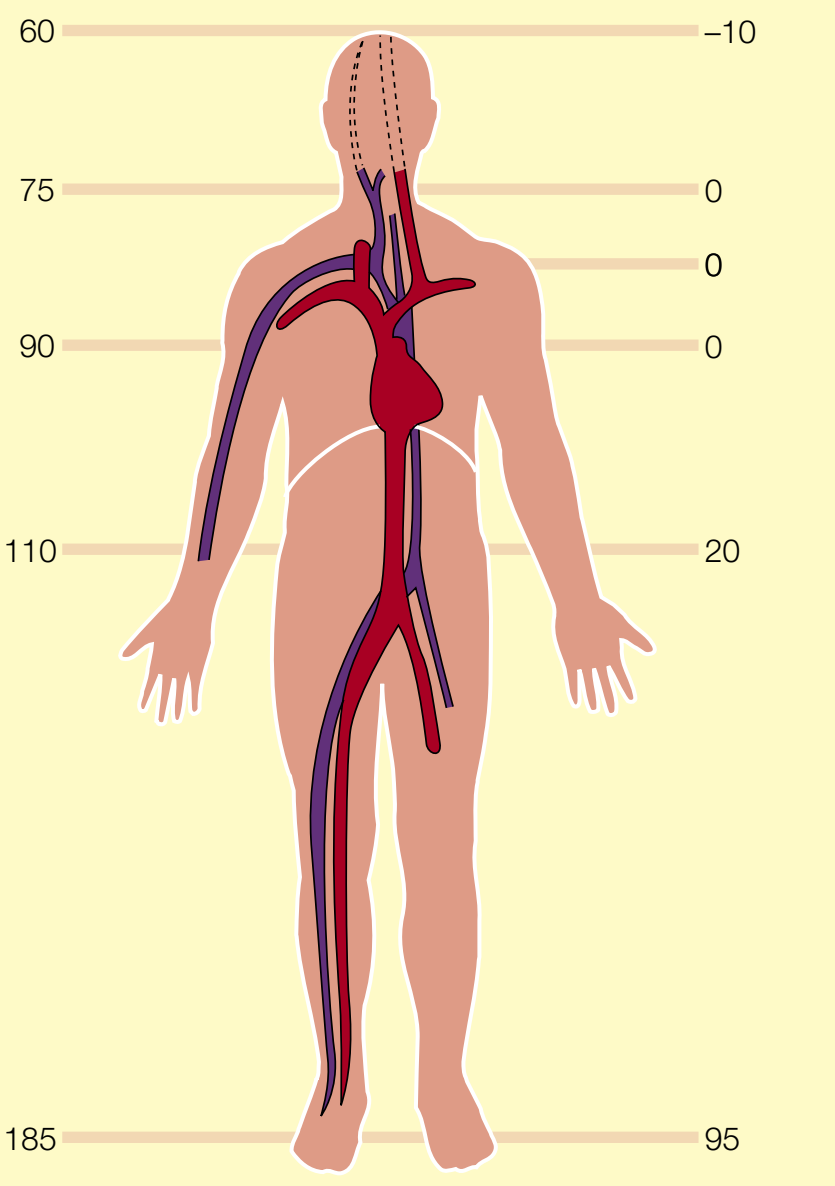
Responses to postural change

Figure 3 gives examples of typical arterial and venous pressure in a person standing motionless. Gravity imposes large pressure gradients, for example the low cerebral perfusion pressure and the high subdiaphragmatic venous pressures. The venous gradients result in the translocation of 0.5 litre or more from the central circulation into dependent veins. Of equal importance is the progressive loss of fluid from the dependent, distended capillaries to the tissues. This also can amount to another 0.5 litre or more within 5 minutes of being upright. The venous pooling and fluid loss result in cardiac output falling by about 25%.

The responses depend on whether the subject stands actively or is tilted using a tilt table. Active standing involves muscular exercise and there may also be some degree of straining (see above). Typically, there is an initial heart rate increase followed by a short-lasting, but often sharp, fall in blood pressure due at least partly to vasodilatation in the working muscle. Passive head-up tilting does not normally lead to a fall in blood pressure but diastolic pressure usually increases with little change in systolic pressure. The fall in pulse pressure, despite the unchanged or even increased mean pressure, provides the change to baroreceptor stimulation. Reflex responses cause vascular resistance and heart rate to increase.

Prolonged standing, particularly standing still so that the 'venous pump' is ineffective, or head-up tilting may lead to venous pooling and capillary fluid loss progressing to the point at which venous return is inadequate and syncope results. Syncope is often associated with a vasovagal reaction where sympathetic vasoconstrictor drive abruptly ceases, causing inappropriate vasodilatation, and vagal activity markedly increases, causing bradycardia or even asystole. On becoming supine, venous return increases and recovery is normally rapid.

Arterial and venous pressures in a motionless upright individual



Gravity causes pressure gradient along vertical axis of body. Arterial pressure is particularly low in the head and vulnerable to further falls. Venous pressures are high in abdomen and legs, resulting in accumulation of blood in distended veins and increased fluid loss from dependent capillaries.

Source: Hainsworth R. Arterial Blood Pressure. In: Enduby G E H, ed. *Hypotensive Anaesthesia.* Edinburgh: Churchill Livingstone, 1985: 993–1029.

3

Weightlessness

The problems encountered during gravitational stress are avoided when the individual is recumbent, immersed in water or in space away from earth's gravity. Several adaptive changes take place, particularly over the first few days, as the result of the absence of hydrostatic pressure gradients. There is no longer the accumulation of blood and tissue fluid in dependent regions, and the blood volume in the thorax and upper parts of the body increases. The increase in thoracic blood volume is at least partly responsible for inducing a diuresis as the result of atrial receptor stimulation. This causes a decrease in extracellular fluid volume including blood volume. Cardiac output decreases and there is also some evidence for impairment of cardiovascular reflexes. Prolonged weightlessness leads to muscle deconditioning and wasting. There is also a slow but persistent demineralization of the bony skeleton.

Changes caused by weightlessness are largely adaptive processes to the absence of work by the cardiovascular and locomotive systems against gravitational forces and, therefore, result in few problems while the subject is in the weightless state. On returning to gravity, however, the adaptive changes result in the subject being unable to induce normal responses. The smaller blood volume, the increased amount of venous pooling in the deconditioned individual and the impaired cardiovascular reflexes result in a greatly impaired orthostatic tolerance, with a greatly increased risk of fainting.

Astronauts attempt to minimize these effects by taking regular exercise while weightless and attempting to expand blood volume by drinking large quantities of saline before returning to earth.

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Blood Cells, Haemoglobin, Haemostasis and Coagulation

David S Minors

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RBCs (erythrocytes)

Characteristics, formation and destruction

The average red cell count is 5.4 x 10^{12}/litre in men and 4.5 x 10^{12}/litre in women. Each RBC is a biconcave disc, which has an average diameter of 7.2 μm and is 2 μm thick at its edges. RBCs lack intracellular organelles. The shape of the RBC is physiologically important, because it maintains a high surface area:volume ratio, which aids transmembrane diffusion (particularly of oxygen), while minimizing the intracellular distance over which oxygen must diffuse to combine with haemoglobin (see below). The shape of the RBC, together with the considerable flexibility of its plasma membrane, also allows the cell to flex and distort, which is often necessary as it traverses the capillaries. The normal shape of the cell is maintained by a membrane skeleton, consisting of four proteins, of which spectrin is the most abundant. A deficiency of these proteins leads to an abnormal shape; for example, a deficiency of spectrin, which is found in hereditary spherocytosis, results in RBCs that are more spherical than normal.

Because they lack intracellular organelles, RBCs have a limited life in the circulation (about 120 days) and must derive energy anaerobically through the glycolytic (Embden–Meyerhof) pathway. About 5% of glycolysis also occurs through the hexose monophosphate shunt, using glucose-6-phosphate dehydrogenase (G6PD), and resulting in the generation of NADPH. G6PD deficiency makes RBCs extremely susceptible to damage by oxidants, resulting in haemolytic anaemia.

The events leading to the death of RBCs remain obscure but, at the end of their life, they are removed by macrophages of the reticuloendothelial system, especially in the bone marrow, and also in the liver and spleen. This removal appears to be triggered by changes in the membrane that alter its flexibility, and any disease that leads to a change in this (e.g. hereditary spherocytosis) results in an accelerated removal of the cells and haemolytic anaemia.

In health, the continuous removal of old RBCs is balanced by the formation of new cells (erythropoiesis). In the early fetus until about 7 months' gestation, erythropoiesis is performed by the liver and spleen. After that time, and throughout childhood and adult life, the bone marrow becomes the sole site of erythropoiesis. Whereas in children all bone marrow is capable of erythropoiesis, in adults it is limited to the marrow of the bones of the trunk and the proximal end of long bones. Within the marrow, RBCs are derived from common pluripotent cells that give rise to a series of progenitor (committed stem) cells which, in turn, form the several blood cell types. The progenitor cells of the erythroid series divide and differentiate into pronormoblasts, which are large cells with a large central nucleus. Through a number of cell divisions, the pronormoblasts give rise to series of progressively smaller normoblasts, which become invested with haemoglobin. In the final stage of maturation, the nucleus is extruded and immature RBCs – reticulocytes – are released into the bloodstream. The rate of erythropoiesis is regulated by the hormone erythropoietin, which is a glycoprotein hormone secreted by the peritubular network of the kidney. Erythropoietin increases RBC formation by enhancing the proliferation of the erythroid progenitors and their differentiation into pronormoblasts. The sole regulator of erythropoietin secretion appears to be the rate of oxygen delivery to kidney; erythropoietin production increases as oxygen delivery falls. A fall in oxygen delivery can occur not only with deficient oxygenation of the blood, but also in haemoglobin deficiency (anaemia) or in the presence of an abnormal haemoglobin which is unable to give up oxygen normally.

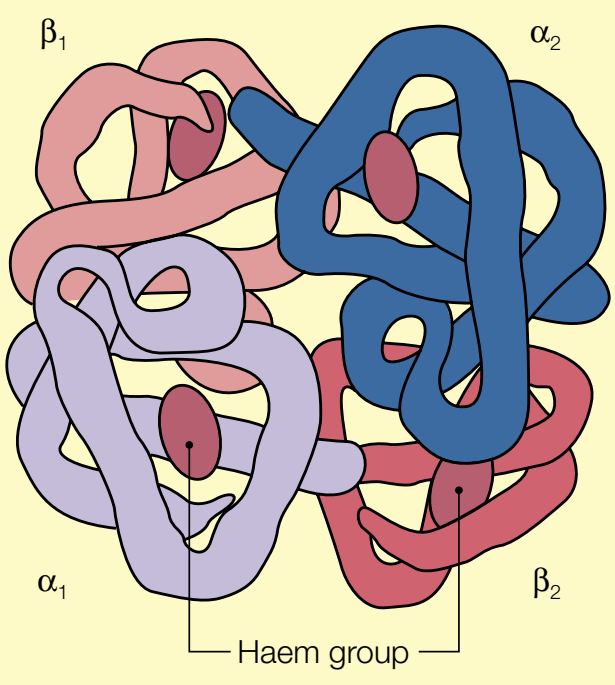
Functions

Functionally, the most important contents of the RBC are carbonic anhydrase and haemoglobin. Carbonic anhydrase catalyses the hydroxylation of carbon dioxide to H^+ and HCO_3^-. The HCO_3^- formed in the RBC then diffuses into the blood plasma in exchange for Cl^- (the chloride shift) and accounts for 90% of the way in which carbon dioxide is carried in blood. The major role of haemoglobin derives from its ability to combine reversibly with oxygen. In addition, it is responsible for the carriage of a small proportion of carbon dioxide in the blood (as carbamino compounds) and it is a buffer, accepting the H^+ released with HCO_3^- formation (see above).

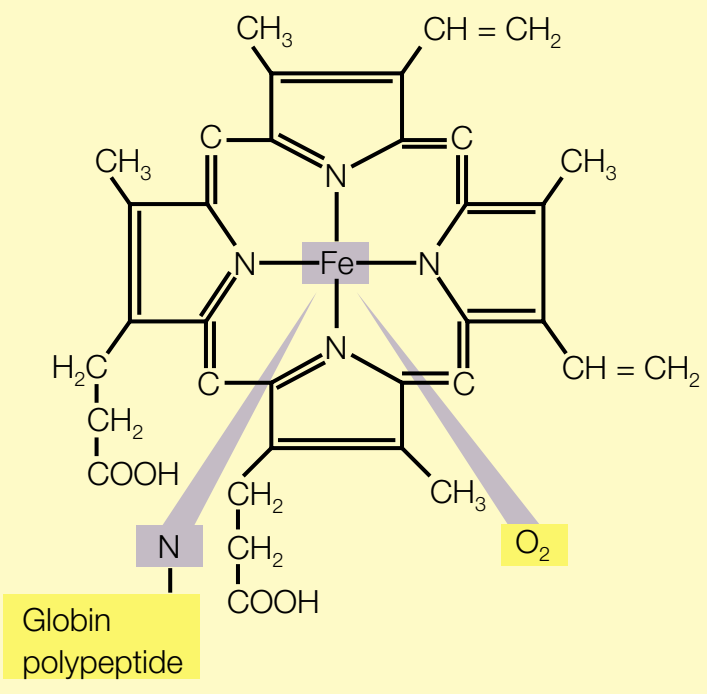
Haemoglobin has a molecular mass of 64,450 and its concentration in blood is normally about 16 g/dl in men and 14 g/dl in women. Physiologically, it exists as a tetramer. Each of the four subunits consists of a polypeptide (globin) chain conjugated to the iron-containing porphyrin, haem, in which the iron is found in the reduced Fe^{2+} state (Figure 1). In the tetramer, there are two pairs of globin chain which differ in their amino-acid sequence. In adults, most haemoglobin (96–98%) possesses two α and two β chains, and is referred to as HbA ($\alpha_2\beta_2$). In addition, there are also small amounts (1–3%) of HbA_2, in which the β chains are replaced by δ chains. In fetal haemoglobin (HbF; $\alpha_2\gamma_2$), the β chains are replaced by γ chains, which results in the higher binding affinity of HbF for oxygen. Most HbF synthesis is switched to HbA production 6–8 months postnatally, though very small amounts of HbF synthesis persist into adult life. The genes for the γ, δ and β chains are situated on chromosome 11, whereas the α gene is found on chromosome 16, where it is duplicated (α_1 and α_2 genes). As with any other genetically determined trait, mutants can arise, resulting in the formation of abnormal or deficient haemoglobin (see below).

In the oxygenation of haemoglobin, each haem moiety binds one oxygen molecule (Figure 1), and thus 1 mole of the tetramer can bind 4 moles of oxygen. The binding of oxygen to one subunit causes an allosteric change in the remainder of the molecule. In the deoxy state, the haem is in the tense or T state, and there are numerous salt bridges between the four globin chains. When oxygen binds to one haem, some salt bridges are broken, leading to a small movement of the globin chains. This causes haem to change to its relaxed or R state, which favours oxygen binding. In this way, binding of one oxygen molecule favours binding of further oxygen until all haem moieties are saturated, which explains the sigmoid shape of the oxyhaemoglobin dissociation curve. As the haemoglobin gives up its oxygen to the tissues, the salt bridges re-form. The resulting movement of the globin chains causes haem to revert to its T state and allows 2,3-diphosphoglycerate (2,3-DPG) to gain access to a central cavity in the haemoglobin molecule. 2,3-DPG decreases the affinity of haemoglobin for oxygen and a rise in the intracellular concentration of 2,3-DPG thus shifts the oxyhaemoglobin dissociation curve to the right.

Model of the adult haemoglobin (HbA) molecule



Chemical structure of the haem moiety showing bound oxygen



Anaemia

Anaemia is normally defined as a haemoglobin concentration of less than 13.5 g/dl in men and 11.5 g/dl in women. It has a number of causes, which can be categorized into anaemias resulting from:

- a decreased life-span of the RBC – haemolytic anaemias
- impairment of RBC formation.

These anaemias are in addition to the anaemia that will follow some hours after a haemorrhage. The haemolytic anaemias include those in which a congenital defect results in abnormal RBCs that are removed by the recticuloendothelial system at an accelerated rate (e.g. hereditary spherocytosis, G6PD deficiency, sickle cell anaemia). In addition, acquired defects (e.g. haemolytic transfusion reaction, some drugs, malaria) can also lead to premature destruction of RBCs.

Anaemias resulting from impairment of RBC formation are equally varied in cause. They are most commonly caused by a deficiency of one of the factors required for normal erythropoietic activity (e.g. iron deficiency, which is required for haemoglobin synthesis, and vitamin B_{12} or folate deficiency, which is required for incorporation of thymidine into DNA). In addition, they can be caused by diseases of the bone marrow – the aplastic anaemias, which can be congenital, acquired or secondary. Causes of secondary damage to marrow include ionizing radiation, cytotoxic drugs such as busulphan and cyclophosphamide, chemicals such as benzene, and myeloid leukaemia, though the latter only rarely results in aplastic anaemia.

Haemoglobinopathies: over 500 haemoglobinopathies, which result from the formation of an abnormal globin chain, have been reported. Most are rare, asymptomatic and harmless, and result from a single-point mutation in one of the globin genes, giving rise to a single amino-acid substitution in one of the globin chains. Some of the more commonly occurring haemoglobinopathies are summarized in Figure 2. Of these, the most common and clinically significant is sickle cell haemoglobin (HbS). HbS is far less soluble and, in the deoxygenated state, crystallizes and then polymerizes into long chains, causing distortion of the RBC into a characteristic sickle shape.

Common haemoglobin variants caused by a single amino-acid substitution on the β chain

Haemoglobin variant	Amino-acid substitution[1]	Clinical abnormality
HbS	GLU(6) → VAL	Sickling of RBCs on deoxygenation due to haemoglobin polymerization, leading to severe haemolytic anaemia and painful crises
HbC	GLU(6) → LYS	Decreased solubility of haemoglobin and reduced RBC flexibility on deoxygenation, leading to mild haemolytic anaemia
HbD	GLU(121) → GLN	Mild haemolytic anaemia
HbE	GLU(26) → LYS	Small RBCs with low intracellular haemoglobin concentration, but seldom anaemia
HbM (Milwaukee)	VAL(67) → GLU	Oxidation of iron in haem to Fe^{3+}, known as methaemoglobinaemia

[1]The amino acid shown before the arrow is the amino acid (and its position on the β chain) that is substituted by the amino acid indicated after the arrow. GLU, glutamic acid; VAL, valine; LYS, lysine; GLN, glutamine.

In an individual homozygous for the HbS gene, more than 80% of circulating haemoglobin is HbS. Such individuals have sickle cell anaemia, which is a haemolytic anaemia resulting from accelerated destruction of the sickled cells, with sickling occurring even at oxygen tensions normally found in venous blood. The individual may also suffer painful crises due to sickled cells blocking the microcirculation and causing tissue infarction. Such crises can be triggered by infection, dehydration, acidosis, and conditions that can cause further deoxygenation of haemoglobin. Careful management of such individuals during general anaesthesia is critical.

Heterozygous individuals have the sickle cell trait. They are generally asymptomatic and do not usually suffer sickling because the RBCs contain less than 45% HbS. Severe hypoxia (haemoglobin saturation < 40%) can, however, still result in sickling in these individuals, who should be considered 'at risk' during general anaesthesia.

As yet, there is no cure for sickle cell anaemia, though treatment with hydroxyurea, which increases HbF production, has been shown to decrease the number of crises. In addition, recent research has attempted transplants of healthy stem cells into the early fetus, before erythropoiesis is transferred to the bone marrow and immunity has developed. These stem cells would then divide further, produce normal RBCs and, it is hoped, might eventually displace native stem cells possessing the sickle cell gene.

Thalassaemia: in this condition, either α or β chain synthesis is decreased due to gene deletions. Since the αgene is duplicated, in α-thalassaemia one, two, three or four genes can be deleted. α^+ and α^0 thalassaemia, in which there is deletion of one or two genes, respectively, are usually asymptomatic. When three genes are deleted, which is termed HbH disease, there is a chronic haemolytic anaemia and, when four genes are deleted, there is usually intrauterine death (Hb Bart's hydrops foetalis syndrome).

β thalassaemias are classified as β thalassaemia major, in which the individual is homozygous, and β-thalassaemia trait, in which the individual is heterozygous. The trait normally results in no or mild anaemia, whereas the major condition results in a severe anaemia as a result of precipitation of the abnormal haemoglobin. The trait can coexist with other haemoglobin variants (e.g. HbS, HbE and HbD).

WBCs (leucocytes)

Unlike RBCs, WBCs are not homogeneous, but are differentiated on the basis of their physiological function and histology. They are broadly divided into lymphocytes, monocytes and granulocytes. Granulocytes, which derive their name from the presence of cytoplasmic granules, are further subdivided into neutrophils, eosinophils and basophils by the staining affinity of the granules. In health, the normal total white cell count is about 4–11 x 10^9/litre.

Like RBCs, WBCs are formed initially from pluripotent stem cells in the bone marrow. These give rise to separate progenitor cells for the eosinophils and basophils, and a common progenitor for monocytes and neutrophils. The two types of lymphocytes also arise from a common progenitor in bone marrow, but postnatally many lymphocytes are formed at other sites.

Neutrophils

Neutrophils are the most abundant WBCs, contributing 50–70% of the total circulating leucocyte population, and have a half-life of about 7 hours. They are easily identifiable in a blood smear by virtue of their multilobular nucleus.

Neutrophils are phagocytic cells and are the body's first line of defence against bacterial infection. In bacterial infection, they migrate through the capillary endothelium (diapedesis) and are attracted towards bacteria or the site of an inflammatory response by chemotactic substances released from damaged tissues and by components of the plasma complement system, particularly C5a. The neutrophils then bind to and phagocytose the bacterium or damaged cell. The binding is facilitated by bacteria that have been opsonized (coated) by antibodies of the IgG class, or by the C3b complement component. (Neutrophils possess receptors for C3b and the Fc component of IgG.) Once ingested by the neutrophil, the foreign material within the phagocytic vacuole is killed and ingested by two pathways, one being oxygen-dependent and the other non-oxygen-dependent. In the oxygen-dependent pathway, superoxide and hydrogen peroxide, which are oxidants that kill bacteria, are generated through activation of a NADPH oxidase. In addition, hydrogen peroxide reacts with myeloperoxidase in the neutrophil to convert intracellular halides to hypothalous acids that also kill bacteria. The non-oxidative pathway involves a fall in pH and release of lysosomal enzymes into the phagocytic vacuole.

Monocytes

Monocytes constitute about 5% of circulating WBCs and are identifiable in a blood smear by their large central nucleus that is oval or indented. They spend only about 72 hours in the circulation before they migrate into the tissues to become tissue macrophages, an important component of the reticuloendothelial system. They may remain in the tissues for several months.

Like neutrophils, monocytes are phagocytic, and kill and digest microorganisms and cellular material using mechanisms similar to those used by neutrophils. In addition, they play a role in presenting foreign antigens to the immune system (see below).

Eosinophils

Eosinophils are so called because of the affinity of their cytoplasmic granules for acidic dyes. They constitute about 2% of circulating WBCs, but their number increases in patients with allergic diseases. The half-life of eosinophils in the circulation is about 6 hours, after which they enter the tissues. They are especially abundant in the mucosa of the respiratory and gastrointestinal tracts, where they probably have a role in mucosal immunity.

Eosinophils participate in the killing of parasites that are too large to be ingested by phagocytes and regulate immediate-type hypersensitivity (allergic) reactions, releasing leukotriene C_4 and platelet activating factor (PAF), which are both inflammatory mediators.

Basophils

Basophils are often absent from the bloodstream. They are similar to mast cells, and contain heparin and histamine. When coated with IgE, basophils can react with specific antigens and are essential for immediate-type hypersensitivity reactions. Once activated, they release histamine, leukotrienes and proteases, which are inflammatory mediators.

Lymphocytes

Circulating lymphocytes are divided into three groups: T cells (60–80%); B cells (30%); and null cells (2–10%). Although postnatally some lymphocytes are formed from stem cells in the bone marrow, most are formed in the lymph nodes, thymus and spleen from cells that originally came from bone marrow, and enter the circulation via the lymphatics. T cells undergo some transformation in the thymus before their appearance in peripheral blood. In birds, there is also processing of B cells by the bursa of Fabricius, but whether or not there is any equivalent processing of B cells in man is unclear.

The plasma membranes of lymphocytes possess specific antigen-recognizing receptor molecules. Thus, they participate in, and give specificity to, immune responses.

B cells are responsible for antibody secretion (i.e. humoral immunity) and thus aid in defence against bacterial infection. Their membrane receptor is similar in structure to the antibody that they will secrete and which will recognize a specific antigen. On exposure to antigen, B cells that recognize that antigen release several cytokines that cause them to proliferate and differentiate into antibody-secreting plasma cells or into so called memory B cells. With primary antigen exposure, the specific antibody released from the plasma cell is usually an IgM. In a secondary response, when the memory B cells are activated and differentiate into plasma cells, most antibody secreted is IgG. Recognition of the specific antigen by the B cell can be aided by antigen-presenting cells and helper T cells (see below).

The physiology of T cells is complex. They are responsible for cell-mediated immunity and thus participate in delayed hypersensitivity reactions and transplant rejection. In addition, cell-mediated immunity is a major defence against viral and fungal infections. Several types of T cell are found. First, they are subdivided by the presence or absence of one of two cell-surface protein markers termed CD4 and CD8. CD4+ cells (possessing the CD4 marker) are further divided into helper cells and memory cells. CD8+ cells are subdivided into suppressor cells and cytotoxic cells. Unlike B cells, T cells are unable to bind to antigen in free solution, and the antigen must be 'presented' to the T cell in association with proteins of the major histocompatibility complex (MCH). Two classes of MCH protein exist. Class I MCH proteins are present on the surface of all nucleated cells and are recognized by CD8+ cells, whereas class II MCH proteins are recognized by CD4+ cells and are present on the surface only of certain cells, including specialized macrophages, termed antigen-presenting cells (APCs).

Helper cells 'help' in the immune response to bacterial infection. Once bacteria have been engulfed by APCs, peptide products of the digested antigen are complexed by class II MCH proteins on the cell surface. Helper cells possessing receptors specific to the antigen bind the MCH-antigen complex, which activates the helper cell. On activation, the helper cell releases various cytokines (in particular interleukin 2), and results in the proliferation of other T cells (including memory cells) and activation of further APCs. Helper cells also participate in the differentiation of B lymphocytes into plasma cells.

Cytotoxic cells play a major role in defence against viral infection. Once a cell is infected by a virus, some viral proteins are broken down to peptides which complex with MCH I proteins on the cell surface. Here, the antigen associated with MCH I is 'recognized' by cytotoxic cells, which then become activated and secrete cytotoxic substances that lyse and thus kill the infected cell. Suppressor cells, which are activated by the same mechanism but more slowly, 'switch off' cytotoxic and helper cells when the infection is no longer a threat. Memory T cells, like those of B cells, differentiate into effector cells on subsequent exposure to the antigen.

Null cells include natural killer (NK) and killer (K) cells. The function of NK cells is similar to that of cytotoxic cells, though they are activated by a different process, and they kill tumour cells and cells with a viral infection. K cells lyse cells that have been coated with antibody and antibody-coated viruses. Together the NK and K cells thus form the first line of defence against viral infection.

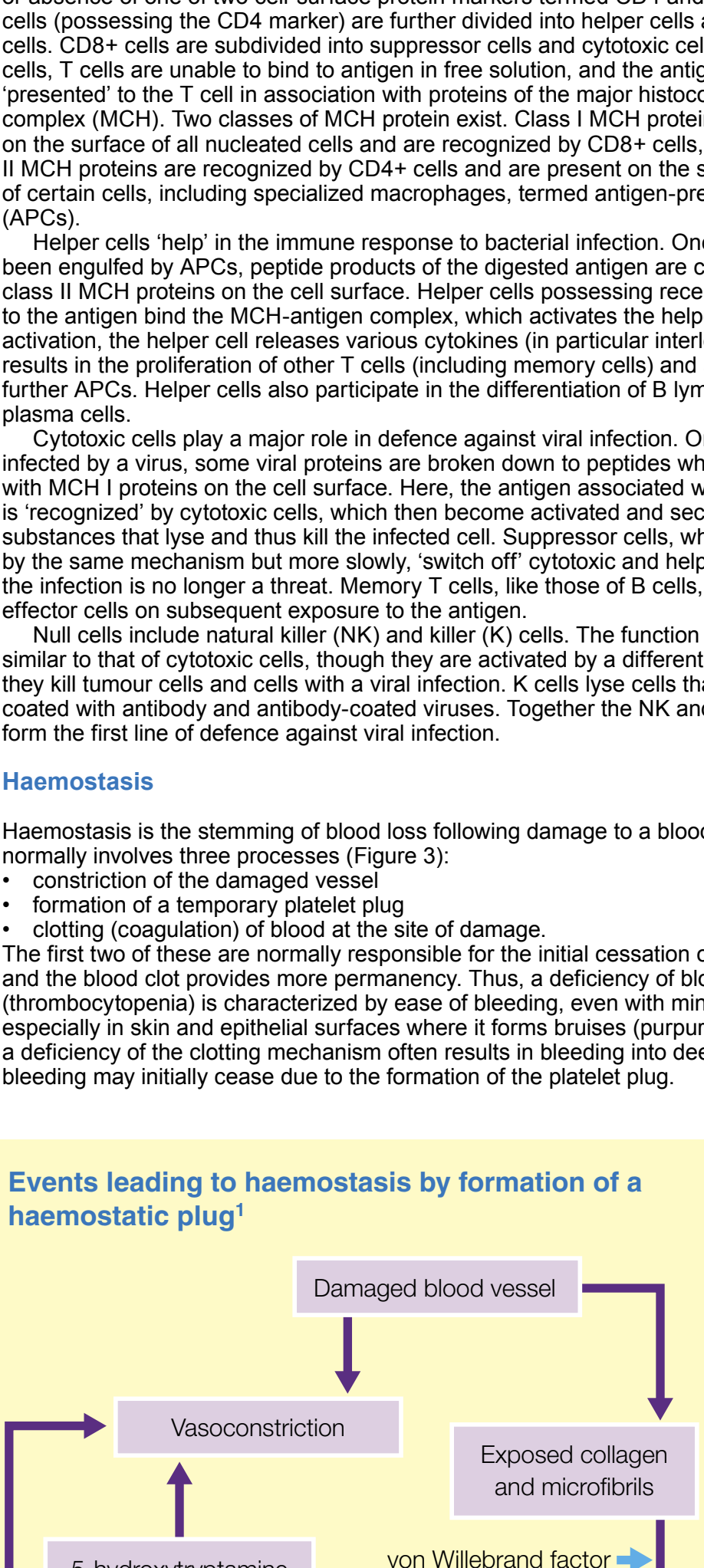
Haemostasis

Haemostasis is the stemming of blood loss following damage to a blood vessel; it normally involves three processes (Figure 3):

- constriction of the damaged vessel
- formation of a temporary platelet plug
- clotting (coagulation) of blood at the site of damage.

The first two of these are normally responsible for the initial cessation of blood loss, and the blood clot provides more permanency. Thus, a deficiency of blood platelets (thrombocytopenia) is characterized by ease of bleeding, even with minor damage, especially in skin and epithelial surfaces where it forms bruises (purpura). By contrast, a deficiency of the clotting mechanism often results in bleeding into deep tissues and bleeding may initially cease due to the formation of the platelet plug.

Events leading to haemostasis by formation of a haemostatic plug[1]



[1]Green arrows indicate positive feedback activation

Platelet function and formation of the platelet plug
The normal platelet count is about 3 x 10^{11}/litre. Platelets are incomplete cells formed from megakaryocytes in the bone marrow. Formation of platelets involves 'pinching off' bits of cytoplasm from the megakaryocyte, with each megakaryocyte giving rise to about 1000 platelets.

The structure of platelets is complex. Normally they are discoid in shape and bounded by a complex plasma membrane. This membrane is extensively invaginated, forming a canalicular system, and contains numerous glycoproteins (GP), including GPIa, GPIb and GPIIb/IIIa, that act as adhesion molecules and play an important part in platelet function. Intracellularly, the platelet contains numerous microfilaments, a dense tubular system and two types of granules:

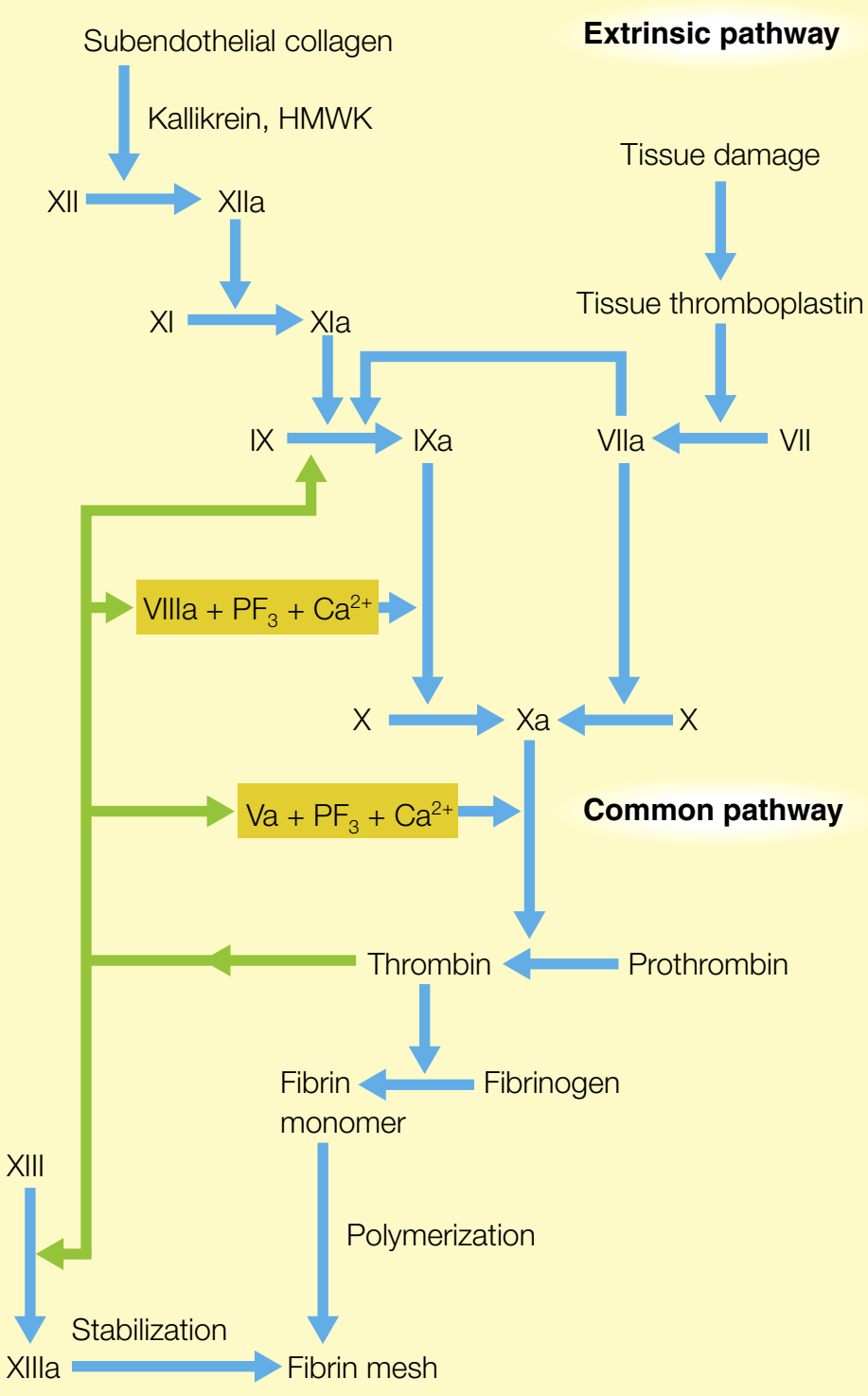
- α-granules, which contain fibrinogen, von Willebrand factor (vWF), a heparin antagonist (PF_4) and a platelet growth factor
- dense-granules, which contain certain adenosine nucleotides (including ADP) and 5-HT.

Normally, platelets do not adhere to the smooth endothelial lining of blood vessels. When the vasculature is damaged, however, this exposes the blood to subendothelial collagen and microfibrils. Platelets bind to this collagen via GPIa and further binding is facilitated by vWF. vWF forms a bridge between subendothelial microfibrils and platelets via the membrane GPIb. Binding of GPIa and GPIb exposes GPIIb/IIIa, which binds fibrinogen and vWF. Following this adhesion, the platelet becomes activated, changes shape to become more spherical, and sends out pseudopodia that enhance platelet–platelet interaction (platelet aggregation). Platelet aggregation is aided by fibrinogen that binds to GPIIb/IIIa and forms a bridge between adjacent platelets. On activation, platelets also release their granules (platelet release reaction). The 5-HT which is released acts as a potent vasoconstrictor. In addition, there is exposure of a membrane phospholipid, platelet factor 3 (PF_3) and release of arachidonic acid from the phospholipids. The arachidonic acid is converted within the platelet to thromboxane A_2 (TxA_2), which is a potent vasoconstrictor and aids the localized vasoconstriction. In addition, TxA_2, together with ADP released from the dense granules, further enhances platelet activation, aggregation and release (Figure 3). In this way, an aggregate of platelets that plugs the damaged blood vessel is rapidly built up. Spreading of this plug away from the site of injury is prevented by the production of prostacyclin (PGI_2), which is a potent inhibitor of platelet aggregation and release, in the normal endothelium in adjacent areas. (The release and aggregation reactions are also inhibited by aspirin, which inhibits TxA_2 synthesis, and thus explains, in part, the anticoagulant activity of aspirin.)

Coagulation
The platelet plug provides a nidus around which the blood clots form a more definitive haemostatic plug. The fundamental reaction in the formation of the blood clot is the conversion of the soluble plasma protein fibrinogen into insoluble fibrin under the action of thrombin. Thrombin splits off two polypeptide chains from the fibrinogen molecule to form fibrin monomer, which polymerizes to form a meshwork of strands. Initially, the strands are held together weakly by hydrogen bonds, but activation of factor XIII by thrombin leads to the formation of covalent cross-bridges between fibrin chains, thus strengthening them.

The conversion of prothrombin, the inactive precursor of thrombin, to thrombin involves a series of plasma serine proteases (collectively referred to as clotting factors) that normally exist in an inactive, proenzyme form, becoming activated in a cascade sequence. As shown in Figure 4, classically, the activation of the clotting factors proceeds down two pathways that converge at factor X to a common pathway. The intrinsic pathway can be activated *in vivo* by exposure of blood to collagen in the subendothelium. This activates the first factor in this pathway, factor XII, which can also be activated by exposure of blood to any electronegative wettable surface (e.g. glass). The extrinsic pathway is activated by release of lipoproteins, referred to as tissue thromboplastin or tissue factor, from damaged tissue. Although initially it was thought that the two pathways operated independently, this is now known not to be the case and interactions occur. Thus, as indicated in Figure 4, active factor VII formed in the extrinsic pathway can directly activate factor IX, thus bypassing the early stages in the intrinsic pathway. In addition, thrombin has positive feedback effects, since thrombin activates factors V and VIII, which act as co-factors in the formation of thrombin and factor Xa, respectively, and factor IX. Blood platelets also play an essential role in clotting since they provide phospholipid PF_3 and activation of factor X by factor IX and the conversion of prothrombin to thrombin by factor X take place, in part, on the surface of platelets in association with PF_3. In this association, the relevant co-factor (V or VIII) in the reaction is bound to PF_3 along with calcium ions, and greatly increases the activity of the co-factor.

The clotting cascade



The active form of the various clotting factors is suffixed 'a'. Green arrows show some of the positive feedback actions of thrombin. Reactions shown in yellow boxes take place on the surface of platelets in association with the platelet, platelet factor 3 (PF_3), and calcium ions. HMWK, high molecular weight kininogen.

4

Tests for clotting deficiency
Two tests are commonly used to detect clotting deficiency.

- The activated partial thromboplastin time (APTT) is a measure of the integrity of the intrinsic pathway and is performed by mixing blood with kaolin (which provides an electronegative surface), a phospholipid (as a substitute for PF_3) and calcium. The normal APTT is 30–32 seconds.
- The prothrombin time measures the integrity of the extrinsic pathway and is performed by adding blood to tissue thromboplastin derived from brain tissue and calcium. Since there are differences in the efficacy of different batches of the thromboplastin, the test is also run against an international reference standard. The prothrombin time is then expressed as a ratio, the international normalized ratio (INR), in which the time for the sample blood to clot is expressed relative to the control sample. In oral anticoagulant therapy (e.g. with warfarin), the dose is adjusted to maintain the INR in the range 2–4.

Anticlotting mechanisms and fibrinolysis
In vivo, there is a natural tendency for blood to clot. This is balanced by various naturally occurring anticoagulants. The most important of these is antithrombin III, which inhibits the activity of factors IX, X, XI and XII as well as thrombin. This inhibition is greatly facilitated by heparin.

Coagulation is also inhibited by thrombomodulin, which is secreted by intact endothelial cells and binds thrombin. The thrombomodulin–thrombin complex then activates a proenzyme protein C, found in plasma, to its enzymatic form and this, together with a co-factor protein S in plasma, results in the inactivation of factors V and VIII. Therapeutically, warfarin is used as an anticoagulant. This coumarin derivative is a vitamin K antagonist – vitamin K being required in the synthesis of several of the clotting factors (prothrombin and factors VII, IX and X).

Fibrinolyis, the dissolution of fibrin also occurs, through the action of plasmin, which degrades fibrin and fibrinogen into fibrin-degradation products. Plasmin is present in plasma as an inactive precursor, plasminogen. Its conversion to plasmin is brought about primarily by tissue-type plasminogen activator (t-PA), a protein released from endothelium. The activity of t-PA is inhibited in plasma due to the presence of plasminogen activator inhibitor-1 (PAI-1). However, this inhibitor is itself inhibited by activated protein C.

FURTHER READING
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Body Temperature and its Regulation

Andrew Sean Weller

Andrew Sean Weller is a Senior Scientist at the Defence Evaluation and Research Agency (DERA) Centre for Human Sciences (CHS). He obtained his doctorate investigating the influence of cold exposure on thermoregulation and metabolism in man at the University of Nottingham, UK. His current research interests are centred around mechanisms of fatigue during exercise in environmental extremes.

Man is a homeotherm and as such deep body (core) temperature must be maintained within narrow limits throughout life, despite greater fluctuations in the ambient temperature. Although core temperature fluctuates by about 0.5°C throughout the day, only during prolonged exercise, illness and extreme exposure to hot and cold environments will it deviate outside the normal range of 36.1–37.8°C. Core temperature is normally in a state of dynamic equilibrium as a result of a balance between factors that add and subtract body heat. These factors are evident in the body heat balance equation:

Heat storage = metabolic heat production ± conductive, convective and radiant heat exchange – evaporative heat loss

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Conductive, convective and radiant heat exchange are positive if heat is gained from the environment, and negative if heat is lost to the environment. Heat storage is zero (i.e. core temperature is constant) when heat production is balanced by heat loss.

Hyperthermia is associated with a net increase in body heat content (i.e. positive heat storage), whereas hypothermia is associated with a net decrease in body heat content (i.e. negative heat storage). Homeostasis of body core temperature is accomplished through two parallel processes: behavioural temperature regulation and physiological temperature regulation. Behavioural temperature regulation operates through conscious behaviour and may employ any means available. Physiological temperature regulation operates through responses that do not rely on conscious voluntary behaviour.

Effector responses

sThe physiological effector responses facilitating homeostasis of body core temperature may be described in terms of their ability to influence heat loss and heat production.

Heat loss

The surface of the body exchanges heat with the environment by conduction, convection, radiation and evaporation.

- Conduction involves the transfer of heat from one material to another through direct molecular contact. For example, the heat generated deep in the body core can be conducted through adjacent tissue until it reaches the body surface. It can then be conducted to clothing or air that is in direct contact with the skin. Conversely, if the matter in direct contact is hotter than the skin, heat will be conducted to the skin.
- Convection involves the transfer of heat by the motion of a gas or liquid across the heated surface. For example, air circulates around the body (even when trapped in clothing layers) and sweeps away the air molecules that have been warmed by contact with the skin. The greater the movement of air (or liquid, such as water), the greater the rate of heat removal by convection. In combination with conduction, convection can also cause the skin to gain heat in a hot environment. Although conduction and convection continuously remove heat when skin temperature is higher than air temperature, their contribution to overall heat loss is relatively low (about 10–20%). However, due to the high specific heat capacity of water, the rate of heat loss by conduction and convection is considerably greater in cold turbulent water compared with air at an equivalent temperature.
- Radiation is the primary means of dissipating heat at rest and, at normal room temperature (about 21–25°C), the nude body may lose up to 60% of its excess heat by this means. Radiant heat is emitted as infrared rays and the body continuously radiates heat to cooler objects (e.g. clothing and walls), but it may also gain radiant heat from warmer surrounding objects. The sun is a powerful radiator and direct exposure to it may cause heat gain.
- Evaporation accounts for about 20% of heat loss at rest, but may increase to about 80% during exercise. Thermal energy is required to transfer water from the liquid to the vapour state. Thus, when water vaporizes from body surfaces (e.g. lungs, mucosa and skin), the heat required to drive the process is removed from the surface, thereby cooling it. In the absence of sweating, water is lost by diffusion through the skin (insensible heat loss) and accounts for about 10% of heat loss, irrespective of the level of activity. However, as body temperature rises, sweat production increases and may reach a rate of 2–3 litres/hour for a short time. Sweating requires the active secretion of fluid by sweat glands which are under sympathetic control. However, high sweat rates do not necessarily translate into high cooling rates, if sweat evaporation is restricted. This is evident when the ambient vapour pressure is high (i.e. high relative humidity), or when clothing that is relatively impermeable to water vapour transfer is worn.

Heat loss by conduction, convection and radiation is largely determined by the temperature difference between the skin surface and the environment. To help explain heat exchange, the body is divided into two compartments: a core of deep tissues (e.g. brain, thoracic and abdominal organs) and a shell of peripheral tissues (e.g. subcutaneous fat and skin). The insulating capacity of the shell may be altered by vasomotor control and this contributes to core homeothermy. In a hot environment (and particularly during exercise), above a threshold body core temperature, active vasodilatation occurs which increases skin blood flow and reduces tissue insulation. This ensures that blood carries heat from the core to the skin, which has two effects. First, skin temperature is increased and thus the potential for dry heat loss (i.e. through conduction, convection and radiation) is maximized. Second, if sweating occurs, it delivers the heat necessary to evaporate the sweat. Although venomotor changes are not usually thought of as being thermoregulatory responses, dilation of superficial veins increases the efficiency of heat convection from core to skin by the blood. In the limbs, deep veins receive blood from the muscles, whereas superficial veins receive blood primarily from the skin; there are also many communicating veins between the deep and superficial veins. Unlike the deep veins, the superficial veins are relatively well innervated by sympathetic fibres. Consequently, dilation of superficial veins favours the return of blood via these vessels and increases the time available for heat exchange between the blood and skin. Both these effects promote the transfer of heat from the core to skin. However, in a cold environment, enhanced sympathetic activity causes vasoconstriction, which reduces the cutaneous blood flow and increases tissue insulation. Skin temperature, and therefore dry heat exchange, will be reduced. Although this heat-conserving mechanism helps to maintain body core temperature, the reduction in peripheral temperature (especially in the extremities) will result in discomfort and reduced performance of fine motor tasks, and may lead to peripheral cold injury (i.e. frost bite).

In a cold environment, clothing is an important component of temperature regulation in humans. The skin loses heat to the air layers trapped in the clothing; the clothes in turn pick up heat from the inner layer and transfer it to the external environment. The thermal insulating value of clothing is primarily determined by its thickness. If the thermal insulation of clothing is inadequate and when vasoconstriction is maximized, the ability to maintain thermal balance largely depends on the thickness of the subcutaneous fat layer. Individuals with a relatively thick layer of subcutaneous fat are able to maintain a large thermal gradient between the core and skin surface. This is particularly important during immersion in cold water, which has high thermal conductivity.

Heat production

Although heat conservation by enhanced vasoconstriction is an important physiological adjustment to cold stress, unless the cold stress is mild, the body must additionally increase its rate of heat production through shivering to maintain thermal balance. Shivering thermogenesis is controlled by motor innervation, and many aspects of this process are unusual and complicated. It is an involuntary response of skeletal muscles which are normally under voluntary control. Shivering can be influenced by conscious control, and it can start or stop abruptly irrespective of changes in skin temperature. Heat production is optimized during shivering as it has low mechanical efficiency and most of the heat generated appears as heat. However, compared with vasomotor responses, it is an energy-demanding process, the increase in blood flow to the shivering musculature will reduce tissue insulation, the associated limb movement will increase convective heat loss, and the performance of fine motor tasks will be impaired. Shivering thermogenesis can potentially increase the rate of heat production up to five times the resting level during cold exposure, although typically, three- to four- fold increases are observed.

Non-shivering thermogenesis is the increase in heat production independent of muscle activity. The site and mechanism of non-shivering thermogenesis in man is controversial. However, it is likely to be confined to the release of the hormones adrenaline, noradrenaline and thyroxine, which all increase the metabolic rate. Nevertheless, the contribution of non-shivering thermogenesis to heat production in the cold is minimal compared with shivering thermogenesis.

Body temperature heterogeneity

Fundamental to the study of temperature regulation is the assessment of body core temperature (the regulated variable). However, there is no one representative body core temperature, because the temperatures of sites within the body core are slightly different from each other. Nevertheless, temperatures at all sites are within about 1°C of central blood temperature at thermal steady state. Brain temperature cannot be measured directly in man, and body core temperature is usually measured at the oesophagus, rectum, mouth, tympanum and auditory meatus.

Oesophageal temperature, which is assessed by a sensor passed through the nose and throat to the level of the left atrium, is recognized as the best non-invasive index of body core temperature, because it responds rapidly to changes in central blood temperature. However, it cannot be tolerated for long periods, and it is influenced by anything ingested while measurements are being made.

Rectal temperature, which is measured by placing a flexible sensor 5–20 cm beyond the anal sphincter, is about 0.2–0.5°C higher than the temperature of the blood leaving the left side of the heart, and responds more slowly to thermal transients (it has a time lag of 5–10 minutes). However, it is well tolerated for long periods and is recognized as a reliable measure
of body core temperature in conditions of thermal steady state.

Sublingual temperature is widely used in the clinical setting because the tongue's high blood flow makes it an efficient heat exchanger with central blood and it is convenient to measure. However, oral temperature may be biased by head and facial skin temperature.

Tympanic temperature is assessed by a sensor placed on the tympanic membrane, which is uncomfortable and may occasionally result in damage to the membrane. Consequently, most researchers have chosen to measure the temperature of the external auditory meatus. Owing to the large temperature gradient along the wall of the meatus, the sensor must be placed near the tympanic membrane and insulated from the environment with a plug of cotton wool. The temperature of the tympanic or auditory meatus responds faster to changed core temperature than rectal temperature and, because this region receives the same blood supply (internal carotid artery) as the hypothalamus, it has been suggested that it is a valid measure of the blood influencing the central thermoreceptors (see page 197).

Although skin temperature is not the regulated variable, it contributes to the effector responses both directly and indirectly. Skin temperature influences the effector response even if the temperature at the site where the effector response is measured is unchanged. Therefore, the skin temperature over the rest of the body contributes to the reflex control of the effector response. Consequently, the contribution of the skin temperature to thermoregulation is usually expressed in terms of a suitably weighted mean temperature. This is more important in a cold environment, where skin temperature varies substantially between extremity and proximal body sites.

Physiological temperature regulation

Most physiologists subscribe to a theory of body temperature regulation, with properties similar to a servomechanism. The key elements of this classic biological control system are evident in Figure 1. Perturbations in body temperature (i.e. body core and skin temperature) arising from changes in metabolic rate (exercise being the most powerful influence) or changes in the external environment are sensed by thermoreceptors and sent to a controller or integrator within the CNS. The central controller compares this afferent information with a reference (or set point) and generates an error signal (load error signal). This load error signal activates corrective effector responses influencing heat loss and heat production via efferent pathways. As a result of controller action, body temperature is kept close to, and may even return to, its original value before the perturbation.

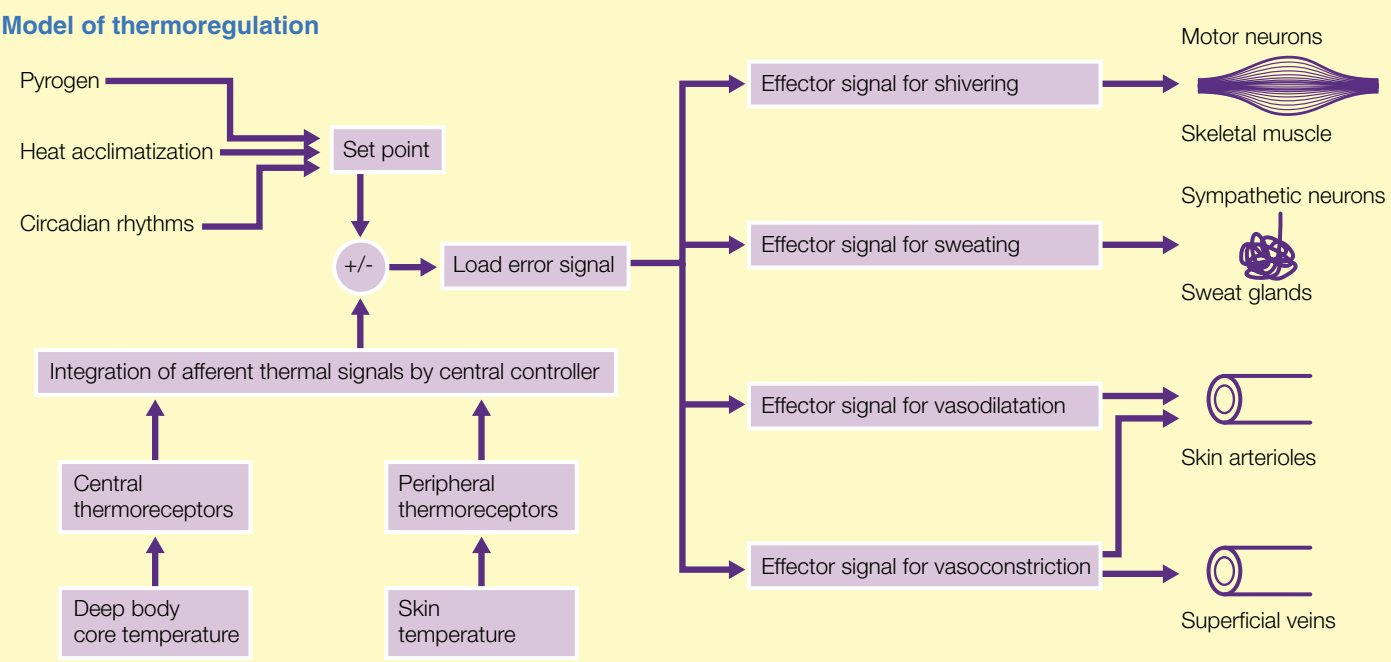
Although the exact neurophysiological mechanisms responsible for this complicated biological control system have not been fully elucidated, the following features are known. The firing rates of thermoreceptors reflect the temperature of the regional blood supply. Warm and cold sensitive thermo-receptors are grouped into those located within the core (central thermoreceptors), and those in skin and certain mucous membranes (peripheral thermoreceptors). Central thermoreceptors are unevenly distributed, though they are concentrated in the hypothalamus, where much of the integration also occurs. With regard to investigation, minor temperature changes in the anterior preoptic area of the hypothalamus induce substantial changes in thermoregulatory effector responses. However, the hypothalamus cannot account for all thermoregulatory integration and control, and other, unidentified, structures within the CNS are also likely to be involved. Other core sites that have been shown to display thermosensitivity include the spinal cord, the heart and major blood vessels. The peripheral thermoreceptors

are characterized by a sudden discharge frequency on stimulation followed by a rapid adaptation to a new static discharge. The transient discharges that occur at the beginning of heating and cooling give the central integrator information about changes in skin temperature as they occur. This feature may be responsible for the sensitivity of sweating not only to skin temperature, but also to the rate of change in skin temperature. The distribution of warm and cold receptors varies in different regions of the body surface, and is dense in the facial skin.

Temperature regulation is an example of a 'proportional control system', which means that the magnitude of changes in responses are proportional to the displacement of the regulated variable from some basal value. For sweating, skin blood flow and forearm venous volume, the response depends on both body core and mean skin temperature. Each response has a core threshold, which is influenced by the mean skin temperature. At any given mean skin temperature, each response is proportional to body core temperature, and increasing the mean skin temperature lowers the threshold level of core for the response (therefore increasing the response at any given core temperature). A change of 1°C in core temperature elicits about a nine-fold greater change in thermoregulatory response as does a 1°C change in mean skin temperature. However, as skin temperature varies over a wider range than core temperature, the importance of mean skin temperature in thermoregulatory control is greater than the 9:1 ratio suggests. The responsiveness of the thermoregulatory system to changes in core temperature is necessary to keep the controlled variable relatively constant, and the system's sensitivity to mean skin temperature allows it to respond appropriately to large changes in environmental temperature while permitting little change in core temperature.

The notion of a single load error signal in thermoregulation is supported by the similar contributions of core and mean skin temperature as inputs to all the heat-dissipating responses, and by the fact that thresholds for different thermoregulatory responses are altered simultaneously and by approximately the same degree by factors such as fever, circadian rhythms and heat acclimatization. The simultaneous shift in the thresholds for a collection of thermoregulatory responses represents a shift in thermoregulatory 'set point'. Ion concentrations, osmolality and vascular pressures may also influence the thermoregulatory set point.

Model of thermoregulation



Modified from Sawka M N, Wenger C B. Physiological Responses to Acute Exercise-Heat Stress. In: Pandolf K, Sawka M, Gonzalez K eds. *Human Performance Physiology and Environmental Medicine in Terrestrial Extremes.* Indianapolis: Benchmark, 1988: 97–151.

Examples of set point shifts

In pyrogen-induced fever, the thermoregulatory set point rises, initially causing a negative load error. This inhibits heat dissipating responses and stimulates heat production. The relationship between metabolic rate and core temperature, and skin blood flow and core temperature, are shifted during fever. Core temperature rises to correct the load error and achieve a new thermal balance in which heat production and heat loss are similar to prefebrile levels. The circadian rhythm in core temperature is also the result of a shift in set point. Core temperature and thresholds for forearm vasodilatation sweating follow each other during a 24-hour cycle. Heat acclimatization is a physiological procedure that decreases the thermoregulatory set point. A reduction in resting core temperature is associated with reduced thresholds for sweating and peripheral vasodilation.

It has been suggested that the increase in core temperature during exercise is an example of an increase in set point. However, core temperature increases during exercise because of increased heat production, which facilitates a sustained load error signal (not corrected as in fever), that is sufficient to drive heat loss responses at a rate to attain a new thermal steady state.

FURTHER READING

Sawka M N, Wenger C B. Physiological Responses to Acute Exercise-Heat Stress. In: Pandolf K, Sawka M, Gonzalez K, eds. *Human Performance Physiology and Environmental Medicine in Terrestrial Extremes.* Indianapolis: Benchmark, 1988; 97–151.

Capillary Dynamics and Interstitial Fluid Lymphatic System

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Fluid is continually being exchanged between the vascular space and the interstitium, and is returned to the vascular space via the lymph. The net balance of this movement determines the amount of fluid in the tissue. If there is too little fluid in the tissue, it becomes dehydrated, while excessive fluid collection causes oedema. Knowledge of the forces governing this movement, and the ability to define the alteration that has occurred, increases our understanding of the patient's condition and enables the response to treatment to be predicted.

Site of fluid exchange: capillaries and post-capillary venules

Fluid exchange between the vascular and interstitial spaces occurs at the capillaries and post-capillary venules, where the barrier between the blood and interstitial fluid is sufficiently narrow to allow exchange of a number of substances. The walls of these vessels are made up of a single layer of endothelial cells and their basement membrane. In addition, there is a network of fibrous molecules or glycocalyx coating the endothelial cells. Furthermore, the interstitium contains a meshwork of long-chain polymers (glycosaminoglycans, proteoglycans and glycoproteins), which can also contribute to the barrier in some tissues. The end result is a barrier that allows water and small solutes to pass through, but severely restricts the movement of larger molecules (e.g. the larger proteins). The degree of restriction depends, to some extent, on the type of capillary (see below) and the effects of a range of vasoactive mediators, such as histamine, bradykinin, 5-HT and even noradrenaline from the sympathetic nerves.

The capillaries fall into three classes.

- In continuous capillaries, the endothelium forms a continuous layer with narrow clefts between the cells giving 'tight' junctions. Such capillaries are found in skin, muscle, fat and connective tissues, with 'super tight' junctions in the brain.
- In fenestrated capillaries, the endothelial cells are perforated by small pores or fenestrae, allowing relatively free passage of salts and water. These capillaries are found in tissues that transport fluid, such as renal glomeruli, gut mucosa and exocrine glands.
- In discontinuous capillaries, wide, leaky, intercellular gaps permit easy transfer of larger proteins and even RBCs. These capillaries are found in tissues such as liver, spleen and bone marrow.

Fluid movement across the capillary wall

The traditional view

Movement of fluid across the walls of the capillaries and post-capillary venules is governed by a group of four forces known collectively as Starling forces (named after the physiologist who first described them). These forces can be subdivided into two groups – hydraulic or hydrostatic pressures and osmotic or oncotic pressures.

The fluid in the capillary is subject to hydraulic or hydrostatic pressure (Pc), which forces fluid across the wall and out of the capillary. This is opposed by the hydrostatic pressure in the interstitial fluid outside the capillary (Pi), which attempts to force fluid into the capillary.

The capillary wall acts as a semipermeable membrane, which produces much greater restriction on the movements of larger protein molecules than water. As a result, the protein in the plasma exerts an osmotic (often called oncotic) pressure (πc) to draw water into the capillary. This, in turn, is offset by the oncotic pressure of the interstitial fluid (πi), which also contains some protein.

The net force driving water out of the capillary is the difference between the hydrostatic pressure gradient across the wall (attempting to move fluid out) and the oncotic pressure gradient (attempting to draw fluid in). Finally, the rate at which water moves across a given area of capillary wall is dependent not only on the net force (described above), but also on the permeability of the capillary wall to water, which is expressed as the capillary filtration coefficient (Kc). The net rate of fluid movement out of the capillary is represented by Equation 1.

Flow per unit area = $Kc [(Pc – Pi) – (\pi c – \pi i)]$ 1

where: Kc = capillary filtration coefficient, Pc = capillary hydrostatic pressure, Pi = interstitial hydrostatic pressure, πc = capillary oncotic pressure, and πi = interstitial oncotic pressure.

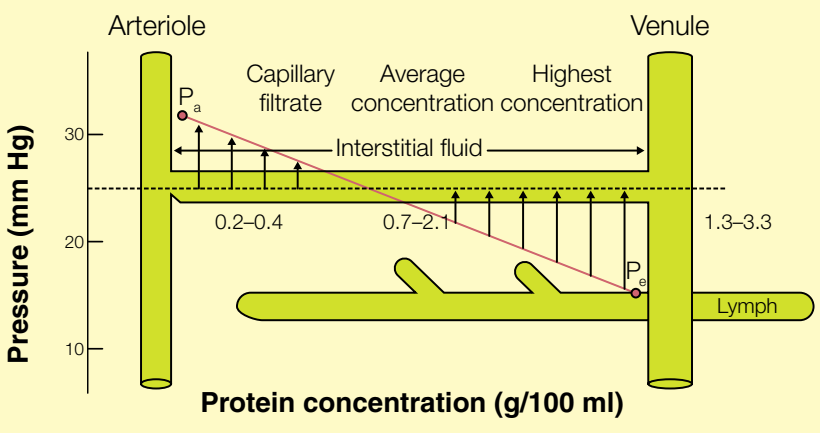
By convention, physiologists consider movement of fluid out of the capillary; thus, Equation 1 has a positive value if fluid is moving out of the capillary and a negative value if fluid is moving into the capillary. The significance of the permeability of the capillary wall is emphasized by considering the different types of capillaries; the continuous capillaries have a fairly low capillary filtration coefficient, while that of the fenestrated capillaries is high.

Equation 1 allows calculation of the transcapillary movement of fluid at any single point on the capillary wall. However, since blood is flowing along the capillary, down its hydrostatic pressure gradient, the hydrostatic pressure will fall from the arteriolar to the venular end of the capillary (Figure 1a). Most physiology textbooks argue that fluid moves out of the capillary at the arteriolar end, but is drawn back in at the venular end, with any excess fluid being returned to the cardiovascular system via the lymph.

Filtration–reabsorption pattern along the length of an 'average' capillary

a Traditional view

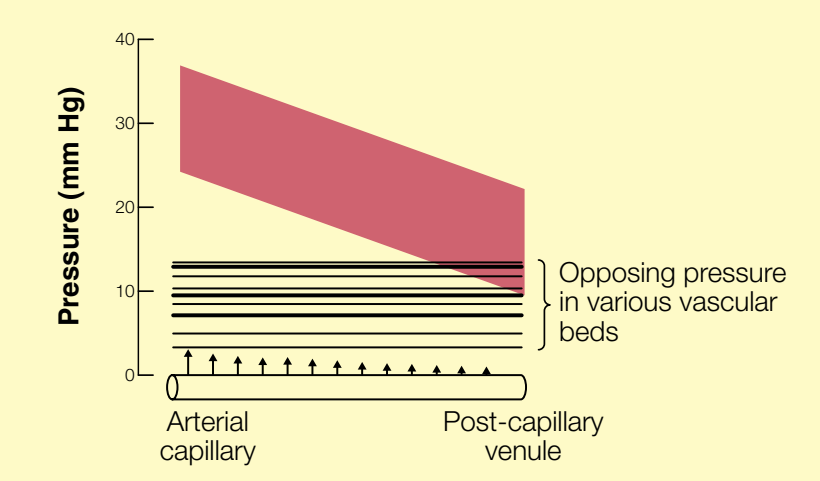
Traditional view with filtration at the arteriolar end and absorption at the venular end. The net effect is a small degree of filtration with return via lymph



Source: Folkow B, Neil E. *Circulation.* London: Oxford University Press, 1977.

b Modern view

Modern view emphasizing the importance of interstitial forces. Predominantly filtration along entire length of the capillary. The net effect is greater filtration than with traditional view, again with return via lymph



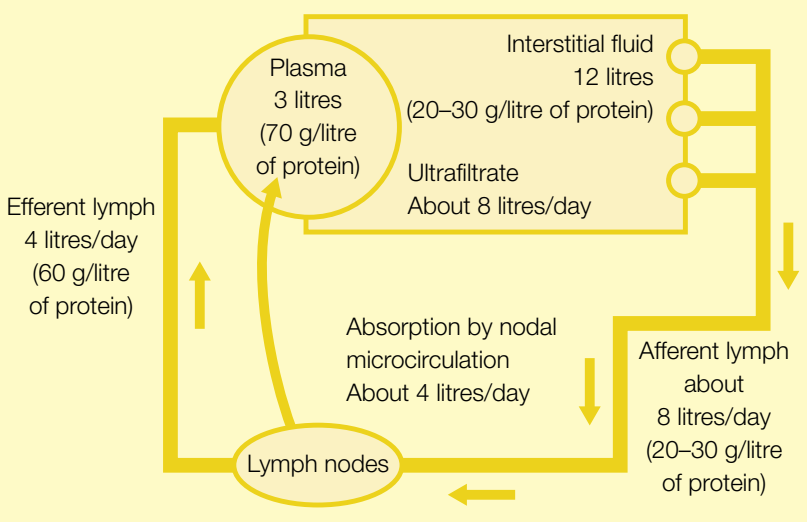
Source: Levick J R. Changing Perspectives on Microvascular Fluid Exchange. In: Jordan D, Marshall J, eds. *Cardiovascular Regulation.* London: Portland Press, 1999.

1

Recent developments

Magnitude of lymph flow: most general textbooks of physiology argue that the Starling forces lead to the production of about 4 litres of lymph per day in a 'normal' adult; this figure is derived from measurements of lymph in the thoracic ducts. However, the rate of lymph production and the flow in the pre-nodal afferent vessels is likely to be substantially higher (Figure 2), because up to 50% of the water is reabsorbed into capillaries from the lymph in the lymph nodes (again under the influence of Starling forces). This results in a reduction in lymph volume being delivered to the post-nodal (efferent) vessels and an increase in its protein concentration. As a consequence of this finding and recent advances in techniques for measuring interstitial pressures, the idea of net filtration at the arteriolar end and absorption of fluid at the venular end of capillaries has been reconsidered. Current ideas suggest that, in a large number of capillaries, there is little reabsorption under normal conditions. The balance is therefore shifted much more in favour of filtration than was thought previously, accounting for the higher rate of lymph production. As will be shown below, these new ideas represent a development of the Starling hypothesis rather than a contradiction.

Overview of the extravascular circulation of fluid in a 65 kg adult



Source: Levick J R. Changing Perspectives on Microvascular Fluid Exchange. In: Jordan D, Marshall J, eds. *Cardiovascular Regulation.* London: Portland Press, 1999: 127–52.

2

Interstitial forces: most general textbooks of physiology view the interstitial forces as negligible. However, this is an oversimplification – not only do they make a significant contribution to the transcapillary movement of fluid, but they are also variable and thus provide a dynamic modulation of flow. Our appreciation of the importance of the extravascular forces has been increased by the advent of new techniques to measure these pressures accurately. The following section will consider the interstitial oncotic and hydrostatic pressures.

Interstitial oncotic pressure – it has been known for many years that plasma proteins are found in peripheral lymph. These proteins enter the lymph by leaking out of the capillaries into the interstitium and so the capillary wall, in most cases, is not completely impervious to the proteins. This occurs because the 'pores' in most capillary walls are small enough to make it extremely difficult for the proteins to leak out, but not so small as to make a slight leak impossible. This effect can be quantified by assessing the ratio of the oncotic pressure actually exerted by a given concentration of protein to the oncotic pressure exerted if the membrane was perfectly semipermeable (impermeable to the protein, but permeable to water). This ratio is called the reflection coefficient. A perfect semipermeable membrane would therefore have a reflection coefficient of 1, while a coefficient of 0 would indicate that the membrane was freely permeable to the solute, which would therefore exert no osmotic effect. Most continuous and fenestrated capillaries have a reflection coefficient of 0.8–0.95, with values of 1 being found in only a few areas (e.g. the brain). Because the reflection coefficient is less than 1, the oncotic pressure exerted by the proteins is proportionately less than it would be otherwise, and the Starling equation needs to be modified to take this into account (Equation 2).

Flow per unit area = $Kc [(Pc – Pi) – (\pi c – \pi i)]$ 2

where: Kc = capillary filtration coefficient, Pc = capillary hydrostatic pressure, Pi = interstitial hydrostatic pressure, πc = capillary oncotic pressure, πi = interstitial oncotic pressure and πi = reflection coefficient.

In a number of tissues (e.g. muscle, skin), because of the protein leak into the interstitium, the interstitial oncotic pressure is 30–60% of the plasma oncotic pressure, which is higher than previously reported. The magnitude of the forces favouring movements of water back into the capillary is therefore diminished compared with the traditional view.

Interstitial fluid pressure is defined as the interstitial pressure that is not attributable to the oncotic pressure exerted by the interstitial proteins. It is difficult to measure accurately because the interstitial space consists of a mesh of small molecular chains, the glycosaminoglycans, and water, which together constitute a gel. Recent measurements of the interstitial fluid pressure indicate that it is zero or negative (subatmospheric) in many normal tissues, and therefore can contribute to 'sucking' water from the capillary to the interstitium. This is because the interstitial glycosaminoglycans exert their own osmotic effect.Gravity has little effect on this pressure because of the gel-like composition of the interstitium. Thus, tissue fluid pressure contributes little to driving fluid back into the capillaries in a number of normal tissues, even when the tissue is below heart level with respect to gravity, and in some circumstances may aid movement of fluid out of the capillary.

Old versus new: a shift in balance

Current ideas suggest that the forces favouring movements of water into the capillary (see Equation 2) are smaller than originally thought. Consequently, it is now considered that, at steady state, there is net filtration along almost the entire length of the capillary in many tissues (Figure 1b), rather than filtration at the arteriolar end and absorption at the venular end (Figure 1a). This explains why the filtration of fluid into tissues is much greater than was originally supposed. However, it should be stressed that it is possible to achieve net absorption during transient non-steady states in most tissues, and sustained absorption in some tissues (see below).

Interdependence of filtration rate and Starling forces: changes from the steady state

Interstitial oncotic pressure helps to determine, and is affected by, the capillary filtration rate. A change in filtration rate would alter the amount of water added to the interstitium, the interstitial protein concentration and thus the interstitial oncotic pressure. Conversely, any alteration in the interstitial oncotic pressure would change the filtration rate (see Equation 2). This interdependence promotes stability within the tissue and leads to a buffering of any change in filtration rate as a consequence of altered intravascular forces. To illustrate this, two situations will be considered.

A fall in capillary hydrostatic pressure (Pi) leading to transient fluid absorption (e.g. following haemorrhage): during mild or moderate haemorrhage, the arterial baroreceptor reflex maintains mean arterial blood pressure. However, this reflex results in an increase in sympathetic vasoconstrictor drive to the arterioles. The consequent increase in arteriolar vascular resistance leads to a fall in the downstream capillary hydrostatic pressure (see Equation 2). This can be sufficient to reduce the force moving water out of the capillary (Pc – Pi) below that favouring inward movement (πc – πi), leading to net absorption. However, the absorptive state is usually transient, because the removal of water from the interstitium in turn causes the interstitial oncotic pressure to rise, thus opposing capillary absorption and re-establishing filtration, albeit at a reduced rate. This effect is also aided by tissue dehydration causing a reduction in the interstitial hydraulic pressure. Although the absorptive state is transient, some studies have shown it to be sufficient to add up to about 500 ml of interstitial water to the plasma over about 30 minutes. Finally, it is important to note that some tissues with active arteriolar vasomotion, such as skin and skeletal muscle, spend considerable time in the non-steady state, alternating between absorption during arteriolar constriction and filtration during arteriolar dilatation. This mechanism may help to remove considerable quantities of fluid from the interstitium.

Increases in capillary hydrostatic pressure (Pc) causing increased filtration: mean capillary hydrostatic pressure can be elevated either as a result of reduced arteriolar constriction or increased venous pressure (e.g. as a consequence of heart failure). The result of this increase in hydrostatic pressure (see Equation 2) is to increase net filtration. However, the increased filtration is soon buffered, because the resulting addition of water to the interstitium decreases interstitial oncotic pressure and thus reduces one of the forces favouring movement of water out of the capillary. A new steady state is therefore re-established, albeit at a slightly elevated level of filtration.

Sustained absorption

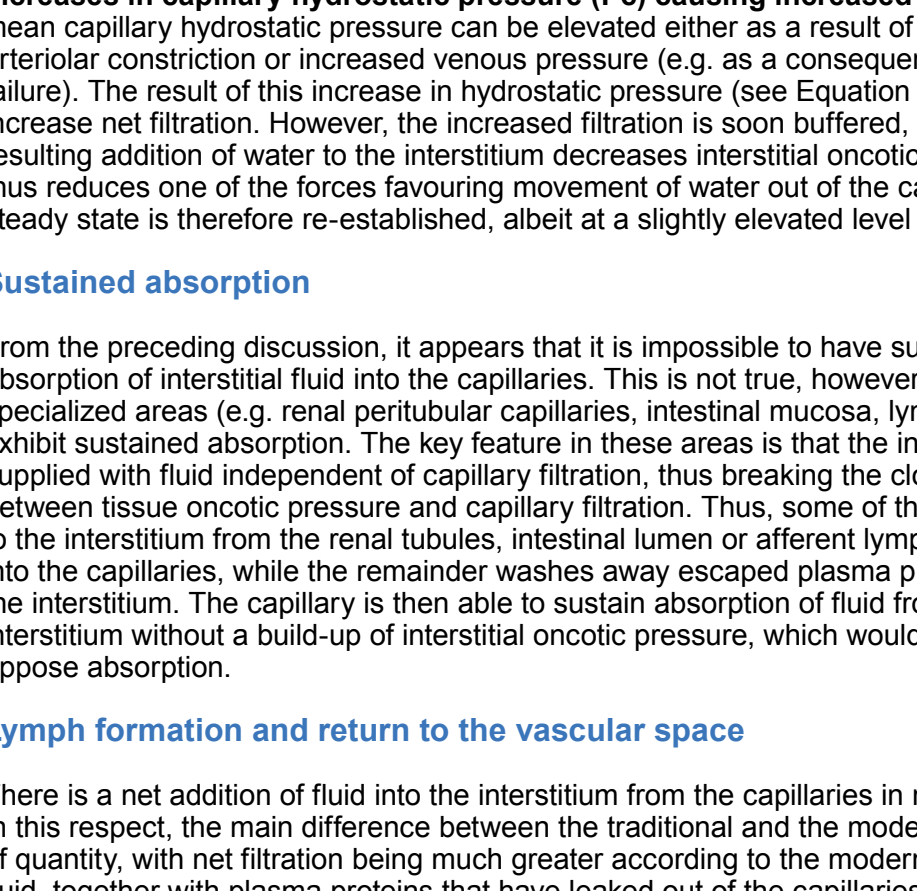
From the preceding discussion, it appears that it is impossible to have sustained absorption of interstitial fluid into the capillaries. This is not true, however, as some specialized areas (e.g. renal peritubular capillaries, intestinal mucosa, lymph nodes) exhibit sustained absorption. The key feature in these areas is that the interstitium is supplied with fluid independent of capillary filtration, thus breaking the close relationship between tissue oncotic pressure and capillary filtration. Thus, some of the fluid added to the interstitium from the renal tubules, intestinal lumen or afferent lymph is absorbed into the capillaries, while the remainder washes away escaped plasma proteins from the interstitium. The capillary is then able to sustain absorption of fluid from the interstitium without a build-up of interstitial oncotic pressure, which would otherwise oppose absorption.

Lymph formation and return to the vascular space

There is a net addition of fluid into the interstitium from the capillaries in most tissues. In this respect, the main difference between the traditional and the modern view is one of quantity, with net filtration being much greater according to the modern view. This fluid, together with plasma proteins that have leaked out of the capillaries, must now be removed from the interstitium by the lymphatic system to prevent build-up of interstitial fluid and tissue oedema.

The lymphatic system consists of the afferent lymphatic vessels, lymph nodes and the efferent lymphatic vessels, with the largest lymphatic vessel being the thoracic duct which ultimately returns fluid to the blood. The filtrate initially enters the fine lymphatic capillaries, which are similar in appearance to blood capillaries in that they consist of an endothelial cell layer, but they also have large intercellular pores and are thus highly permeable to both water and larger molecules, such as protein. The capillaries merge with the larger afferent lymphatic trunk, and fluid movement is aided along the vessel by contractions of smooth muscle within the lymphatic vessel (Figure 3). Where the lymph vessels travel through skeletal muscle, activity in surrounding skeletal muscle also aids fluid movement analogous to the muscle pump moving blood in the veins. These contractions transiently increase pressure within segments of the lymphatic vessels and, because of the presence of one-way valves in the lymph vessels, the fluid can only move away from the lymphatic capillaries (Figure 3) and is returned to the blood circulation mainly via the thoracic duct.

Lymphatic system



Interstitial fluid and proteins enter the low pressure terminal lymphatic and are propelled forward through the one-way valves towards the thoracic ducts by contraction of surrounding smooth and skeletal muscle

Source: Holliday M A. Extracellular Fluid and its Proteins: Dehydration, Shock and Recovery. *Pediatr Nephrol* 1999; **13:** 989–95.

3

Clinical sequelae

The Starling forces are important in a number of clinical situations and responses associated with daily life in addition to acute hypovolaemia (e.g. following haemorrhage) and heart failure, which have already been discussed. It must, however, be acknowledged that clinical reality is often complex and the following descriptions are, of necessity, simplified.

Orthostasis

The effect of gravity can cause marked changes in the fluid content of tissues. Venous blood and lymph being columns of fluid, unlike interstitial fluid, are particularly affected by gravitational forces. Thus, in the upright individual, blood and lymph pool in the veins and lymphatic vessels, respectively. During quiet standing or sitting, this is unopposed and capillary hydraulic pressure is increased, leading to elevated net capillary filtration (see Equation 2). The increased capillary filtration is further enhanced by increased leakage of albumin from the capillary, partly because of increased convection with the increased movement of fluid through the large pores, and partly because of increased permeability to albumin as a consequence of enhanced sympathetic activity. The increased permeability to albumin, in turn, increases filtration because of a reduction in the difference between capillary and interstitial oncotic pressure, and a reduced reflection coefficient. The increased filtration, coupled with an initial reduction in lymph drainage, leads to increased fluid content of the dependent tissues, which continues until tissue expansion causes a sufficient increase in interstitial hydraulic pressure to return filtration to normal levels. Many readers will have been painfully aware of this when re-applying shoes at the end of a long flight. A recent study indicated that as much as 20% of the plasma volume may move out of the vascular space after 15 minutes of quiet standing.

Increased capillary permeability following trauma

Following trauma, there can be periods of tissue hypoxia as a result of hypovolaemia and haemodynamic changes initiated by the response to tissue injury and subsequent nociception. This, coupled with subsequent reperfusion during resuscitation, can lead to reperfusion injuries and an inflammatory response. In some circumstances, the inflammatory response can become widespread. Additionally or alternatively, there may be an inflammatory response in the lungs leading to adult respiratory distress syndrome. One consequence of the inflammatory response is increased vascular permeability to protein. The increased leakage of protein from the vasculature causes a reduction in the forces opposing filtration of fluid out of the capillary and thus tissue oedema. Following burn injuries, this is a particular problem at the sites of the burn, and to a lesser extent elsewhere, due to the presence of circulating vasoactive agents, leading to oedema with a high albumin content.

Reduction in plasma protein concentration

There are a number of situations in which plasma protein levels are reduced markedly. In nephrotic syndrome, there is a sudden reduction in plasma albumin (and thus plasma oncotic pressure) with profound proteinuria and loss of albumin into the interstitial fluid. In other situations, the liver is unable to synthesize adequate quantities of plasma proteins for a variety of reasons, including severe malnutrition with a carbohydrate-rich, protein-poor diet (kwashiorkor). Predictably, the reduced plasma oncotic pressure leads to increased capillary filtration (see Equation 2) and tissue oedema.

ACKNOWLEDGEMENT

The authors are grateful to Dr Chris Snowden, Consultant Anaesthetist and Senior Lecturer, Freeman Hospital, Newcastle upon Tyne for constructive criticism of this review.

Cell Biology and Gene Expression

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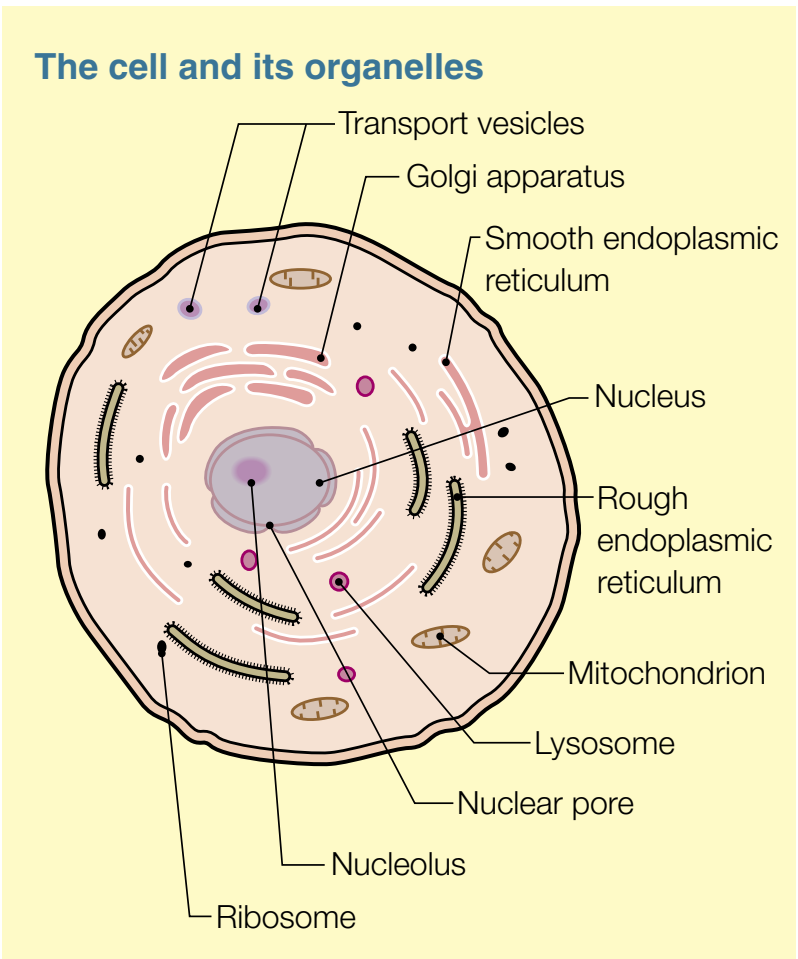
Cell biology

Cells are the individual units of life. They are made up of protoplasm surrounded by a membrane that separates them from their environment. Cells contain structures or organelles that carry out functions vital for the cell's survival. Each structure or organelle is also surrounded by, or composed of, membrane which allows compartmentalization of the various cell functions. Protoplasm within the cell is known as cytoplasm. Cells also contain genetic material that directs activity, and machinery for obtaining energy. Energy in the form of nutrient macromolecules is taken into vacuoles by the process of endocytosis and digested by enzymes contained in lysosomes. Energy is released in discrete packages of ATP via aerobic respiration in the mitochondria.

Cell theory states that all organisms are made up of cells and their products; new cells arise only from existing cells; all cells have the same fundamental make-up and chemical processes; the activity of the organism results from the interdependence and cooperative work of groups of cells.

The eukaryotic cell is divided into two regions: the nucleus, a spherical or oval structure usually situated near the centre containing the genetic material, and the cytoplasm in which lie the other organelles and the fluid surrounding them (the cytosol). Metabolic processes within the cell synthesize (and degrade) proteins for use by the cell or for export. These processes are catalysed by enzymes, which are proteins. Cells differ in their structure depending on their function and no cell can be described as typical. However, there are features common to most cells and the various organelles are found in most body cells (Figure 1).



1

Cell membranes

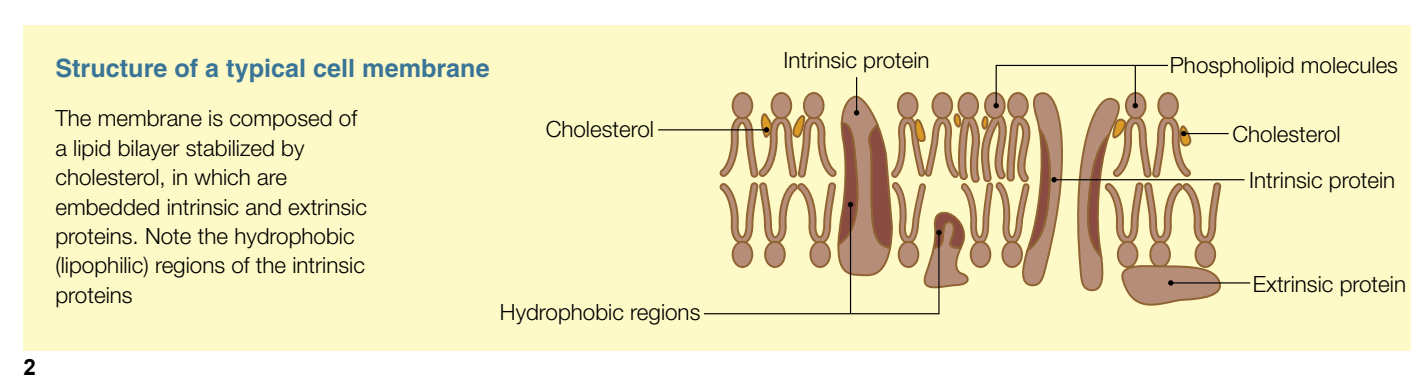
The membranes surrounding the nucleus and the organelles are composed typically of 50% protein and 50% lipid, though the precise proportions vary depending on the cell's function. At one extreme, the membranes of Schwann cells, which provide support and insulation for neurons, are only 18% protein whereas the inner mitochondrial membrane, with its mass of enzymes involved in energy metabolism, is 76% protein. Carbohydrate is also found bound to proteins (glycoproteins) and to lipids (glycolipids) but constitutes only 2–10% of the membrane. The membrane is a selective barrier between the cell and its surrounding medium; it regulates the passage of substances between the cell and its environment. It also detects chemical messengers arriving at the cell surface (e.g. hormones), provides links to adjacent cells and anchors various intra- and extracellular proteins and filaments involved in the generation and transmission of force.

The amphipathic features of the phospholipid molecules that make up most of the structure of a membrane are discussed on page 149. It is this propensity to form bilayered sheets that constitutes the structure of the membrane. Each of the phospholipid molecules can rotate on its own longitudinal axis and move around rapidly within the sheet. They can also move between the two layers of the sheet, but this is less common because it involves the hydrophilic head of the molecule moving across the inner hydrophobic region of the membrane. The fatty acid molecules can also flex and the whole structure is very fluid. It is stabilized, in part, by cholesterol (Figure 2), which may contribute up to 20% of the total lipid. This is a weak amphipathic molecule; it has an -OH group attached but is otherwise hydrophobic. The -OH group lies in the hydrophilic surface of the membrane and its hydrophobic ring structure interacts with the hydrocarbon chains of the phospholipid molecules. Other phospholipids in the membrane include phosphatidylethanolamine, phosphatidylserine, phosphatidyl-inositol and sphyngomyelin. These phospholipids are not distributed evenly throughout the membrane; the composition of the inner and outer membranes often differs.

Protein molecules are embedded in, or lie on the surface of, the phospholipid layers and contribute to the functional characteristics of the membrane. They form the receptors for chemical signals (e.g. hormones) and channels that open and close to allow passage of specific ions (e.g. Na^+, K^+) (Figure 2). Membrane proteins are of two types, intrinsic (or integral) and extrinsic (or peripheral). Intrinsic proteins lie embedded in, and many span the full thickness of, the membrane, allowing transduction of signals and passage of ions and molecules from the outside to the inside of the cell. The intrinsic proteins account for about 70% of total membrane protein. They are amphipathic molecules with their hydrophobic side chains buried in the lipid bilayer and their hydrophilic parts exposed to the aqueous regions outside the bilayer, or buried within the folds of the protein molecule itself. Like the lipid molecules they can move around within the cell membrane, though their freedom of movement may be controlled by interaction with extrinsic or peripheral proteins on the membrane surface or with components of the cytoskeleton of the cell (see page 155). This two-dimensional model of a bilayered phospholipid membrane with embedded proteins is known as the fluid mosaic model.

Extrinsic or peripheral proteins do not lie within the lipid parts of the membrane. They are not amphipathic but hydrophilic and lie on the surface, mostly on the cytoplasmic surface attached via hydrostatic and hydrogen bonds to the polar parts of intrinsic membrane proteins and to the polar phosphate heads of the phospholipids. These are relatively weak interactions, therefore it is much easier to separate extrinsic proteins from cell membranes compared with intrinsic molecules.

Most carbohydrates associated with cell membranes (90%) are found on the surface and in the external half of the bilayer (Figure 2). They are hydrophilic structures and unlike proteins, which are constituted by the folding of a linear molecule, carbohydrates are made up of multiple branching structures. They are associated mainly with proteins in the cell membrane (glycoproteins) though some are associated with lipid molecules (glycolipids). They are important in cell-to-cell recognition processes and, in conjunction with the proteins, function as membrane receptors for extracellular chemical messengers (e.g. hormones). The branching structure provides infinite possibilities in the construction of specific receptor sites.



2

The nucleus

The nucleus is the site where the nucleic acids – deoxyribo-nucleic acid (DNA) and ribonucleic acid (RNA) – are made. DNA makes up the chromosomal material. A gene is a portion of DNA containing the instructions for assembly of a particular polypeptide that makes up a protein. The genome comprises all the genes. DNA contains the instructions for synthesizing the proteins and other macromolecules that the cell needs to carry out its specific function in the body. The instructions are taken to the organelles via RNA. DNA is necessary for the independent existence and function of the cell and for cell reproduction. It is a long unbranched molecule composed of a double strand of bases in the form of an alpha helix. The DNA from one cell, if unravelled, would be about 1 m long. The DNA is tightly packed into the nucleus wrapped round proteins known as histones. Histones have positively charged side chains that bind to negative ions on the phosphate groups of the DNA. DNA is packed to form the chromosomes, of which the human cell has 23 pairs. In the resting state, DNA is relatively uncoiled and the chromosomes are unrecognisable. It is only when the cells divide that individual chromosomes become apparent.

RNA is synthesized in the nucleus from DNA. It travels as messenger RNA (mRNA) via pores in the nuclear membrane to ribosomes, structures that synthesize protein and are composed of ribosomal RNA (rRNA) and protein.

The nucleolus is a prominent area within the nucleus not surrounded by membrane, but composed of large loops of DNA and concerned with the synthesis of rRNA.

The nuclear membrane is a double membrane which appears to be continuous with the endoplasmic reticulum. Ribosomes are attached to its outer layer on its cytoplasmic face. The nuclear membrane contains pores about 9 nm in diameter through which small molecules can pass.

The cytosol

The cytosol contains the various organelles, the precursors for macromolecules to be synthesized by the cell, enzymes and energy stores in the form of glycogen and lipid droplets containing triglycerides. 20% of the cytosol is protein and it forms a highly viscous solution.

Ribosomes and endoplasmic reticulum

Ribosomes are the protein-making structures of the cell. They may be free in the cytosol or attached to the endoplasmic reticulum (ER) forming the 'rough' ER. If they occur in groups in the cytosol they are known as polysomes. Ribosomes are composed of roughly equal weights of rRNA and protein. mRNA takes the information about the precise make-up of a protein (polypeptide) from the nucleus to the ribosome, and transfer RNA (tRNA) transfers the appropriate amino acids to the ribosome.

The ER is a complex interconnected system of folded membranes enclosing a space or lumen. Rough ER has ribosomes attached to it and is concerned with protein synthesis. Smooth ER is concerned with lipid synthesis. Rough ER is prominent in cells that secrete polypeptide hormones and smooth ER in cells that synthesize and secrete steroid hormones. In muscle cells, the ER is important in the storage of calcium ions.

Many ribosomes that occur free in the cytosol become attached to the ER when they become involved in protein synthesis. Polypeptides, synthesized by ribosomes attached to the ER, are formed from amino acids in the cytosol. The polypeptide chain is extruded into the lumen of the ER and may be modified by the addition of carbohydrate to become a glycoprotein. Proteins synthesized by free ribosomes remain in the cytoplasm. Proteins destined to be membrane proteins are trapped in the wall of the ER during synthesis which prevents further movement of the polypeptide into the ER lumen.

Lipids are synthesized in the smooth ER. They are formed from precursors in the cytosol by enzymes that are part of the ER membrane. They may be complexed with proteins in the lumen of the ER to form lipoproteins. Completed proteins destined for export are moved in vesicles formed from the ER membranes to the Golgi complex for processing before export out of the cell, or for storage if the protein is to be used in the cell. Likewise, lipids synthesized in the smooth ER are transported to the Golgi apparatus before moving to the cell membrane or the membranes of other organelles in the cell.

Golgi complex

The Golgi complex is a collection of smooth membranes that look like flattened sacs. Its function is to modify macromolecules synthesized in the ER before they are transported to the cell surface or returned to the cytosol. One side of the complex faces the ER with transition vesicles shuttling synthesized molecules between the two structures. The mature face of the Golgi apparatus faces the plasma membrane, particularly in secretory cells. Secretory vesicles move the newly processed molecules from the Golgi complex towards the cell membrane for export. The modification that occurs in the Golgi complex involves largely polysaccharide chains added to the polypeptides in the ER. The precise size and shape of the complex varies between different types of cells.

Exocytosis, endocytosis and membrane recycling

The cell extrudes macromolecules by the process of exocytosis; the substance is transported in a membrane-bound vesicle to the surface and extruded. The membrane of the vesicle may then form part of the cell membrane. Likewise, during endocytosis, when macromolecules are ingested, part of the cell membrane becomes internalized. It may ultimately be returned to the plasma membrane or directed to the lysosomes with its ingested particle for digestion where it might also be broken down into its component proteins and lipids, which then become deposited in the precursor pool in the cytoplasm.

Lysosomes
Lysosomes are membrane-bound vesicles that contain about 50 digestive enzymes. They allow cells to break down any macromolecule in the body, but are kept within these membrane-bound organelles that originate from the Golgi complex. The enzymes they contain originate from the rough ER. They fuse with the endocytotic vesicles to digest substances taken in by the cell, but are also used in the breakdown and recycling of the cell's organelles.

Peroxisomes
Peroxisomes form as buds from the ER and contain catalase, which degrades hydrogen peroxide, a potentially harmful by-product of oxidative reactions. They were originally defined as organelles that carry out oxidation reactions leading to the production of hydrogen peroxide. A number of substances are oxidized in peroxisomes, including uric acid, amino acids and fatty acids.

Mitochondria
The mitochondrion is the powerhouse of the cell and provides it with energy. It is a double-membraned structure, cylindrical, and about 0.5–1 μm in diameter. The outer membrane is smooth and unfolded but the inner membrane has well-developed infoldings or cristae that project into the lumen thereby increasing the surface area. Most of the body's energy is obtained by the oxidation of carbohydrate, fat and protein. The greatest energy (ATP)-producing mechanism is the Krebs' tricarboxylic acid cycle. This occurs in the mitochondrial matrix, which contains about 120 different enzymes, some RNA and a few DNA molecules. Oxidative phosphorylation, the final stage of the ATP production process, takes place on the inner folded wall of the mitochondrion.

The cytoskeleton
Special proteins in the cytosol (tubulin, actin and myosin) form microtubules, intermediate filaments and microfilaments, which constitute a cytoskeleton and give the cell its shape. They maintain the position of the internal organelles and mediate movement of both the cell and the organelles within the cell. Microtubules are dynamic structures and their distribution within the cell is subject to change with circumstances, whereas the intermediate filaments are more stable. Myosin is seen mainly in muscle cells but it also occurs in non-muscle cells.

Gene function and gene expression

The molecular basis of the different tissues is in the structure of their proteins. Proteins are made by the cell. Cells of different tissues make or express different proteins. The instructions for each cell are contained in the DNA in the chromosomes. All cells of an organism have the same set of chromosomes constituting the genome. Thus, potentially every cell in the body could make all, and the same, proteins, but they all make different ones. Each cell therefore has more information than it needs and most of it is suppressed. Only certain genes in each cell are used to make the proteins appropriate to that particular cell's function.

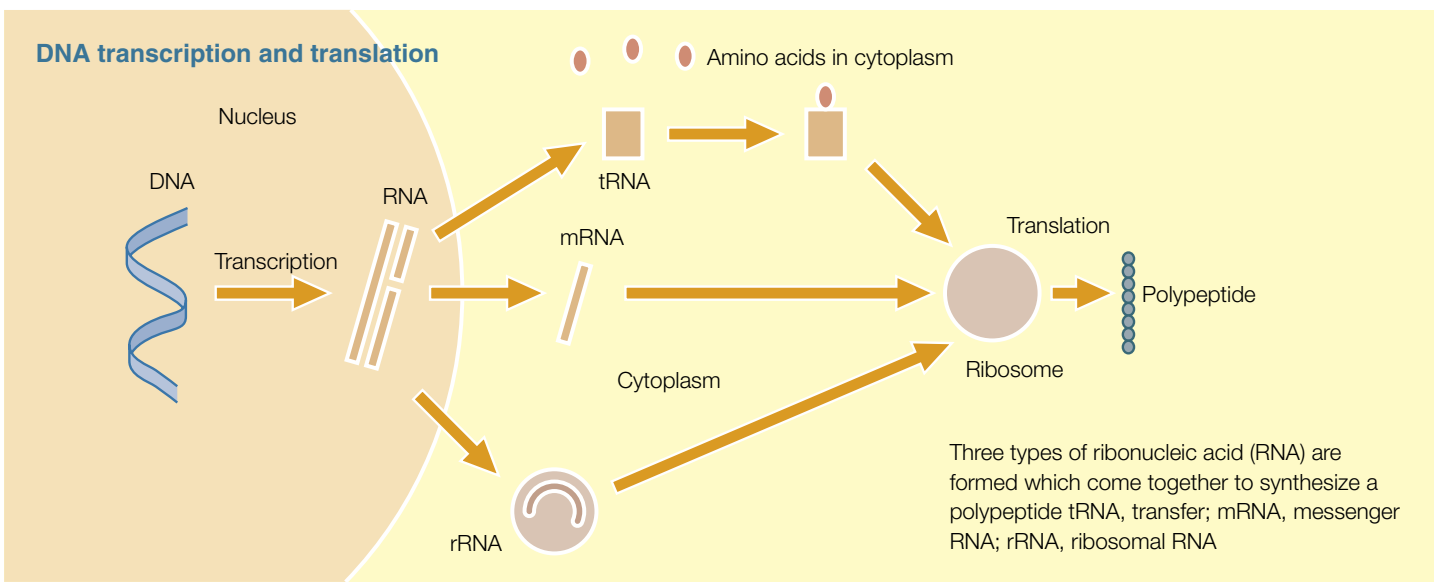
The nucleic acids are composed of nucleotides of which there are four types. Combinations of these nucleotides code for the 20 different amino acids and the order in which they are arranged to form polypeptides and thus proteins. A nucleotide is made up of phosphate groups, a sugar (ribose or deoxyribose) and a specific chemical group called a base (a nitrogen-containing ring structure derived from either purines or pyrimidines), so called because they are all proton acceptors. In DNA, the pyrimidine bases are thymine and cytosine and in RNA they are uracil and cytosine. The purine-derived bases in both DNA and RNA are adenine and guanine. The nucleotides are linked to form DNA and RNA via the phosphate groups attached to carbons 3 and 5 of each sugar molecule (Figure 3). Thus, any nucleotide chain (i.e. any gene) has a 3' end and a 5' end. Nucleotides forming nucleic acids each have only one phosphate group. The phosphate and deoxyribose groups, the so-called sugar–phosphate backbone of the nucleic acid, form the strands of the double helix and are oriented so that their bases are inside the column of the helix and close to the bases from the other strand. Hydrogen bonds can thus form between the bases in the two strands. Each turn of the helix has 10 base pairs. The variable part of the nucleic acid, corresponding to the amino acids that make up a protein (i.e. the order of the amino acids in the polypeptide chain) is the sequence of bases. The bases forming the links across the double helix do so specifically with only one of the other bases – adenine with thymine and guanine with cytosine. Each amino acid that will eventually go to make up the protein is coded for by a sequence of three bases. There are 64 possible combinations of three of each set of four bases and 20 common amino acids. Of the 64 possible triplet combinations, 61 specify a particular amino acid and some amino acids are specified by more than one triplet. The triplet specifying methionine has a special role in starting polypeptide synthesis and the three sets of triplets that do not specify any amino acids are used to stop synthesis.

The information required for protein synthesis is transferred to the ribosome by mRNA following the process of DNA transcription (i.e. the synthesis of the various types of RNA from the DNA template). Each of the bases on the DNA molecule binds only with its corresponding pair and so acts as a template for synthesis of RNA, though adenine in DNA links to uracil in RNA (instead of thymine). rRNA is synthesized in the nucleolus whereas tRNA and mRNA are synthesized in other parts of the nucleus. Several RNA molecules may be synthesized on a single DNA template at the same time. Transcription of a given gene starts when the RNA polymerase binds to a 'promoter' site on the DNA. This is a specific sequence of nucleotides immediately before the 3' end of the gene and it stops when it reaches the 'terminator' site, again a specific sequence of nucleotides towards the 5' end. The promoter sequence determines which strand of the double-stranded DNA is transcribed.

This process of DNA transcription is carried out by an enzyme – RNA polymerase. There are three types of polymerase – one for each type of RNA. RNA undergoes further processing (post-transcriptional modification) in the nucleus and other chemical groups are added to each end. In the RNA strand there are sequences of nucleotides that have no useful information; these are known as introns. They are cut out and the remaining lengths of RNA are spliced together before being exported to the cytoplasm as mature RNA.

RNA is thus synthesized from the DNA template by this process of transcription. Each triplet of bases on the DNA represents a specific amino acid. Following transcription the corresponding series of three bases on the RNA is known as a codon.

Protein synthesis



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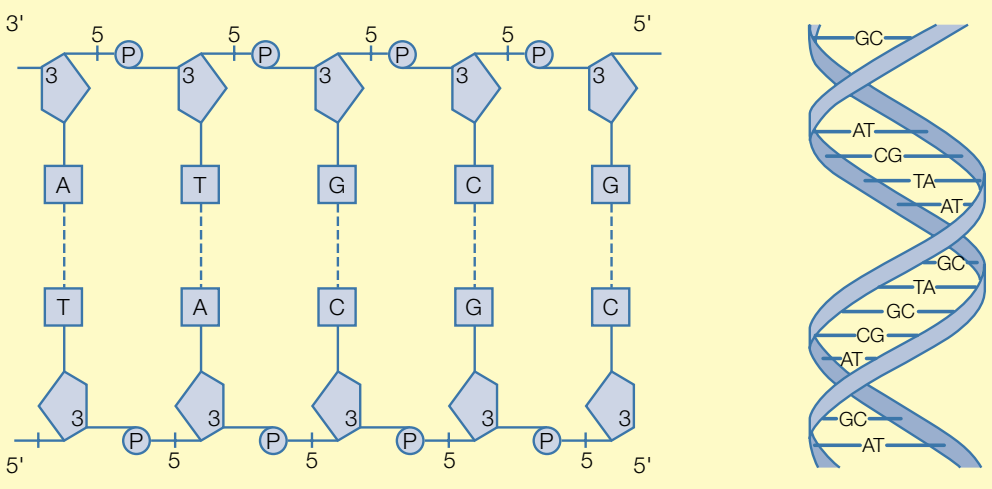
The several steps that involve the translation of the information in the mRNA into the synthesis of a polypeptide take place in the ribosome following the instructions contained in the mRNA (Figure 4). Free amino acids in the cytoplasm are coupled to the 3' end of the ribose ring of the tRNA. This coupling involves an enzyme (amino acyl-tRNA synthetase – AAS) and the expenditure of energy. Each molecule of tRNA has two important sites: one for the attachment of the amino acid, the other for the anti-codon, the triplet of bases complementary to a codon on a molecule of mRNA. For an amino acid to participate in protein synthesis it has to be attached to tRNA and each amino acid has its own AAS and one specific tRNA. mRNA binds to the ribosome, and tRNA molecules transport their amino acids to the ribosome where the polypeptide is assembled. The polypeptide is assembled in accordance with the sequence of codons on the mRNA. The amino acids are joined by peptide bonds by peptide transferase and the tRNA is ejected. Several ribosomes may attach to a single mRNA strand forming a polysome. Translation of the mRNA and polypeptide synthesis cease when a stop codon is encountered in the mRNA sequence. Polypeptides also undergo some degree of post-translational modification in the Golgi apparatus before they become mature proteins.

Gene expression is regulated at the level of transcription rather than translation (i.e. RNA formation rather than protein synthesis). This is performed by repressor and inducer molecules that prevent or allow transcription to occur (i.e. turn the gene on or off), though the mechanism is unclear.

Structure of the DNA helix

The sugar–phosphate backbone, the 3' and 5' ends of the nucleotide chain and the interrelationships of the bases are shown. A, adenine; G, guanine; T, thymine; C, cytosine



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The Cell Membrane and Receptors

James Waterhouse

James Waterhouse is Senior Lecturer at the Research Institute of Sport and Exercise Sciences, Liverpool John Moores University. He qualified as an animal physiologist from Oxford University and gained his DPhil there. His research interests are circadian rhythms, with particular reference to jet lag and assessing the clock-driven components of measured circadian rhythms.

The cell membrane, the plasmalemma, separates the intracellular fluid (ICF) from the surrounding extracellular fluid (ECF), and acts as an interface between the cell's environment and its contents. Because the ICF and ECF differ in composition, the cell membrane must act as a barrier; however, the metabolism of the cell requires the entry of raw materials and the exit of waste products, therefore the membrane must also allow certain substances to cross it. Cells that manufacture a product that is required elsewhere, have to secrete it across the cell membrane in some way. The cell membrane is also the link between the anatomical structures inside the cell (the microtubules and microfilaments of the cytoskeleton) and those outside it (the basal lamina and other cells), and is the site where external signals first exert their influence on the cell.

It is not surprising, therefore, that the structure of the cell membrane is complex, and that into this complexity is also built specificity, by which only some cells respond to a particular stimulus, and those cells that do respond do so in a specific way.

Membrane composition and the role of lipid

The cell membrane is composed of about equal amounts, by weight, of phospholipids and protein, with a small amount of carbohydrate. The molecular weight of the phospholipids is much less than that of the proteins and there are about 50 phospholipid molecules for each protein molecule. The exact properties of the membrane bilayer depend on the nature of the lipids involved, and change according to the amount of cholesterol, the length and the degree of branching of the lipid chains, and the level of unsaturation of the lipids. The lipids from cell membranes in different regions of the body differ also; for example, those in the brain contain sphingomyelins. The mixture of lipids is such that the cell membrane behaves as a solid just below its melting point; its molecules do not lose their parallel alignment, but the whole is to be regarded as a vibrating rather than a static structure.

The lipid bilayer forms a barrier between the ICF and the ECF to the passage of water-soluble molecules in either direction. However, such a barrier is leaky to small molecules such as water. Some of this leak is probably through gaps that form transiently between the vibrating lipid molecules. If there is an osmotic gradient across the membrane, there is a net flux of water by osmosis; if there is no such gradient, water movement across the membrane occurs, but is equal in both directions (i.e. there is a dynamic equilibrium between influx and efflux). Other small molecules, including the dissolved oxygen, carbon dioxide and nitrogen also pass across the cell membrane, possibly by the same mechanism. However, for other water-soluble substances, including ions, glucose and amino acids, the membrane forms a barrier. For these substances to cross the membrane requires various channels and carriers, which are made of protein.

Role of proteins in the cell membrane

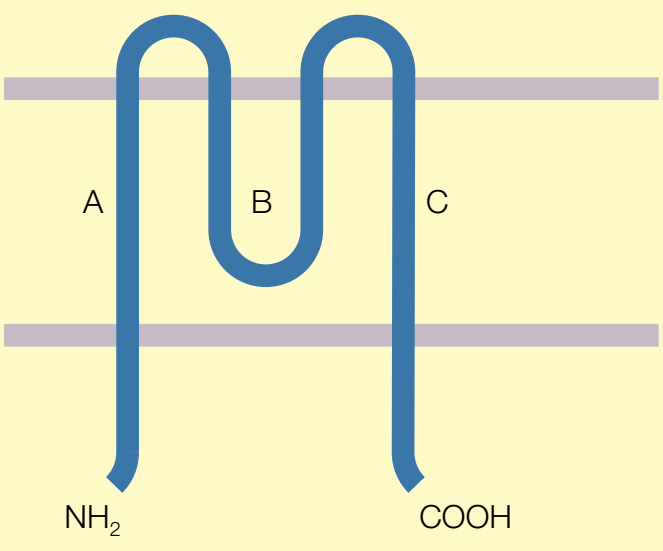
As well as providing a barrier to the free passage of water-soluble molecules, the membrane allows the passage of specific ions and other water-soluble substances; it is selectively permeable. These functions are achieved by the proteins of the cell membrane, which provide the required receptor and channel specificity. The main roles of proteins in allowing the transfer of specific molecules across the membrane are as channels (pores), carriers, receptors, and in the processes of endocytosis, pinocytosis and exocytosis. Proteins also have an important structural role and, in conjunction with carbohydrate moieties, have a role in the immune system.

Transmembrane channels

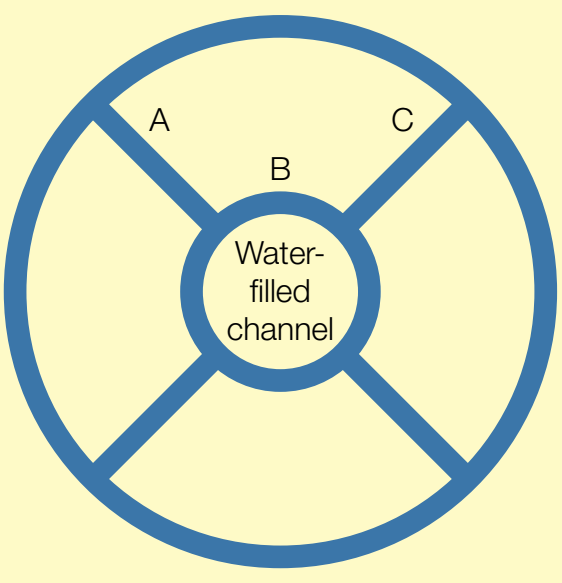
The best known transmembrane channels allow the passage of Cl^-, Na^+, K^+ and Ca^{2+} ions. These channels are fundamental to the functioning of excitable tissues. The channels differ not only in their specificities, but also in whether they are normally open or closed, and in the kind of stimulus that can cause them to open or close. The channels are produced by a set of subunits, each of which spans the membrane and produces a hydrophilic region in the membrane. A set of subunits (generally four or more) combines to form a hydrophilic, water-filled channel or pore, through which a specific ion can pass when the channel is open (Figure 1). The detailed properties of a channel that give it its specificity are not fully understood. Important factors appear to be the size of the channel and its charge, and also the distribution of charge density along the channel. At a physiological pH, some amino acids show a net positive, and some a net negative, charge; these are responsible for the charge along the channel.

The main chloride channel is always open, allowing the movement of Cl^- ions down their electrochemical gradient. The sodium, potassium and calcium channels, by contrast, are often shut, and are said to be gated. Channels can be opened either by changes in the electrical potential across the membrane (voltage-gated), by chemical signals, transmitters or hormones reaching the cell (ligand-gated), or by both mechanisms (Figure 2). For voltage-gated channels, the gate (which determines if the channel is open or closed) is probably a charged part of the protein molecule that is free to swing and whose position is determined by the prevailing electrical gradient. The ligand-gated channels are considered further when the action of membrane receptors is discussed.

Simple ion channel



The position of one subunit in the membrane. It spans the membrane several times. Regions A and C are lipophilic, and region B contains a hydrophilic section that forms part of the wall of the channel



Four subunits combine to form a water-filled channel. The positions of the parts of the subunit (A–C) are shown

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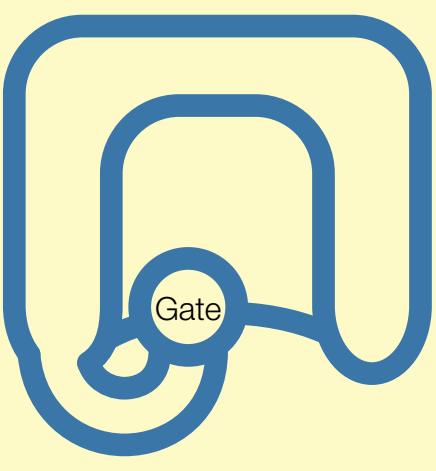
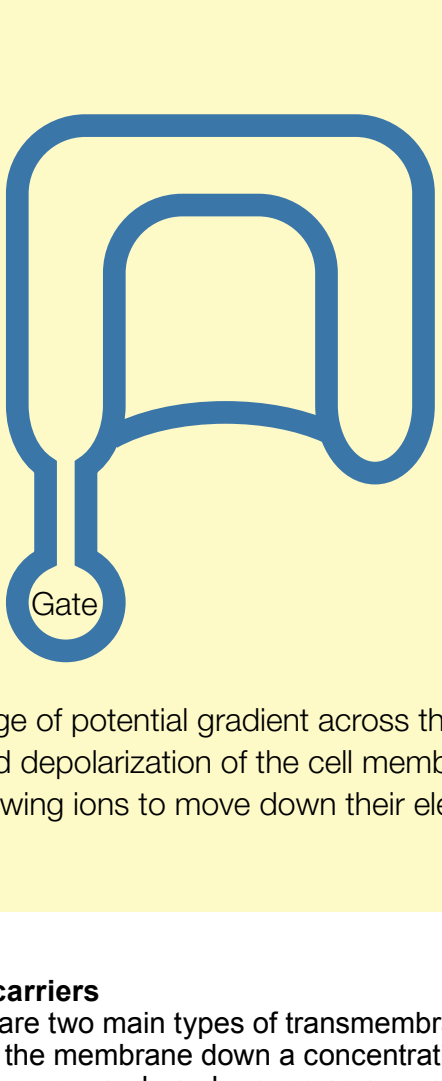
Voltage-gated channel

Closed channel



The gate blocks the channel and prevents ion movement

Open channel



Following a change of potential gradient across the channel (a supra-threshold depolarization of the cell membrane), the gate swings open, allowing ions to move down their electrochemical gradient

2

Transmembrane carriers

Functionally, there are two main types of transmembrane carriers. The first transfers substances across the membrane down a concentration gradient by facilitated diffusion. It does not require energy, and can be seen as a means to overcome the impermeability of the membrane conferred by its lipid structure. Well-known examples are those that involve the transfer of glucose and amino acids into the cell. The molecule seems to be passively transferred to the inside of the cell by conformational changes in the molecule-receptor complex.

The second type of carrier transfers molecules against a concentration gradient, and thus requires energy. The best-known example is the membrane-bound Na^+/K^+-activated ATPase (the sodium pump), which exchanges $3Na^+$ on the cytoplasm side of the cell for $2K^+$ in the ECF. Because the pump moves more positive charges out of the cell than into it, it is also described as an electrogenic system.

Membrane receptors

There are also receptors on the outer surface of the cell membrane, the function of which is to bind with external signals from, for example, blood-borne hormones or neurotransmitters. With blood-borne hormones, the specificity of the receptor–hormone interaction arises from the complex structures of the hormone and its receptor. For neurotransmitters, the receptor–transmitter complex is likely to be formed only in the localized regions into which the transmitter is released. These receptors sometimes contain carbohydrate moieties.

After binding to the receptor has taken place, one change that can occur is the opening of a calcium channel (a ligand-gated channel), allowing calcium influx. Another change is to initiate a series of events that begins with the activation of G proteins (proteins associated with the inner surface of the cell membrane). These G proteins then activate 'second messengers', the effects of which spread into the cytoplasm. Among these second messengers are derivatives of inositol phosphate, but one of the best known is cyclic AMP. This is formed by the action of the enzyme adenylyl cyclase, another protein found at the inner surface of the membrane. Second messengers often cause the release of intracellular calcium. The properties of the different types of membrane transport proteins are summarized in Figure 3.

Some roles of transport proteins

Channels

- Open (Figure 1)
- Voltage-gated (Figure 2)
- Ligand-gated: after binding to the receptor, the ligand causes the channel to open

Carriers

- Facilitated transport: the molecule that is to be carried, after binding with the receptor, causes a conformational change in the complex. The molecule moves down a chemical (diffusion) gradient, no energy being required
- Active transport: the process is the same as that in facilitated transport, except that the molecule moves against an electrochemical gradient. Energy is therefore required and is obtained from the breakdown of ATP, often by the carrier itself, part of which is an ATPase

Receptors

- After the ligand has bound to the receptor, G proteins are activated on the inner surface of the cell membrane. This causes the release of second messengers.
  Two common possibilities are:
  - release of inositol triphosphate from the cell membrane, which diffuses into the cytoplasm causing the release of calcium from the endoplasmic reticulum
  - activation of membrane-bound adenylyl cyclase, which converts ATP into cAMP, leading to the activation of protein kinases which diffuse through the cytoplasm

Endocytosis, pinocytosis and exocytosis

Endocytosis and pinocytosis are processes by which portions of the ECF and its contents can be transported into or out of the cell. A common example of endocytosis is the ingestion of material by phagocytosis. An example of exocytosis is the secretion of stored products, (e.g. hormones). In endocytosis, the cell membrane engulfs the material that is to be taken in and forms a vesicle round it. The process is initiated by an interaction between the signal molecule(s) and a specific membrane protein, some of which are called clathrins. The vesicle can then be discharged into the cytoplasm. Pinocytosis is similar, except that the vesicle contains only ECF and the proteins involved are caveolins; vitamins are taken up by this method. In exocytosis, the process is essentially the same but in the opposite direction; a secretory vesicle, bounded by a structure like the cell membrane, fuses with the inside of the cell membrane with the help of a docking protein. The process is often initiated by a secretagogue that causes calcium influx. This promotes the movement of vesicles to the exit site, a process that involves microfilaments and microtubules, and the proteins kinesin and dynein.

These three processes enable relatively large amounts of material to cross the membrane without allowing continuity between the ECF and ICF. If continuity occurred, it might damage the cell, allowing unwanted material to enter, or required material to escape. This would have catastrophic consequences for ionic gradients.

Structural and immune functions

The proteins in the cell membrane add structural stability to it, and can be considered as a type of scaffolding. In addition, other proteins (cell adhesion molecules) bind cells together at tight junctions, gap junctions, desmosomes and terminal bars. Laminins are proteins that bind the cell membrane to the basement membrane, and other proteins anchor the cell membrane to the internal cytoskeleton.

The external part of the cell membrane contains complex glycoproteins that extend into the ECF. They are the cell's natural antigens, and are the basis of the recognition of self by the immune system.

Modification of membrane function

The membrane is a dynamic interface between the ICF and ECF. There is some regulation of membrane function; for example, frequent exposure of a cell to a particular secretagogue can decrease the sensitivity of the cell to this signal (down-regulation), because it decreases the number of free receptor molecules on the outer surface of the cell membrane (internalization). Exocytosis increases the amount of cell membrane; therefore, the membrane has to be recovered to form more intracellular structures for refilling with transmitter or secretory material.

Transport processes, both those involving carriers and channels, can be modified by natural substances as well as by drugs. Insulin, for example, changes the properties of the glucose carrier, and aldosterone increases the number of functional sodium pumps in the kidney. Many drugs modify membrane function, such as ouabain (the sodium pump), tetrodotoxin (the sodium channel) and atropine (muscarinic receptors).

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Characteristics of Special Circulations

Roger Hainsworth

Roger Hainsworth is Professor of Applied Physiology at the University of Leeds and Honorary Consultant Cinical Physiologist. He trained in Leeds and San Francisco. His research interests centre around the control of the cardiovascular and respiratory systems in normal subjects and patients with cardiorespiratory diseases.

Blood flow through any region is controlled by physical principles. Poiseuille's equation, which relates to the laminar flow of a Newtonian fluid through a non-distensible tube, is given as:

$$Q = \frac{(P_1 - P_2)}{\eta \times l} \times r^4$$

where: Q = flow, $P_1 - P_2$ = the pressure gradient, η = viscosity, l = length of the tube and r = radius of the tube.

However, Poiseuille's equation can be used only in a descriptive sense in relation to the cardiovascular system. This is partly because blood is not a Newtonian fluid and its viscosity varies with the velocity of movement, largely as a result of the axial streaming of the cells. Furthermore, the vascular system is not a single tube, but a complex system of interconnecting tubes of various diameters. Nevertheless, the equation provides an insight into the main factors influencing blood flow.

Pressure gradient is the driving force for blood flow and an adequate arterial pressure is essential. In many situations (e.g. in the skin and liver), P_1 and P_2 represent arterial and venous pressure, respectively, with P_2 being usually much lower than P_1. In other regions, the pressure gradient may not be arterial–venous, but be related more to capillary pressure which, importantly, may be influenced by the tension in the surrounding tissues. This particularly applies to blood flow to contracting muscle, including that to the left ventricle.

Poiseuille's equation emphasizes the importance of vessel radius, because this is raised to the fourth power. The most significant vessels in this respect are normally the precapillary resistance vessels (essentially microscopic arteries and arterioles), because they contain a high proportion of vascular smooth muscle and are under neurochemical control. The largest pressure drop occurs across these vessels. There is usually a minimal flow-related pressure drop along the conducting arteries and veins. However, this is not always the case, particularly when conducting arteries are narrowed by disease. In the coronary arteries, for example, a narrowing of about 70% of the diameter allows adequate flow during resting conditions with a relatively small pressure gradient, but during increased demand when the precapillary vessels dilate, flow through the narrowed segment becomes the limiting factor.

The diameter of the lumen of resistance vessels is dependent on the degree of contraction of the vascular smooth muscle. There is usually an inherent muscle tone which can be enhanced or inhibited by neural, humoral or local chemical influences. The principal vasomotor nerves are sympathetic vasoconstrictors. These supply most regions of the body and their activity is largely dependent on reflex inputs, particularly from baroreceptors. Vasomotor nerves are noradrenergic, though their effects may be modulated by the co-transmitters, ATP and neuropeptide Y. Vasodilator nerves also exist in some regions. Parasympathetic nerves cause increases in blood flow in association with glandular secretion. Cholinergic sympathetic vasodilator nerves are found in the cutaneous circulation and blood flow increases with sweating. However, contrary to previously held views, there are no cholinergic sympathetic vasodilator nerves supplying skeletal muscle in humans. Circulating hormones, particularly catecholamines, angiotensin II and vasopressin, have widespread actions. Noradrenaline is a vasoconstrictor, but adrenaline has different actions in that it dilates vessels supplying muscle and mainly constricts those elsewhere.

Flow through highly metabolically active regions, such as working muscle, including the myocardium, is mainly regulated by local mechanisms. These mechanisms are essentially the results of metabolism, which reduces oxygen tension and increases the production of metabolites. The principal vasodilators are carbon dioxide, adenosine, phosphates, and potassium and hydrogen ions. Osmotic forces increase as large molecules are broken up into smaller molecules. The local temperature also increases. These factors combine to cause relaxation of vascular smooth muscle and an increase in flow. A metabolic mechanism can also explain autoregulation of flow. An increase in perfusion pressure immediately leads to an increase in flow, which washes out metabolic products, thereby reducing their local concentration. Flow is therefore restored close to its former level. The other hypothesis for autoregulation is myogenic, whereby vascular muscle reacts by contracting when its tension increases.

When considering the factors influencing regional flow, it is important to recognize that the vascular endothelium is a source of potent vasoactive substances. Endothelial-derived relaxing factor, believed to be nitric oxide, is one such substance. It is released in response to shear stress or pulsatility of the blood and has potent effects on vascular smooth muscle. Other agents released by the endothelium include endothelin, a potent vasoconstrictor, and prostaglandins.

Both neurohumoral and local factors influence the state of constriction of resistance vessels in most vascular beds, and the resultant tone is a balance between local factors (mainly dilator) and neural control (mainly constrictor). The relative importance of the various factors differs widely in the various regions and at different times in the same region.

Coronary circulation

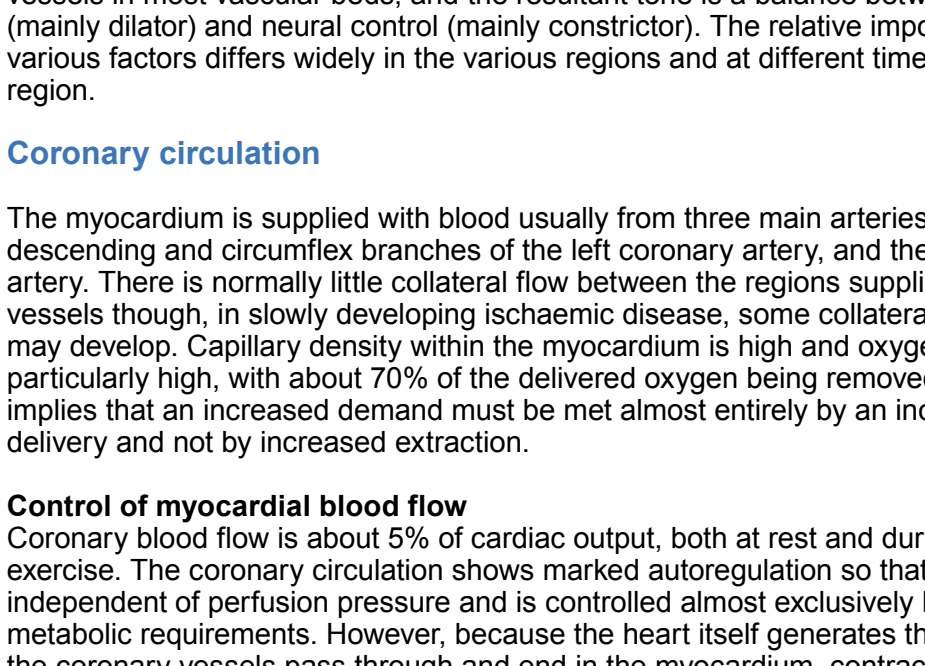
The myocardium is supplied with blood usually from three main arteries: the anterior descending and circumflex branches of the left coronary artery, and the right coronary artery. There is normally little collateral flow between the regions supplied by these vessels though, in slowly developing ischaemic disease, some collateral circulation may develop. Capillary density within the myocardium is high and oxygen extraction is particularly high, with about 70% of the delivered oxygen being removed at rest. This implies that an increased demand must be met almost entirely by an increase in oxygen delivery and not by increased extraction.

Control of myocardial blood flow

Coronary blood flow is about 5% of cardiac output, both at rest and during exercise. The coronary circulation shows marked autoregulation so that flow is largely independent of perfusion pressure and is controlled almost exclusively by myocardial metabolic requirements. However, because the heart itself generates the pressure, and the coronary vessels pass through and end in the myocardium, contraction of the heart has a major effect on the phasic characteristics of flow, particularly flow to the left ventricle (Figure 1). The high intramyocardial tension, especially at the start of systole, prevents and may even transiently reverse coronary flow. Flow is, therefore, maximal in early diastole when perfusion pressure is greatest and intra-myocardial tension relaxes. Coronary flow is thus dependent on both diastolic pressure and its duration. Intra-myocardial tension increases from epicardium to endocardium. Normally, this has little effect on flow, but when flow is restricted by coronary disease, it is the inner wall of the ventricle that is most susceptible to ischaemia.

Activity in cardiac nerves has little direct effect on coronary flow; activity in sympathetic and parasympathetic nerves causes small decreases and increases in flow, respectively. These effects are, however, transient because of the associated changes in cardiac work, which have far more potent effects. Increases in the metabolic activity of the myocardium result in decreases in tissue oxygen tension and increases in the concentrations of metabolic products, of which adenosine is a particularly potent vasodilator. The magnitude of this dilatation can be appreciated by considering that the changes required when going from rest to exercise typically cause a five-fold increase in both cardiac output and coronary flow, accompanied by a marked reduction in diastolic duration. Coronary flow is almost linearly related to heart rate and is also affected by arterial blood pressure due to its effect on cardiac work. Both of these factors are increased by exercise, which explains why stress testing is an effective method for assessment of coronary insufficiency.

Pressures in the aorta and left ventricle, and flow in left coronary artery during the cardiac cycle



Vertical lines A–B indicate the ventricular isovolumic contraction phase and C the onset of ventricular diastole. Note that coronary flow abruptly ceases during isovolumic contractions and is greatest during diastole

1

Cerebral circulation

The brain is supplied with blood through the carotid and vertebral arteries, which anastomose in the circle of Willis. This anastomosis may allow for adequate flow if one vessel is obstructed, though with age and vascular disease adequate perfusion may be dependent on the patency of all vessels. Perfusion pressure is the arterial–venous difference and the effects of gravity need to be considered when the body position changes. Cerebral venous sinuses, unlike other veins, do not collapse at low pressures so that, in the upright position, perfusion may be assisted by negative venous pressures.

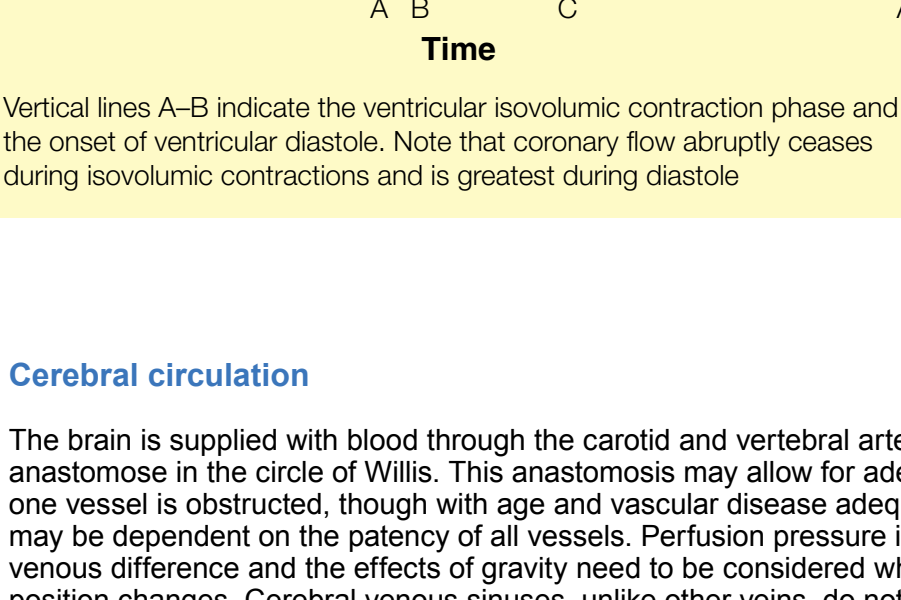
Control of cerebral blood flow

Cerebral blood flow is about 55 ml/minute/100 g, which is about 15% of the resting cardiac output. Flow overall normally remains relatively constant, though localized increases in flow occur in response to various activities. For example, shining a light in the eye causes hyperaemia in the visual cortex.

The cerebral circulation is autoregulated; flow is relatively constant at mean pressures of 60–130 mm Hg. Innervation of cerebral vessels is relatively weak, though there may be cerebral vasospasm in some circumstances. The level of carbon dioxide in the cerebral blood does, however, have a marked effect on cerebral flow. An increase in the partial pressure of carbon dioxide from its normal level of 5.3 kPa to 7 kPa doubles the flow, whereas a decrease to about 3 kPa reduces the flow by half. The level of carbon dioxide influences autoregulation of cerebral flow (Figure 2). During hypercapnia, autoregulation is largely lost, whereas during hypocapnia blood flow remains low at all perfusion pressures.

It should be noted that the brain can tolerate complete ischaemia for only a few seconds and a 50% reduction in flow results in consciousness starting to be lost. This level could be reached by hyperventilation or by a fall in mean cerebral arterial pressure to about 40 mm Hg. In the upright position, this is equivalent to a brachial pressure of about 60 (80/50) mm Hg.

Effects of cerebral perfusion pressure and arterial carbon dioxide on cerebral blood flow



During normocapnia (partial pressure of carbon dioxide, 5.3 kPa), there is effective autoregulation of flow at pressures above 60 mm Hg. During hypercapnia, autoregulation is largely lost and flow markedly increases. During hypocapnia, flow remains low at all pressures

2

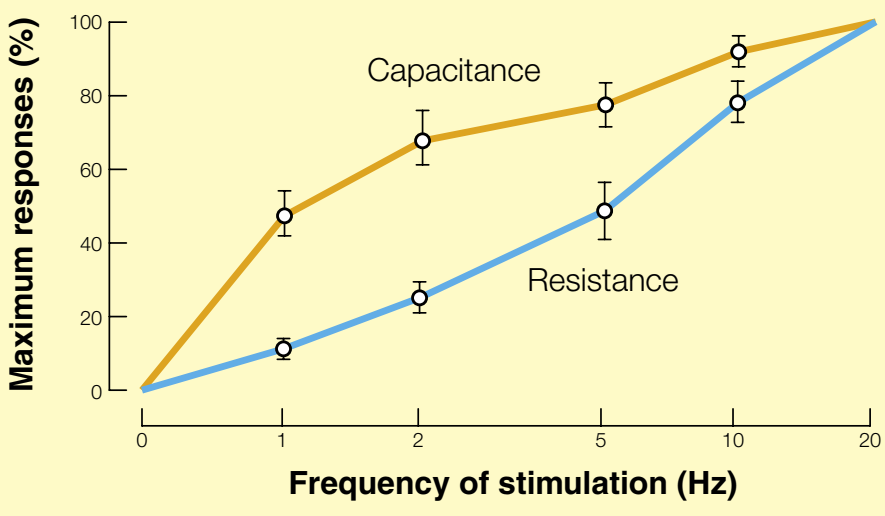
Hepatosplanchnic circulation

The gastrointestinal tract from stomach to large intestine receives blood from the coeliac, and the superior and inferior mesenteric arteries. Splanchnic blood flow, which is about 1.2 litres/minute, passes through the portal vein to the liver. Hepatic arterial flow is about 0.4 litres/minute and the combined outflow is through the hepatic veins. The hepatosplanchnic circulation provides for the secretory and absorptive functions of the digestive system. It is also a large vascular bed, which is important in reflex circulatory control.

Control of splanchnic flow
Splanchnic flow increases in response to food in the gastro-intestinal tract. This is partly due to local mechanisms resulting from the increased metabolic activity associated with secretion, digestion and absorption. Humoral factors, such as gastrin, cholecystokinin and insulin, cause vasodilatation, and food products, particularly glucose and fatty acids, also contribute.

Apart from increases in flow due to food digestion, splanchnic flow is regulated by sympathetic vasoconstrictor nerves which in turn are controlled by reflexes, particularly baroreceptors. The high resting splanchnic blood flow means that it has the potential to be significant in the control of total peripheral vascular resistance. Of particular importance, however, is its role in vascular capacitance. The hepatosplanchnic circulation contains about a quarter of the blood volume. The capacitance vessels (veins) are highly distensible so they can passively constrict or expand if blood is transferred to or from other regions, or if blood volume changes. They also possess adrenergic innervation, which can cause active constriction and thereby enhance inflow to the heart; this is a capacitance effect. The gut vessels are highly distensible and are responsible for most of the 'passive' volume changes in the region. This region accounts for most of the active capacitance of the body, with the liver being of particular importance. One feature of the responses to sympathetic nerve stimulation is that, at low levels of activity, capacitance responses dominate and only at higher levels do resistance vessels show large changes (Figure 3).

Capacitance and resistance in the hepatosplanchnic circulation to graded stimulation of efferent sympathetic nerves



Total responses at stimulation frequency of 16 Hz are taken as 100%. Note that at low frequencies (1–2 Hz) capacitance responses predominate, whereas higher frequencies are needed to induce large responses of vascular resistance

3

Renal circulation

The blood flow to the kidneys is about 1.2 litres/minute and is extremely high in relation to their size. Renal arteries supply the glomerular capillaries via afferent arterioles and then drain to efferent arterioles. This arrangement maintains the high glomerular capillary pressure required for filtration. Efferent arterioles supply the peritubular capillaries, which drain into the renal veins. Juxtaglomerular cells synthesize and release renin in response to decreases in local blood pressure, decreases in sodium delivery (actually detected by cells in the macula densa of the distal convoluted tubules) and to sympathetic nerve stimulation.

Control of renal blood flow
Renal blood flow is autoregulated and is thus largely independent of blood pressure down to mean levels of about 80 mm Hg. Myogenic mechanisms are thought to be involved, but there is also a tubuloglomerular feedback mechanism whereby the flow of fluid in the distal tubule is sensed by the macula densa. This regulates various vasodilator or vasoconstrictor factors that act on afferent arterioles to control both blood flow and glomerular filtration. The agents responsible are not precisely known, though angiotensin II, prostaglandins and adenosine have been implicated. Sympathetic nerve activity reduces renal blood flow mainly by constriction of afferent arterioles. This effect may be augmented by angiotensin II, formed as a result of increases in renin release.

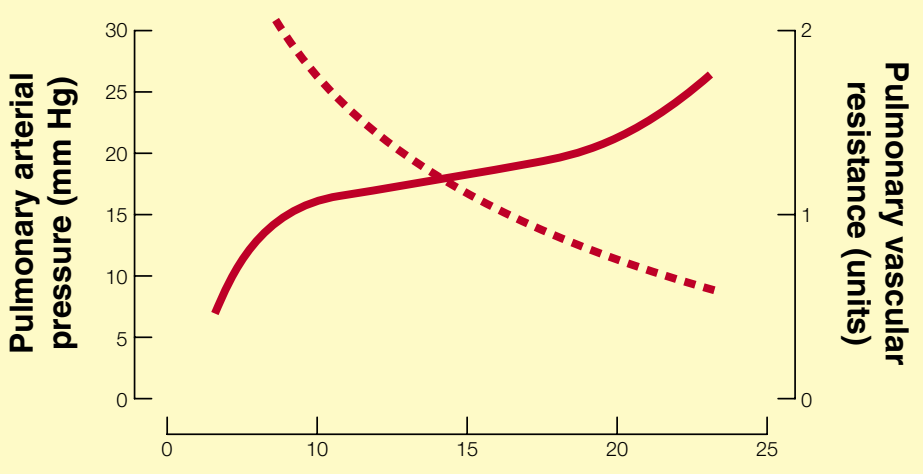
Pulmonary circulation

The pulmonary vascular bed is a low-resistance network in series with the systemic circulation, but with only about one-sixth of the arterial pressure. Because pulmonary arterial pressure is so low (systolic pressure about 20 mm Hg), both pulmonary pressures and flow are greatly influenced by gravity so that, at rest in the upright position, there is little or no flow at the apices, and the greatest flow at the bases. The uneven distribution of flow is partly, but not completely, offset by a similar distribution of ventilation. Pulmonary capillary pressure is about 10 mm Hg, which is considerably less than plasma colloid osmotic pressure. Nevertheless, some filtration does take place, resulting in lymph formation. This is because the tissue protein concentration in the lungs is high, thereby reducing the absorptive gradient.

The volume of blood in the pulmonary circulation is about 0.5 litres. This can vary to allow for changes in blood distribution. For example, standing upright or the Valsalva manoeuvre results in most of this blood being transferred elsewhere. The reservoir function also allows for temporary imbalances between the right and left ventricles as occurs at the start of exercise.

Factors influencing pulmonary vascular resistance
Unlike regions of the systemic circulation, overall pulmonary flow is not regulated but depends solely on systemic flow. The characteristics of the pulmonary circulation allow flow to be increased five-fold with only a small change in arterial pressure (Figure 4). This is partly because of the high degree of distensibility of the pulmonary vessels and also because a small pressure change results in more perfusion of the apical regions. Pulmonary arterioles possess some smooth muscle, which has sympathetic innervation. Stimulation of peripheral arterial chemoreceptors results in pulmonary vasoconstriction. Hypoxia also increases pulmonary vascular resistance by a direct effect on the blood vessels. This is the opposite of what occurs in the systemic circulation. Localized hypoxic vasoconstriction has the beneficial effect of diverting blood away from inadequately ventilated regions. Generalized hypoxia, however, leads to pulmonary hypertension and possibly oedema; this can be countered by administration of oxygen.

Effects of changes in pulmonary blood flow (cardiac output) on pulmonary artery pressure and pulmonary vascular resistance



Resistance is perfusion pressure (pulmonary artery – left atrial pressure). Note that increasing cardiac output from resting levels (typically 5 litres/minute) to exercise levels (25 litres/minute) is associated with only a small increase in pulmonary arterial pressure ▬ and a large decrease in pulmonary vascular resistance ▪ ▪ ▪

4

FURTHER READING

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Digestive Functions

Adrian Thomas

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Most foods cannot be absorbed in the form in which they are present but require digestion into smaller compounds that can be more easily absorbed. The basic process of digestion for the three major foods (carbohydrates, proteins, fats) is hydrolysis. Most absorption takes place in the small intestine and the absorptive surface is increased about 1000-fold by:

- valvulae conniventes (mucosal folds)
- villi (finger-like projections composed of epithelial cells, blood supply and a central lacteal)
- microvilli (finger-like projections on the surface of epithelial cells).

Absorption of ions and water

Sodium is actively transported from inside the epithelial cell through the basal and lateral cell walls into the paracellular spaces. Intracellular sodium is replaced by sodium from the chyme moving down the electrochemical gradient. In addition, some potassium and hydrogen ions are transported in the opposite direction in exchange for sodium ions, and some chloride ions are transported in the same direction with the sodium ions. Osmotic equilibrium is maintained by water following sodium through the epithelial membrane. In the colon, the junctions between the epithelial cells are much tighter than those in the small intestine. This prevents back diffusion of ions and water, allowing more complete absorption of sodium, especially when under the influence of aldosterone.

A typical adult ingests 2000 ml/day of fluid. In addition, about 7000 ml/day of fluid is secreted into the gastrointestinal tract. Of this 9000 ml, only about 1500 ml enters the colon and only about 200 ml is lost in the stool. Similarly 5–8 g/day of sodium is ingested and 20–30 g/day is secreted into the gastrointestinal tract, but less than 0.5% is lost in the faeces. If the absorptive mechanisms are overwhelmed (e.g. in severe diarrhoea) dehydration and electrolyte depletion can occur rapidly.

The epithelial cells in the ileum and large intestine can absorb chloride ions in exchange for bicarbonate ions, which are secreted. Calcium, iron, magnesium, potassium, phosphate and other ions are all actively absorbed from the small intestine.

Carbohydrates

The main carbohydrates in the diet are sucrose, lactose, starch and cellulose (Figure 1). However, cellulose cannot be digested by humans.

Starch is digested by salivary amylase (ptyalin) in the mouth and upper stomach. Ptyalin is inhibited by the low gastric pH but carbohydate digestion is continued in the small intestine by pancreatic amylase, which is more powerful than salivary amylase. Starch digestion produces maltose and short chains of glucose molecules. These, together with ingested sucrose and lactose, are broken into monosaccharides by luminal enzymes (lactase, sucrase, maltase, α-dextrinase). Fructose crosses the epithelium by facilitated diffusion, while glucose and galactose undergo secondary active transport coupled to sodium. Thus, the final products of carbohydrate digestion are all monosaccharides, which are absorbed immediately into the portal blood. Most ingested carbohydrate is digested and absorbed in the first 20% of the small intestine.

Carbohydrates in food

Monosaccharides	Disaccharides	Polysaccharides
Glucose	Sucrose (glucose + fructose)	Starch
Fructose	Lactose (glucose + galactose)	Cellulose
Galactose	Maltose (glucose + glucose)	Glycogen

1

Proteins

Pepsin precursors (pepsinogen I and II) are activated by gastric acid and inactivated by alkali in the duodenum. Proteins are broken down to peptides in the stomach and by the major proteo-lytic pancreatic enzymes (trypsin, chymotrypsin, proelastase) in the small intestine. The peptides are further digested to free amino acids by carboxypeptidase (pancreatic), aminopeptidase and several dipeptidases (in the small intestinal brush border). D amino acids are absorbed by passive diffusion. L amino acids are actively absorbed by basic, neutral and amino acid transporters (the latter two are coupled with sodium). Dipeptides and tripeptides are absorbed by secondary active transport coupled with hydrogen ions, are hydrolysed to amino acids in the epithelial cell, then enter the blood by facilitated diffusion. Occasionally, large peptides and whole proteins are absorbed intact by endocytosis and subsequent exocytosis. This can result in severe allergic reactions and declines with age. Overall about 50% of digested protein originates from food, 25% from digestive juices and 25% from desquamated cells.

Fats

Triglycerides are the main dietary fat. They are emulsified by bile salts, lecithin and monoglycerides and the process is assisted by agitation in the small intestine. Procolipase is secreted by the pancreas and is activated by trypsin. It displaces emulsifying agents and binds lipase to the fat droplets. Lipase (lingual, gastric, pancreatic) produces free fatty acids, glycerols, monoglycerides and diglycerides. Cholesterol esters and phospholipids are hydrolysed by pancreatic cholesterol ester hydrolase and phospho-lipase A_2 to release cholesterol, monoglycerides and fatty acids. Lipids and bile salts interact to produce micelles, which contain fatty acids, monoglycerides and cholesterol. Micelles facilitate fat digestion in three ways:

- they lower the concentration of monoglycerides and free fatty acids thereby allowing triglyceride hydrolysis to continue
- they move down the concentration gradient to the brush border where the lipids diffuse into the epithelial cells and are esterified
- they are essential for cholesterol absorption.

The bile salts are released back into the chyme and are re-absorbed in the terminal ileum, to be re-used to form micelles. Medium chain fatty acids (10–12 carbon atoms long) enter the portal blood directly. Longer fatty acids are re-esterified to triglycerides and together with cholesterol esters are coated with protein, cholesterol and phospholipid to form chylomicrons, which enter the lymphatics within the villi. Fat absorption occurs mainly in the proximal small intestine but also, to some extent, in the ileum. Overall, about 95% of ingested fat is digested and absorbed.

Malabsorption

The causes of malabsorption are summarized in Figure 2. ◆

Reasons for malabsorption

Loss of absorptive surface
- Surgical resection of small intestine (short bowel syndrome)
- Villous atrophy (e.g. coeliac disease)

Specific enzyme defects
- Lactase deficiency

Motility disorders
- Intestinal pseudo-obstruction

Inflammatory disorders
- Crohn’s disease

Pancreatic insufficiency
- Cystic fibrosis

Hepatobiliary dysfunction
- Cirrhosis

2

Gastrointestinal Secretions and Vomiting

Adrian Thomas

Adrian Thomas is Consultant Paediatric Gastroenterologist at Booth Hall Children's Hospital, Manchester. He qualified from Manchester where he also completed an honours BSc in physiology. His training in paediatric gastroenterology was completed in Manchester, London and Sydney, Australia. His research interests include inflammatory bowel disease and nutritional support.

The two main gastrointestinal secretions are mucus and digestive enzymes. There are numerous pits or crypts throughout the gastrointestinal tract containing specialized secretory cells (e.g. crypts of Lieberkuhn in the small intestine). Tubular glands are present in the stomach (e.g. oxyntic glands) and proximal duodenum. Specialized glands include the salivary glands, pancreas and liver.

The presence of food in the gastrointestinal tract causes direct stimulation of mucous (goblet) cells and nearby glands, which release digestive enzymes. The mucus protects the epithelium and acts as a lubricant. Mucous cells and glands are also stimulated by local enteric reflexes in response to distension or irritation. Parasympathetic stimulation increases secretion from salivary, oesophageal, gastric, pancreatic, duodenal Brunner's and distal large intestinal glands. Secretion from the rest of the small intestine and proximal large intestine is controlled predominantly by local neural and hormonal stimuli. Sympathetic stimulation alone slightly increases gastrointestinal secretion, but in the presence of parasympathetic or hormonal stimulation can reduce secretion because it induces constriction of splanchnic blood vessels.

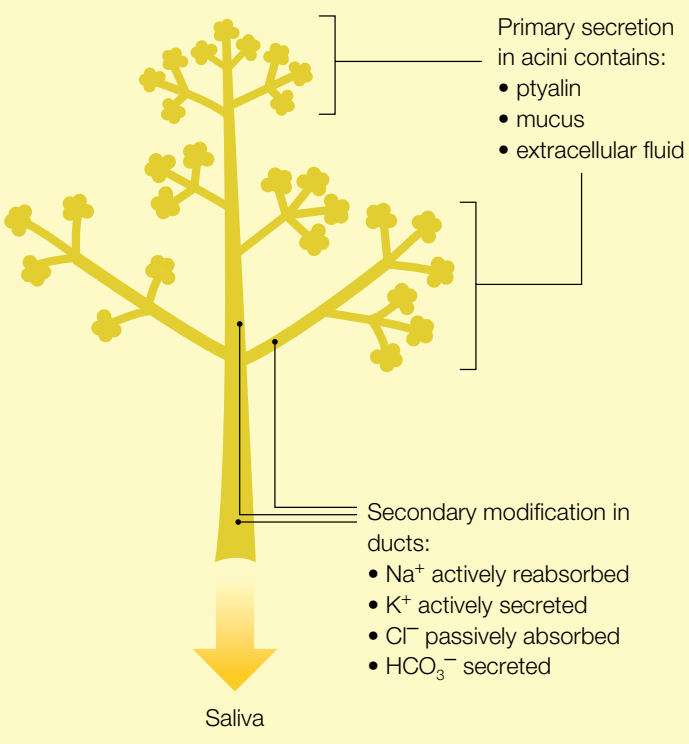
Basic mechanism of glandular secretions
Organic substances: synthesis of enzymes and other organic substances takes place in the endoplasmic reticulum of glandular cells. These are modified in the Golgi apparatus and stored in secretory vesicles until neural or hormonal signals induce their release by exocytosis.

Water and electrolytes: hormonal or neural stimulation is thought to initiate active transport of chloride across the basal membrane, positive ions then follow the electrical gradient, the increased intracellular osmolality draws in water, resulting in increased intracellular pressure and cell swelling. This disrupts the secretory border allowing leakage of water and electrolytes.

Saliva
Saliva helps to maintain oral hygiene because it:
- washes away bacteria and food
- contains bactericidal agents (e.g. thiocyanate)
- contains proteolytic enzymes (e.g. lysozyme)
- contains antibodies.

Saliva comprises a serous secretion containing ptyalin and a mucous secretion. The parotid gland secretes only serous fluid, the submandibular and sublingual glands secrete both and the numerous buccal glands secrete only mucus. Together they secrete 800–1500 ml/day of saliva. Ptyalin and/or mucin are secreted in the acini (Figure 1); as the fluid passes through the ducts, sodium is actively reabsorbed in exchange for potassium, bicarbonate is secreted and chloride is reabsorbed. Therefore, saliva contains high concentrations of potassium and bicarbonate and low concentrations of sodium and chloride. When the rate of salivation is increased, the rate of flow through the ducts also increases, reducing reabsorption and secretion.

Salivary gland



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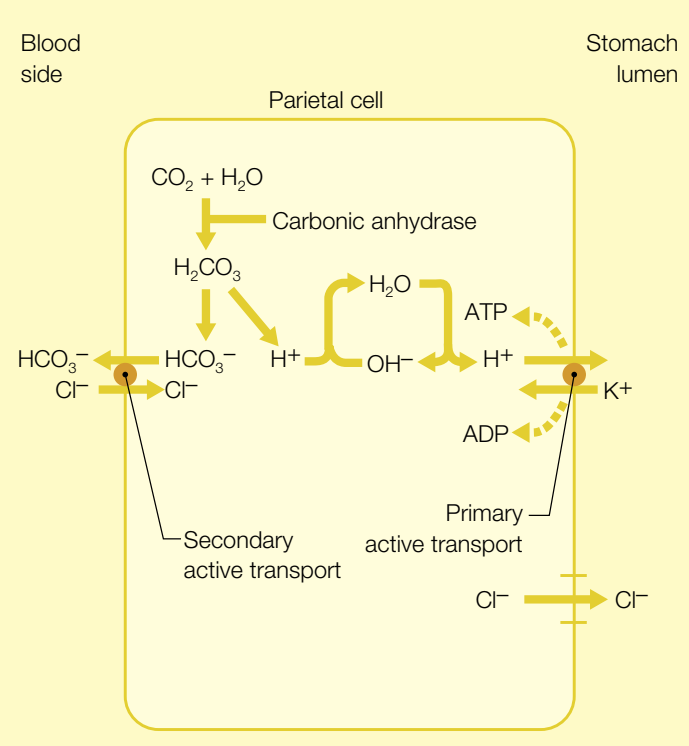
Regulation of secretion: the salivary glands are controlled mainly via the parasympathetic nervous system from the superior and inferior salivary nuclei in the brainstem. They are influenced by the adjacent medulla and pons, which are stimulated by taste and touch sensors in the mouth, tongue and pharynx. They are also influenced by the appetite area in the amygdala, prefrontal cortex and adjacent hypothalamus. Reflex salivation also occurs in response to gastrointestinal irritation.

Gastric secretion
Mucous cells line the gastric mucosa. Oxyntic (gastric) glands occur in the fundus and body of the stomach. The pyloric glands are confined to the antrum.

Mucous cells secrete large amounts of viscid alkaline mucus to protect the gastric mucosa from acid.

Oxyntic glands contain three types of cells: mucous neck cells (secreting mainly mucus but also some pepsinogen), peptic (chief) cells (secreting pepsinogen) and parietal (oxyntic) cells (secreting hydrochloric acid and intrinsic factor). The basic mechanism of pepsinogen and mucus secretion is described above. Pepsinogen is activated to pepsin in the presence of hydrochloric acid and pepsin. In an acid environment, pepsin is a powerful proteolytic enzyme. Intrinsic factor is necessary for absorption of vitamin B_{12} in the terminal ileum. During the secretion of hydrochloric acid (Figure 2) hydrogen ions from water in the parietal cell are actively secreted into the gastric lumen in exchange for potassium ions. The remaining hydroxyl ions are neutralized by hydrogen ions from carbonic acid. Bicarbonate ions diffuse from the cell to the extracellular fluid in exchange for chloride ions. Chloride ions are also transported into the lumen. Water passes into the lumen by osmosis.

Secretion of hydrochloric acid by parietal cell



2

Pyloric glands contain mainly mucous cells, but also secrete gastrin and small amounts of pepsinogen.

Regulation of gastric secretion: acetylcholine, gastrin and hist-amine bind to specific receptors on the secretory cells. Acetylcholine stimulates secretion of pepsinogen by the peptic cells, hydrochloric acid by the parietal cells and mucus by the mucous cells. Gastrin and histamine stimulate secretion of hydrochloric acid by the parietal cells but have little effect on the other cells. Amino acids, caffeine and alcohol also have weak stimulatory effects on gastric secretion.

Acid secretion – neural stimulation of acid secretion is initiated by higher CNS centres via the vagus nerve or by local reflexes. Local reflexes are triggered by gastric distension, acid pH and products of protein digestion. The nerves release acetyl-choline, except for those supplying the gastrin-secreting cells (G cells) in the pyloric glands where an intermediate neuron secretes gastrin-releasing peptide. Gastrin enters the bloodstream and travels to the oxyntic glands in the body of the stomach where it stimulates the parietal cells to release hydrochloric acid and to a lesser extent the peptic cells to release pepsinogen. Acetylcholine, gastrin and histamine alone have little effect on gastric secretion. Histamine is continually present in small amounts and exerts its effect via the H_2-receptors on the parietal cells. This, together with vagal stimulation (either from higher CNS centres or local reflexes when food enters the stomach), releases gastrin and acetylcholine thus promoting large quantities of gastric acid to be released. Excess acidity produces neural inhibition of gastric secretion and blocks the secretion of gastrin from the G cells.

Pepsinogen secretion – pepsinogen is released from the peptic cells in response to neural stimulation (releasing acetylcholine) and the presence of gastric acid.

Phases of gastric secretion
Cephalic phase – this results from the thought, sight, smell or taste of food. Neural stimuli arise in the cerebral cortex, appetite centre or hypothalamus and are transmitted through the vagus.

Gastric phase – food entering the stomach elicits long vaso-vagal reflexes, local enteric reflexes and release of gastrin. This phase accounts for about 70% of total gastric secretion.

Intestinal phase – food mixed with gastric secretions (chyme) entering the proximal small intestine can stimulate modest gastric
secretion. Mechanisms include duodenal gastrin release, absorbed amino acids, other hormones and reflexes.

Inhibition of gastric secretion: although chyme stimulates gastric secretion during the intestinal phase, it inhibits it during the gastric phase. This is initiated by the enterogastric reflex and gastrointestinal hormones, including secretin, in response to distension, hyper- or hypo-osmolar fluid, acid, protein breakdown products, fat or irritation in the duodenum.

Exocrine pancreatic secretion
The exocrine pancreas is structurally similar to the salivary glands. Digestive enzymes are secreted by the pancreatic acini and sodium bicarbonate is secreted by the ductules and ducts leading from the acini. Secretion is stimulated primarily by chyme in the duodenum.

Pancreatic enzymes: the pancreas secretes enzymes for:
- protein digestion (trypsin, chymotrypsin, carboxypeptidase)
- carbohydrate digestion (pancreatic amylase)
- fat digestion (pancreatic lipase, cholesterol esterase, phospho-lipase).

The proteolytic enzymes are produced in inactive forms (trypsinogen, chymotrypsinogen, procarboxypeptidase) which become active only in the gastrointestinal tract. Trypsinogen is converted to trypsin by enterokinase. Trypsin converts chymo-trypsinogen to chymotrypsin, other proenzymes into active forms and can also activate trypsinogen (autocatalysis). The pancreatic enzymes are prevented from activation before reaching the gastrointestinal tract (which would cause destruction of the pancreas) by trypsin inhibitor.

Bicarbonate ions produced from carbon dioxide and water by carbonic anhydrase, are actively secreted (in exchange for chloride ions) by the ductular epithelial cells. The remaining hydrogen ions are exchanged for sodium ions in the bloodstream, the sodium ions continue into the duct to maintain electrical neutrality. Water follows by osmosis.

Regulation of secretion: pancreatic secretion is stimulated by acetylcholine (from parasympathetic nerves), cholecystokinin (from proximal small intestine when food enters) and secretin (from proximal small intestine when acid enters). Acetylcholine and cholecystokinin primarily stimulate the production of pancreatic enzymes from the acinar cells whereas secretin primarily stimulates the production of large quantities of sodium bicarbonate solution by the ductal cells, which is largely responsible for neutralizing the gastric acid. Pancreatic secretion occurs in three phases: cephalic, gastric and intestinal in the same way as gastric secretion.

Intestinal secretions
Mucus is secreted by Brunner's glands in the proximal small intestine. Throughout the intestine are numerous crypts of Lieberkuhn containing goblet cells (which produce mucus) and, in the small intestine, enterocytes (which produce large quantities of water). Enterocytes in the small intestinal villi also produce peptidases, disaccharidases and lipase.

Nausea and vomiting

Nausea is a conscious awareness of arousal of the vomiting centre or related areas of the brain. It often precedes vomiting and may be initiated by higher CNS centres or local irritation in the gastrointestinal tract.

Vomiting can be initiated by overdistension or irritation of the upper gastrointestinal tract, resulting in afferent impulses transmitted via the parasympathetic (vagus) and sympathetic nervous systems to the vomiting centre in the medulla. It can also be initiated by stimulation of other areas of the brain, especially the chemoreceptor trigger zone.

Certain drugs (including morphine) induce vomiting by direct stimulation of this area. In motion sickness, impulses arise from receptors in the labyrinth and are transmitted to the vestibular nuclei, then the cerebellum, before reaching the chemoreceptor trigger zone and eventually the vomiting centre. Higher CNS centres can also stimulate the vomiting centre (e.g. in states of psychological distress).

The vomiting centre initiates vomiting by transmitting impulses via cranial nerves V, VII, IX and X to the upper gastrointestinal tract and through the spinal nerves to the diaphragm and abdominal muscles. Antiperistalsis begins as far distally as the terminal ileum and rapidly propels the contents of the small intestine back to the stomach and duodenum, which contract vigorously. The vomiting centre then initiates a deep inhalation, opening of the upper oesophageal sphincter, closure of the glottis and lifting of the soft palate to prevent nasal reflux. The diaphragm and abdominal muscles contract and the lower oesophageal sphincter relaxes allowing vomiting to occur. ◆

Gut Motility, Sphincters and Reflex Control

Adrian Thomas

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The gastrointestinal tract is made up of layers of serosa, longitudinal muscle, circular muscle, submucosa and mucosa. The muscle layers are composed of bundles of smooth muscle fibres joined together at multiple points so that action potentials can travel along the length of the gastrointestinal tract. The two basic types of electrical activity are slow waves and spike potentials (spikes). Slow waves are minor depolarizations (5–15 millivolts) occurring 3–12 times/minute. They mainly modify the spikes and cause contractions only in the stomach. Spikes occur when the resting membrane potential becomes more positive than about –40 millivolts. The frequency varies from 1 to 10 spikes/minute and is regulated by the slow waves. The higher the slow wave potential rises above –40 millivolts the greater the spike frequency. Many factors influence the resting membrane potential. Gastrointestinal hormones, acetylcholine, parasympathetic stimulation and stretching of the muscle make it more positive and more excitable whereas noradrenaline, adrenaline and sympathetic stimulation make it more negative and less excitable. Muscle contraction is initiated by calcium entering the muscle fibres.

Gastrointestinal movements and secretions are controlled by the enteric nervous system. This comprises two plexuses:
- the myenteric (or Auerbach's) plexus between the longitudinal and circular muscle layers
- the submucosal (or Meissner's) plexus in the submucosa.

The plexuses are influenced by the sympathetic and para-sympathetic innervation of the gastrointestinal tract.

The two types of movement in the gastrointestinal tract are propulsive or peristaltic and mixing movements or local constrictive movements). Peristalsis is a ring of contraction moving from the proximal gastrointestinal tract distally; the usual stimulus is distension of the lumen.

Chewing and swallowing

Chewing (mastication) breaks food up into small particles, increasing the surface area for digestion and absorption. Swallowing is a complex action requiring the coordinated activity of 26 muscles of the mouth, pharynx and oesophagus, six cranial nerves, the brainstem and cerebral cortex. It consists of two voluntary phases (oral preparatory, oral) and two involuntary phases (pharyngeal, oesophageal). In the oral preparatory phase, food is formed into a bolus. In the oral phase, the bolus is propelled backwards by the tongue. When the bolus passes the anterior fauces into the pharynx the swallowing reflex is triggered and from this point the process is involuntary. In the pharyngeal phase, the soft palate rises against the posterior pharyngeal wall to prevent aspiration into the nasopharynx. The bolus is propelled by the peristalsis of the pharyngeal constrictors to the cricopharyngeal sphincter, which then relaxes. The larynx is raised, closing the glottis, which is then covered by the epiglottis, preventing food entering the trachea. In the oesophageal phase, the upper oesophageal (pharyngo-oesophageal) sphincter relaxes and a wave of peristalsis then propels food down the oesophagus, the lower oesophageal (gastro-oesophageal) sphincter relaxes and food enters the stomach. Receptive relaxation occurs in the stomach and duodenum so that they become relaxed before the peristaltic wave reaches them and they are ready to receive food.

A number of factors help to prevent reflux of irritant gastric or small intestinal juice back into the oesophagus. The lower oesophageal sphincter is usually constricted (except during swallowing). Increased intra-abdominal pressure (especially when walking or coughing) causes the intra-abdominal portion of the oesophagus to collapse.

Motor function

The stomach

The stomach has three main motor functions.

Storage: food entering the stomach induces relaxation of the muscular wall via a vasovagal reflex. This allows the stomach to expand to accommodate food up to a volume of about 1.5 litres.

Mixing: food is mixed with gastric secretions by means of mixing or constrictor waves. These are weak peristaltic waves originating from slow waves occurring in the stomach wall. They are each 15–20 seconds long and spread towards the antrum. Some of these peristaltic waves become more intense (constrictor rings) and force the antral contents towards the pylorus. The pylorus contracts to slow gastric emptying and results in further mixing of gastric contents.

Emptying: the more intense peristaltic waves promote antral emptying. As the stomach empties, these constrictor rings begin further up in the body of the stomach promoting further gastric emptying. The pylorus allows fluid, but not usually solid, gastric contents to enter the duodenum. The rate of gastric emptying is regulated by gastric (weak influence) and duodenal (strong influence) factors.

Gastric factors include the gastric food volume and gastrin, which is released in response to gastric stretching, and the presence of certain foods. Carbohydrates remain in the stomach for the shortest time, proteins are intermediate and fats remain for the longest time.

Duodenal factors include enterogastric neural reflexes. These are stimulated by the acidity and osmolality of duodenal juice, the presence of digested proteins, duodenal distension and irritation. Cholecystokinin and other hormones (released particularly in response to duodenal fats) also have a role.

Small intestine

Mixing (segmentation) contractions: distension with chyme elicits regularly spaced contractions each 20–30 seconds. When relaxation occurs in these areas, contractions occur in intervening areas. These alternating contractions mix the chyme with small intestinal secretions and help to propel it distally.

Propulsive movements: peristalsis spreads chyme throughout the absorptive surface of the small intestine and propels it towards the ileocaecal valve. This slows the flow of chyme, often for several hours, until the next meal is eaten and the gastroenteric (gastroileal) reflex increases ileal peristalsis. Peristalsis slows from the proximal to the distal small intestine. Most peristaltic waves last for 3–10 cm and small intestinal transit time is 3–5 hours. Peristaltic activity is promoted by the entry of chyme into the duodenum, by the gastroenteric reflex secondary to gastric distension and by various gastrointestinal hormones including gastrin and cholecystokinin. Secretin and glucagon inhibit small intestinal motility. During fasting a 'migrating motor complex' or peristaltic wave passes down the upper gastrointestinal tract every 90 minutes to prevent any accumulation of secretions. Severe intestinal inflammation can result in intense and rapid peristalsis (peristaltic rush).

Ileocaecal valve

The ileocaecal valve slows the flow from the ileum to the caecum and prevents backflow from the caecum into the ileum. Distension or irritation of the caecum results in a reflex increase of tone in the ileocaecal valve and inhibition of ileal peristalsis, thereby delaying ileal emptying.

Colon

Proximal colonic movements are slow, which promotes reabsorption of fluid and electrolytes. Simultaneous contractions of the circular muscle and longitudinal muscle strips (taeniae coli) result in outward bulging of the bowel wall in between (haustrations). As in the small intestine, alternating areas of contraction and relaxation result in mixing of the colonic contents. Slow forward propulsion also occurs. In the distal colon, modified peristaltic waves or 'mass movements' 1–3 times/day move the faeces towards the rectum. These movements are initiated by colonic inflammation and by gastrocolic and duodenocolic reflexes resulting from gastric and duodenal distension following meals.

Defecation

The internal anal sphincter consists of circular involuntary smooth muscle whereas the external anal sphincter consists of striated voluntary muscle, which is continually contracted unless consciously inhibited. Faeces entering the rectum, initiate an intrinsic defecation reflex mediated by the myenteric plexus. This results in peristalsis in the descending colon/rectum and relaxation of the internal anal sphincter. The intrinsic defecation reflex is weak and usually requires reinforcement by a parasympathetic defecation reflex, mediated via the sacral segments of the spinal cord and the pelvic nerves. This amplifies the peristaltic waves and relaxes the internal anal sphincter. Deep inhalation, closure of the glottis and contraction of the abdominal muscles are also initiated via the spinal cord. Defecation can be inhibited by conscious control over the external anal sphincter.

Gastrointestinal hormones

Several hormones influence gastrointestinal motility and secretions. The two main 'families' of gastrointestinal hormones are gastrin and secretin. The gastrin family includes gastrin and cholecystokinin (CCK), which are polypeptides with the same terminal five amino acids. The secretin family includes secretin, glucagon, glicentin, vasoactive intestinal peptide (VIP) and gastric inhibitory peptide (GIP), which all have similar structures. The functions of the most important gastrointestinal hormones are summarized in Figure 1. ◆

Principal gastrointestinal hormones

	Gastrin	Cholecystokinin (CCK)	Secretin
Where produced	Gastric antrum	Small intestine	Small intestine
Stimuli for release	Peptides and amino acids in stomach	Amino acids and fatty acids in small intestine	Acid pH in small intestine
Effect on stomach	Stimulates acid secretion and growth	Inhibits acid secretion	Inhibits acid secretion
Effect on exocrine pancreas	Stimulates growth	Stimulates growth and enzyme secretion Potentiates secretin	Stimulates growth and bicarbonate secretion Potentiates CCK
Effect on hepatobiliary system		Potentiates secretin Stimulates gallbladder contraction	Stimulates bicarbonate secretion
Effect on intestine	Stimulates small intestinal growth, motility, colonic motility		

1

Hormonal Control of Metabolism: Regulation of Plasma Glucose

Anna Casey

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Blood glucose concentration represents the net flux of glucose entering and leaving the blood. Glucose is delivered to the blood from the liver following ingestion of carbohydrate, from the breakdown of glycogen (the storage form of glucose) and from endogenous glucose synthesis. Glucose is removed from the blood by a number of organs and tissues, notably the brain, skeletal muscle, liver and adipose tissue. With this variety of means of entry and exit from the blood, and the complications arising from too high or too low a glucose concentration, the regulation of blood glucose is complex.

Many factors affect the delivery of glucose to, and its removal from, the blood. These include dietary carbohydrate and fat, the circulating free fatty acid concentration, exercise, hypoxia and the actions of several hormones. The postprandial blood glucose concentration is about 4–5.5 mmol/litre or 70–100 mg/100 ml, but arterial concentrations vary throughout the day from about 3.5 mmol/litre after exercise to 9 mmol/litre following a meal. For the purposes of this article, it is the plasma fraction of blood glucose that is of most interest, because the plasma glucose concentration is the driving force behind the diffusion of glucose molecules across the capillary wall into the interstitial space.

Glucose disposal

The plasma glucose concentration is regulated by the opposing actions of a number of hormones (Figure 1), the net effect of which depends on their relative concentration in the blood at a given time. Some, such as insulin, promote the clearance of glucose from the plasma, while others, including glucagon, growth hormone, and catecholamines, stimulate the production and release of glucose into the blood.

The most important hormone involved in the regulation of plasma glucose is insulin, a polypeptide secreted by the β-cells of the islets of Langerhans in the pancreas. It promotes the uptake of glucose from plasma, and is used parenterally in the treatment of diabetes mellitus. A rise in plasma glucose concentration, for example after a meal, stimulates the release of a number of gut hormones, known as incretins, which promote insulin secretion by pancreatic β-cells. Glucagon-like peptide-1-(7-36)amide (GLP-1), and glucose-dependent insulinotropic peptide (GIP), secreted from endocrine cells in the intestinal mucosa, are the incretins of major interest. GLP-1 is released within a few minutes of carbohydrate ingestion, mediated by an unknown signalling pathway, and may form the first line of defence against hyperglycaemia. This is followed by a sharp decline in GLP-1 release, the timing of which is related to the glucose load (i.e. the larger the glucose load, the slower the decline in GLP-1 release)

Tight control of GLP-1 helps to prevent excessive insulin secretion and the development of hypoglycaemia. GLP-1 also inhibits the release of glucagon, and probably downregulates gastric emptying of carbohydrates. Insulin secretion is also regulated by somatostatin, a pancreatic hormone, which is released in response to increases in the plasma concentration of glucose, amino acids and fatty acids, and which acts locally within the pancreas to inhibit insulin secretion.

An increase in circulating insulin promotes the uptake of glucose into insulin-sensitive tissues, primarily skeletal muscle, liver and adipose tissue. Skeletal muscle is the primary site of insulin-stimulated glucose disposal in the fed state. As a consequence, the insulin sensitivity of skeletal muscle, which accounts for about 40% of body mass, is an important factor in the regulation of the plasma glucose concentration. The rate of glucose uptake from the plasma is largely dependent on the transfer of glucose across the plasma membrane of the muscle fibres (sarcolemma). Glucose transport across the sarcolemma occurs by facilitated diffusion, involving at least two glucose transporter isoforms, GLUT-1 and GLUT-4. The GLUT-4 isoform has emerged as the most important transporter in skeletal muscle. It is located in an intracellular compartment, and translocates to the plasma membrane in response to insulin and muscle contractions. The fastest rate of glucose uptake from the plasma occurs within the first few hours after muscular exercise. During this period, insulin sensitivity of the muscle is acutely increased, as is the number of GLUT-4 transporters in the sarcolemma.

The action of insulin is mimicked by a number of related peptides. Insulin-like growth factor 1 (IGF-1) is a peptide with similar (though less potent) effects to insulin, the expression and secretion of which is regulated by growth hormone. The primary site of IGF-1 production was thought to be the liver, but it is now clear that IGF-1 is produced by several tissues, including skeletal muscle and adipose tissue. A large, acute dose of IGF-1 produces hypoglycaemia, but prolonged IGF-1 therapy reduces hyperglycaemia in type 1 and type 2 diabetes mellitus, and in some insulin-resistance states. The effects of IGF-1 and insulin on glucose disposal are additive.

Proinsulin, the insulin precursor, is cleaved within β-cells releasing equimolar amounts of insulin and connecting(C)-peptide into the circulation. The concentration–time curve of plasma C-peptide is often used as a marker of insulin secretion, and C-peptide itself is traditionally thought to be biologically inactive. However, there is some evidence to suggest that C-peptide stimulates plasma glucose uptake into skeletal muscle in a dose-dependent manner. The mechanism is unclear, but it is known that binding to insulin receptors on the plasma membrane does not occur. Unlike IGF-1, the effects of C-peptide and insulin are not additive.

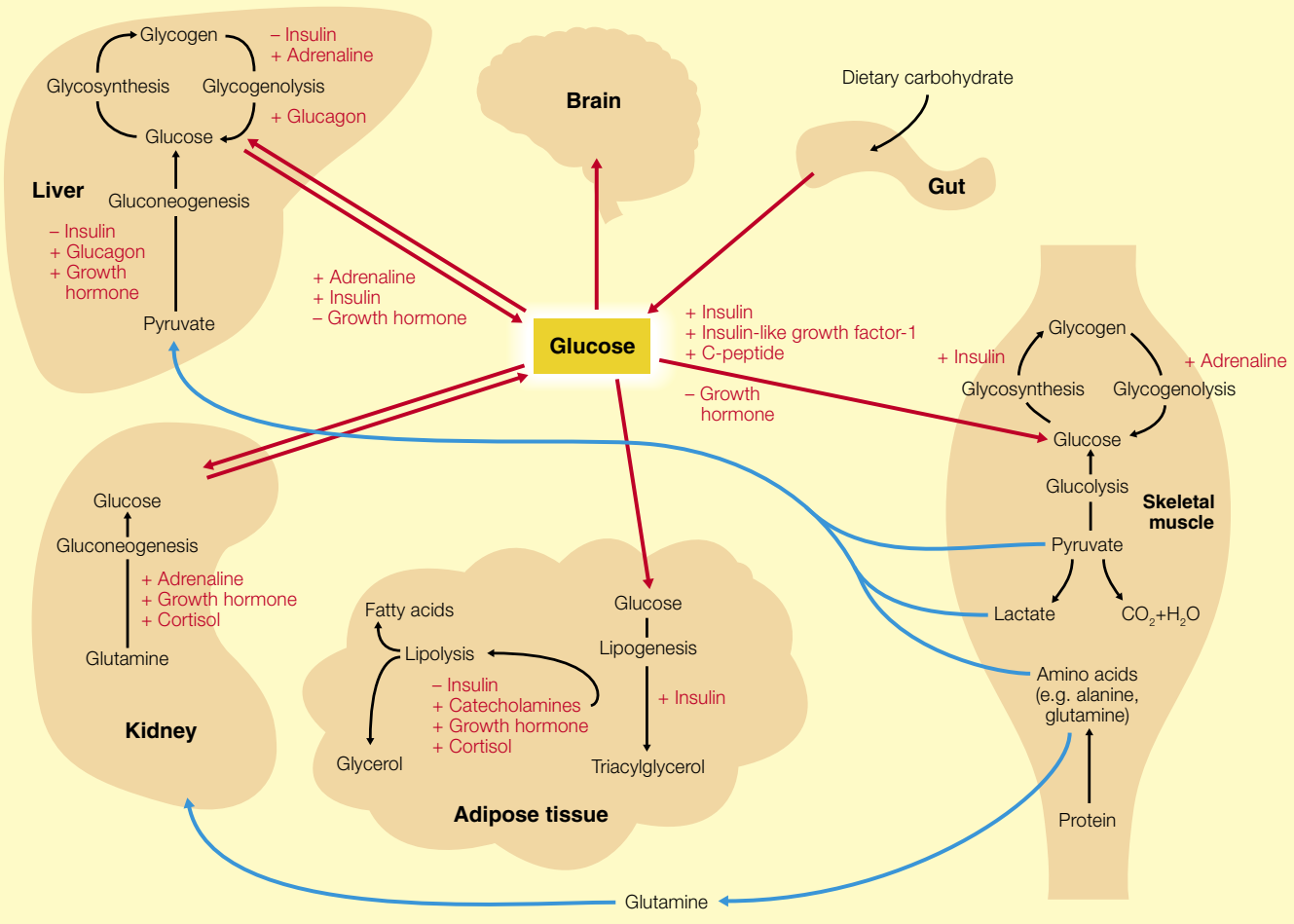
Recently, interest has surrounded the role of leptin, a hormone produced by adipose tissue which acts via the hypothalamus to decrease food intake and to regulate energy stores. Leptin is also reported to have peripheral effects, including stimulation of lipolysis, and insulin-like, though probably indirect, effects on plasma glucose uptake. This increase in glucose disposal appears to be independent of changes in food intake, and is likely to be secondary to a leptin-mediated decline in muscle triglyceride levels.

In contrast to muscle, the plasma membranes of hepatic cells are freely permeable to glucose, enabling a rapid response to changes in blood glucose availability. An increase in plasma insulin concentration reduces the rate of hepatic glycogenolysis (the breakdown of glycogen to glucose) and gluconeogenesis (glucose synthesis from non-sugar sources), thereby inhibiting the production and release of free glucose into the circulation.

Once inside a cell, glucose is phosphorylated to form glucose-6-phosphate (G6P), a process that traps the glucose molecule and prevents it from recrossing the plasma membrane. In the liver, this is a reversible reaction, allowing free glucose to leave the cell and re-enter the circulation, but the requisite enzyme, glucose-6-phosphatase, is missing from skeletal muscle, thus muscle G6P is not a source of free glucose. Instead, G6P either enters glycolysis, resulting in the formation of pyruvate which is oxidized or converted to lactate, or it is converted to glycogen and stored as a future source of energy.

One of the major functions of insulin is the activation of glycogen synthase, the rate-limiting enzyme in glycogen synthesis, by means of a signalling cascade that begins with the binding of insulin to receptors on the plasma membrane. The long-held view is that insulin does not enter the cell and exert any direct effects, though there is some evidence to the contrary.

Hormonal regulation of plasma glucose



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Glucose production

A fall in plasma glucose concentration evokes a number of counter-regulatory measures designed to restore plasma glucose levels, and avoid the debilitating and potentially fatal effects of hypoglycaemia. At the most basic level, this response involves an increase in the release of glucose into the circulation, and a decrease in tissue glucose uptake.

In healthy individuals, a common cause of a fall in plasma glucose concentration is prolonged exercise. Exercise presents a considerable challenge to glucose homeostasis, because it is common for values to fall below 3.0 mmol/litre at the end of prolonged, fatiguing exercise, and values as low as 2.5 mmol/litre have been recorded. Muscle glycogen is an important fuel for this type of exercise, but stores are limited, and it is now clear that, as the availability of muscle glycogen declines, oxidation of carbohydrate from alternative sources is increased to meet the energy demands of muscle contraction. Plasma glucose is the major source, and it is supplied to skeletal muscle via carbohydrate ingestion, hepatic glycogenolysis and/or gluconeogenesis from 3-carbon precursors, including alanine, glycerol, lactate and pyruvate. In contrast to glycogenolysis, which is rapid, gluconeogenesis is a lengthy process that takes place over several hours. In the absence of exogenous carbohydrate, therefore, hepatic glycogenolysis is the principal means of maintaining euglycaemia during exercise, and the rate of glycogenolysis is directly related to the hepatic glycogen content. However, the store of liver glycogen is also limited and, as exercise progresses, the plasma glucose concentration soon falls in the absence of carbohydrate ingestion.

The key processes described above are skeletal muscle glycogenolysis, hepatic glycogenolysis, and hepatic gluconeogenesis. The existence of muscle gluconeogenesis is debatable, but there is evidence to suggest that glucose synthesis from lactate may occur when the muscle glycogen concentration is low and the lactate concentration is high, for example after exercise. Quantitatively, however, gluconeogenesis is more important during prolonged fasting and starvation. These processes are controlled by several hormones released in response to stressors such as exercise, and to a fall in plasma glucose concentration, notably adrenaline, noradrenaline, glucagon, cortisol, somatostatin and growth hormone (Figure 2).

Role of the principal hormones in regulating plasma glucose

Effects of a rise in plasma glucose

Hormone	Main effects
Increase in insulin	• Peripheral glucose uptake increases • Glycogen synthesis increases • Hepatic glycogenolysis and gluconeogenesis decrease • Lipogenesis increases • Lipolysis decreases
Increase in GLP-1	• Insulin secretion increases • Glucagon secretion decreases
Increase in glucose-dependent insulinotropic peptide	• Insulin secretion increases
Increase in insulin-like growth factor-1	• Peripheral glucose uptake increases
Increase in C-peptide	• Skeletal muscle glucose uptake increases?
Increase in somatostatin	• Insulin secretion decreases

Effects of a fall in plasma glucose

Hormone	Main effects
Increase in glucagon	• Insulin secretion decreases • Hepatic glycogenolysis and gluconeogenesis increase
Increase in adrenaline	• Insulin secretion decreases • Skeletal muscle and hepatic glycogenolysis increase • Hepatic glucose release increases • Renal gluconeogenesis increases
Increase in growth hormone	• Lipolysis increases • Peripheral glucose uptake decreases • Hepatic gluconeogenesis increases
Increase in cortisol	• Potentiates effects of glucagon and adrenaline
Decrease in insulin	• Hepatic glycogenolysis increases

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The catecholamine hormones, adrenaline and noradrenaline, are secreted by the adrenal medulla in response to stress. Catecholamines inhibit insulin secretion, thereby helping to preserve plasma glucose. Adrenaline activates adenyl cyclase, an enzyme in the plasma membrane, which leads to the activation of phosphorylase, the enzyme controlling glycogenolysis in muscle and liver tissues. An increase in plasma catecholamines also activates hepatic glucose-6-phosphatase, resulting in the rapid conversion of G6P to glucose, and the release of glucose into the circulation. In the absence of glucose-6-phosphatase, muscle G6P enters glycolysis, resulting in the formation of pyruvate. If it is not used as a substrate for oxidative metabolism, pyruvate is converted to lactate, which is transported to the liver and used as a precursor for hepatic gluconeogenesis.

Hepatic glucose production is regulated by anterior pituitary growth hormone, which stimulates hepatic gluconeogenesis, and reduces hepatic and peripheral (principally muscle) insulin sensitivity. The subsequent impairment of glucose uptake is probably secondary to a growth hormone-mediated increase in lipolysis, rather than a direct effect on glucose transport and metabolism. Glucagon, secreted by pancreatic α-cells, has a similar inhibitory effect on insulin secretion, and stimulates hepatic glycogenolysis and gluconeogenesis very rapidly – hence its use in the treatment of hypoglycaemia resulting from exogenously administered insulin. Unlike adrenaline, glucagon has no effect on muscle glycogenolysis. Blunted glucagon responses to hypoglycemia are noted in adults a few years after developing type 1 diabetes mellitus, and the problem seems to be worse in children, in whom impaired autonomic responses appear to reduce or abolish the glucagon response, even following profound nocturnal hypoglycaemia. Cortisol, a corticosteroid hormone secreted by the adrenal cortex, and the most potent of the naturally occurring glucocorticosteroids, potentiates the effects of glucagon and adrenaline on hepatic gluconeogenesis.

In the post-absorptive state, the kidney, another gluconeogenic organ, accounts for about 20% of plasma glucose disposal. This decreases by a small amount during hypoglycaemia. More importantly, renal glucose release has been shown to increase three-fold under these conditions, suggesting that the role of the kidney in the counter-regulation of hypoglycaemia has been underestimated. Animal studies suggest that renal gluconeogenesis is probably stimulated by adrenaline, with additional effects of growth hormone and cortisol after 2–3 hours. In humans, adrenaline, but not glucagon, has been shown to increase renal gluconeogenesis, probably by increasing the fractional extraction of primarily glutamine.

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Hypothalamic and Pituitary Function

Adrian Heald

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Hypothalamus

The hypothalamus can be regarded as the coordinating centre of the endocrine system. It consolidates signals from higher cortical centres, autonomic afferents, environmental cues (e.g. light, temperature) and peripheral endocrine feedback. It delivers precise signals to the pituitary gland which releases hormones that influence most of the endocrine systems in the body. The hypothalamus is also involved in several neuroendocrine functions including temperature regulation, control of appetite and regulation of the autonomic nervous system.

The hypothalamic hormones are small peptides. They are secreted in a pulsatile fashion and reach their target cells rapidly and in high concentration via the hypothalamo-hypophyseal portal venous circulation. The anterior pituitary lacks a major direct arterial supply and is bathed in a dense capillary network of blood containing hypothalamic hormones released from the median eminence of the hypothalamus, together with paracrine and autocrine factors released from the anterior pituitary cells. The capillary plexus empties into the petrosal sinuses and then into the internal jugular veins. The concentration of hormones in the petrosal sinuses is therefore representative of anterior pituitary production and the petrosal sinuses may be catheterized to assess pituitary function. Control of anterior pituitary hormone production is by negative feedback from hormones produced in target endocrine glands in the periphery and by hypothalamic releasing or release-inhibiting factors that are subject to negative feedback from the periphery.

Anterior pituitary hormones

Adrenocorticotrophin (ACTH)

ACTH stimulates the adrenal cortex to secrete cortisol, adrenal androgens and mineralocorticoids. Corticotrophin releasing hormone (CRH) from the hypothalamus and antidiuretic hormone (ADH) stimulate ACTH secretion.

Structure: ACTH is a 39 amino acid peptide. It is synthesized as part of a large precursor molecule pro-opiomelanocortin (POMC) (241 amino acids). Derivatives of POMC are ACTH, β-lipotrophin (β-LPH) (which is converted to lipotrophin and β-endorphin) and melanocyte stimulating hormone (α-MSH). The first 18 amino acids of ACTH have full biological activity and the first 24 amino acids are identical in all mammals. Synthetic $ACTH_{(1–24)}$ (synacthen) has a longer half-life than native ACTH. Concentrations of β-LPH are increased in renal failure because of slower clearance. The hyperpigmentation observed in ACTH hypersecretion, for example in Addison's disease and uraemia, is a result of the MSH-like activity of β-LPH and ACTH on melanocytes.

Secretion*:* ACTH is secreted in bursts that are maximal in the last hours before waking and in the first hour after waking. Light is one of the most important regulators of the circadian rhythm of ACTH. Activators of ACTH secretion are hypoglycaemia (used in the insulin tolerance of cortisol reserve), fever and stress (psychological or physical).

ACTH actions: immediate actions include stimulation of the initial and rate-limiting step of conversion of cholesterol to pregnenolone with increased supply of free cholesterol ester for cortisol biosynthesis. Prolonged actions include increased adrenal protein synthesis including the enzymes involved in steroidogenesis.

ACTH deficiency presents almost exclusively as the resulting cortisol deficiency. Cortisol is necessary to maintain blood pressure and is involved in the maintenance of hepatic glucogenesis and in salt and water balance. In the most severe form this leads to vascular collapse and death. In the less severe form, there is postural hypotension, tachycardia and hyponatraemia. Baseline screening for ACTH deficiency with a short synacthen test is recommended in all patients with pituitary adenoma.

ACTH excess: increased circulating ACTH from the pituitary represents about 60% of cases of Cushing's syndrome. Ectopic ACTH secretion with consequent glucocorticoid excess is characterized by a short history, pigmentation, weight loss, profound muscle weakness, hypokalaemia and plasma ACTH concentrations greater than 200 ng/litre.

Prolactin

Prolactin is a 199 amino acid peptide. It is synthesized from the fifth week of gestation.

Regulation: prolactin release is under tonic hypothalamic inhibition by dopamine. Probable releasing factors are thyro-tropin releasing hormone (TRH) and vasoactive intestinal peptide (VIP). Oestrogen positively regulates prolactin gene expression (levels of prolactin rise during menarche and pregnancy).

Actions*:* prolactin stimulates initiation and maintenance of lactation (this also requires oestrogen, progesterone and several placental mammotrophic hormones). It regulates hypothalamic dopamine turnover and suppresses gonadotropic releasing hormone (GnRH) secretion in the hypothalamus.

Hyperprolactinaemia results in galactorrhoea (spontaneous or expressible), oligomenorrhoea, decreased libido and headaches. It is caused by disruption of the hypothalamus or hypothalamo-hypophyseal stalk by tumour or trauma, prolactin-secreting adenoma, drugs that decrease dopamine synthesis (e.g. neuroleptics), nipple stimulation, stress and primary hypothyroidism.

Growth hormone (GH)

The gene for GH is located on chromosome 17. GH is a single- chain 191 amino-acid non-glycosylated peptide. It exists in several forms including 22 kDa, 20 kDa and at least one acidic form. Oligomers exist in the peripheral blood. Abnormalities in the cDNA encoding the GH receptor result in the GH resistance of Laron dwarfism. A high-affinity binding protein exists leading to a ten-fold longer half-life for bound GH.

Regulation: GH releasing hormone increases transcription of GH messenger RNA. Somatostatin regulates the timing and amplitude of GH pulses. Insulin-like growth factor-I inhibits GH synthesis. GH secretion is greatest during adolescence and decreases with age. GH secretion rises during sleep and is augmented in fasting, stress, exercise, anorexia nervosa, type I diabetes mellitus and hepatic cirrhosis.

Actions: the somatomedin hypothesis proposes that IGF-I is the mediator of GH effects at the cellular level. The effects of GH are anabolic (positive nitrogen balance), lipolytic (redistributed body fat) and decreased carbohydrate utilization.

Growth hormone imbalance in children leads to short stature with low growth velocity in the absence of a systemic cause. In adults, GH deficiency (often secondary to pituitary tumours or pituitary surgery) results in decreased energy, centripetal obesity and affective disturbance. Symptomatic growth hormone deficiency following pituitary surgery and radiotherapy can be treated with daily GH supplementation. GH excess in children (if acquired before epiphyseal fusion) causes gigantism. In adults it causes acromegaly with progressive increase in the size of hands and feet, thick greasy skin, macroglossia and prognathism, hypertension and glucose intolerance.

Glycoprotein hormone family

The glycoprotein hormone family includes thyroid stimul-ating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH). The α subunit is common to all three hormones, while the β subunit confers biological specificity.

TSH: thyrotrophs are the least common anterior pituitary cell type (5%). TRH stimulates TSH release. Intracellular tri-iodothyronine (T3) regulates TSH release but plasma thyroxine (T4) correlates better with TSH levels in health and hypothyroidism (T4 correlates better in hypothyroid patients receiving thyroxine replacement). In the treatment of primary hypothyroidism with thyroxine, levels of TSH may lag behind changes in serum T4 levels.

Deficiency occurs relatively late in the development of hypopituitarism. The clinical presentation of TSH deficiency is of thyroxine deficiency with lethargy, weight gain, constipation and cold intolerance.

LH, FSH and β-human chorionic gonadotropin (hCG): both LH β subunits and FSH β subunits are composed of 115 amino acids and have two carbohydrate side-chains. The structure of the β subunit of LH is similar to hCG except that the β subunit of hCG has an additional 32 amino acids and additional carbohydrate residues.

GnRH interacts with a membrane receptor to regulate LH and FSH synthesis and release. The timing of GnRH pulses is crucial. One GnRH pulse per hour maintains LH and FSH pulse secretion, above this level LH is preferentially stimulated; while one GnRH pulse every 3 hours causes FSH to be preferentially stimulated.

Oestradiol and androgens suppress GnRH secretion by the hypothalamus. Progesterone slows the GnRH pulse generator.

Inhibin suppresses LH and FSH secretion. It is a member of a large family of glycoprotein hormones including transforming growth factor (TGF)-β and mullerian inhibiting substance that are important in cellular differentiation. It is synthesized by the Sertoli cells of the testis, granulosa cells of the ovary, placenta, pituitary gonadotrophs and the brain. Thus, it may operate as a gonadal feedback hormone and locally in the hypothalamus and pituitary in a paracrine fashion.

In women, gonadotrophin deficiency leads to ovarian hypofunction with anovulation and consequent amenorrhoea and infertility, together with decreased oestrogen production leading to premature menopause with flushing/sweating, vaginal dryness and increased risk of osteoporosis in the long term. In men, it results in testicular hypofunction with infertility, diminished libido and decreased energy.

Posterior pituitary

The posterior pituitary secretes two major peptides: antidiuretic hormone (ADH) and oxytocin. Both are synthesized in the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus. Both are nonapeptides. The precursor molecule includes a specific neurophysin which is the carrier protein within the neuronal tracts. The molecular weight of ADH is 1.084 kDa and of oxytocin is 1.007 kDa. Both circulate unbound to proteins and have half-lives of 5–15 minutes.

ADH

Control of secretion: the principal determinant is osmolality, sensed in the organum vasculosum of the lamina terminalis. Increased plasma osmolality leads to an increase in ADH release which reduces water excretion and leads to lower plasma osmolality. Decreased blood pressure or blood volume leads to an increase in ADH. This is mediated by baroreceptors in the carotids, aorta, heart and great veins.

Actions: the main action is the reduction of solute-free water excretion. This effect is mediated by the receptor coupled to adenylate cyclase in the distal collecting tubule and leads to an increase in the permeability to water of the distal convoluted tubule and the collecting duct. ADH stimulates ACTH combined with chronic renal failure (V_{1B} receptor). At high concentration it contracts blood vessels, gut and renal tract (V_{1A} receptor).

Deficiency of ADH leads to diabetes insipidus. This presents with polyuria, excessive thirst and polydipsia developing after pituitary tumour, pituitary surgery or recent head injury. The diagnosis is confirmed by a water deprivation test with failure to concentrate urine after dehydration but concentration of urine after desmopressin. Treatment is with desmopressin (DDAVP), which is usually administered intranasally.

Excess ADH causes the syndrome of ADH excess. This presents with hyponatraemia (serum sodium less than 130 mmol/litre) with inappropriately low plasma osmolality and inappropriately high urine osmolality. Clinical features become increasingly severe as the serum sodium decreases, ranging from mild drowsiness to convulsions, coma and death. There are many causes, including pneumonia, lung neoplasm, brain tumour or abscess, head injury, subarachnoid haemorrhage and drugs (particularly carbamazepine and selective serotonin reuptake inhibitors).

Oxytocin

Oxytocin production is controlled by stimulation of the nipple and cervical distension of the pregnant uterus (Ferguson reflex). It causes contraction of the myoepithelial cells around the breast ducts and contraction of the uterine myometrium in labour and expulsion of the placenta.

There is low affinity of oxytocin to the V_2 vasopressin receptor. Therefore, it is suggested that care is taken when oxytocin infusion is administered with large amounts of intravenous fluid because this could lead to hyponatraemia. ◆

The Immune System

Peter J Wood

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The mammalian immune system has evolved to provide protection against infectious agents (pathogens). Although the immune system may provide protection against tumours, the main evolutionary driving force has been the battle with pathogens.

Innate and specific immunity

The immune system has historically been divided into the innate and specific systems. The innate immune system includes:

- physical and chemical barriers to infection (e.g. skin, hydrochloric acid in the stomach)
- cells (e.g. macrophages, neutrophils, mast cells)
- soluble factors (e.g. the complement proteins, acute phase proteins).

The cellular components of the specific immune system are the lymphocytes. Lymphocyte precursors originate from the bone marrow and some differentiate in the thymus into T lymphocytes which are responsible for cellular immunity. Other lymphocyte precursors differentiate into B lymphocytes in the fetal liver and after birth in the bone marrow. B lymphocytes are responsible for humoral immunity. Most of the processing of lymphocytes occurs during fetal and neonatal life, but there is a slow continuous production of new lymphocytes from stem cells in adults. After differentiation, the lymphocytes migrate to the lymph nodes and other lymphoid tissue. The two main types of T cells are CD4 and CD8. Although morphologically indistinguishable the three types of lymphocyte perform different functions. One of the main features distinguishing specific from innate immunity is that specific immunity is not present before infection. Following initial infection with a pathogen it takes about 4 days to produce antibody against it.

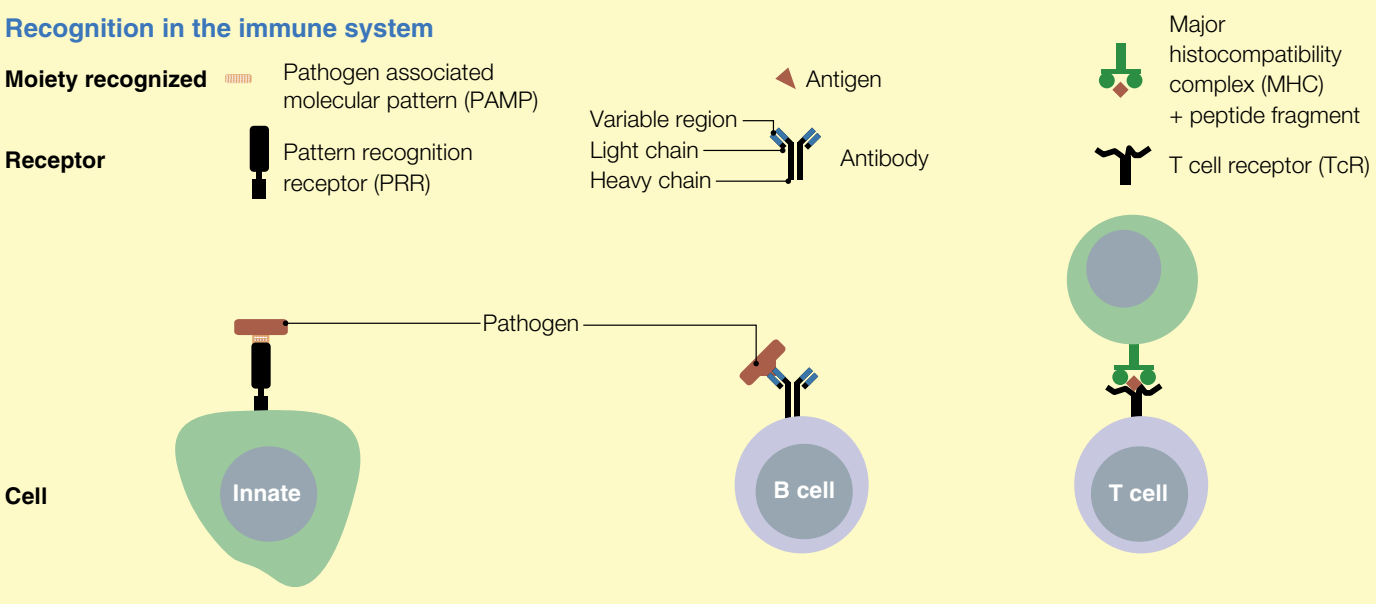
The innate immune system used to be regarded as a primitive defence system of limited effectiveness, found in vertebrates and invertebrates. The specific immune system is found in vertebrates only and was thought to be the main defence mechanism. It is now known that the innate immune system does more than provide the first line of defence and plays an important role in determining the type of specific immune response that is mounted against infectious agents.

Self/non-self discrimination

Both the innate and specific immune systems can distinguish between foreign entities (e.g. pathogens) and the body's cells and tissues. Recognition is achieved by molecules of the immune system that bind only to foreign molecules associated with pathogens and not to self-molecules.

Innate immune system: cells and proteins of the innate immune system can recognize certain molecules on the surface of path-ogens (pathogen-associated molecular patterns – PAMPs) as foreign. PAMPs are large molecules with a significant non-protein component and examples include lipopolysaccharides, peptido-glycans, lipotechoic acids and mannans. They are found only on microbes and are essential for microbial survival, therefore they cannot stop manufacturing them as a way of avoiding recognition by the innate immune system. The cell receptors that recognize PAMPs are called pattern-recognition receptors and include toll-like receptors and lectins such as the mannose receptor (Figure 1). Soluble factors recognizing PAMPs include mannose-binding lectin and C-reactive protein.

Recognition in the immune system



There is a limit to the number of receptors that can evolve to recognize foreign PAMPs and, given the quicker replication of pathogens compared with mammals, some pathogens will evolve ways of escaping recognition by the innate immune system. For example, avirulent streptococci are recognized and eliminated by the innate immune system and therefore do not cause disease. However, virulent streptococci synthesize a waxy carbohydrate outer coat that is not recognized by the innate immune system and therefore to eliminate them a specific immune response is required.

Specific immune system

B lymphocytes and antibody – B lymphocytes have antibody molecules on their cell surface. Antibody molecules consist of two identical heavy chains and two identical light chains forming a Y-shaped structure (Figure 1). Each heavy chain molecule consists of a variable (V) region at the N-terminal amino acid end and a constant region at the C-terminal end consisting of three domains. Light chains have a variable region and a constant region consisting of one domain. The variable regions of the heavy and light chain fold together to form a structure that is responsible for recognizing and binding to molecules on a microbial cell surface or soluble protein made by a microbe. The molecules to which antibody binds are called antigens. Special molecular mechanisms cause part of the gene coding for the V region of the antibody to be randomly altered. Therefore each antibody molecule has a different amino acid sequence in the part of the molecule that recognizes antigen and thus each antibody can bind to some antigens but not others. Enzyme digestion can split antibodies into an antigen-binding fragment (Fab) and a crystallizable fragment (Fc). There are a number of different classes of antibody (IgM, IgG, IgA, IgE, IgD). The class is determined by the Fc region of the heavy chain. There are also two types of light chain called κ and λ. Each class of heavy chain can associate with either κ or λ light chains. The class of heavy chain determines the function of the antibody, the light chain type has no effect on function.

T lymphocytes have receptors for antigen on their surface. Although related to antibody, the T cell receptor for antigen (TcR) is coded for by different genes. The TcR consists of two transmembrane glycoprotein chains (α and β), linked by disulphide bonds. The chains have a constant region proximal to the cell surface and a V region distal to the cell surface. Different V regions are generated on different T cells by the same molecular mechanisms used by B cells, therefore different T cells recognize different antigens.

The TcR does not recognize intact antigen (as antibody does) but recognizes fragments of peptides, 8–20 $\alpha\alpha$ in length derived from microbial proteins. The TcR does not recognize these peptide fragments in isolation but in association with self-molecules of the major histocompatibility complex (MHC) (Figure 2). The MHC is a complex of over 100 genes located on chromosome 6 in humans, where it is also called HLA. There are three classes of MHC.

- Class I MHC genes are called HLA-A, HLA-B and HLA-C. They code for similar proteins with the same function.
- Class II MHC includes three genes (HLA-DP, HLA-DQ, HLA-DR). They code for proteins with similar structure and function.
- Class III MHC genes code for a variety of products, most of which have immune function but which are not related to each other. Examples include the cytokine tumour necrosis factor-α (TNF-α) complement components C2 and C4 and heat shock proteins.

Antigen processing and the major histocompatibility complex (MHC)

The peptide fragments are generated from whole protein by antigen processing (see Figure 2). This involves proteolytic degradation of the whole protein. The two proteolytic pathways deal with extracellular and intracellular antigen in different ways. Extracellular antigen is taken up by endocytosis (phagocytosis, pinocytosis or receptor-mediated endocytosis) into an endocytic vesicle and is degraded by the lysosomal pathway. The antigen peptide fragments generated associate with class II MHC in special transport vesicles and the peptide/class II MHC complex is transported to the cell surface. Intracellular antigens, produced in the cytosol, are degraded in special proteolytic structures called proteosomes. The fragments generated are transported to the rough endoplasmic reticulum where they associate with class I MHC and are transported to the cell surface. CD4 T cells recognize antigen in association with class II MHC and CD8 T cells recognize antigen in association with class I MHC. ◆

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Immunological Response to Infection: Inflammatory and Adaptive Immune Responses

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When a microbe enters the body, it or its products encounter tissue macrophages. If the macrophage recognizes the pathogen it is activated to release a range of factors.

- Nitric oxide causes vasodilatation and has antimicrobial activity.
- Oxygen radicals have antimicrobial activity.
- Prostaglandins and leukotrienes are important inflammatory mediators that cause vasodilatation and increased vascular permeability, and are chemotactic for (attract) neutrophils and eosinophils.
- Platelet-activating factor causes platelet aggregation and is chemotactic for neutrophils and eosinophils.
- Cytokines are hormone-like molecules involved in immune responses. They are small proteins and act in an autocrine and paracrine manner but seldom in an endocrine fashion. Three of the most important cytokines secreted by macrophages in an inflammatory response are interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α).

Tissue damage and damage to the endothelium, which often accompany infection, result in activation of the clotting, kinin, fibrinolytic and complement systems. Activation of these systems leads to the generation of factors with many biological functions (Figure 1) including vasodilatation, increased vascular permeability and activation of mast cells. Activated mast cells degranulate, releasing the contents of their granules into the surrounding tissue. The granules contain histamine, heparin and degradative enzymes. Histamine is a powerful mediator of vasodilatation and increased vascular permeability. The net result is increased blood flow to the area and the recruitment of blood proteins and cells to the site. Cytokines released in the area increase the expression of adhesion molecules on the endothelium, and chemokines (chemotactic cytokines) attract neutrophils and monocytes to the site. The neutrophils and monocyte/macrophages attempt to phagocytose and kill the infectious microbes and monocyte/macrophages also remove dead cells and damaged tissue.

Systems activated during inflammatory responses

System	Component cleavage product	Function of component or
Clotting	Hageman factor	Activates clotting, fibrinolytic and kinin systems
	Fibrin	Forms clot
	Fibrinopeptides	Increase vascular permeability, neutrophil chemotaxis
Kinin	Bradykinin	Vasodilatation, smooth muscle contraction, pain
Fibrinolytic	Plasmin	Breaks down clots, activates complement system, activates Hageman factor
Complement	C1	Binds to antibody (C1q). Serine proteases (C1r,C1s)
	C4	Inflammatory mediator (C4a), binds C2
	C2	Serine protease (C2a)
	C3	Activates mast cells (C3a) Opsonin (C3b)
	C5a	Activates mast cells, chemotactic for neutrophils, monocytes, eosinophils and basophils
	C5–C9	Formation of pores in microbial cell walls causing cell lysis

Acute phase response

If the inflammatory response is large enough, cytokines produced by macrophages appear in the bloodstream in sufficient concentrations to affect other tissues and organs.

Brain – IL-1 acts on the hypothalamus to stimulate prostaglandin secretion which causes fever, somnolence and anorexia.

Bone marrow – IL-6 and TNF-α stimulate stromal cells and macrophages in the bone marrow to release factors that stimulate increased production of leukocytes.

Liver – IL-6 stimulates hepatocytes to produce increased amounts of acute phase proteins, which are secreted into the blood and travel to sites of inflammation. Plasma levels of some of these proteins increase 100–1000-fold:

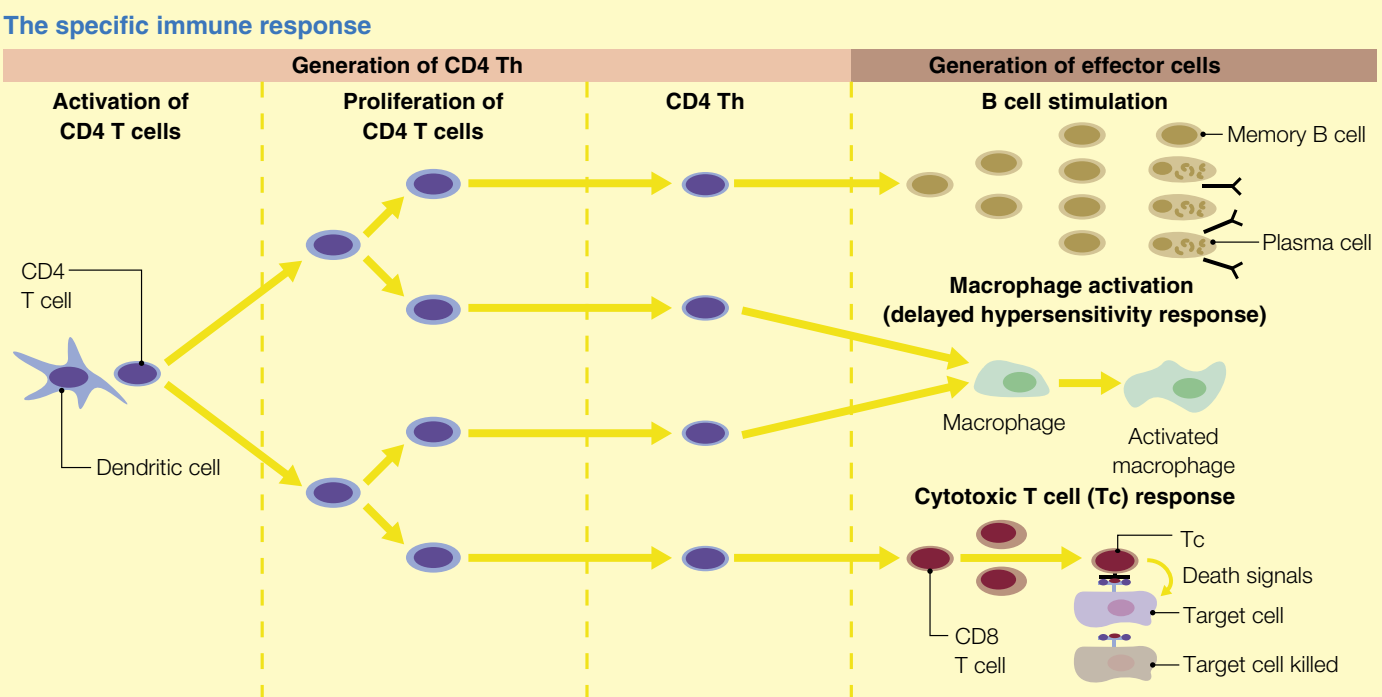
- serum amyloid A inhibits fever and platelet activation and provides a negative feedback loop
- C-reactive protein binds to phosphoryl choline present on bacteria and some fungi and can act as an opsonin in a similar fashion to antibody (see below). Plasma levels of other factors increase only 2–5-fold:
- fibrinogen is involved in clotting and some of its breakdown products (the fibrinopeptides) are chemotactic for (attract) phagocytes (Figure 1)
- complement protein C3 has a number of biological activities including activation of mast cells and promoting phagocytosis (Figure 1)
- mannose-binding lectin can bind mannose-containing molecules on the surface of microbes and activate complement.

Generation of the specific immune response

The local inflammatory and acute phase responses may be enough to resolve an infection. If not, the next response of the immune system is to generate a specific immune response, which can be divided into two stages (Figure 2):

- activation of CD4 T cells so that they divide and differentiate into helper T (Th) cells
- generation of effector cells and molecules that mediate the removal or neutralization of the pathogen (the generation of these cells is controlled by Th cells produced in the first stage of the response).

The specific immune response



Generation of Th cells

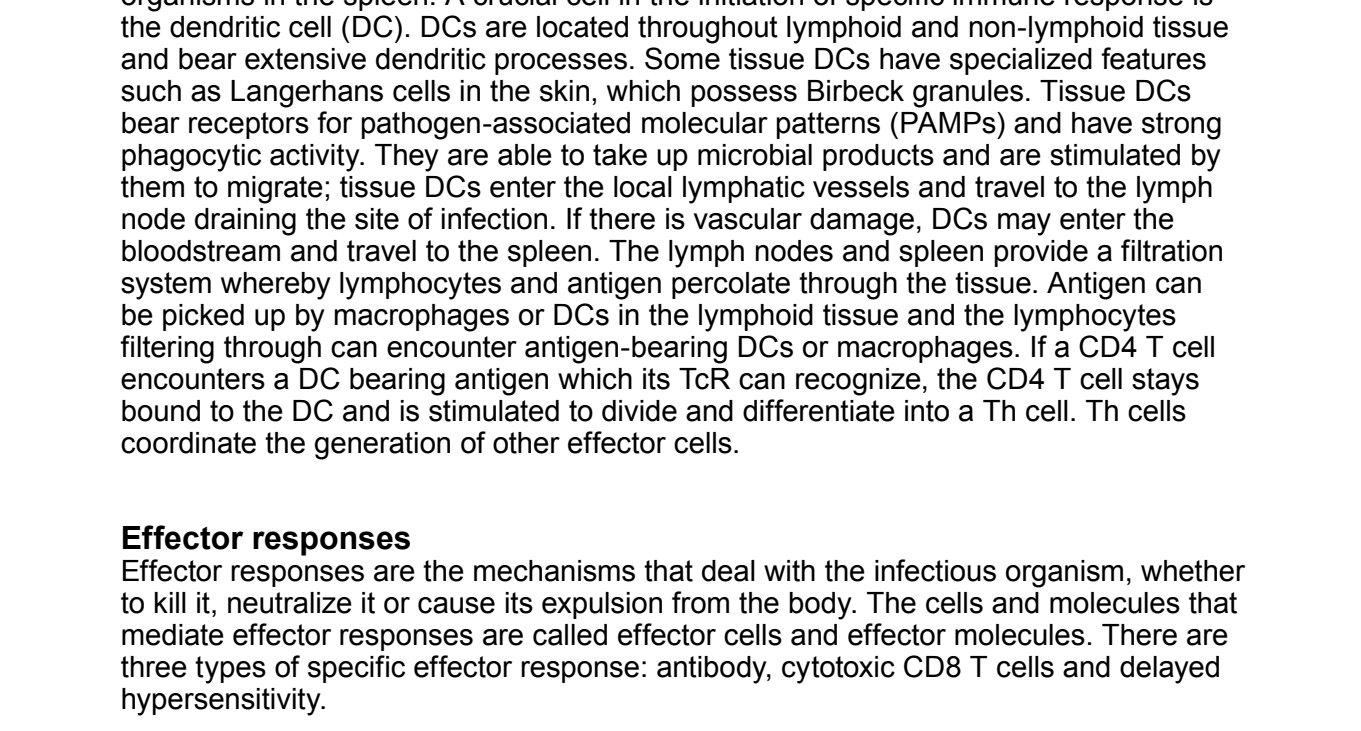
Specific immune responses occur in specialized lymphoid tissue. Responses against tissue pathogens generally occur in lymph nodes and responses against blood-borne organisms in the spleen. A crucial cell in the initiation of specific immune response is the dendritic cell (DC). DCs are located throughout lymphoid and non-lymphoid tissue and bear extensive dendritic processes. Some tissue DCs have specialized features such as Langerhans cells in the skin, which possess Birbeck granules. Tissue DCs bear receptors for pathogen-associated molecular patterns (PAMPs) and have strong phagocytic activity. They are able to take up microbial products and are stimulated by them to migrate; tissue DCs enter the local lymphatic vessels and travel to the lymph node draining the site of infection. If there is vascular damage, DCs may enter the bloodstream and travel to the spleen. The lymph nodes and spleen provide a filtration system whereby lymphocytes and antigen percolate through the tissue. Antigen can be picked up by macrophages or DCs in the lymphoid tissue and the lymphocytes filtering through can encounter antigen-bearing DCs or macrophages. If a CD4 T cell encounters a DC bearing antigen which its TcR can recognize, the CD4 T cell stays bound to the DC and is stimulated to divide and differentiate into a Th cell. Th cells coordinate the generation of other effector cells.

Effector responses

Effector responses are the mechanisms that deal with the infectious organism, whether to kill it, neutralize it or cause its expulsion from the body. The cells and molecules that mediate effector responses are called effector cells and effector molecules. There are three types of specific effector response: antibody, cytotoxic CD8 T cells and delayed hypersensitivity.

Antibody response: B cells that encounter antigen for which their surface Ig is specific are guided by chemokines to the region of the lymph nodes or spleen where CD4 T cell–DC interactions take place. This brings into proximity the B cells and Th cells. B cells express class II major histocompatibility complex (MHC)/antigen on their surface and if the Th cell is specific for the class II MHC/antigen it will be stimulated to produce cytokines which will cause proliferation and differentiation of the B cell. Interaction of CD40 on the B cell surface with CD154 on the Th cell surface is also required for all but IgM production. The proliferating B cells and some of the Th cells form a structure called a germinal centre in the lymph node or spleen. In germinal centres, B cells divide rapidly and undergo class switch and somatic mutation in their Ig genes. Class switch means that instead of expressing IgM and IgD on their cell surface, B cells express IgG, IgA or IgE. This is due to a change in the constant region of the H-chain but it is important to appreciate that the V region, and hence antigen specificity, of the B cell does not change during class switch. Somatic mutation within the Ig genes is a mechanism that results in the production of antibody with much higher affinity (stronger binding) for the antigen. High affinity antibody is more efficient at carrying out the biological activities of antibody listed below. The final step in the B cell response to antigen is differentiation into plasma cells or memory B cells (Figure 2). Plasma cells secrete large amounts of antibody. Memory B cells, because they have already undergone class switch and somatic mutation, provide increased numbers of high affinity B cells. They are long lived and ensure that if the same pathogen is encountered again there is a faster, bigger and better antibody response. Antibody is able to provide protection in a number of ways (Figure 3).

Antibody effector mechanisms



Opsonization – phagocytes have receptors for the Fc part of the antibody molecule. Antibody bound to a microbe can be bound to the phagocyte, promoting uptake and phagocytosis.

Neutralization – by binding to toxins, viruses or bacteria, antibody can prevent them binding to cellular receptors thereby preventing entry into cells.

Activation of complement – the complement system is a cascade of proteins that have a number of biological functions (Figure 1). Antibody binding to antigen undergoes a conformational change that enables the Fc part of the antibody to bind the first component of complement C1, leading to activation of later components. Complement can also be activated in an antibody-independent fashion by the acute phase protein, mannose-binding lectin, and by certain microbial products (e.g. zymosan in yeast cell walls).

Antibody-dependent cell-mediated cytotoxicty (ADCC) – macrophages and natural killer (NK) cells (a type of lympho-cyte) have receptors for the Fc part of the antibody. Antibody bound to an organism can be bound by the macrophage or by the NK cell, which triggers the cell to kill the organism in an extracellular manner. Macrophages and NK cells can kill infected host cells and tumour cells by ADCC. There is evidence that eosinophils can kill helminth worms *in vitro* in the same way.

Generation of CD8 cytotoxic T cells: Th cells also help in the generation of CD8 cytotoxic T cells (Tc), which are capable of killing other cells expressing antigen on class I MHC (Figure 2). In the lymph node or spleen, DCs expressing antigen on their class II MHC to CD4 T cells can also express antigen derived from the same pathogen on their class I MHC. If a CD8 T cell, percolating through the lymph node or spleen, has a TcR specific for the antigen plus class I MHC it will bind to it and receive a signal for activation. The cytokine, IL-2, secreted by the CD4 T cell stimulates the CD8 T cell to divide and differentiate into a Tc. The Tcs migrate through the body and if they encounter any cell type expressing the same antigen on its class I MHC they kill the cell.

Delayed hypersensitivity (DTH) responses: initially considered a pathological response, DTH is now recognized as an important protective response against some intracellular pathogens, especially those that can live in macrophages. Usually DTH responses are generated in response to tissue-dwelling pathogens. Th cells generated in the lymph node draining the site of infection re-enter the bloodstream and travel to the site of infection where they leave the bloodstream and enter the tissue. Infected macrophages, present at the site of infection, can present antigen on class II MHC on their cell surface and this stimulates the Th cells to release cytokines. Among these cytokines, TNF-α increases the expression of adhesion molecules on the local endothelium thereby aiding the recruitment of monocytes from the blood. The monocytes and tissue macrophages are activated by other cytokines, particularly interferon-γ and TNF-α to differentiate into activated macrophages which are better able to kill the pathogens (Figure 2). However, extensive activation of macrophages can also lead to tissue damage and hence the original description of the response as a hypersensitivity reaction. Much of the damage caused in chronic infections (e.g. tuberculosis, leprosy) is due to DTH reactions. ◆

Immunology of Transplantation

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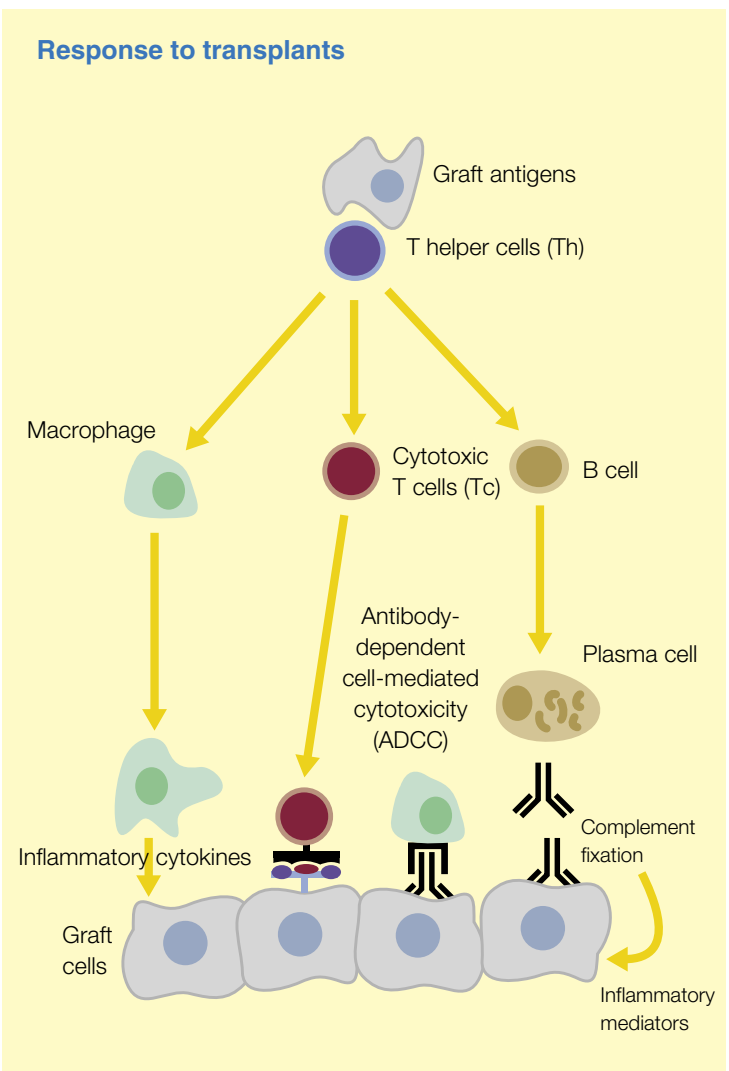
The immune response to transplants is fundamentally no different from that previously described for pathogens elsewhere. The main difference is in the nature of the antigens. Cells of a transplant bear both class I and class II major histocompatibility complex (MHC) molecules on their surface. Because of the enormous variation of class I and class II genes between individuals, unless the transplant is from a relation, it almost certainly bears variants of class I and class II molecules that are not possessed by the transplant recipient. For reasons that are not fully understood, foreign MHC molecules stimulate a much higher number (10–100-fold) of T cells than foreign antigen presented by self-MHC and therefore the immune response against foreign MHC transplantation antigens is much stronger than that seen against pathogens. In addition to foreign MHC molecules (major transplantation antigens), transplants have many proteins that are a variant of the recipient's equivalent proteins. These are called minor transplantation antigens and, though they do not stimulate as strong an immune response as foreign MHC, they can stimulate rejection of the transplant, unless the response against them is suppressed.

Transplants stimulate the same type of effector responses as pathogens (see page 130). In non-immunosuppressed patients antibody is produced particularly against class I MHC, but also against class II MHC and other unidentified antigens on the graft. CD4 T cells respond to foreign class II MHC on the graft and also to minor histocompatibility antigen presented by self class II MHC, and develop into helper T (Th) cells. Similarly CD8 T cells respond to foreign class I MHC and develop into cytotoxic T cells (Tcs).

Therefore, damage to the graft can be brought about by antibody-mediated damage, CD8 Tc killing of graft cells and Th-mediated induction of delayed hypersensitivity (DTH) responses (Figure 1). Histologically, graft rejection resembles DTH most closely, but it is likely that without immunosuppression all three types of effector response will be brought against the graft.



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Types of graft rejection

Hyperacute rejection occurs within minutes or hours of a vascularized graft and is caused by pre-existing antibodies against the graft which bind to the transplant, activating the complement and clotting pathways, leading to massive clotting throughout the graft. It is prevented by matching blood types and testing the recipient for pre-existing antibodies against the graft (cross-matching).

Acute rejection is the result of the generation of an immune response against the graft as described above. It is treated with immunosuppressive drugs. Without immunosuppression, acute rejection occurs 1–2 weeks after transplantation.

Chronic rejection is a major cause of later graft loss and is seen as slow deterioration of graft function, usually beginning years after transplantation. Although it differs from organ to organ, one of the main features is arterial intimal thickening due to myofibroblast migration and proliferation. This results in progressive narrowing of the arterial lumen, which eventually becomes occluded, leading to tissue anoxia. Current immunosuppressive drugs do not prevent chronic rejection. ◆

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Inflammatory Response: Vascular Endothelium

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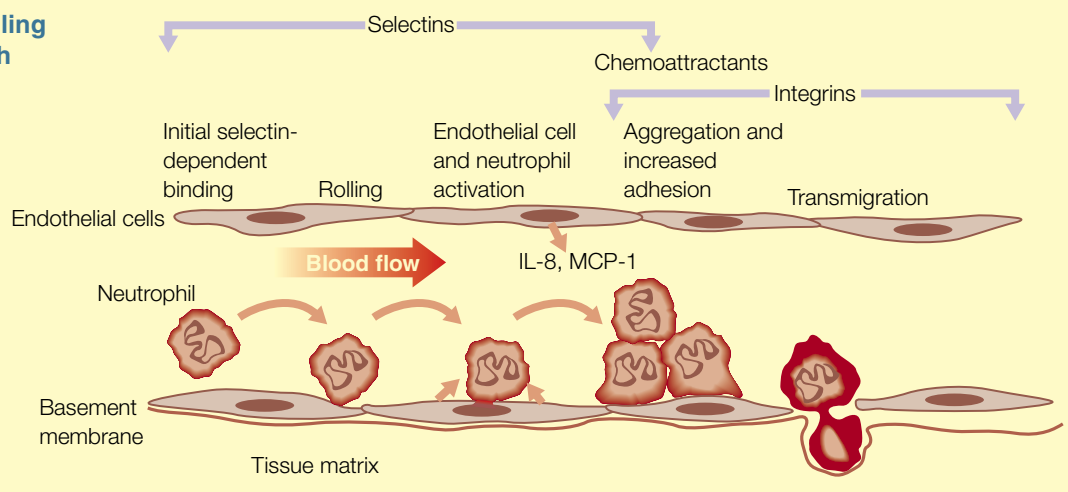
The vascular endothelium forms a barrier between the blood-borne leucocytes, which play a key role in the inflammatory response, and the underlying tissue. Current ideas suggest that the endothelium orchestrates the inflammatory process, directing the leucocytes to the site of tissue damage or infection to produce a localized response while preventing the spread of the inflammation. As part of this response, the endothelium at the site of inflammation becomes damaged, with both the leucocytes and the endothelial cells providing essential ingredients for this damage. Provided this process remains localized it is beneficial because it plays a part in removing infected or devitalized tissue and leads to healing. However, if the process becomes unregulated and widespread it leads to whole-body inflammation, coagulopathy and organ dysfunction associated with the systemic inflammatory response syndrome (SIRS) and eventually multi-organ failure and death. This contribution discusses the localized process, the potential for spreading of the response and the consequent problem with vascular control and oxygen delivery to cells.

Endothelium–leucocyte interaction

Movement of leucocytes from the blood stream into the damaged and/or infected tissue is an essential part of the inflammatory process. It takes place mainly across the wall of the post-capillary venules, though in some areas, such as the lungs, the process can also occur in the capillaries. The entire process is depicted in Figure 1 and involves complex interactions between the endothelium and the leucocytes. There is a carefully timed sequence of molecular expression and regulation leading to the key steps of leucocyte margination (attraction to the endothelium), rolling (along the endothelium) and finally transmigration (penetration) between the endothelial cells into the tissue.

Leucocyte margination, rolling and transmigration through the endothelium



IL-8, interleukin-8; MCP-1, monocyte chemotactic protein-1

Adapted from: Lentsh A B, Ward P A. Regulation of Inflammatory Vascular Damage. *J Pathol* 2000; **190:** 343–8.

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Leucocyte margination and rolling

An essential first step for leucocyte margination and rolling is the appearance of a group of glycoproteins known as selectins on the surface of both the endothelial cells and the leucocytes. Of particular importance are three selectins: P- and E-selectins on the endothelium and L-selectin on neutrophils. The appearance of the selectins on the cell surfaces, in turn, can be triggered by a variety of pro-inflammatory mediators.

In some organs, such as the lungs, a number of injurious stimuli can result in the activation of resident macrophages to produce pro-inflammatory mediators such as tumour necrosis factor (TNFα) and interleukin-1 (IL-1). These mediators, as well as histamine, thrombin-activated complement, leukotrienes and oxygen radicals, cause the endothelial cells to re-distribute P-selectin, normally stored in Wiebel–Palade bodies within the cell, to the cell surface. Expression of P-selectin in this way is normally maximal within 20 minutes of stimulation and declines after 1 hour. By contrast, expression of E-selectin requires *de novo* synthesis and E-selectin is not seen at the cell surface until 2 hours after stimulation. A complementary ligand (binding molecule) for P-selectin, P-selectin glycoprotein ligand 1 (PSGL-1), is found on the surface of neutrophils (and other cells such as monocytes, natural killer cells and memory T lymphocytes). L-selectin on the leucocytes is thought to act as a ligand for both P- and E-selectins.

As a consequence of the interaction between endothelial cell P- and E-selectins with leucocyte PSGL-1 and L-selectin there is a series of intermittent low-affinity binding between the leucocytes and the endothelium leading to leucocyte margination to the endothelium and subsequent rolling along the endothelium. Concurrent with this series of pro-inflammatory events, the host activates a series of anti-inflammatory processes that limit margination and rolling. These include secretion of endocrine substances (e.g. glucocorticoids, IL-10) and paracrine/autocrine substances (e.g. adenosine, nitric oxide (NO), prostacyclin (PGI_2), lipocortin-1).

At this point, the balance of the pro- and anti-inflammatory mechanisms decides whether the inflammatory process proceeds to the next step of transmigration (penetration) or is stopped by detachment of the leucocytes from the endothelium.

Leucocyte activation and transmigration

Assuming that the inflammatory response proceeds, the next step is transmigration. The first step involves an interaction between a further group of endothelial and leucocyte surface molecules to produce high-affinity binding and an arrest of the rolling behaviour. The molecules on the endothelial cells belong to the immunoglobulin supergene family and include intercellular adhesion molecules 1 and 2 (ICAM-1 and ICAM-2), vascular cell adhesion molecule 1 (VCAM-1) and platelet-endothelial cell adhesion molecule 1 (PECAM-1). The best studied of these is ICAM-1, the expression of which is up-regulated by TNFα and IL-1 within 6–9 hours of the stimulus. ICAM-1, in turn, becomes bound to members of the β_2-integrin family of adhesion molecules on the leucocytes, examples of which are leucocyte function associated antigen 1 (LFA-1 or CD11a/CD18) found on all leucocytes, and macrophage-1 antigen (Mac-1 or CD11b/CD18) found particularly on monocytes and neutrophils.

Endothelial cells that have been activated to express ICAM-1 also express chemokines such as IL-8, which leads to activation of the adherent leucocytes. The endothelial cells retract resulting in gaps between the cells, which increase vascular permeability and lead to local oedema. Facilitated by the gaps between the endothelial cells the leucocytes transmigrate out of the blood vessel into the tissue. This process is aided by PECAM-1, which is found along the intercellular junctions of the endothelial cells and is under the control of chemotactic factors such as IL-8 and complement C5a.

The entire process leads to damage of the endothelial cells, with both the activated neutrophils and the endothelial cells playing a role as described in the next section.

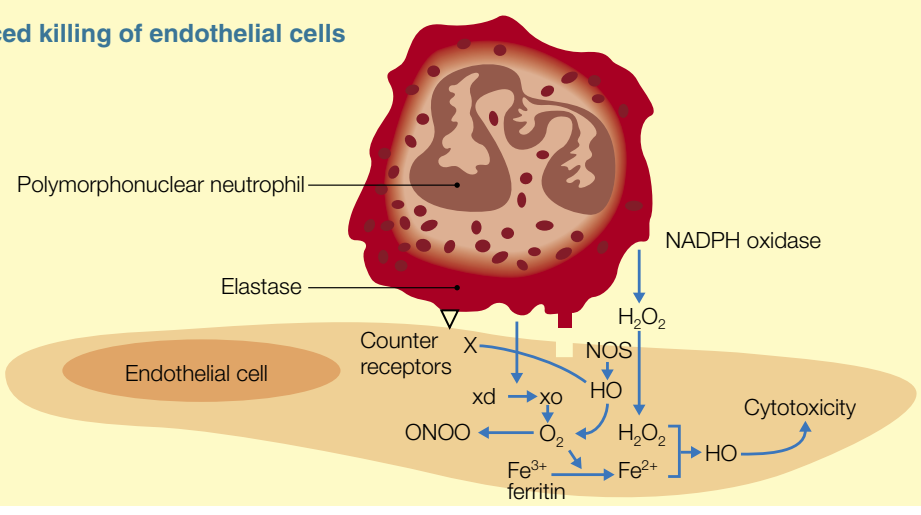
Endothelial cell damage

Evidence suggests that the endothelial cells are damaged by the pro-inflammatory cytokines (e.g. TNFα, IL-1), which serve as triggers for the endothelial–leucocyte interaction, as well as by the activated neutrophils. The cytokines are thought to induce apoptosis (programmed cell death) in the endothelial cells.

The interaction between the activated neutrophils and the endothelial cells is better understood. The mechanism underlying the killing of endothelial cells by activated adherent neutrophils is summarized in Figure 2. The neutrophil secretes an enzyme, elastase, which enters the endothelial cell to convert an intracellular enzyme xanthine dehydrogenase (XD) to xanthine oxidase (XO). XO in turn acts on xanthine (a breakdown product of adenosine triphosphate, ATP) to form the superoxide O_2* which in turn reduces bound Fe^{3+} to Fe^{2+}. Fe^{2+} then reacts with hydrogen peroxide (produced by the neutrophils) to yield the highly cytotoxic oxygen free radical HO* within the endothelial cell, causing damage and death.

Neutrophil-induced endothelial cytotoxicity is limited by nitric oxide (NO*). This is formed in the endothelial cell by nitric oxide synthase (NOS) from L-arginine. The protective effect of NO* is twofold. Firstly, it reduces the adhesion between the endothelial cell and the neutrophil. Secondly, NO* scavenges O_2*, forming the peroxynitric anion ONOO*, thus attenuating the formation of Fe^{2+} which is needed to form the cytotoxic oxygen free radical. Endothelial cells from different tissues have different abilities to form NO* and hence different vulnerabilities to injury by oxidants and neutrophil-mediated killing.

Mechanism of neutrophil-induced killing of endothelial cells



NADPH, nicotinamide adenine dinucleotide phosphate; NOS, nitric oxide synthase; xd, xanthine dehydrogenase; xo, xanthine oxidase.

Adapted from: Lentsh A B, Ward P A. Regulation of Inflammatory Vascular Damage. *J Pathol* 2000; **190:** 343–8.

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Natural mechanisms limiting inflammation

Although the inflammatory response is destructive locally, it is beneficial to the whole organism because it is the first step towards healing, provided it is localized and prevented from causing secondary damage elsewhere. It is therefore not surprising that there are several powerful mechanisms that down-regulate the pro-inflammatory mechanisms. Among the most studied mediators are the cytokines IL-10 and IL-13 and secretory leucocyte protease inhibitor (SLPI).

IL-10 and IL-13, in the lung, have been shown to act on alveolar macrophages to reduce the secretion of TNFα and IL-1. SLPI acts on the vascular endothelium to reduce the expression of ICAM-1 and hence reduce neutrophil adhesion. This effect is thought to be mediated by a modulation of the signal transduction mechanism in the endothelial cell, which leads to the activation of NFκB (a transcription factor involved in the production of adhesion molecules). By preventing the activation of NFκB there is a reduced expression of ICAM-1. This effect of SLPI appears to be part of a physiological mechanism limiting inflammation, because blockade of SPLI leads to an enhancement of lung vascular damage (increased permeability) during an inflammatory response.

Widespread inflammation and SIRS

Despite the mechanisms limiting inflammation there are circumstances when the inflammatory response becomes widespread. The precise mechanism is unclear and is likely to be multi-factorial. Some studies have suggested that the endothelium plays a role in this widespread response, with aberrant adhesion molecule expression causing pathological interaction between endothelium and leucocytes. The resulting endothelial damage causes widespread tissue damage and oedema, limiting oxygen delivery to the cells and an exacerbation of the problem. A confounding factor in these cases is disseminated intravascular coagulation (DIC), which again involves the endothelium.

Disseminated intravascular coagulation

Post-mortem findings from victims of SIRS indicate widespread fibrin microthrombi even in vessels with intact endothelium. This has led to the suggestion that the endothelial anti-coagulant mechanisms have become disrupted. Under normal circumstances, the endothelium possesses three anticoagulant mechanisms.

- Cell surface expression of thrombomodulin providing a negative feedback mechanism for thrombin generation, and activated protein C-induced degeneration of an inhibitor of plasminogen activator, thus promoting plasmin formation and hence fibrinolysis.
- Heparin sulphate, which is associated with the endothelial cell surface.
- Secretion of prostacyclin (PGI_2) and adenosine, which inhibits platelet aggregation.

A disturbance of these mechanisms leads to the anticoagulant role of the endothelium being attenuated and reduced fibrino-lysis. Concurrently, the pro-inflammatory cytokines induce the synthesis and surface expression of tissue factor, which in turn causes the endothelium to initiate the extrinsic coagulation cascade giving widespread, unopposed, pro-coagulant activity. The resulting impairment of microvascular flow causes further reduction in tissue oxygenation and hence additional tissue damage.

Impairment of local vasomotor control

The vascular endothelium plays an important physiological role in regulating arteriolar vascular resistance and hence microcirculatory haemodynamics. A detailed description of this role is beyond the scope of this review, however, there are a number of excellent accounts of this topic (see Further Reading). Briefly, the endothelium secretes a number of vasoactive agents, some of which are vasodilator (e.g. NO) and some of which are vasoconstrictor (e.g. endothelin).

NO is among the most thoroughly studied of these mediators. It has been implicated in vascular regulation and dysregulation during sepsis (the systemic inflammatory response to infection). With regard to normal vascular regulation there is a basal synthesis and release of NO by endothelial cells. The NO then diffuses to the underlying smooth muscle cells where it activates guanylate cyclase leading to an elevation of guanosine 3',5'-cyclic monophosphate (cGMP), triggering a series of intracellular events culminating in falls in free calcium levels and hence muscle relaxation. Thus, in arterioles, NO causes vasodilatation and a fall in vascular resistance.

The physiological release of NO by endothelial cells is modulated by a number of chemical (e.g. acetylcholine, 5-HT, thrombin) and mechanical (e.g. shear stress) influences on the endothelium, serving to 'fine tune' local vascular resistance and hence blood flow. In sepsis it has been argued that there is an overproduction of NO and hence widespread vasodilatation.

NO is produced from L-arginine by the action of the enzyme nitric oxide synthase (NOS). There are three isoforms of NOS:

- eNOS found in the endothelium
- nNOS in neurons
- iNOS, an inducible form found in a number of locations (e.g. macrophages, smooth muscle, endothelium).

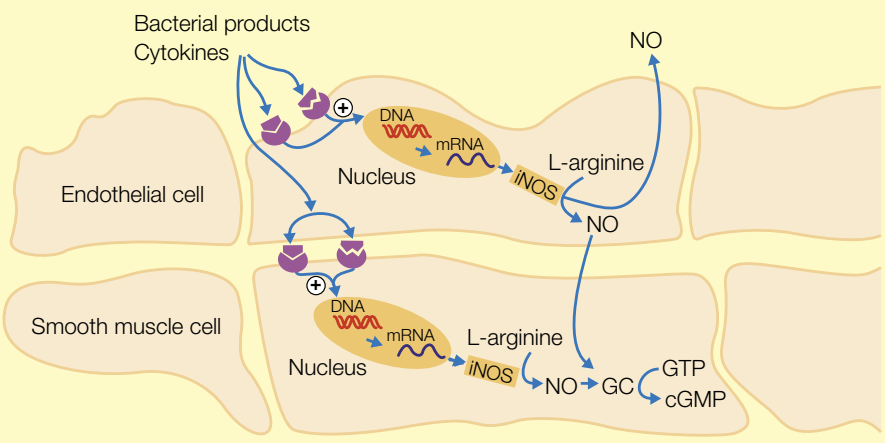
eNOS and nNOS are constitutive enzymes and are sometimes grouped under the title cNOS. In contrast, the expression of iNOS is induced by several stimuli such as those associated with inflammation and sepsis (Figure 3).

Expression of iNOS

Nitric oxide–cGMP pathway producing vascular smooth muscle relaxation

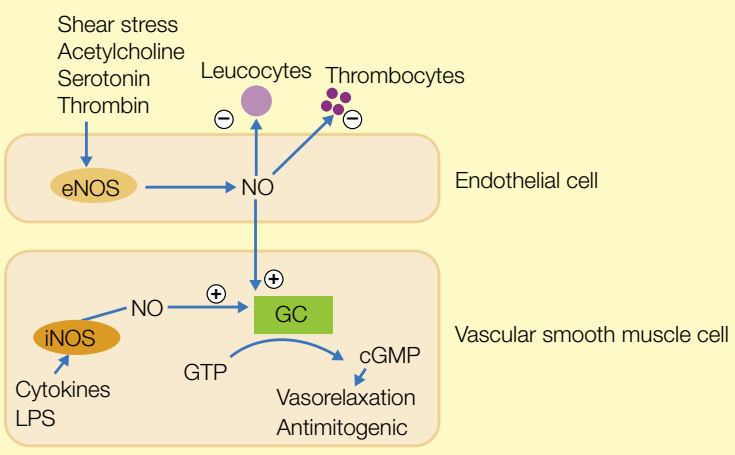
iNOS is not usually present under normal physiological conditions but is induced during inflammation and sepsis

cGMP, cyclic guanosine monophosphate; GC, guanylate cyclase; GTP, guanosine triphosphate; LPS, lipopolysaccharides (endotoxin); NOS, nitric oxide synthase.



Induction and activation of iNOS during sepsis

cGMP, cyclic guanosine monophosphate; GC, guanylate cyclase; GTP, guanosine triphosphate; LPS, lipopolysaccharides (endotoxin); NOS, nitric oxide synthase.



Adapted from: Kirkeboen K A, Strand O A. The Role of Nitric Oxide in Sepsis – An Overview. *Acta Anaesthesiol Scand* 1999; **43:** 275–88.

There are several important differences between cNOS and iNOS, perhaps the most important of which is that cNOS generally produces small amounts of NO and the rate of secretion is rapidly controlled. By contrast, iNOS produces much greater amounts of NO, and its activation is sustained sometimes for several days. During widespread inflammation and sepsis it is argued that the pro-inflammatory cytokines (e.g. TNFα, IL-1) as well as bacterial components such as endotoxin lead to the induction of iNOS over a period of several hours, thereby causing excessive production of NO. This may produce extensive vasodilatation, a fall in total peripheral resistance and hypotension. Additionally, widespread vasodilatation is likely to be detrimental for matching regional oxygen delivery to demand because it may lead to a 'stealing' of blood flow from areas which most need it to those that do not.

The role and potential therapeutic treatment of NO over-production in human sepsis is currently a 'hot topic'. The balance of evidence suggests that there is overproduction of NO, though this is not universally accepted. The therapeutic potential is more contentious. A large number of animal and a small number of human studies have investigated the effects of NOS inhibition using analogues of L-arginine (e.g. L-NAME, L-NMMA) which affect both cNOS and iNOS, and more selective inhibitors of iNOS. These studies have produced mixed results ranging from benefit to no effect and even increased mortality. Perhaps this is not surprising given the complexity of the system in which NO is widespread and subserves many functions.

Current issues include the relative importance of NO during sepsis in different species, type of inhibitory agent and dose used and whether they are given as a series of boluses or a continuous infusion.

One final area of concern is that some studies have indicated that inhibition of cNOS by L-NAME in healthy volunteers had differential effects on vascular resistance in various organs possibly involving vasoconstriction in the splanchnic and renal circulations but not in skeletal muscle or skin. If this finding was also true in sepsis then any increase in total peripheral resistance (and hence blood pressure) would result in a redirection of blood flow from vital organs with a greater need for oxygen towards skeletal muscle and skin where the need for oxygen might be less. The end result is a potential hypoperfusion of gut and kidney and resulting organ damage. This potential problem emphasizes the danger of becoming fixated on attempts to improve arterial blood pressure when the main concern should be ensuring adequate regional blood flow and oxygen delivery to meet tissue demand.

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Intermediary Metabolism

Iain Campbell

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Energy is obtained from the oxidation of the macronutrients carbohydrate, fat and protein. The structure of these macro-nutrients and the whole body quantification of their metabolism are described on page 115. The end-products of fat and carbohydrate metabolism are carbon dioxide and water only. The end-products of protein metabolism are carbon dioxide, water and a number of nitrogen-containing compounds excreted in the urine, mainly urea, but also creatinine, uric acid and ammonia. About 80% of urinary nitrogen is normally present as urea.

Energy release

Energy released by oxidation is not used directly by the cells but goes into the formation of bonds between phosphoric acid residues and certain organic compounds and is thus 'stored' as discrete packets. When these bonds are hydrolysed the energy is released for use in muscle contraction, membrane transport or protein synthesis.

'Oxidation' involves the loss of electrons, but organic molecules do not give up electrons easily and oxidation of a complex molecule such as glucose normally involves the loss of an entire atom, usually hydrogen. The oxidation (dehydrogenation) of a compound such as glucose results in the production of the low-energy compound carbon dioxide and the acceptance of electrons (hydrogen atoms), ultimately by oxygen, to produce water. As hydrogen ions are released in the intermediate parts of the oxidation process they are taken up transiently by co-enzymes, most commonly flavine adenine dinucleotide (FAD, derived from vitamin B2) to form FADH2 and nicotinamide adenine dinucleotide (NAD, derived from nicotinamide also a B group vitamin) to form NADH. ATP is synthesized from a series of electron transport proteins situated on the inner wall of the mitochondrion, the flavoprotein-cytochrome (respiratory) chain. The electrons (hydrogen atoms) enter this enzyme chain via FADH2 and NADH. They are passed down the respiratory chain, from one enzyme to the next, each enzyme having a greater affinity for electrons than the previous one. Free energy is released and is used to drive hydrogen ions (protons) across the inner mitochondrial membrane into the intermembrane space to create an electrochemical gradient across the inner membrane. The protons then pass back down this gradient into the mitochondrion, driving a reversible ATPase in the membrane. It is this ATPase that synthesizes ATP from ADP and inorganic phosphate.

Other high-energy phosphate compounds are also used as immediate sources of energy; they include creatine phosphate, large quantities of which are found in muscle, as well as other purines and pyrimidines (e.g. guanosine triphosphate, cytidine triphosphate, inosine triphosphate). 90% of whole body oxygen consumption in the basal state is mitochondrial and 80% of it is coupled to ATP synthesis. About 30% of ATP is used for protein synthesis, 25% by Na/K ATPase in cell membranes, 10% for gluconeogenesis and 3% for ureagenesis. ATP is also the precursor for cyclic AMP

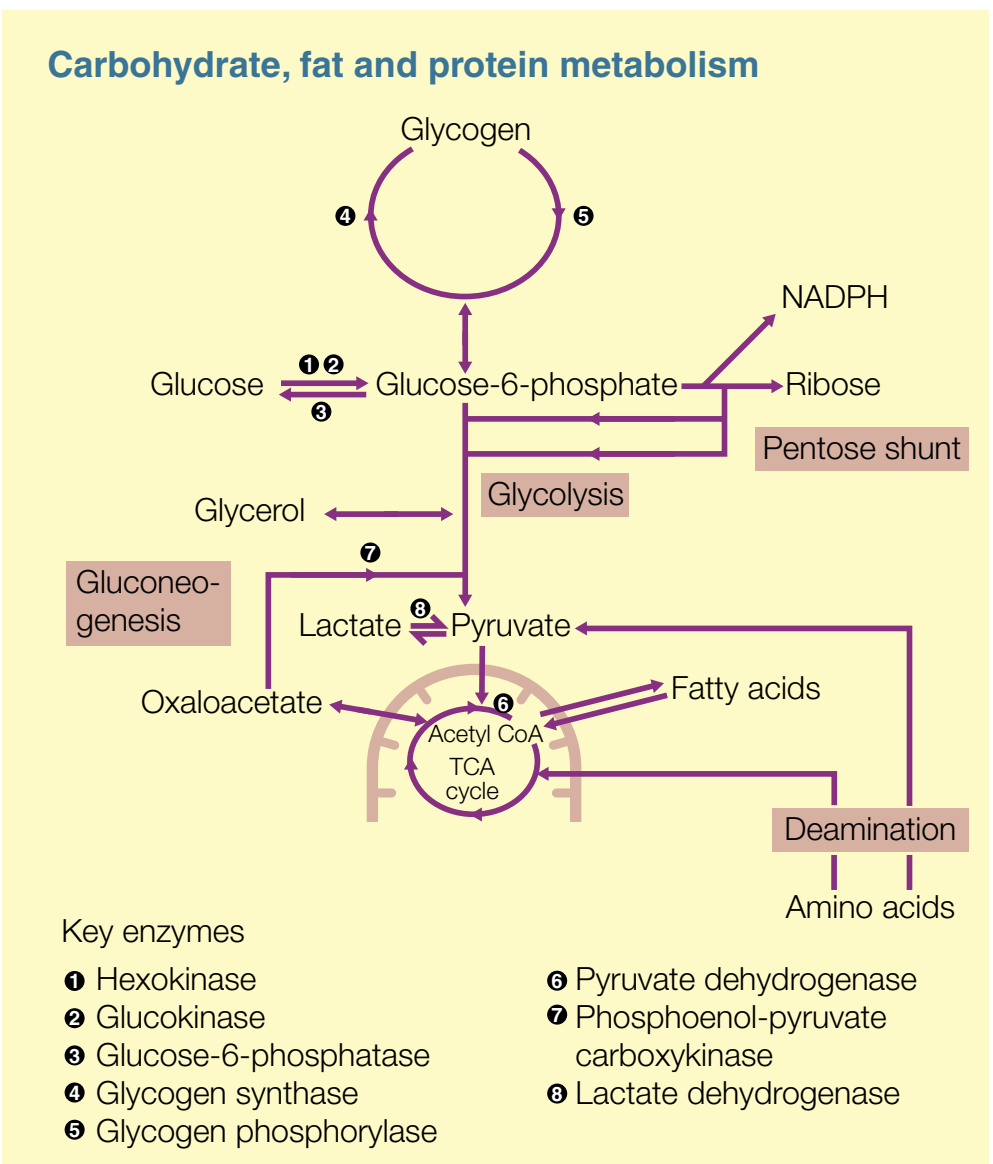
Carbohydrate, fat and protein metabolism

Carbohydrate is the immediate most usable form of energy, fat is the body's main energy store and protein constitutes the structure of the body.

Carbohydrate metabolism

The principal carbohydrate is glucose, but other monosaccharides include fructose and galactose. Glucose is absorbed from the gastrointestinal tract via the portal vein. It passes to the liver where in times of excess, such as after a large meal, some is synthesized into glycogen. The rest passes into the general circulation where it is metabolized in the tissues, or may be stored as glycogen, particularly in muscle. In starvation, most tissues, including muscle (both skeletal and cardiac), can obtain their energy needs from fatty acids alone, but some, such as the CNS and RBCs are obligatory users of glucose.

Glucose is oxidized via two sequential metabolic pathways – the Embden–Meyerhof or glycolytic pathway, which occurs in the cytoplasm, and the Krebs' or tricarboxylic acid (TCA) cycle, which takes place in the mitochondria (Figure 1).



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Glycolysis is the first stage of glucose breakdown; it is a six-stage metabolic pathway in which metabolism of one molecule of glucose results in the production of two molecules of pyruvate, which enter the TCA cycle. Absorbed glucose is phosphorylated in the tissues by hexokinase (and in the liver by glucokinase) to glucose-6-phosphate (G6P), which is then either converted to glucose-1-phosphate prior to glycogen synthesis or enters the glycolytic pathway. During the course of glycolysis the 6-carbon molecule is split into two 3-carbon fragments – glyceraldehyde-3-phosphate and dihydroxyacetone. Dihdroxyacetone phosphate undergoes isomerization to glyceraldehyde-3-phosphate and it is this 3-carbon molecule that eventually forms pyruvate, but dihydroxyacetone can also be converted to glycerol and thus provides a link with fat metabolism, though, in terms of energy flux, this pathway is minor.

Most of the reactions in glycolysis are reversible, but some are not and these irreversible reactions direct the flow of metabolites through the system. Reversal of these steps in the pathway requires different enzymes.

- The conversion of glucose to G6P by hexokinase (or glucokinase). This is reversed by glucose-6-phosphatase.
- The conversion of fructose-6-phosphate to fructose 1:6 diphosphate in the middle of the glycolytic pathway by phosphofructokinase. This is reversed by fructose 1:6 di-phosphatase.
- The conversion of pyruvate (3 carbons) to acetyl CoA (2 carbons; 1 molecule of carbon dioxide is released) by pyruvate dehydrogenase for entry into the TCA cycle. This step cannot be reversed.

Four molecules of ATP are produced in glycolysis, but two are used in the process so the net gain in glycolysis is two molecules of ATP. 36 molecules are eventually synthesized from the complete oxidation of a molecule of glucose via the glycolytic pathway and the TCA cycle so these two represent about 5% of the total amount of energy ultimately available.

Pentose monophosphate shunt is an alternative pathway for glucose metabolism. This starts with G6P and its main function is to supply pentose sugars, essential in the synthesis of nucleotides and nucleic acids, as well as reduced nicotinamide-adenine dinucleotide phosphate (NADPH), a phosphorylated form of NADH used in a number of biosynthetic pathways. Excess ribose-5-phosphate not required for nucleotide synthesis returns to the glycolytic pathway as fructose-6-phosphate and phosphoglyceraldehyde. The pentose shunt does not use ATP or oxygen. Whether glucose is metabolized via this route or via the glycolytic pathway appears to depend on whether the cell is engaged in biosynthesis (e.g. fatty acid synthesis).

TCA cycle is a sequence of reactions that result in the production of most of the ATP derived from both fat and carbohydrate oxidation. The reactions occur within the matrix of the mitochondrion. With carbohydrates, pyruvate is transported across the inner mitochondrial membrane and is then oxidatively decarboxylated to acetyl CoA. This reacts with the 4-carbon acid oxaloacetate to produce the 6-carbon tricarboxylic acid citrate. In a subsequent series of seven reactions, oxaloacetate is regenerated and two carbon dioxide molecules are produced. A number of other intermediate compounds are generated (oxoglutarate, malate, fumarate) but the oxidation of the acetyl groups to carbon dioxide is coupled to the reduction of NAD and FAD to NADH and FADH2 which enter the flavoprotein-cytochrome chain in the mitochondrion to produce ATP.

Entry of glucose into the cells is via a number of specialist receptors. Some such as GLUT4 in muscle are insulin dependent, others such as GLUT 2 in the liver are not and glucose follows the concentration gradient. Hexokinase activity is not affected by insulin but glucokinase activity is and insulin stimulates both glycolysis and glycogen synthesis. Glycogen is a branched glucose polymer and is synthesized from glucose by glycogen synthase. Glycogen is a short-term store or buffer for glucose and, in the short term, maintains blood glucose levels in the absence of a glucose intake. Glycogen breakdown to glucose is performed by glycogen phosphorylase which is converted from its inactive b form to its active a form via cyclic AMP and protein kinase A which catalyses the phosphorylation and activation of phosphorylase. Protein kinase also inhibits glycogen synthase, which is active in its dephosphorylated form and inactive when phosphorylated. The balance of glycogen synthesis (glycogenesis) and glycogen breakdown (glycogenolysis) is determined by the balance of the anabolic hormone insulin and the catabolic hormones glucagon, adrenaline and noradrenaline. The balance of insulin and glucagon controls the normal cycle of glycogen synthesis/breakdown, the catecholamines come into play during 'stress'.

Muscle does not contain glucose-6-phosphatase, therefore muscle glycogen does not contribute to blood glucose levels. When muscle glycogen is mobilized the glucose is metabolized by glycolysis. In severe exercise or 'shock' the rate of glycolysis exceeds the oxygen supply and the rate at which pyruvate enters the TCA cycle. Pyruvate goes to form lactic acid, catalysed by the enzyme lactate dehydrogenase. Pyruvate receives hydrogen ions from NADH with the consequent development of a metabolic acidosis. When the oxygen supply is restored to balance the rate of substrate utilization (the 'shock' is treated, or the intensity of exercise diminishes) pyruvate is resynthesized.

Fat metabolism

Fatty acids are also metabolized in the mitochondrion via the TCA cycle. Two carbon fragments at a time are split off the fatty acid chain from the carboxyl end (see page 116) by the process of β oxidation to form acetyl CoA which then enters the TCA cycle. Short and medium-length fatty acid chains can enter the mitochondrion directly, but the long chain molecules need to be bound to carnitine before they can cross the inner mitochondrial membrane. When large quantities of acetyl CoA from fat become available ketone bodies (acetoacetic acid and β-hydroxybutyric acid) are formed. They are synthesized in the liver from free fatty acids and are seen most commonly in starvation, but pathologically in diabetes. In starvation they are used by many tissues in place of glucose, but in diabetic ketoacidosis, in which they are produced in huge quantities, they contribute to a metabolic acidosis. Acetoacetic acid is formed from the condensation of two molecules of acetyl CoA. It is converted to β hydroxybutrate and to acetone (excreted in the breath).

Fatty acids can be synthesized (lipogenesis) from acetyl CoA in the presence of excess glucose, which may occur if a high glucose intravenous feed is given in excess of requirements. High insulin concentrations in response to the glucose load stimulates the process. Lipogenesis occurs principally in the liver and in adipose tissue and takes place in the cytosol. NADPH derived from the pentose phosphate pathway is involved as the source of hydrogen. Fatty acid synthesis stops when the carbon chain reaches 16C and, in adipose tissue depots, fatty acids combine with glycerol to form triglyceride.

Whether or not lipogenesis takes place is determined also by the patient's nutritional status and is most evident in the well-nourished individual with a high proportion of carbohydrate in the diet. In the presence of a fat intake of more than 10–15% of the diet there is little conversion of carbohydrate to fat.

Protein metabolism

Proteins are made up of chains of amino acids. Interconversions can take place between amino acids and products of fat and carbohydrate metabolism involving transfer of the amino groups to other ketoacids by transamination, or oxidative deamination can take place with the formation of N_H^4+ which is in equilibrium with ammonia. Most of the N_H^4+ formed by deamination in the liver is converted to urea. Removal of the amino group from amino acids produces the corresponding ketoacids, most of which undergo oxidative metabolism via pyruvate or the various intermediates in the TCA cycle. Some amino acids are ketogenic in that their ketoacids are converted to acetoacetate, but most are glucogenic and are converted to glucose via gluconeogenesis.

Gluconeogenesis occurs in the liver and the kidney as part of the normal adaptation to starvation and in response to stress. The driving force is the fall in insulin and the rise in the counter-regulatory hormones (glucagon, adrenaline, noradrenaline, cortisol) and, in trauma and sepsis, the release of cytokines that affect peripheral and hepatic metabolism. All of the TCA cycle intermediates potentially act as gluconeogenic precursors but, as stated earlier, the reaction catalysed by pyruvate dehydrogenase which takes pyruvate into the TCA cycle is irreversible. The key enzyme for gluconeogenesis is phosphoenolpyruvate carboxy-kinase, which converts oxaloacetate to phosphoenolpyruvate, the final product of the glycolytic pathway before pyruvate. Glucose is then synthesized via reversal of the various steps in glycolysis, bypassing the 'irreversible' ones referred to earlier.

Amino acids are transferred to the liver and kidney, about 50% of them as alanine (the amino acid corresponding to pyruvate) and glutamine (the amino acid corresponding to α-ketoglutarate, a constituent of the TCA cycle). Transamination takes place in the periphery, mostly by transfer of amino groups from the branch chain amino acids, valine, leucine and isoleucine. Other gluconeogenic precursors are lactate and glycerol. Lactate is synthesized to glucose in the liver and glycerol via dihydroxyacetone phosphate, one of the constituents of the glycolytic pathway.

Ions: Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-

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Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, and HCO_3^- are ions present within all body fluids. Ions are substances that conduct an electrical current in solution and they are often referred to as electrolytes. The balance of ion species between the inside and the outside of the cell is of fundamental importance to physiological function (Figure 1).

The kidney is pivotal in controlling the total body electrolyte content, while transmembranous pumps in conjunction with the physical properties of the cell membranes govern their distribution. The organization of these systems enables the body to take advantage of the electrochemical properties of ions in order to maintain equilibrium.

Summary of the roles of ions

Na^+
- Major determinant of extracellular fluid (ECF) volume and osmolality
- Actively transported from cells – high concentration in ECF, low concentration in intracellular fluid (ICF)
- Resting cell membrane is relatively impermeable to Na^+
- In excitable cells the large concentration gradient for Na^+ to move intracellularly is utilized for propagation of the action potential

K^+
- Major determinant of ICF volume and osmolality
- Actively transported into cells – low concentration in ECF, high concentration in ICF
- Diffusion of K^+ out of the cell is responsible for the resting membrane potential

Ca^{2+}
- Regulates cell metabolism
- Serves as the link between electrical activity in muscle and contraction
- Influences neuromuscular excitability
- Required for blood clotting

Mg^{2+}
- Activates intracellular enzyme systems, including glycolysis, oxidative phosphorylation and protein synthesis
- Required for the function of the Na^+/K^+ pump
- Influences neuromuscular excitability

Cl^-
- Predominantly in the ECF accompanying Na^+
- Present in gastric juice as hydrochloric acid
- Important in secreting and absorbing cells in the kidney and alimentary tract

HCO_3^-
- Primarily found in the ECF
- Principal role in the transport of CO_2 from the tissues
- Important in the regulation of blood pH

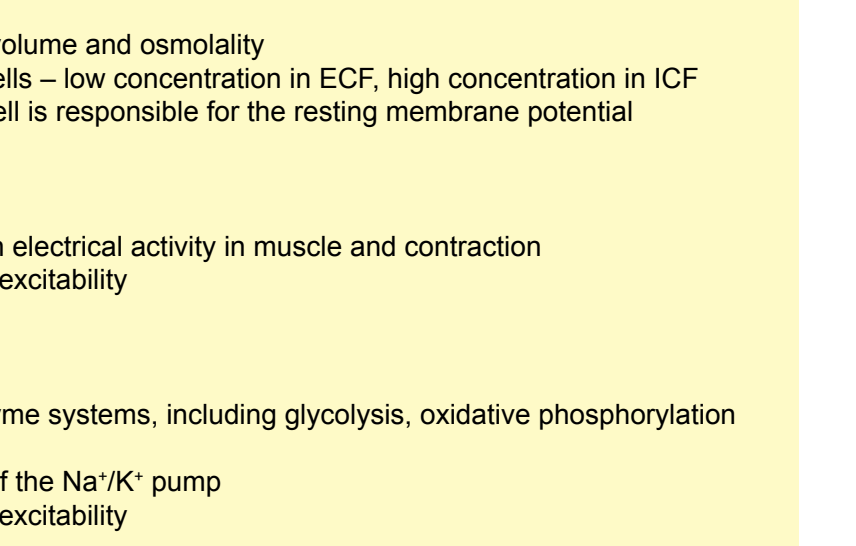
1

Ionic contents of body fluid compartments

The distribution of ions between the major body fluid compartments – the extracellular fluid (ECF) and the intracellular fluid (ICF) – determines their volume (Figure 2). Osmotic forces, primarily generated by the electrolytes, drive water across the semipermeable cell membrane that separates the ECF and ICF. Therefore, the osmolality of the ECF and ICF is equal; the normal range is 275–290 mosmol/kg. However, owing to the differential permeability of the cell membrane and specific transport mechanisms, the electrolyte content of each compartment is different (Figure 3). The most striking contrast is that the concentrations of the predominant ions in each compartment (Na^+ in the ECF and K^+ in the ICF) are nearly opposite.

Distribution of body water in adults

a Total body water expressed as a percentage of total body weight. In women, the total body water accounts for a smaller proportion of body weight because they have more adipose tissue than men. **b** Total body water comprises extracellular fluid (ECF) and intracellular fluid (ICF). **c** ECF is subdivided into interstitial fluid (ISF) and the intravascular compartment or plasma. There is no gender variance in the percentage of body weight taken up by the ECF.



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Ionic composition of the extracellular fluid (plasma) and the intracellular fluid

Extracellular fluid – Plasma			Intracellular fluid	
Cations	**Concentration (mmol/litre)**		**Cations**	**Concentration (mmol/litre)**
Na^+	130–155	Capillary membrane / Interstitial fluid / Cell membrane	Na^+	10–35
K^+	3.2–5.5		K^+	150–155
Ca^{2+}	2.1–2.9		Ca^{2+}	< 0.1
Mg^{2+}	0.7–1.5		Mg^{2+}	12–28
Anions			**Anions**	
Cl^-	95–110		Cl^-	3–10
HCO_3^-	23–32		HCO_3^-	7–20
PO_4^{3-}	0.7–1.6		PO_4^{3-}	31–105

The capillary membrane is freely permeable to all plasma solutes except protein and lipids. The cell membrane is a selectively permeable barrier that is freely permeable to water

3

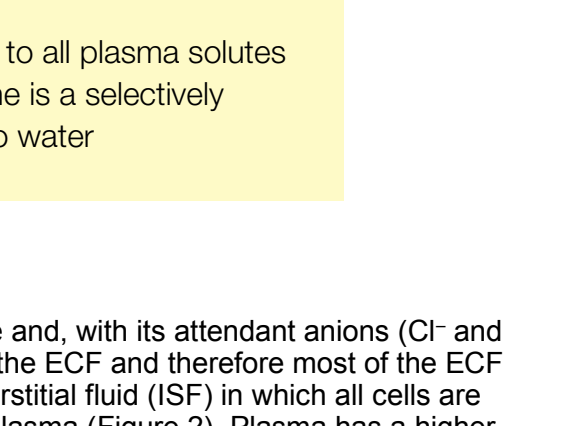
ECF
Na^+ is the main determinant of the ECF volume and, with its attendant anions (Cl^- and HCO_3^-), accounts for 90–95% of all solutes in the ECF and therefore most of the ECF osmolality. ECF can be subdivided into the interstitial fluid (ISF) in which all cells are bathed and the intravascular compartment or plasma (Figure 2). Plasma has a higher protein content than ISF; this does not equilibrate because the capillary endothelium, which separates the two compartments, is not freely permeable to protein. Since, at an arterial pH, protein bears multiple negative charges, electrical neutrality is maintained across the two subcompartments by a redistribution of ions; a slight increase in Na^+ and K^+, and a slight decrease in Cl^- and HCO_3^- in plasma compared with ISF.

ICF
Intracellular osmolality, and thus volume, is determined by the main ICF ion, K^+. There is a large concentration gradient for K^+ to diffuse out of the cell and for Na^+ to move into the cell (Figure 3). However, these ions do not equilibrate because their distribution across the cell membrane is maintained by the Na^+/K^+ pump (Figure 4). The exact composition of the ICF is not consistent across all cell types. In muscle, the most prevalent cell in humans, the Na^+ and Cl^- concentration is 3–4 mmol/litre. In comparison, the Na^+ and Cl^- content of RBCs is 20 and 90 mmol/litre, respectively. The Cl^- concentration is greater than that of Na^+ because during the transport of CO_2, Cl^- enters the RBC in exchange for HCO_3^-.

ICF ions are not always distributed evenly throughout the cell. Ca^{2+} is sequestered in the sarcoplasmic reticulum of muscle cells and is released into the ICF in response to a muscle membrane action potential. The increased Ca^{2+} concentration in ICF activates myofibrillar ATPase that results in contraction. At rest, the cell Ca^{2+} concentration is only 0.1 µmol/litre and a high concentration gradient exists for Ca^{2+} to move from the ECF to the ICF compartment.

Distribution of Na^+ and K^+ across the cell membrane

The intracellular K^+ concentration is maintained by active transport of K^+ in exchange for Na^+ (in a ratio of 3:2). The immediate ionic asymmetry across the cell membrane results from the resting cell membrane being relatively permeable to K^+, but not to Na^+. K^+ moves down a concentration gradient out of the cell and establishes a cell membrane potential difference (–70 to –90 mV in excitable cells, nerve and muscle)



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Na^+/K^+-ATPase pump

Na^+/K^+-ATPase is a transmembranous enzyme that plays a central role in regulating the internal environment of every body cell. This enzyme acts as a Na^+/K^+ pump that utilizes energy from the hydrolysis of ATP to transport $2K^+$ into the cell and $3Na^+$ out of the cell, against their respective concentration gradients. In humans, the work of the Na^+/K^+ pump is responsible for 45% of the resting metabolic rate. Other primary cation pumps that operate in the body include; H^+/K^+-ATPase; Ca^{2+}/H^+-ATPase, Na^+/H^+-ATPase and Ca^{2+}/Mg^{2+}-ATPase.

The Na^+/K^+ pump usually maintains the osmolality between the fluid compartments. If the pump becomes impaired, such as in hypoxia and septicaemia, Na^+ will accumulate within the cell. This sets up an osmolar gradient across the compartments causing the cell to swell. To compensate, K^+ diffuses down its electrochemical gradient from the intracellular to the extracellular compartment resulting in hyperkalaemia.

The primary functions of tissues specialized in ion transport (brain, kidney, intestine, muscle) depend on the Na^+/K^+ pump, the concentrations of which are over 100 times greater than in other cells, generating dramatic osmolar gradients. For example, the Na^+/K^+ pump on the basolateral surface of epithelial cells lining the proximal tubule of the kidney, maintains a low intracellular Na^+ concentration. This facilitates the active reabsorption of Na^+ (about 25,000 mmol/day), and the co-transport of glucose and amino acids with Na^+ from the tubule lumen. By the same mechanism, the Na^+/K^+ pumps on the basolateral surface of enterocytes enable nutrient molecules to be co-transported with Na^+ from the small intestine. Being an osmotically active transportable solute, Na^+ also has a major influence on water absorption.

Generation of membrane potentials
The characteristics of the cell membrane are of prime importance in the generation of membrane potentials. The resting cell membrane is relatively impermeable to Na^+ and relatively permeable to K^+. K^+ diffuses out of the cell along its electrochemical gradient, generated by the Na^+/K^+ pump. As Na^+ cannot readily move into the cell, the membrane becomes polarized where the inside is negative with respect to the outside (Figure 4). The magnitude of the potential difference depends on the particular cell type; it is greatest in excitable cells ranging from –70 to –90 mV in nerve and muscle, and is lower in nonexcitable cells, for example –40 mV in the hepatocytes of the liver.

The large concentration gradient required for Na^+ to move intracellularly is utilized by phasic changes in the permeability of the cell membrane to Na^+, which results in transient membrane depolarization and the transmission of an action potential. Changes in plasma Na^+ concentration have little effect on the resting membrane potential. Both decreases and increases in the K^+ concentration of ECF (hypokalaemia and hyperkalaemia, respectively) affect the resting cell membrane potential, particularly of nerve and myocardium, resulting in muscle weakness and cardiac arrhythmias.

The excitability of cell membranes is influenced by the presence of other ions, in particular Ca^{2+} and Mg^{2+}. Both hypocalcaemia and hypomagnesaemia result in neuromuscular hyperexcitability and cardiac arrhythmias, and are often associated with hypokalaemia. Conversely, hypercalcaemia and hypermagnesaemia both increase the threshold for membrane depolarization.

Ions and acid–base balance

Ion shifts occur in response to changes in H^+ concentration, in order to maintain electrical neutrality between the body fluid compartments. Acidosis causes H^+ to enter cells and displace K^+, leading to hyperkalaemia. Alkalosis causes K^+ to move from the ECF into cells, resulting in hypokalaemia.

The plasma calcium concentration is directly influenced by the pH of the ECF. About 40% of the plasma calcium is bound to plasma proteins, 10% is complexed with bicarbonate, citrate and phosphate, and the remaining 50% exists as Ca^{2+} and constitutes the physiologically active component. As the Ca^{2+} binding to protein is modulated by pH, the plasma Ca^{2+} concentration rises and falls in response to acidosis and alkalosis, respectively.

Some ions function directly as buffers. HCO_3^- is quantitatively the most important buffering mechanism within the ECF, and is also of prime importance in the transport of CO_2 from the tissues to the lungs. HCO_3^- and H^+ are created by the dissociation of carbonic acid, which is formed by the hydration of CO_2. This reversible reaction system is catalysed by the enzyme carbonic anhydrase, the presence of which is of prime importance in RBCs and renal tubular epithelium.

$$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

The unique aspect of the carbonic acid–bicarbonate buffer system is that carbonic acid can be rapidly excreted in the form of CO_2 in response to an increase in H^+ concentration. The kidneys are involved in the longer-term control of this buffer system by regulating plasma HCO_3^- concentration and excreting H^+. Importantly, organic acids other than carbonic acid can be eliminated from the body only by the kidneys. Electrical balance is maintained by the reabsorption of Na^+ when H^+ is actively secreted into the tubule lumen of the kidney. Other interconnected blood-buffering systems, including haemoglobin, plasma proteins and phosphates are important in limiting changes in blood H^+ concentration but cannot be regulated in response to blood pH changes.

A disruption in the reabsorption of HCO_3^- along the proximal tubule can lead to a depletion of both Na^+ and HCO_3^- in the ECF. A reduction in ECF Na^+ results in ECF volume depletion. In response, the kidney increases Na^+ reabsorption, which is reabsorbed as NaCl. This leads to effective replacement of HCO_3^- deficit with Cl^- giving rise to hyperchloraemia and low bicarbonate.

Ion reserves
Only a certain amount of each element within the body is exchangeable with the ions in the body fluid compartments. Exchangeable ions act as buffers in response to changes in plasma ion concentrations. The primary reservoir for Na^+, K^+, Ca^{2+} and Mg^{2+} is bone. Normal ECF electrolyte concentrations are achieved through a variety of complex mechanisms, for example the ECF Ca^{2+} concentration is controlled by the interaction of calcitropic hormones with bone, kidney and intestine similar to that of Mg^{2+}.

The ECF ion concentration does not necessarily reflect the total body electrolyte content; for example, only 1–2% of total body K^+, the major cation of the ICF, is present in the ECF. An abrupt decrease in the plasma K^+ concentration should be considered as acute hypokalaemia, whereas a prolonged reduction may be termed chronic hypokalaemia, which reflects a reduction in the total body stores as well as plasma levels. As there are no regulatory mechanisms for controlling the intake of electrolytes, the kidneys function to regulate the ionic balance between input and output.

Na^+ balance: plasma Na^+ concentration is a reflection of both total body Na^+ and total body water. The plasma osmolality is determined by the ratio of Na^+ and water, whereas the ECF volume is determined by the absolute amounts of Na^+ and water that are present. Plasma volume and osmolality homeostasis, are primarily maintained by the kidneys. Total body sodium and hence ECF volume, is regulated by maintaining the balance between sodium input and output. Since the body cannot directly monitor total body sodium, indicators of extracellular volume, atrial stretch, renal perfusion and blood pressure act as signals of total body sodium to the kidneys. Plasma osmolality is sensed by osmoreceptors in the hypothalamus. These receptors affect both water excretion and water intake by influencing antidiuretic hormone secretion and thirst, respectively. Hypernatraemia and hyponatraemia simply indicate that relatively more or less Na^+ is present per unit volume of body fluid. These terms give no insight into any change in the volume of body fluid compartments.

K^+ balance: is regulated by K^+ secretion in the kidneys and is mediated by aldosterone, which conserves Na^+ and promotes K^+ excretion. The regulation of the ratio of intracellular and extracellular K^+ is a function of the Na^+/K^+ pump. To an extent, uptake or release of K^+ from cells buffers changes in the concentration of the ECF K^+.

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Macronutrients, Minerals, Vitamins and Energy

Iain Campbell

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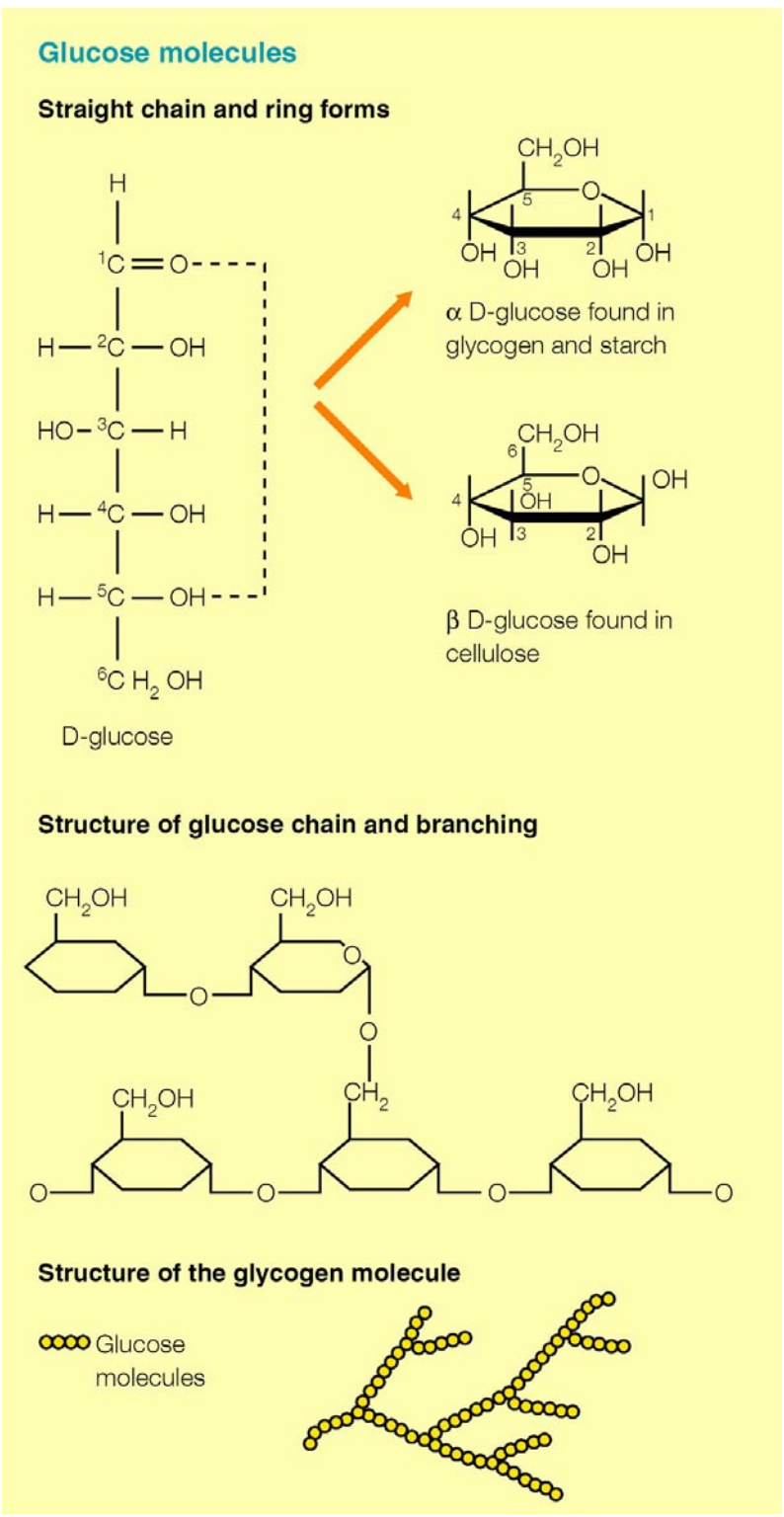
Macronutrients

Carbohydrate, fat and protein make up most of the body's soft tissue structure. These complex molecules are also the form in which protein and energy are ingested (macronutrients). What allows their formation is the ability of the carbon atom to form four bonds at once. In simple terms, carbohydrate, usually in the form of glucose (or glycogen), is the energy substrate for immediate use, fat in the form of adipose tissue represents the long-term energy store, and proteins form the 'living' tissue. Carbohydrate, in combination with protein (glycoproteins) and with fat (glycolipids) is also important in the structure of membrane receptors for hormones and other transmitter molecules, and fat is a major structural component of cell membranes. In this article the structure of carbohydrate, fat and protein and their role in the provision of energy are discussed; their metabolic interrelationships are discussed elsewhere.

Carbohydrates
Carbohydrates are classified in three broad groups – mono-saccharides, disaccharides and polysaccharides. They have the general molecular formula $(CH_2O)n$, where n denotes the number of carbon atoms, with an H and an OH group attached to each carbon (Figure 1). Monosaccharides may have three carbons (triose), four (tetrose), five (pentose) or six (hexose). Triose sugars (e.g. glyceraldehyde) are important in intermediary metabolism, such as glycolysis, and pentoses in the pentose shunt, but it is the hexose sugar, glucose, that is the basic unit of carbohydrate storage and energy provision.

Glucose can exist in a straight chain form or as a ring (Figure 1); the aldehyde group on C_1 reacts with the hydroxyl group on C_5 to form a stable covalent bond and gives rise to a six-member ring (Figure 1). In solution, the two forms are in equilibrium but the ring structure predominates. Conventionally, glucose is seen as a flat structure at right angles to the plane of the page with hydrogen atoms and hydroxyl groups above and below the plane of the ring (Figure 1). Pentoses (e.g. ribose and deoxyribose in nucleic acids) form five-member rings as do some hexoses (e.g. fructose). The presence of an asymmetric distribution of atoms or groups around the carbon atoms allows the formation of isomers. In glucose, the biologically important ones arise from the disposition of the H and OH groups around C_5 and C_1. The asymmetry around C_5 denotes the D or L forms, dependent on the rotatory effect they have on polarized light. Most of the glucose in animals is in the D configuration (hence the term dextrose, commonly used for glucose) and the enzymes responsible for its metabolism are specific for this configuration. The isomerism of H and OH around C_1 (α or β) is important in the formation of bonds between glucose units (see later).

Two monosaccharides can combine to form a disaccharide – maltose from two glucose units, lactose from glucose and galactose and sucrose from glucose and fructose. Glucose units can join at C_1 and C_4 to form chains or at C_1 and C_6 to form branching molecules (Figure 1). Starch is the principal carbohydrate store in plants and is made up of a mixture of non-branching chains of α D-glucose (amylose) and of branched chains of 24–30 glucose molecules, the branching occurring at the 1:6 linkage. Glycogen is the carbohydrate store in the animal body (animal starch). It is found predominantly in muscle and liver and has a similar composition to starch but is a much more highly branched structure (Figure 1) of variable and even indeterminate molecular weight. Cellulose found in plants is also made up of glucose units and these are also linked at C_1 and C_4. The glucose making up cellulose is the β isomer of C_1 (see above) and animals do not have an enyme to break this linkage; cellulose is therefore indigestible by enzymes, though it is broken down by fermentation.



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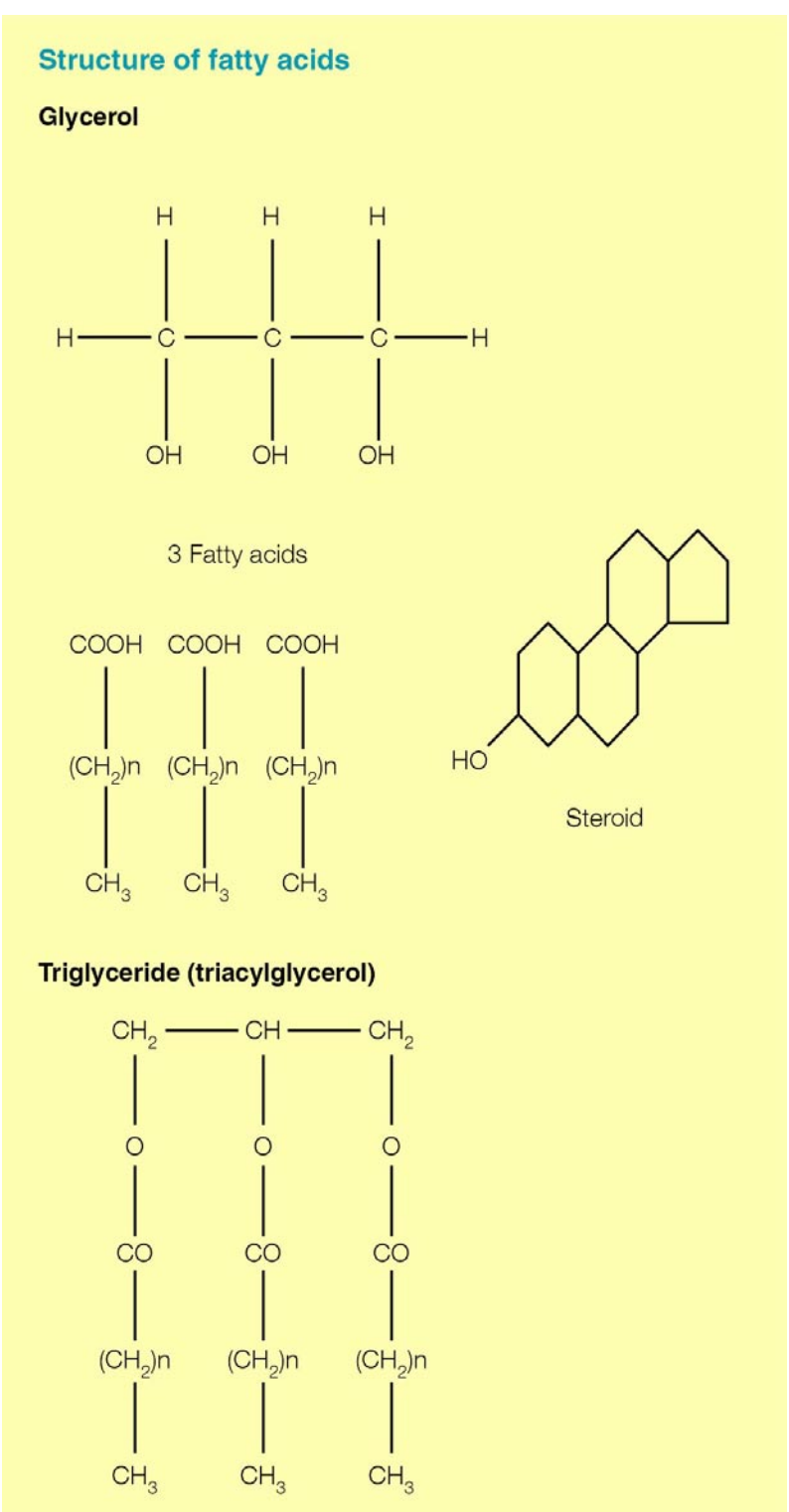
Fats
Fats (lipids) differ from other macronutrients in that they are poorly soluble in water, but highly soluble in organic solvents such as ether or acetone. Like carbohydrates they are composed of carbon, hydrogen and oxygen (Figure 2), but the proportion of oxygen atoms to carbon and hydrogen is lower than in carbohydrate.



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Fatty acids are chains of carbon atoms to which hydrogen atoms are attached with a carboxyl group (COOH) at one end. The carbon atoms are lipophilic and the COOH group hydrophilic. Two of the most common fatty acids in animal cells are palmitic (16C chain) and stearic (18C) acid. Fatty acids are distinguished from one another by the number of carbon atoms in the chains and the number of double bonds. When only single bonds exist the acid is said to be saturated; palmitic and stearic acids are both saturated acids. With one or more double bonds (C=C) the fatty acid is said to be unsaturated. Fatty acids are classified into families according to the position of their first double bond, counting from the noncarboxyl end of the fatty acid molecule. The terms n-3 (or omega-3), n-6 or n-9 denote the three main families. Unsaturated fatty acids include oleic (n-9; one double bond), linoleic (n-6; two double bonds) and arachidonic acids (n-6) which contain four double bonds. Arachidonic acid is an intermediary metabolite in the synthesis of prostaglandins, a group of substances that have a wide range of physiological effects. Dietary n-3 fatty acids (e.g. α linolenic acid found in fish oil) have come to prominence over the last decade for their ability to dampen down inflammatory processes and form part of the lipid structure of cell membranes

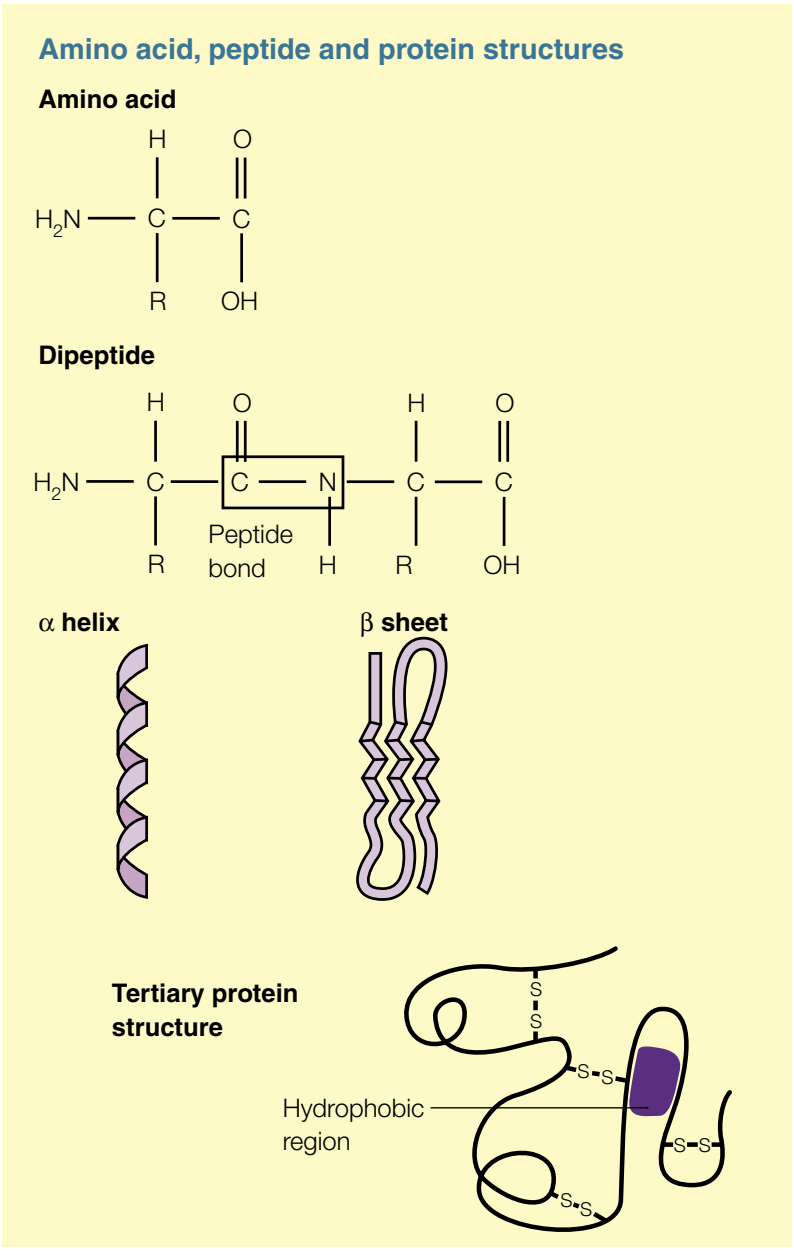
Triglycerides: glycerol is a molecule with three carbon atoms each with an OH group attached. These can form bonds with the COOH groups of the fatty acids to form triglyceride (Figure 2) which makes up adipose tissue. It is in this form that fatty acids are stored until they are required for energy. When needed as an energy source the glycerol–fatty acid bonds are hydrolysed and the fatty acids are released into the circulation loosely bound to albumin as free (or non-esterified) fatty acids.
Phospholipids are important in the formation of cell membranes. The parent compound is glycerol-3 phosphate in which, instead of the OH group on the C_3 of glycerol being linked with a fatty acid, it combines with a phosphate group (PO_4) to form phosphatidic acid and the addition of another chemical group (e.g. choline, serine, inositol) produces a phospholipid. The glycerol phosphate part of this molecule is extremely hydrophilic and the fatty acid part hydrophobic and it is these features that contribute to the structure of cell membranes.

Steroids have a variety of roles including the stabilization of cell membranes and the formation of various hormones, such as male and female sex hormones and the corticosteroids. The steroid nucleus is made up of four interlocking rings of carbon atoms and is amphipathic; the hydrophilic region is an OH group, the main structure of the molecule being lipophilic (Figure 2).

Proteins
Proteins constitute the fundamental structure of a living organism. They have different levels of organization and it is this that determines protein shape; a protein's shape or conformation determines its function. The basic constituent of protein is the amino acid of which 20 are available to make proteins.

Amino acids: the general structure of an amino acid is shown in Figure 3. It consists of an asymmetric carbon atom (the α carbon) with both an amino group (NH_2) and a carboxyl group (COOH) attached, and a side-chain. This gives rise to two isomers D and L, but only the L amino acids are constituents of proteins. At body pH, both the amino and the carboxyl groups are charged. The side-chains distinguish the various amino acids from each other. They are linked by peptide bonds formed between the carboxyl and the amino groups of adjacent amino acids. Two amino acids linked form a dipeptide (Figure 3), three a tripeptide, a chain of eight a polypeptide and proteins are typically made up of 50–2500 amino acids. The number and order of the sequence is what characterizes the protein. Conventionally the amino group is considered to be the start of the chain and the carboxyl group the end (Figure 3).

Amino acids are broadly classified into two groups according to the polarity or hydrophilicity of their side-chains (i.e. water- or fat-soluble). Some amino acids fulfill roles other than protein structure. They include ornithine, citrulline and argininosuccinate (which participate in the formation of urea), tyrosine (which is involved in the formation of thyroid hormones) and glutamate (used in the synthesis of neurotransmitters).



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Protein structure: the primary structure of protein is the sequence in which amino acids join together in chains. These chains are folded on each other, side-chains of the various amino acids linking and giving the protein its ultimate shape, as discussed above (Figure 3). The secondary structure is formed by folding the chain into a specific conformation. This occurs spontaneously as the various side-chains interact with each other. The precise conformation of this secondary structure is predictable and determined by the sequence of amino acids in the polypeptide.

There are a variety of ways in which interactions occur between side-chains to produce the folding. They include hydrogen bonding, the formation of covalent bonds between amino acids and carboxyl groups and between sulphur atoms in the sulphur-containing amino acids (cysteine, methionine), and the disposition of the hydrophilic and hydrophobic groups within the structure of the protein. In general, hydrophobic (lipophilic) groups find a place within the protein molecule and interact with each other (clump together), while the polar groups are on the outside of the molecule and interact with the aqueous environment.

Insulin is an example of the simplest of protein structures, consisting of two polypeptide chains joined by two covalent linkages between cysteine residues within each of the two chains. There are several types of secondary protein structure and these may occur within the same polypeptide chain. In the β helix, the polypetides adopt a spiral shape largely because of the formation of hydrogen bonds. In the α pleated sheet, regions of the polypeptide chain lie alongside one another forming a corrugated surface, hairpins and loops where regions of the polypeptide chain form tight bends and random coils in which there is no recognizable structure, though for any one protein this apparently random structure is always the same. More complex protein molecules have several of the above structures, all within the same polypeptide. This is called the tertiary structure with β helices folded on themselves and lying in close association with β sheets or 'random' coils. Some globular molecules, of which haemoglobin is an example, may consist of several of the above lying in close proximity and linked with each other. This constitutes a so called 'quaternary structure'.

Minerals

A number of minerals are required for normal metabolism and have to be provided in the diet. Some such as calcium, phosphorus, magnesium and sodium have major roles in normal physiology (e.g. bone structure, maintenance of cell membrane potentials) and are required in large quantities. Others such as copper, zinc, selenium, fluorine and chromium are required only in small quantities and are known as micronutrients or trace elements or minerals. Deficiencies in these elements have characteristic effects; lack of zinc causes skin ulcers and depressed immunity, copper deficiency causes anaemia, chromium lack causes insulin resistance, lack of fluorine is associated with dental caries. Some minerals, such as zinc and selenium, are important in the acute phase (systemic inflammatory) response to trauma and infection where circulating concentrations decrease as they are redistributed to active tissues. There is some evidence that supplementation with trace elements can reduce infection rates and promote healing.

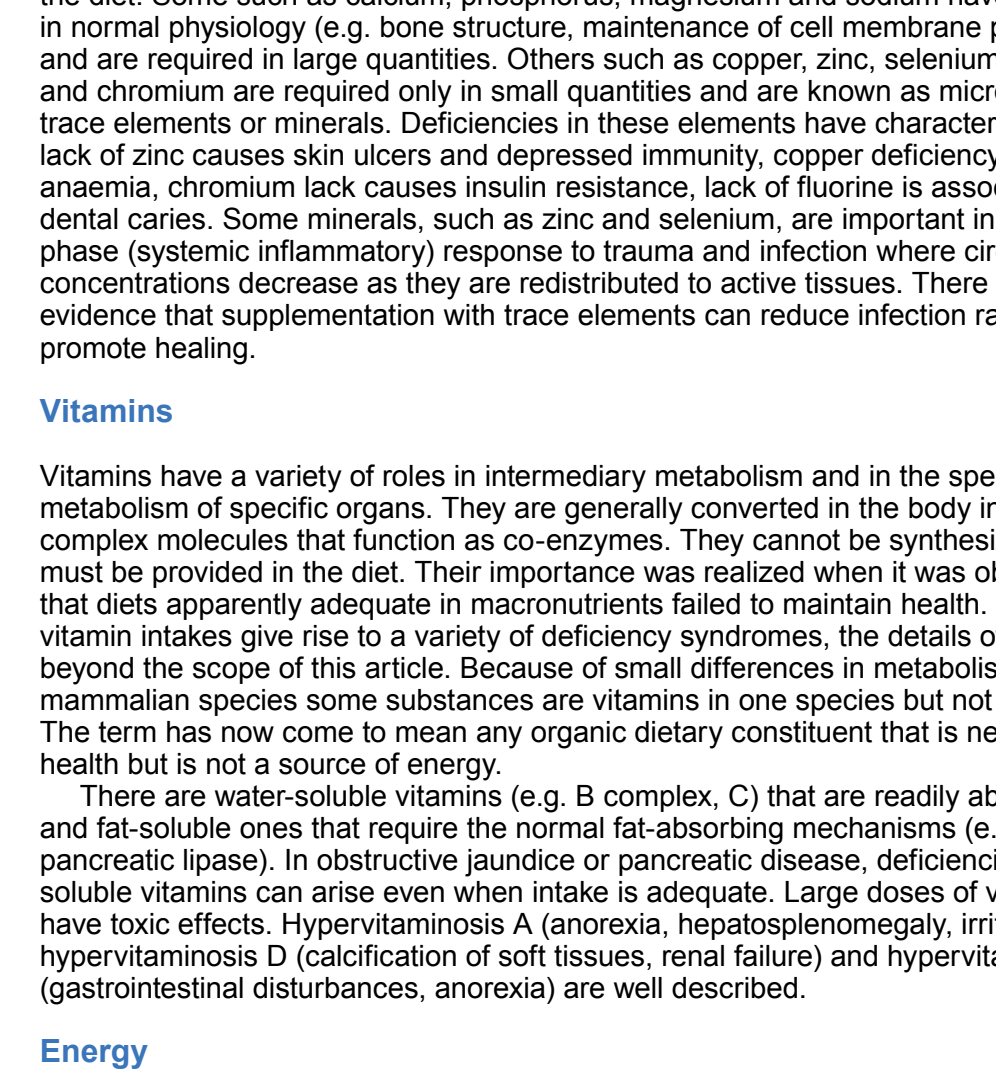
Vitamins

Vitamins have a variety of roles in intermediary metabolism and in the specialized metabolism of specific organs. They are generally converted in the body into more complex molecules that function as co-enzymes. They cannot be synthesized and must be provided in the diet. Their importance was realized when it was observed that diets apparently adequate in macronutrients failed to maintain health. Inadequate vitamin intakes give rise to a variety of deficiency syndromes, the details of which are beyond the scope of this article. Because of small differences in metabolism between mammalian species some substances are vitamins in one species but not in another. The term has now come to mean any organic dietary constituent that is necessary for health but is not a source of energy.

There are water-soluble vitamins (e.g. B complex, C) that are readily absorbed, and fat-soluble ones that require the normal fat-absorbing mechanisms (e.g. bile, pancreatic lipase). In obstructive jaundice or pancreatic disease, deficiencies of fat-soluble vitamins can arise even when intake is adequate. Large doses of vitamins have toxic effects. Hypervitaminosis A (anorexia, hepatosplenomegaly, irritability), hypervitaminosis D (calcification of soft tissues, renal failure) and hypervitaminosis K (gastrointestinal disturbances, anorexia) are well described.

Energy

Energy used by the body is obtained from the oxidation of the macronutrients, 10–15% from protein oxidation, the rest from fat and carbohydrate in roughly equal proportions. The summary equations for fat and carbohydrate are given in Figure 4 in which the energy released is given in units of heat. For technical reasons, heat has always been the traditional unit of energy. Energy is the ability to do work and the unit of work (or energy) is the Joule. This is defined as the work done when a force of 1 Newton (1 kg/second^2) moves through a distance of 1 metre. The calorie is the heat/energy required to raise the temperature of 1 g of water by 1°C. In human metabolism, the conventional unit is the kilocalorie – 1000 times the calorie. The relationship between calories and Joules is given by the mechanical equivalent of heat: 1 calorie = 4.2 Joules. Energy is expended in the maintenance of basal metabolism (i.e. the energy expended in keeping the body alive), in the conduct of external work and in thermoregulation (maintenance of body temperature in the face of thermal (cold) stress).



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Energy intake

The energy values of the various macronutrients can be determined by bomb calorimetry. This entails burning (oxidizing) the dried foodstuffs in an atmosphere of pressurized oxygen and measuring the heat given off. Carbohydrate and fat produce average values of 4 and 9 kcal/g and, because these substances are oxidized completely in the body to carbon dioxide and water, these figures are the same values as are available to the body. In contrast, bomb calorimetry of protein produces 5.4 kcal/g but only about 4 kcal/g are available for metabolic use; oxidation of protein is only partially complete in the body and energy-containing products of metabolism (e.g. urea, creatinine) are excreted in the urine.

Energy derived from bomb calorimetry is described as gross energy and energy available for metabolism as metabolizable energy. Energy available for metabolism is modified further by absorption. In a normal, mixed Western diet about 95% of ingested food is absorbed, though for high-fibre diets the figure is nearer 92%.

In clinical practice, a patient's energy intake is normally assessed by measuring and recording what they eat then calculating the nutrient content (energy, vitamins, minerals) from tables that list the constituents of the various foodstuffs. These values are derived from bomb calorimetry and chemical analysis.

Measuring oxygen consumption and energy expenditure

Energy expenditure can be derived from the measurement of oxygen consumption and carbon dioxide production – indirect calorimetry. VO_2 can be measured with a traditional carbon dioxide absorption technique using a closed-circuit spirometer, or calculated from the analysis of inspired and expired gas volumes. Thus:

$$VO_2 = (V_I \times F_IO_2) - (V_E \times F_EO_2)$$

$$VCO_2 = V_E \times F_ECO_2$$

where V_I and V_E are inspired and expired volumes and FO_2 and FCO_2 the fractional concentrations of inspired and (mixed) expired oxygen and carbon dioxide, respectively. It is simple to measure VCO2. However, measurement of V_{O2} requires the measurement of inspired and expired volumes separately because the expired volume is usually lower than the inspired volume (RQ is normally 0.7–1). This is technically difficult and it is normal practice to measure one and calculate the other from the inspired and expired nitrogen ($_{NI}$ and $_NE$) concentrations. Nitrogen is not measured but is assumed to constitute all the non-$_O2$, non-C_O2 gas in the two volumes. Thus $_{VE}$ = $_VI$ x $_NI/_NE$. This is known as the Haldane transformation. It has limitations in ventilated patients who require high inspired concentrations of oxygen, and at an $_FI_{O2}$ of 1 it does not work. In practice, most indirect calorimeters that use this technique cease to function properly at an $_FI_O2$ of about 0.6–0.7. The use of the Haldane transformation assumes that the system is in a 'steady state' and that 'nitrogen' (non-$_O2$, non-C_O2) does not take part in gas exchange.

Total 24-hour energy expenditure generally depends on how active an individual is. Most energy expended in any given period is that used to maintain basal expenditure such as the work of breathing, heart beat, maintenance of cell membrane potentials and the multitude of other energy-consuming reactions used in the maintenance of life. In a bed-bound individual this may constitute 90% of total expenditure. In a manual labourer it may be only 50%. Factors that raise metabolic rate other than activity are the energy cost of digestion, absorption and assimilation of food, exposure to cold and body temperature. A high-protein meal stimulates metabolism more than fat or carbohydrate. Thus, to measure basal energy expenditure (oxygen consumption) a subject should be fully rested after an overnight fast and be in a thermoneutral environment. Basal energy expenditure can also be predicted from a number of equations, the Harris–Bennedict equation is probably the best known, but in the UK the Schofield equation has been introduced recently. The variables they include are measures of body size (height and weight), gender and age. Metabolic rate decreases with age and for a given body weight is lower in women because of the higher proportion of body fat. Body temperature also affects metabolic rate. A change in core temperature of ^{1}oC is said to increase or decrease metabolic rate by 13%, though more recent measurements made in the clinical environment indicate that this figure may be nearer 6–7%.

Cold stress raises energy expenditure by inducing shivering or increasing muscle tone. Another thermogenic mechanism is non-shivering thermogenesis seen in hibernating rodents and in humans in the first 6 months of life. The site of this increased heat production is brown adipose tissue, found over the kidneys and around the great vessels. It is brown owing to the large numbers of mitochondria that are ‘uncoupled’ (i.e. instead of synthesizing ATP they produce heat). The process is under the control of the sympathetic nervous system.

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Muscle

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Anthony C Wareham was Senior Lecturer in Physiological Sciences at the University of Manchester until taking early retirement in April 2001. He obtained his BSc in Zoology and his PhD from Durham University. His research interests focus on the electrophysiological properties of skeletal muscle during development, denervation and disease, particularly muscular dystrophy.

Morphology

Skeletal muscle

A skeletal muscle is composed of thousands of elongated muscle fibres running in parallel. Fibres are multinucleate cells, formed from the fusion of single nucleated myoblasts. In healthy fibres, the nuclei lie peripherally just under the cell membrane. In large limb muscles, fibres may reach a length of 30 cm with a diameter of 100 μm. The cell membrane (the sarcolemma) surrounds the cytoplasm (the sarcoplasm). The sarcoplasm contains several hundreds to thousands of contractile elements, the myofibrils, each of which is 1–2 μm in diameter. A myofibril is compartmentalized into as many as 10,000 repeating units called sarcomeres joined together by dense material at Z lines. These repeating units in myofibrils endow the muscle fibre with repeated cross striations (easily seen under the light microscope), which leads to the alternative term striated muscle for skeletal muscle. The sarcolemma is invaginated at each sarcomere to form blind-ending transverse tubes (t-tubules) that run into the centre of the fibre and have a crucial role in the activation of contraction. Running longitudinally between the repeating t-tubules are blind-ending membrane tubes or sacs called the sarcoplasmic reticulum. The ends of the tubes of the sarcoplasmic reticulum, terminal cisternae, abut closely to the membranes of the t-tubules, forming triads. A triad is part of a t-tubule and the terminal cisternae on either side and is the site of excitation–contraction coupling.

Fibres are categorized by their speed of contraction, from slow to fast. Primarily, speed of contraction depends on the activity of myosin ATPase. Slow fibres receive a plentiful blood supply and have oxidative metabolism whereas fast fibres can operate anaerobically and do not have such a rich blood supply. All human muscles are composed of a mix of slow and fast fibres, the ratio depending on their function and the amount and type of exercise.

Smooth muscle

Smooth muscle fibres are not striated. They are smaller than striated fibres (5–10 μm in diameter, 30–200 μm long) forming small cells, tapering at each end. They have only one, centrally located nucleus. Cells do not contain ordered sarcomeres, nor is the cell membrane invaginated into t-tubules. The sarcoplasmic reticulum system is present but not as well developed as in striated fibres. The cell surface forms folds or pits called calveolae, which are thought to function in a similar way to t-tubules, and which are associated with tubules of the sarcoplasmic reticulum.

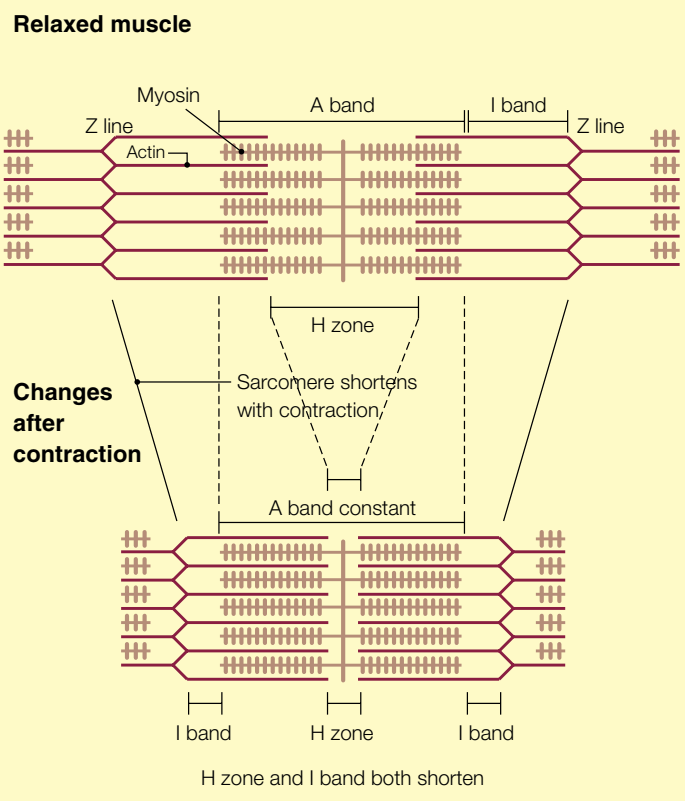
The most common type of smooth muscle is visceral (single unit) muscle, which is composed of smooth muscle cells tightly bound together with gap junctions to form a continuous network. Gap junctions connect the cells together electrically so that an action potential generated in one cell is transmitted to all other cells in the network. Since any smooth muscle cell can be spontaneously active, a sheet of visceral muscle is normally partly contracted and has tone. It is found in the walls of small arteries and veins and lining the hollow viscera. Multi-unit smooth muscle is less common. It consists of individual fibres, each with their own motor nerve endings, and does not function as a network. Multi-unit fibres are found in the walls of large arteries and large airways, in erector pili muscles attached to hair follicles, and in the intrinsic eye muscles.

Ultrastructure

Striated muscle

The contractile proteins are myosin (molecular weight 450 kDa) and actin (molecular weight 43 kDa). Within a sarcomere, filaments of actin are attached to the Z line by actinin. Lying between the thin actin filaments are thick myosin filaments that are not firmly attached to anything. They are kept in place by huge elastic protein molecules of titin (the largest known protein with 25,000 amino acids) which stretch from one Z line to the next. The action of titin and nebulin (an inelastic giant protein lying alongside actin filaments and attached to one Z line of each sarcomere) ensures that actin and myosin exist in a very ordered way (Figure 1). Associated with actin filaments are two inhibitory proteins, troponin and tropomyosin, which prevent any uncontrolled reaction with myosin. The partial overlapping of actin and myosin results in distinct banding across each sarcomere (visible only under the electron microscope) of light areas (I band) where there is no overlap and dark areas (A band), where there is overlap. Actin filaments do not extend across the sarcomere, therefore the central region of the A band is lighter (H zone). The reaction between actin and myosin is responsible for the production of force and movement as the two types of filament are able to slide along each other, thus drawing the Z bands together and shortening each sarcomere and consequently the whole muscle fibre (Figure 1).

Banding patterns seen in striated muscle



1

Smooth muscle

The contractile proteins, actin and myosin, are arranged in long bundles that extend diagonally around the cell, forming a lattice around the central nucleus. Owing to the oblique arrangement of filaments, smooth muscle cells become globular when they contract, rather than simply shortening. Actin filaments are not attached to Z lines but to dense bodies of protein in the cytoplasm at one end and to protein plaques in the cell membrane at the other end. Myosin filaments lie bundled within the long actin filaments. The ratio of actin to myosin filaments is 12:1 compared with 4:1 in skeletal muscle. Smooth muscle does not contain the inhibitory proteins troponin and tropo-myosin.

Proteins involved in contraction

Myosin has at least 10 isoforms. Each myosin molecule consists of two heavy (2000 amino acids) alphahelical protein chains, wound together to form a rod-like tail, and two tadpole-like heads, S1, each connected to a flexible neck, S2. The S1 portion contains the active site that reacts with actin and the S2 portion allows movement of the head. Two lightweight protein chains are associated with each S1 head. Their function is unknown in striated muscle but in smooth muscle they regulate contraction. One molecule of myosin is 150 nm long. About 250 molecules make up a thick filament in a sarcomere. The molecules are wound together in such a way that the S1 heads are clustered at each end of the thick filament, resulting in the central portion being just a bundle of myosin tails.

Actin: the actin molecule is a globular protein (G-actin). The actin of the thin filament in a sarcomere is a polymerized form called F-actin. The thin filament is composed of two F-actin filaments wound together like two strands of beads. Each ‘bead’ of G-actin in the filament has a binding site for a myosin S1 head.

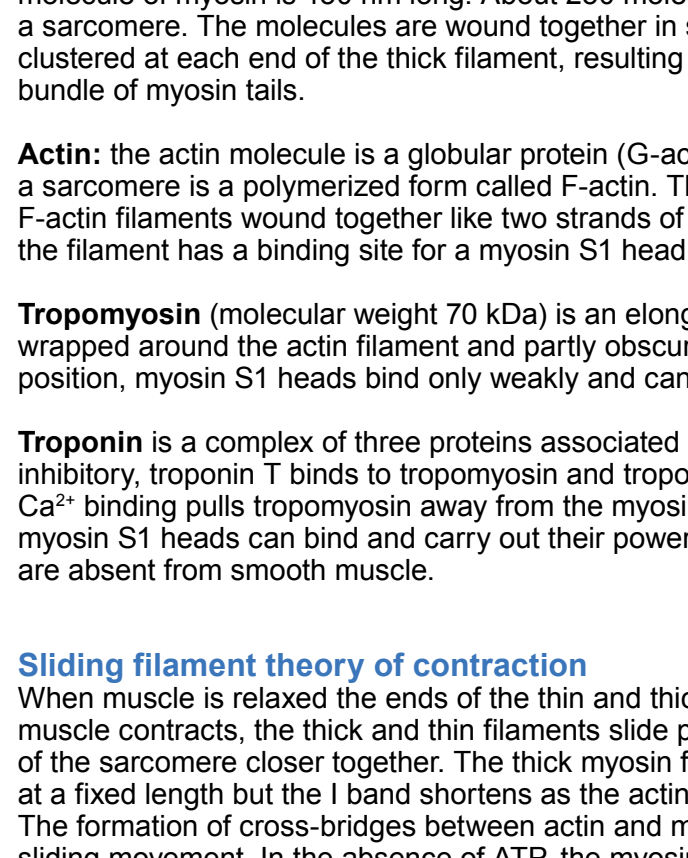
Tropomyosin (molecular weight 70 kDa) is an elongated protein polymer that is wrapped around the actin filament and partly obscures the binding sites. In such a position, myosin S1 heads bind only weakly and cannot create a power stroke.

Troponin is a complex of three proteins associated with tropomyosin. Troponin I is inhibitory, troponin T binds to tropomyosin and troponin C binds reversibly to Ca^{2+}. Ca^{2+} binding pulls tropomyosin away from the myosin-binding sites. In such a position, myosin S1 heads can bind and carry out their power stroke. Troponin and tropomyosin are absent from smooth muscle.

Sliding filament theory of contraction

When muscle is relaxed the ends of the thin and thick filaments overlap slightly. As the muscle contracts, the thick and thin filaments slide past each other, moving the Z lines of the sarcomere closer together. The thick myosin filaments, seen as the A band, stay at a fixed length but the I band shortens as the actin slides into the myosin (Figure 1). The formation of cross-bridges between actin and myosin provides the power for this sliding movement. In the absence of ATP, the myosin S1 head is tightly bound to actin, called the rigor state. ATP, normally present in abundance in resting muscle, binds with the S1 head and releases it from actin (Figure 2). The nucleotide binding site on the S1 head hydrolyses ATP to ADP and inorganic phosphate; both are retained at the site. The energy released rotates the S1 head on the flexible S2 region and it binds to a new site on the actin, one or two positions away from the G-actin where it started. At this point the S2 region is like a stretched spring ready to shorten. The power stroke begins when inorganic phosphate is released and the S2 region pulls the actin filament towards the centre of the sarcomere (Figure 2). To end the contractile cycle, myosin releases ADP and the myosin head is firmly bound to actin. The cycle continues to operate as long as the binding sites for cross-bridge formation are exposed. Therefore, control of contraction is linked to the regulation of troponin and tropomyosin. The contraction cycle is similar in smooth muscle even though it does not have sarcomeres, but the regulation of the cycle is different.

Development of the power stroke of the contractile cycle



2

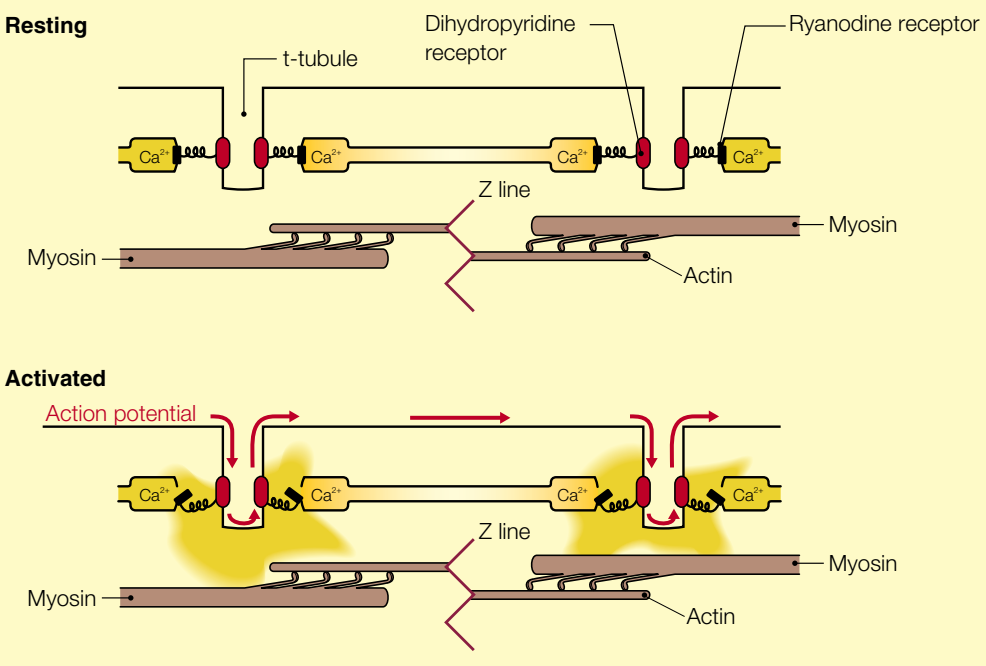
Excitation–contraction coupling

Skeletal muscle

The sarcoplasmic reticulum contains a high concentration of calcium owing to the activity of an inwardly directed calcium pump. The release of this calcium is the link between a muscle action potential and contraction. The sarcolemmal action potential travels into the centre of a muscle fibre along t-tubules. At each triad, the depolarization activates voltage-sensitive dihydropyridine (DHP) binding calcium channels. These activate ryanodine-binding calcium channels on the sarcoplasmic reticulum membrane. This activation, caused by either a physical link between the two types of calcium channel or calcium entering via the activated DHP channel, opens the ryanodine calcium channels and releases calcium from the sarcoplasmic reticulum (Figure 3). The calcium binds to troponin C, which moves tropomyosin on actin, exposes the actin binding sites and starts the contraction cycle. Provided the sarcoplasmic calcium concentration is kept high, by the repeated arrival of action potentials in the t-tubules, the contraction cycle continues. However, as soon as the action potentials cease, calcium is rapidly sequestered back into the sarcoplasmic reticulum system, tropomyosin returns to cover the actin binding sites and the muscle relaxes.

Excitation–contraction coupling

Excitation–contraction coupling is caused by the release of Ca^{2+} from the terminal cisternae of the sarcoplasmic reticulum



3

Smooth muscle

In smooth muscle, initiation of the contraction cycle is different from that of skeletal muscle because it may take up to 500 ms after a smooth muscle action potential to produce the peak of tension. There are several reasons. Some of the calcium required to initiate the contraction cycle comes from the extracellular medium and some from the sarcoplasmic system, therefore the diffusion path is greater. A major cause of delay is that myosin in smooth muscle must be phosphorylated for the activation of myosin ATPase. The pairs of myosin lightweight chains that appear to have no function in striated muscle regulate this process in smooth muscle. Calcium binds to calmodulin, which activates calmodulin-dependent myosin light chain kinase. This catalyses phosphorylation of the myosin S1 site allowing myosin ATPase to be activated and starts the contraction cycle between actin and myosin. Myosin is dephosphorylated by phosphatases in the cell but this does not necessarily lead to relaxation. There appears to be a latch bridge mechanism by which dephosphorylated myosin cross-bridges remain attached for some time after the cell calcium concentration has fallen, producing sustained contractions with little energy expenditure. Smooth muscle is unique in other ways because it is activated by stretch in the absence of external innervation and can adapt its tone to remain constant in the face of different amounts of stretch. ◆

FURTHER READING

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Neurological and Humoral Control of Blood Pressure

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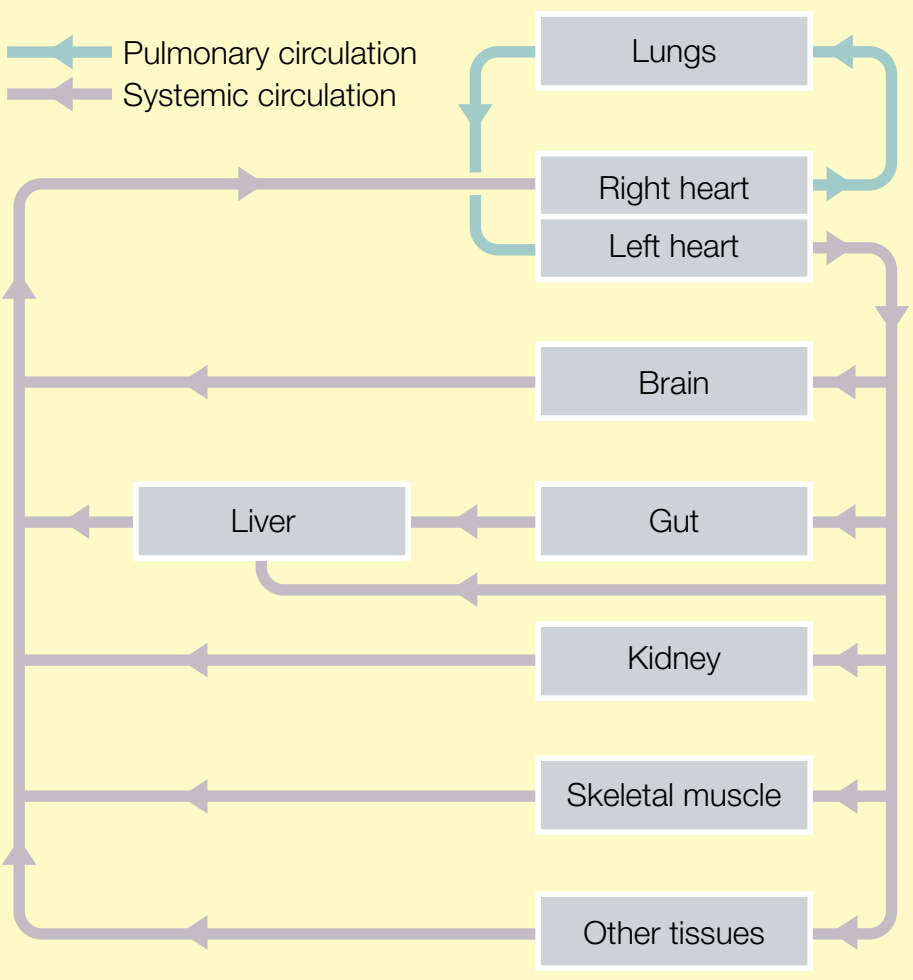
Systemic arterial blood pressure, flow and blood volume are closely regulated by a group of interrelated mechanisms. Perhaps the most important mechanism in the moment-to-moment control of arterial blood pressure is the arterial baroreceptor reflex. This reflex influences blood pressure by modifying a series of cardiovascular parameters: heart rate, cardiac stroke volume and peripheral vascular resistance. The key to understanding how the arterial baroreceptor reflex controls blood pressure is the interrelationship between these parameters as shown by the following equations:

Blood Pressure	= Cardiac Output x Total Peripheral Resistance	1
Cardiac Output	= Heart Rate x Stroke Volume	2
Resistance	$\alpha \frac{1}{(\text{Arteriolar Radius})^4}$	3

The baroreceptor reflex uses negative feedback to maintain constant arterial blood pressure. This normally ensures an adequate pressure to drive blood through individual vascular beds without it becoming high enough to damage the circulation. In simple terms, the vascular beds can be viewed as the blood vessels and circulation through different types of tissue, such as the gut and muscle (Figure 1). There are two circulations in the body: the pulmonary circulation and the systemic circulation. The systemic circulation is made up of a number of vascular beds arranged in parallel. The overall vascular resistance (total peripheral resistance in Equation 1) depends on the vascular resistance of all these beds. Because the beds are arranged in parallel, it is possible to regulate blood flow through specific beds to suit their needs at any given time without causing a similar change in others. For example, blood flow through skeletal muscle is increased during exercise, while that through the gut is reduced, whereas when the same individual is resting postprandially, blood flow through skeletal muscle falls and that to the gut and liver increases. This regulation of blood flow depends on an interplay between reflexes initiated on a whole-body basis.

Thus, blood pressure is dependent on blood flow and vascular resistance. Arterial blood pressure is maintained constant by the regulation of overall flow (cardiac output) and total peripheral resistance. Blood flow through individual organs depends on the peripheral pressure across that vascular bed (difference between arterial and venous pressure) and the vascular resistance. It is important to note, however, that there are some special cases where additional factors are important (e.g. in the cerebral circulation).

The parallel arrangement of some of the vascular beds in the systemic circulation



1

Vascular resistance

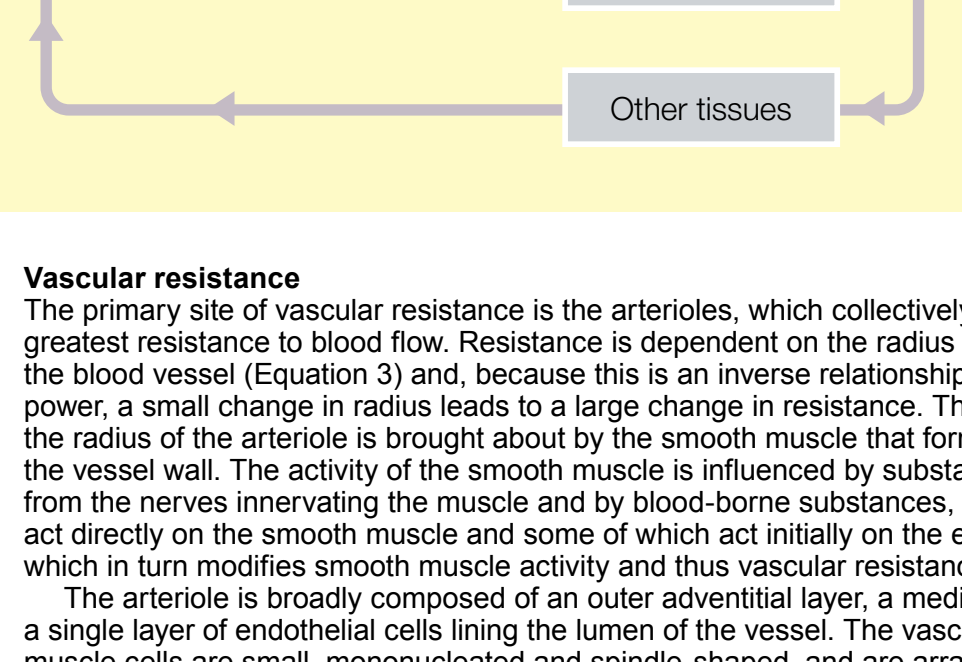
The primary site of vascular resistance is the arterioles, which collectively offer the greatest resistance to blood flow. Resistance is dependent on the radius of the lumen of the blood vessel (Equation 3) and, because this is an inverse relationship to the fourth power, a small change in radius leads to a large change in resistance. The change in the radius of the arteriole is brought about by the smooth muscle that forms part of the vessel wall. The activity of the smooth muscle is influenced by substances released from the nerves innervating the muscle and by blood-borne substances, some of which act directly on the smooth muscle and some of which act initially on the endothelium, which in turn modifies smooth muscle activity and thus vascular resistance.

The arteriole is broadly composed of an outer adventitial layer, a medial layer and a single layer of endothelial cells lining the lumen of the vessel. The vascular smooth muscle cells are small, mononucleated and spindle-shaped, and are arranged in a circular layer around the arteriole in the medial layer, so that when they contract they reduce the radius of the vessel. There is a close association between the endothelium and the smooth muscle cells. Indeed, the endothelium plays an important role in regulating the contractile state of the smooth muscle cells (see *Anaesthesia and Intensive Care Medicine* **2:2:** 77). The arteriole is primarily innervated by the autonomic nervous system; parasympathetic fibres play almost no role in modifying vascular resistance to control arterial blood pressure.

In most organs, the primary transmitter released by the sympathetic nerves is noradrenaline, though there are many other co-transmitters including ATP, neuropeptide Y and adrenaline (Figure 2).

There is clear evidence of sympathetic cholinergic fibres, which release acetylcholine and innervate the resistance vessels of skeletal muscle in some species (e.g. cats), but the evidence is more controversial in man and they are thought not to exist in the rat. The sympathetic fibres run along the adventitial layer forming a plexus. The fibres, now with multiple varicosities along their length, run on into the media and end primarily on the outer surface of the smooth muscle layer without penetrating it. Transmitter is released from the varicosities in response to an action potential travelling along the nerves, and diffuses to reach the smooth muscle cells in the media (Figure 2).

Regulation of vascular tone by perivascular nerves and endothelial cells



NPY, neuropeptide Y; NA, noradrenaline; ATP, adenosine triphosphate; AgII, angiotensin II; VP, vasopressin; H, histamine; EDRF, endothelium derived relaxing factor; ACh, acetylcholine; 5-HT, 5-hydroxytryptamine; SP, substance P; PG, prostacyclin; M, muscarinic cholinergic receptor; P_{2Y} and P_{2X}, purinergic receptors; α, α-adrenoreceptor

Adapted from Burnstock G, Ralevic V. *Br J Plastic Surg* 1994; **47:** 527–43.

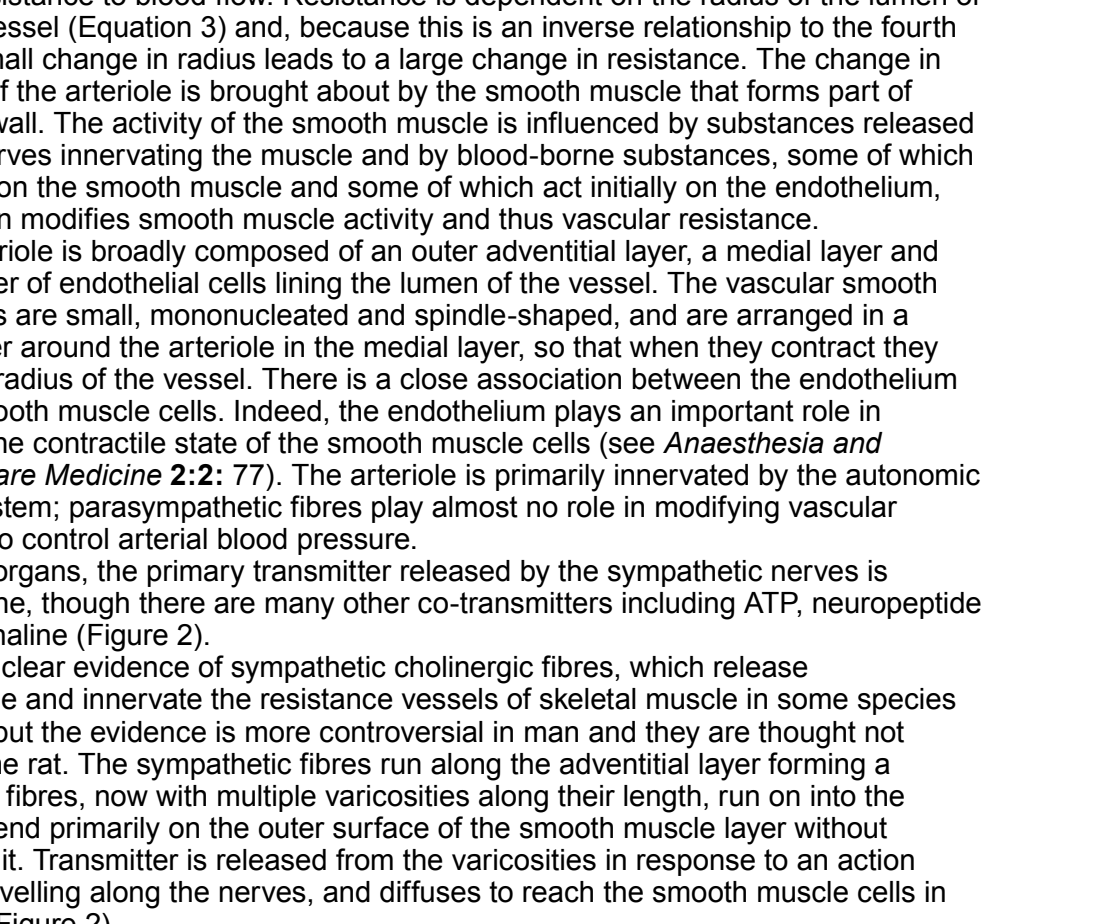
2

Vascular smooth muscle contraction

Vascular smooth muscle contraction takes place by the sliding of actin and myosin filaments over one another. Although there are many similarities between vascular smooth muscle and cardiac and skeletal muscle, there are also some important differences. Compared with skeletal muscle, smooth muscle contracts very slowly, develops high forces and maintains force for long periods of time with low use of ATP.

The sliding of actin and myosin filaments is controlled by the intracellular free calcium ion concentration. The calcium enters the cell via voltage-gated calcium channels and receptor-operated calcium channels (pharmacomechanical coupling), and by release from the sarcoplasmic reticulum (Figure 3). Neurohumoral agents, such as noradrenaline, cause contraction of the vascular smooth muscle primarily by pharmacomechanical coupling. For example, noradrenaline binds to α adrenoceptors on the muscle fibre membrane, which is linked to a membrane-bound regulatory protein called G-protein (guanine nucleotide binding protein). This, in turn, leads to the activation of phospholipase C causing hydrolysis of membrane-bound phosphatidyl inositol bisphosphate to yield inositol triphosphate and diacylglycerol. Inositol bisphosphate then causes the release of calcium from the sarcoplasmic reticulum, which ultimately leads to smooth muscle contraction, reduction in vessel radius and thus increase in vascular resistance.

Excitation–contraction coupling in vascular smooth muscle



ATP, adenosine triphosphate; GP, guanine nucleotide binding protein; PL-C, phospholipase C; PIP_2, phosphatidyl inositol biphosphate; IP_3, inositol triphosphate; DG, diacylglycerol.

Adapted from Berne R M, Levy M N. *Physiology.* 3rd ed. St Louis: Mosby Year Book, 1993.

Calcium and calmodulin activate myosin light chain kinase, which phosphorylates myosin LC_{20} resulting in cross-bridge recycling

3

Blood-borne substances
Blood-borne substances diffuse into the smooth muscle layer across the endothelial layer. Some, such as adrenaline, act directly on the smooth muscle. Vascular β_2 adrenoreceptors are more sensitive to adrenaline than are α adrenoreceptors. Therefore, at low doses or in vascular beds such as skeletal muscle where β_2 adrenoreceptors predominate over α adrenoreceptors, adrenaline causes vasodilatation. However, at high doses or in vascular beds with a predominance of α adrenoreceptors, adrenaline causes vasoconstriction. Other substances, such as acetylcholine, ATP, 5-HT and substance P, are released as paracrine agents from the endothelial cells in response to stimuli such as a shear stress or hypoxia (Figure 2), and act on neighbouring endothelial cells to cause release of endothelium-derived relaxing factor (EDRF), which is now known to be nitric oxide. This in turn diffuses into the smooth muscle layer ultimately to cause a reduction in intracellular calcium ion levels, muscle relaxation and thus vasodilatation, and a fall in vascular resistance.

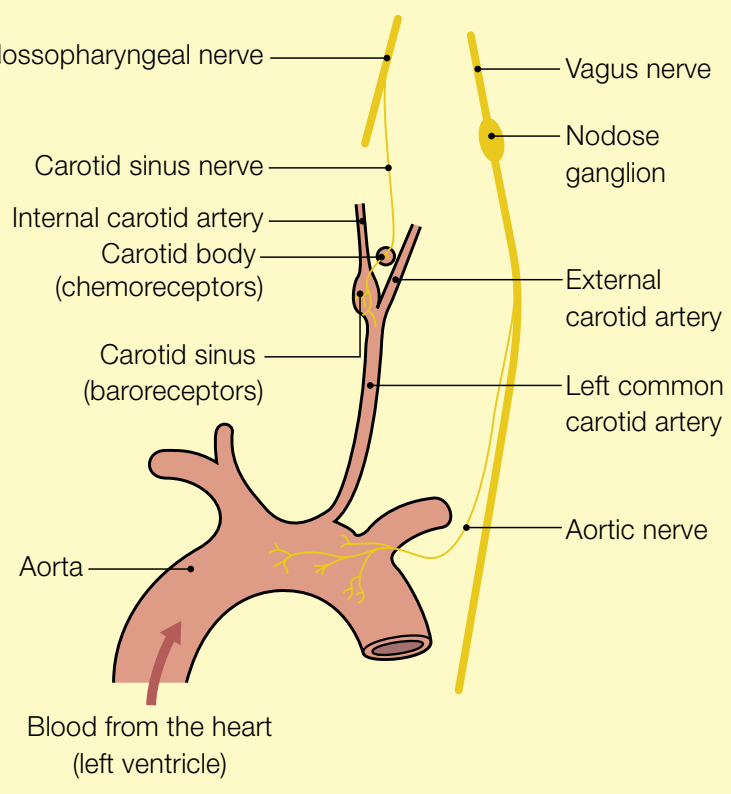
The vascular smooth muscle is therefore constantly under the influence of competing drives and the degree of contraction is the result of the balance of these forces. Generally, there is a tonic basal activity in the sympathetic vasoconstrictor nerves which helps to maintain a degree of vascular tone. By contrast, the sympathetic cholinergic fibres, whenever present, are normally silent and only contribute to vascular regulation during exceptional circumstances, such as the visceral alerting response of the defence reaction (see below).

Arterial baroreceptor reflex

The arterial baroreceptor reflex is a negative feedback reflex, so that any change in arterial blood pressure is detected and a response initiated to reverse the change.

Arterial baroreceptors
Arterial blood pressure is detected by a group of receptors known as the arterial baroreceptors (sometimes called the high-pressure baroreceptors). The baroreceptors are found in parts of the arterial tree with a specialized elastic structure. The main areas are the carotid sinuses at the bifurcation of the internal and external carotid arteries, and the aortic arch (Figure 4), though some are also found along the common carotid arteries, particularly at the origin of the thyroid arteries.

The position and nerve supply of the aortic and carotid baroreceptors



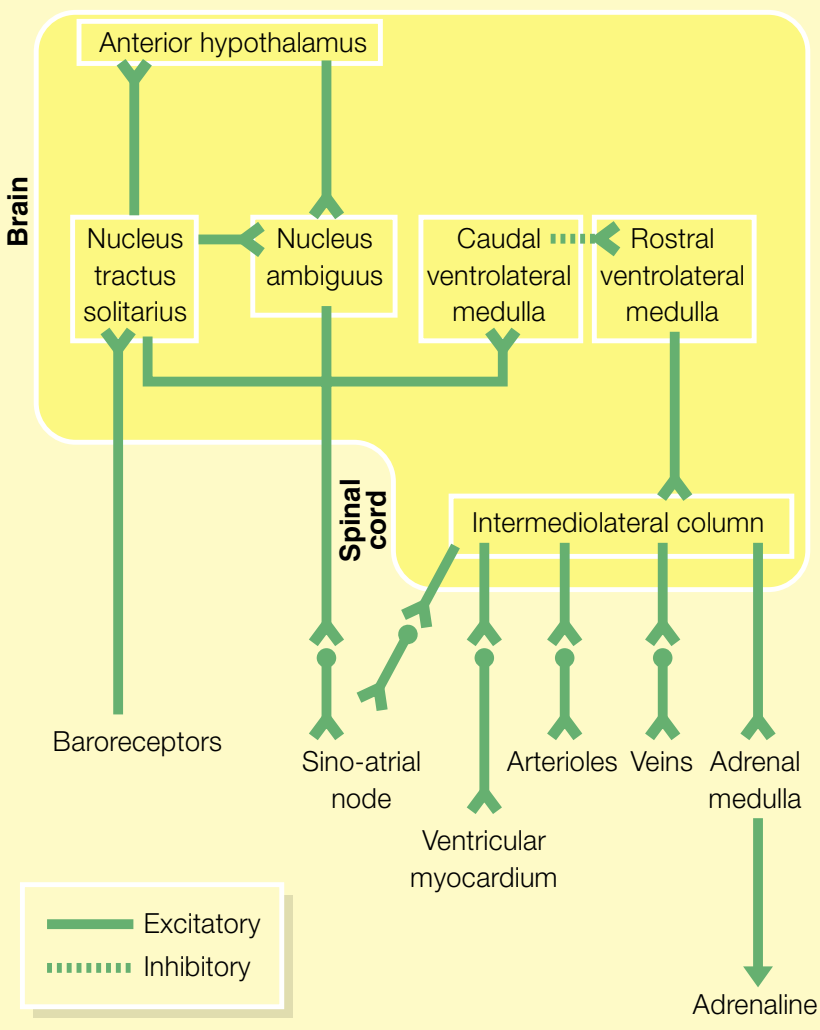
Source: Pocock G, Richards C D. *Human Physiology; The Basis of Medicine.* Oxford: Oxford University Press, 1999: 305Ð10.

4

These receptors are slowly adapting mechanoreceptors represented by nerve endings in the medio-adventitial junction of the barosensitive area. They do not respond to arterial blood pressure *per se*, but rather to the stretch of the arterial wall produced by the intravascular pressure. They are active at normal arterial blood pressures. A rise in arterial blood pressure will cause the receptors to produce an increased frequency of action potentials, while a fall in arterial blood pressure causes an unloading of the receptors and a reduction in action potential frequency. Since they are mechanoreceptors, any mechanical deformation of the barosensitive areas can cause a burst of action potentials to be generated and provoke a baroreceptor reflex response. Although such mechanical interference does not normally occur, it can be seen in clinical practice (e.g. during carotid sinus massage).

Baroreceptor afferent information is conveyed to the brain via myelinated and unmyelinated fibres in the sinus nerve (a branch of the glossopharyngeal nerve) from the carotid sinus and via the vagus nerve from the aortic arch. The cell bodies of these sensory afferents are found in the petrosal and nodose ganglia (from the carotid sinus and aortic arch, respectively). The afferent axons continue into the medulla where the first synapse of the baroreceptor reflex is found (Figure 5).

Baroreceptor reflex arc



5

CNS connections and efferent pathways
The primary relay of the baroreceptor reflex is found in the nucleus tractus solitarius in the medulla (Figure 5). Older physiology textbooks argue that the baroreceptor reflex is integrated in a brainstem 'vasomotor centre'. Although this represents a convenient 'black box' when describing cardiovascular control mechanisms, current evidence argues against this concept and suggests that cardiovascular control is achieved via a number of interrelated pathways.

The efferent pathways mediating the baroreceptor reflex are carried in the vagus nerve (parasympathetic) to the heart (primarily the sino-atrial and atrioventricular nodes), influencing heart rate and the sympathetic nerves to the heart (affecting both heart rate and force of ventricular contraction) and the vasculature. In addition, the adrenal medulla releases adrenaline into the bloodstream to affect both heart and vasculature (see above). The vagus nerve originates from the nucleus ambiguus (NA) and dorsal vagal motonucleus (DVN) in the medulla. There is both a segmental pathway from the nucleus tractus solitarius to the vagal outflow nuclei (NA and DVN) and a longer one, which ascends to the anterior hypothalamus, synapses and descends again to the vagal outflow nuclei. Increased baroreceptor afferent activity arising in the nucleus tractus solitarius leads to excitation of these secondary pathways, which in turn excite the vagal motor neurons, causing increased vagal efferent activity to the heart (Figure 5).

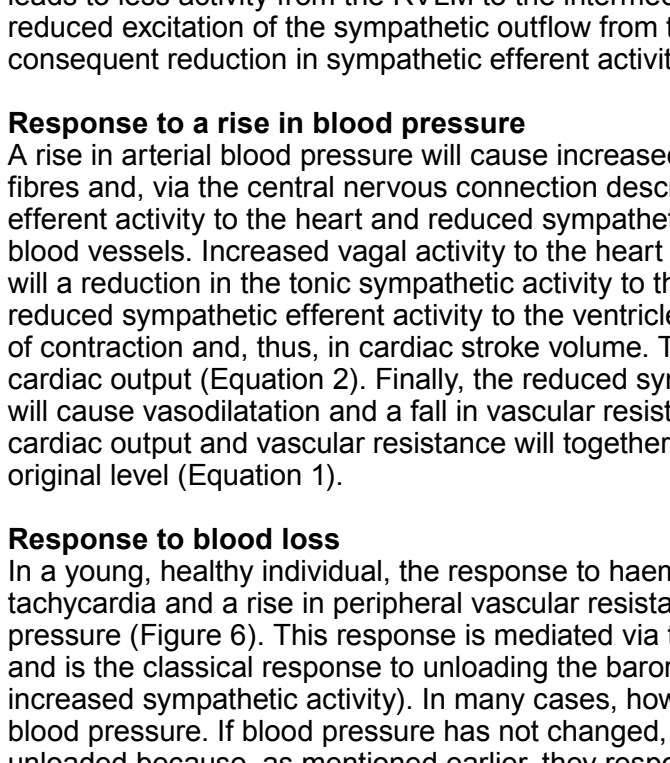
The sympathetic nerves originate from the intermediolateral column of the spinal cord, with pools of neurons that innervate different organs grouped at various levels along the cord. The sympathetic motor neurons receive a tonic descending excitatory drive from a group of neurons in the rostral ventrolateral medulla (RVLM). There is a high degree of viscerotopic organization here, with neurons innervating sympathetic outflow neurons being grouped together according to the type of vascular bed they influence. The RVLM receives an input from a group of neurons in the caudal ventrolateral medulla (CVLM), which receives an input from the nucleus tractus solitarius (Figure 5). Activation of the baroreceptor afferents innervating the nucleus tractus solitarius causes excitation of neurons projecting to the CVLM, which in turn causes excitation of neurons projecting from the CVLM to the RVLM. This causes increased release of transmitter in the RVLM, however, this is an inhibitory transmitter, possibly −aminobutyric acid, which therefore causes inhibition of RVLM neurons. This leads to less activity from the RVLM to the intermediolateral column and thus to reduced excitation of the sympathetic outflow from the intermediolateral column with a consequent reduction in sympathetic efferent activity (Figure 5).

Response to a rise in blood pressure
A rise in arterial blood pressure will cause increased activity in the baroreceptor afferent fibres and, via the central nervous connection described above, lead to increased vagal efferent activity to the heart and reduced sympathetic efferent activity to both heart and blood vessels. Increased vagal activity to the heart will, in turn, cause a bradycardia as will a reduction in the tonic sympathetic activity to the sino-atrial node. In addition, the reduced sympathetic efferent activity to the ventricles will cause a reduction in the force of contraction and, thus, in cardiac stroke volume. Together, these effects will reduce cardiac output (Equation 2). Finally, the reduced sympathetic activity to the vasculature will cause vasodilatation and a fall in vascular resistance (Equation 3). The reduced cardiac output and vascular resistance will together return blood pressure back to its original level (Equation 1).

Response to blood loss
In a young, healthy individual, the response to haemorrhage initially involves a tachycardia and a rise in peripheral vascular resistance to maintain arterial blood pressure (Figure 6). This response is mediated via the arterial baroreceptor reflex and is the classical response to unloading the baroreceptors (decreased vagal and increased sympathetic activity). In many cases, however, there is no fall in mean arterial blood pressure. If blood pressure has not changed, how do the baroreceptors become unloaded because, as mentioned earlier, they respond to the stretch of the arterial wall produced by the intravascular pressure? The baroreceptors respond not only to the absolute or mean pressure, but also to the pulse pressure (difference between systolic and diastolic pressures). Thus, during a mild haemorrhage, there is a reduction in pulse pressure (because stroke volume is reduced). This unloads the baroreceptors and leads to the tachycardia and elevated peripheral resistance, which helps maintain mean arterial blood pressure.

Finally, the aim of the response, namely that arterial blood pressure is maintained constant to preserve blood flow, should be considered. This reveals an apparent paradox, because part of the baroreceptor reflex response involves increased vascular resistance, which would itself cause reduced flow. The answer to this lies in the parallel arrangement of the vascular beds in the systemic circulation. The sympatho-activation is not uniform to all vascular beds; those with the greatest dependence on oxygen generally are subject to the least vasoconstriction, while areas less dependent on oxygen, or more tolerant to transient reductions in oxygen delivery, have the greatest constriction. The baroreceptor is therefore able to deliver the blood to those areas which need it the most.

Changes in heart rate, systolic arterial blood pressure, cardiac output, peripheral vascular resistance and right atrial pressure during a controlled haemorrhage (venesection) and subsequent faint



6
Adapted from Barcroft *et al.* *Lancet* 1944 i: 489.

Regulation of blood volume

Although a detailed discussion of blood volume regulation is beyond the scope of this review, it is pertinent to discuss briefly the effect of the baroreflex on the short-term control of blood volume. It should be noted, however, that this does not include the role of the baroreceptor reflex in the long-term (definitive) correction of blood volume, which involves the kidneys.

In a normal individual, it is estimated that 60–70% of the blood volume at any one time is contained within the veins. It is also known that the veins, especially those of the splanchnic circulation, are very sensitive to low levels of sympathetic activity. It has been suggested that the earliest response to blood loss would be a sympathetically-induced constriction of the veins (veins as well as arterioles receive a sympathetic efferent supply). While this would have only a small effect on the resistance of these vessels, it has been shown that it would have a much greater effect on capacitance, mobilizing an estimated 5 ml blood/kg body weight. Arteriolar vasoconstriction upstream would also reduce blood flow into the veins and thus, it is argued, would produce a further reduction in capacitance of approximately the same magnitude.

Finally, arteriolar constriction leads to a fall in capillary hydrostatic pressure. This disturbs the Starling forces that govern the net movement of fluid across the capillary wall and leads to a transient mobilization of interstitial fluid into the vascular space, with a fall in haematocrit.

Other reflexes influencing the cardiovascular system

Although the arterial baroreceptor reflex is considered to be the principal mechanism regulating the cardiovascular system, there are many other cardiovascular reflexes and responses mediating the neurological and humoral control of blood pressure and blood flow. These mechanisms are able to interact and enable one to predominate. Thus, for a resting individual, the baroreceptor reflex is probably one of the most important regulatory mechanisms, but this changes in other circumstances.

Severe haemorrhage

The response to progressive haemorrhage initially involves a baroreflex-mediated tachycardia in order to maintain blood pressure (Figure 6). As the haemorrhage progresses and becomes severe, however, there is a reflex increase in vagal tone to the heart and thus bradycardia, and sympatho-inhibition leading to a fall in vascular resistance and severe hypotension. At this point, the patient usually faints. This second phase is not the result of the baroreceptor reflex failing, but is due to the activation of a second ‘depressor’ reflex which seems to predominate over the baroreceptor reflex. Until recently, it was thought that this second reflex was a consequence of stimulating mechanoreceptors in the cardiac ventricular wall, which send afferent information via cardiac afferent C fibres in the vagus. More recent evidence argues against this being the afferent pathway, which is currently unknown. It is thought that this reflex may help protect the heart from ischaemic damage when coronary perfusion is low.

Visceral alerting response of the defence reaction

The visceral alerting response of the defence reaction prepares an individual to fight or flee from a threatening stimulus. It is characterized by a rise in both heart rate and blood pressure, with vasoconstriction due to sympatho-activation in many organs such as gut and kidney, but vasodilatation in skeletal muscle. The muscle vasodilatation results from an inhibition of the sympathetic vasoconstrictor activity and elevated blood adrenaline levels in this bed. In addition, the sympathetic cholinergic vasodilator fibres, in species where they exist, are activated. The benefit of this pattern of response is that there is an effective diversion of blood flow towards skeletal muscle in preparation for the increased demand during the ensuing vigorous muscular activity. This pattern is at variance with the baroreceptor reflex (increased blood pressure should cause a bradycardia and sympatho-inhibition in the vital organs as well as skeletal muscle). However, during the visceral alerting response, the baroreceptor reflex is temporarily inhibited at a number of sites in the medulla including the nucleus tractus solitarius and nucleus ambiguus.

Organization of the Body: Control of the Internal Environment

Iain Campbell

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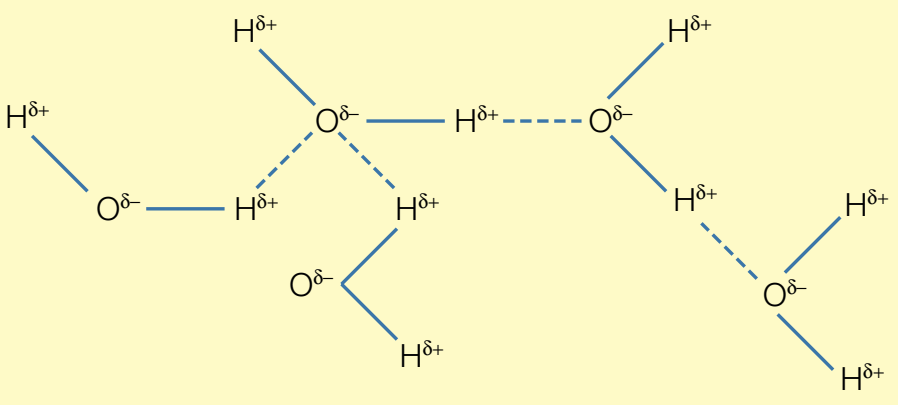
Polar and non-polar molecules

The mammalian cell comprises 70% water, 15% protein, 7% nucleic acids, 2% carbohydrate, 2% lipid, 1% inorganic ions and 3% other small molecules. The predominant substance, water, is made up of two atoms of hydrogen and one of oxygen and is described as 'polar.' A polar molecule has an overall charge, or an uneven distribution of charge on its surface. The most polar of small particles are ions (e.g. Na^+, K^+) which have lost an electron from their outer shell. However, even covalently bound molecules (e.g. water) demonstrate polarity by virtue of the uneven distribution of their electron 'cloud.' In water, the oxygen atom pulls electrons towards itself so the electron cloud is more dense over that part of the molecule, which is thus relatively more negative than it is over the hydrogen atoms. The partial negative charge over the oxygen atom is attracted to the partial positive charge over the neighbouring hydrogen atoms, and this weak 'hydrogen bonding' keeps the molecules together (Figure 1) and gives water its principal characteristic (i.e. a liquid, which, for the size of its molecule, has a relatively high boiling point).

Interactions between water molecules



Owing to the polarity of the water molecule (i.e. an uneven distribution of negative and positive charge) hydrogen bonding occurs between neighbouring molecules. This bonding is weak and bonds are constantly being formed and broken, but it accounts for the fact that water is a liquid whereas larger non-polar molecules such as methane and carbon dioxide are gases

1

The polarity of water contrasts with that of organic molecules, made up entirely of carbon and hydrogen ions (e.g. methane) which are non-polar. The carbon–hydrogen bonds lead to an even distribution of electrons so that the molecules do not interact with each other. Polar and non-polar compounds do not mix well; the water molecules bond together and exclude the non-polar substances, which may pack together because of their lack of interaction. There is some attraction between non-polar compounds, however, as a result of random variations in the density of the electron cloud, which results in minor transient degrees of polarity inducing opposite charges in neighbouring molecules and transient attractions between them; these are known as van der Waal forces. Their effects are small compared with the exclusion by water.

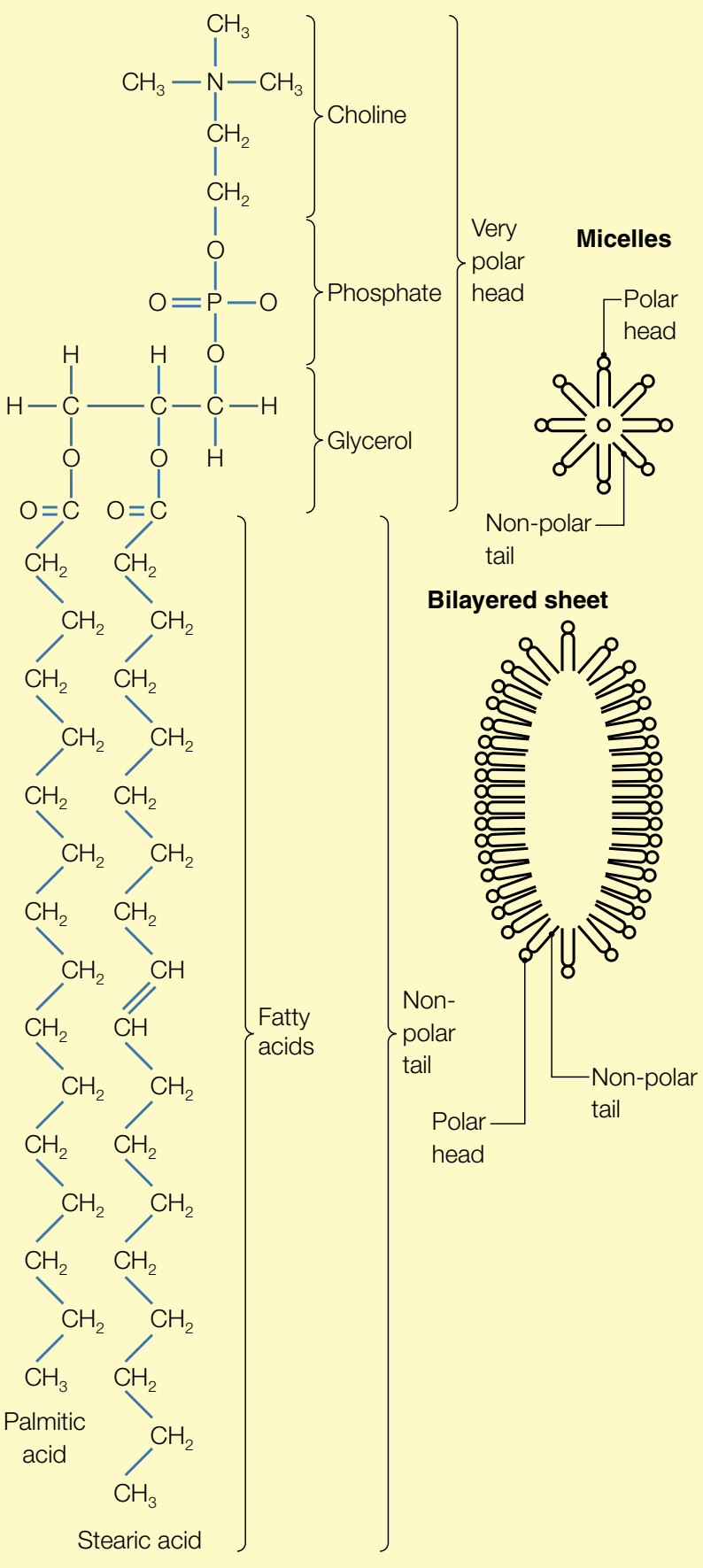
The state of polarity results from the fact that, compared with hydrogen, certain atoms are always electronegative. Biochemically, the important polar atoms are oxygen, phosphorus and nitrogen along with certain functional groups based on these atoms – the hydroxyl group (OH), the amino group (NH_2) and the orthophosphate group (OPO_3). Thus polar compounds, such as glucose (with a large number of OH groups), lactic acid (with a COO group) and other small metabolites, including most amino acids, form hydrogen bonds and are water-soluble.

Molecules that have both polar and non-polar regions, are partly soluble and partly insoluble in water and are described as 'amphipathic.' Amphipathic molecules submersed in an aqueous environment generally take up one of two configurations.

- As micelles they form spherical droplets with their polar heads facing outwards and their hydrophobic tails together in the centre.
- As bilayered sheets or membrane, their water-soluble heads are in the aqueous environment and their hydrophobic tails form the substance of the membrane. An obvious example of this is the phospholipids that make up cell membranes (Figure 2).

Cell membranes comprise two layers of these compounds, with the water-soluble polar phosphate head presented to the aqueous environment and the two layers of hydrophobic non-polar hydrocarbon lipid tails making up the body of the membrane. The structure and function of cell membranes is discussed on page 152. Molecules passing through such membranes have to traverse both the hydrophilic regions (comprising the polar phosphate heads of the phospholipid molecules) and the thickness of the hydrophobic interior (comprising the hydrocarbon chains of the fatty acids). Specific carrier proteins are embedded in the body of the membrane to facilitate these processes. Membrane transport is discussed on page 153, but in general, hydrophobic lipid-soluble substances traverse membranes more easily than do polar water-soluble ones.

Molecular structure of phospholipids



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Body water volumes

In the young adult male, 60% of the body is water; 40% intracellular fluid (ICF) and 20% extracellular fluid (ECF). Of the ECF, 5% is intravascular and 15% extravascular or interstitial (i.e. between the cells). The composition of the ECF resembles that of sea water but is more dilute.

The volumes of the various fluid compartments can be measured using dilutional techniques (Figure 3). A known amount of tracer, which remains in the compartment being measured, is injected or ingested. The volume of dilution (V) can be calculated from the total amount injected (M), from its final dilution in the compartment into which it is injected (m/unit volume) less the amount excreted (E) over the time it takes for mixing to occur: V= M-E/m.

The tracers commonly used for total body water measurement are tritiated or deuterated water, sodium bromide is used for ECF volume, and Evans' blue dye, labelled albumin, or red blood cells, with appropriate corrections made for haematocrit, are used for plasma. Plasma is normally 93% water. ICF volume is calculated from the difference between total body water and ECF volume.

The interstitial ECF bathes the outside of the cells and provides their immediate environment. The intravascular ECF provides the transport system for nutrients and waste products. The ECF is ultimately a medium of exchange between the cells and the external environment. Its principal cation is sodium. Interstitial ECF normally contains little or no protein. Other types of ECF, in addition to plasma, include lymph and CSF and transcellular fluid (e.g. eye humours). ECF makes up the immediate environment of the cells and its nature and composition is tightly controlled by the mechanisms discussed below (page 151). In contrast, the ICF is rich in potassium and poor in sodium. It contains protoplasm, a complex mixture of substances that includes most of the protein in the body and which shows the features of life:

- organization into specific structural units
- ability to enter into chemical activities that include the transformation of energy and the maintenance or synthesis of the protoplasm itself
- ability to respond to changes in the environment
- ability to grow and reproduce.

Tissues, organs and organ systems

Cells are units of protoplasm bounded by phospholipid membranes formed by the interaction of hydrophobic and hydrophilic molecules. Life as a single-celled organism is obviously vulnerable to the vicissitudes of the environment. It is directly exposed to the external world and does not have the physiological resources to protect itself. In multicellular organisms, the cells have differentiated to perform different functions and have taken on different roles such as movement, digestion and reproduction. When groups of cells are closely associated functionally they form a tissue of which there are four types.

Epithelial tissue comprises close-packed sheets of cells that cover the body surfaces and line the various cavities, tubes and hollow viscera. Apart from its structural role, epithelium may also secrete, absorb and filter.

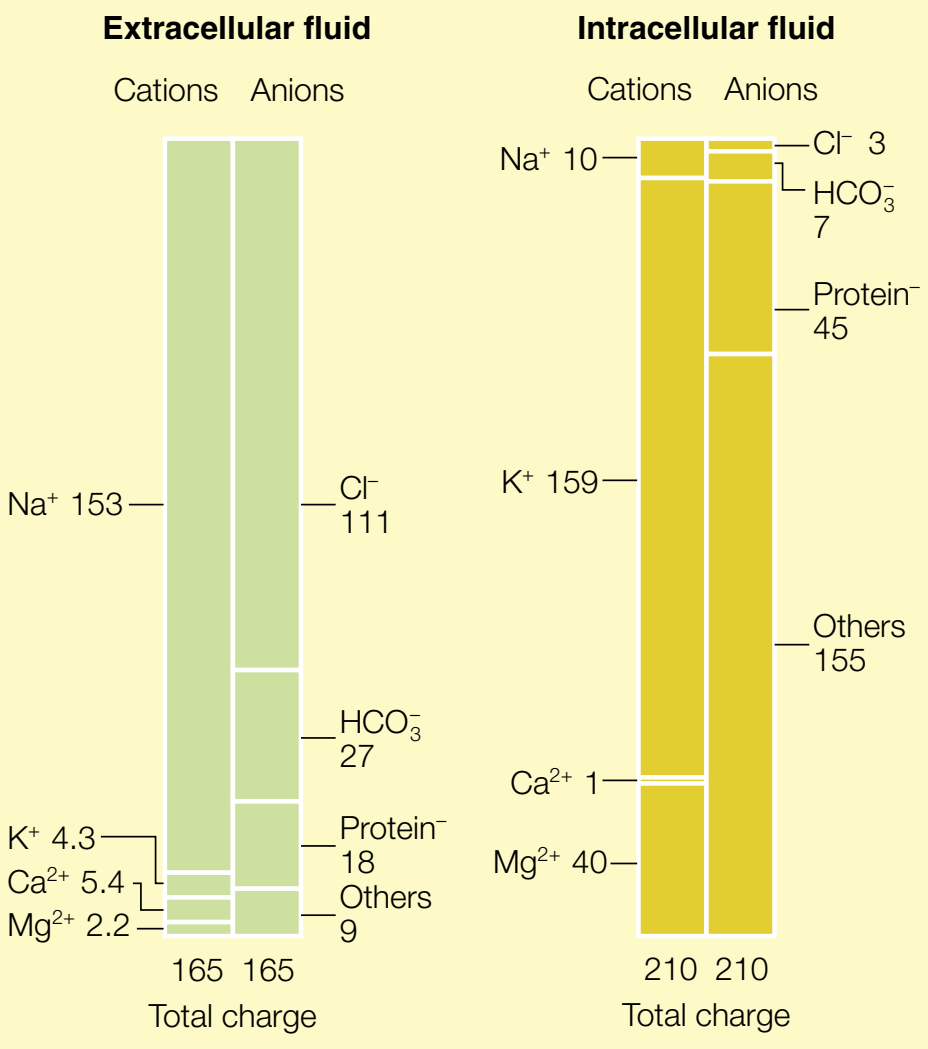
Connective tissue is the most widely distributed tissue in the body. Its cells are loosely arranged and separated by intercellular matrix, which contains fibres, soluble protein and crystalline complexes. It supports and partitions nearly all components of the body and its rearrangement determines growth. Connective tissue includes bone, cartilage, ligaments, blood and adipose tissue.

Muscle – there are three types of muscle. Skeletal muscle enables the body to move and react to external stimuli. Smooth muscle, in part, forms the walls of the gastrointestinal tract, the blood vessels and other hollow viscera (e.g. bladder, uterus). Cardiac muscle pumps blood round the cardiovascular system.

Nervous tissue constitutes the central (brain and spinal cord) and peripheral nervous systems (somatic and autonomic). Neurons are associated with glial tissue, which provides them with structural and metabolic support.

Tissues form organs and a variety of tissues may contribute to the formation of one organ (Figure 4). The gastrointestinal tract and cardiovascular systems, for example, are made of muscle lined by epithelium. The epithelium of the gastrointestinal tract secretes digestive juices and absorbs nutrients, and is under central (autonomic) nervous control with neural networks within the wall of the gut. Organs that share in the performance of related tasks are grouped into systems. These are classified as the cardiovascular, respiratory, gastrointestinal, nervous, locomotor, genitourinary and reticuloendothelial systems.

Constitution of intracellular fluid (muscle) and extracellular fluid (plasma water) and the tracers used to measure the various compartments



Figures are ionic concentrations in mmol/kg water. Total ionic concentrations are greater for intracellular fluid because many of the intracellular anions such as protein are polyvalent molecules. 'Other' intracellular anions are mainly organic phosphates such as creatine phosphate and ATP

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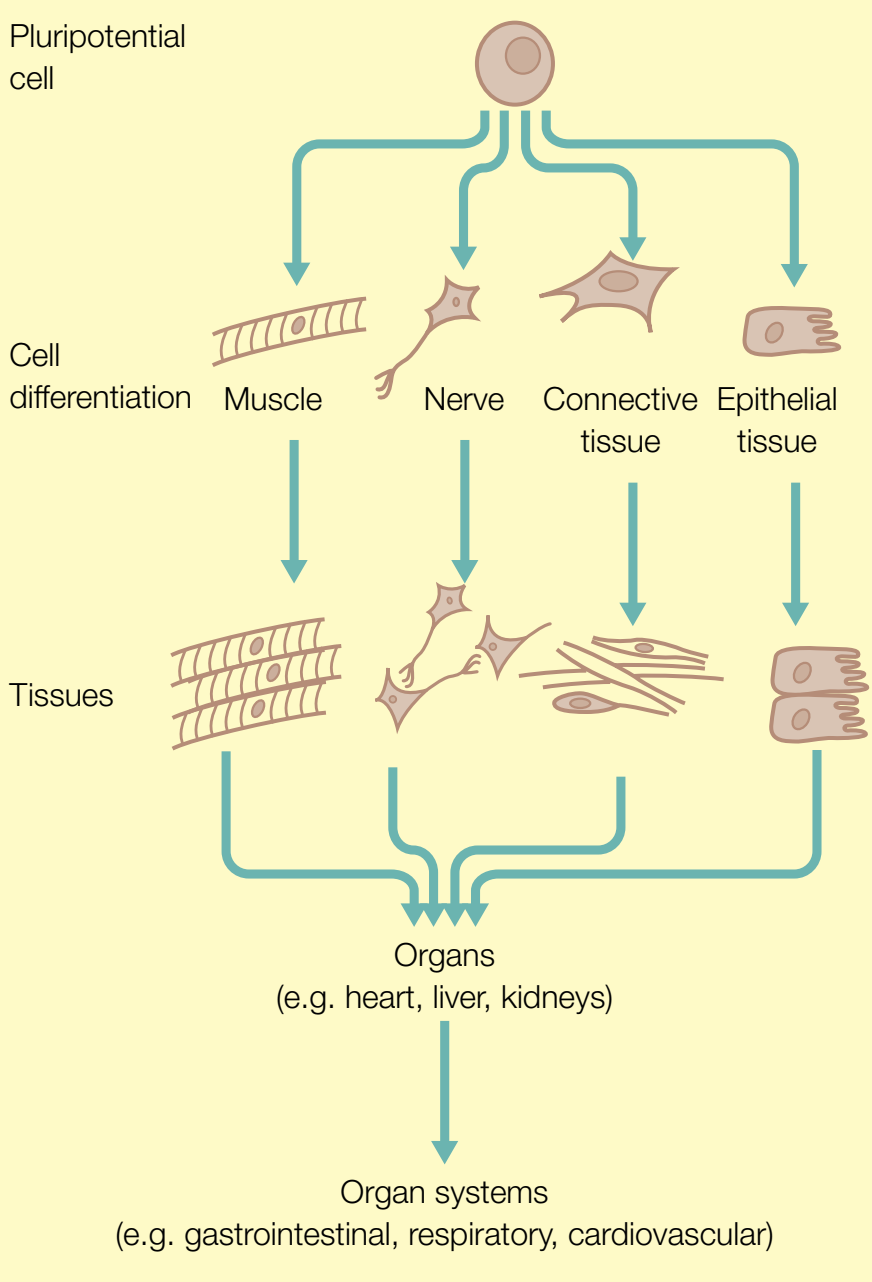
Organization of the body from cells to organ systems



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Control of the internal environment – homeostasis

For a living organism to function optimally, the internal environment (the composition of the ECF) has to be kept constant in terms of the Po_2, PCo_2, pH, osmotic pressure, temperature and concentrations of the various hormones, substrates, waste products and ions. Poikilotherms (e.g. reptiles) are unable to regulate their body temperature and are therefore sensitive to environmental conditions, but mammals maintain their body temperature in the face of wide variations in environmental temperatures and thus remain active under a variety of conditions.

Outside these tightly controlled conditions, function is suboptimal. The molecular basis for this is in the configuration of proteins. Proteins form the structural components of cells, the enzymes that catalyse biochemical reactions and the receptors and channels in cell membranes that connect the inside of the cell and the ECF. To function properly each protein has its own particular configuration or shape, which is a function of pH, temperature and ionic concentration. When conditions move outside of a relatively narrow range, protein configuration is altered and the ability to function properly is diminished or may be lost. Homeostatic mechanisms maintain the stability of the internal environment. They operate principally through the endocrine and nervous systems.

Control systems possess sensors to monitor variables and effectors to enable a response to alterations in that variable. The desired range of any variable is set, usually in the CNS, and any movement outside that range activates mechanisms that bring the variable back within range. For example, a rise in body temperature brought about by exercise results in peripheral vasodilatation and, depending on the severity of the exercise, sweating. This produces increased heat loss and a tendency for body temperature to return to normal. Most control systems are of the negative feedback type and work to restore the variable to the normal value. Some, however, incorporate positive feedback and these tend to destabilize. An example of this is seen when a rise in body temperature increases metabolic rate and thus heat production and raises body temperature further.

Sensors are situated centrally, usually in the hypothalamus, but there are peripheral sensors such as those for Po_2 and blood pressure which are part of, and transmit their signals via, the autonomic nervous system. Stimuli that activate the endocrine system may also be detected in the CNS or by special cells in the periphery, such as those in the pancreas that detect changes in blood sugar. The mechanisms that correct homoeostatic disturbances may be endocrine or neural, but generally the two systems work together.

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Osmolarity and Partitioning of Fluids

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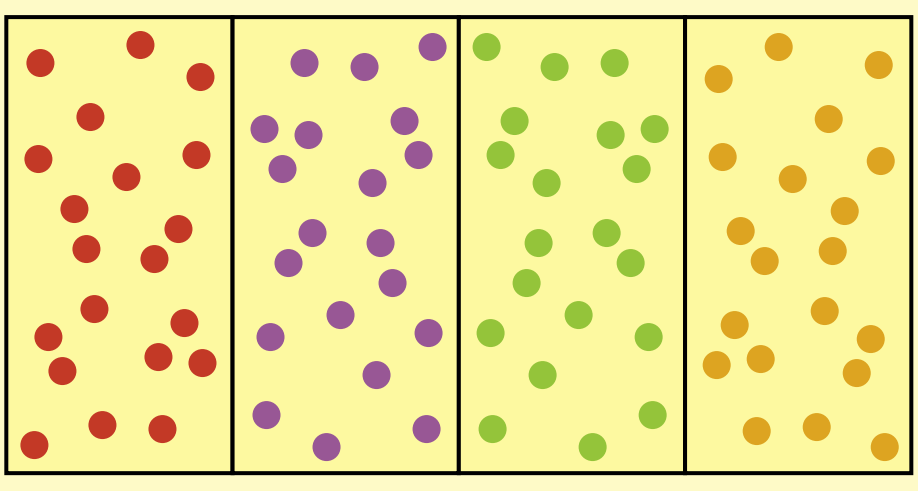
Diffusion

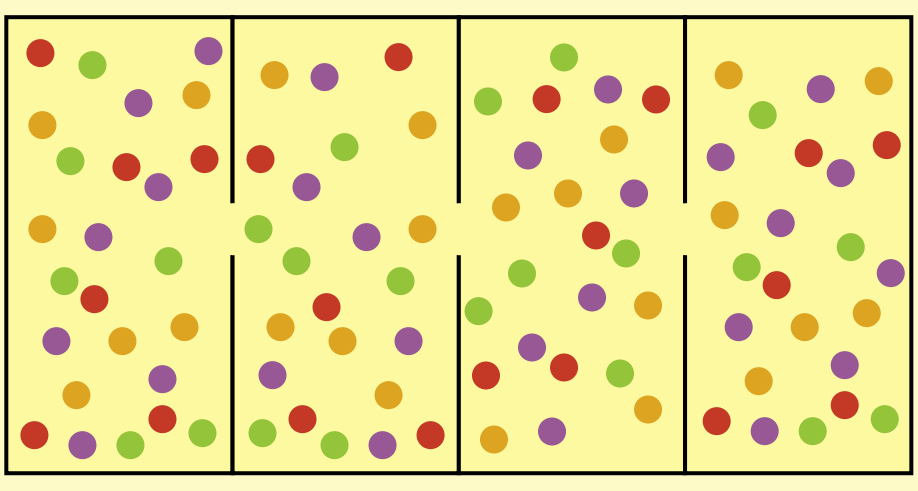
Substances move down concentration gradients. In nature, all molecules are in motion. The rapidity of the motion is proportional to the thermal energy (temperature) of the substance. In fluids (gases and liquids), this movement is random (Brownian motion). When fluids are mixed together, they diffuse down their own concentration gradients and come to a dynamic equilibrium such that the concentrations of the various substances in all parts of the medium are the same (Figure 1). The rate at which they come to equilibrium at a given temperature depends on their relative concentrations and, in the case of solutions, the solubility of the solute in the solvent. Gas molecules also diffuse in proportion to their own concentration gradients (partial pressures), as if they were the only type of molecule present, to become evenly distributed throughout the gas mixture, each contributing its own partial pressure to the whole.

Dynamic quilibrium

Four closed containers holding different gases



The resulting equilibrium if the gases are allowed to mix



Fluids move down their own concentration gradients and come to a dynamic equilibrium with concentrations dispersed equally throughout the medium

1

Diffusion of water (osmosis)
When two aqueous solutions of different concentrations are separated by a semipermeable membrane (permeable to water but not the solute), water moves from the weaker solution to the stronger one by the process of osmosis. In doing so it is moving down its own concentration gradient (i.e. from the solution with the higher water concentration to the solution with the lower water concentration).

The osmotic concentration of a solution depends on the number of particles present. Thus, in a molar solution of glucose, where the molecule stays intact, the osmotic effect is less than that of a molar solution of sodium chloride where the molecule dissociates. Osmotic concentrations are expressed in units called osmoles; in physiological solutions, which are usually weak, the unit is the milliosmole. The relationship between the molarity of a solution and its osmolarity depends on the number of particles derived from each molecule. Thus:

milliosmoles = millimoles x n
where n is the number of particles into which the solute dissociates.

For example, the osmotic concentration of a 60 mmol/litre glucose solution is 60 mosmoles/litre, but the osmotic concentration of a 60 mmol solution of sodium chloride is 120 mosmoles and a 30 mmol solution of calcium chloride is 30 x 3 = 90 mosmoles because calcium chloride dissociates into three particles.

Osmotic pressure is the force that water exerts in passing from a weak solution to a strong one. The osmotic pressure of a solution is given by:

$\pi = RTC$
where π *is* the osmotic pressure, R the ideal gas constant (0.082 litre.atmospheres/degree.mole), T the absolute temperature and C the concentration of a solute expressed in mosmoles/litre.

For a molar solution at 0°C (273° absolute) the osmotic pressure is 22.4 atmospheres. The osmotic pressure of a solution depends on the number of particles in the solution and not on the nature of the solute. The osmotic pressure of pure water is zero.

Osmolarity – the osmolarity of a solution can be measured directly using an osmometer. The freezing point of water is depressed when solutes are present, the extent of the depression being directly proportional to the amount of solute (number of particles), regardless of the nature of the solute. Osmometers work on the principle of freezing point depression. They are usually calibrated to give a readout of mosmoles. The osmolarity of body water is close to 300 mosmoles/litre.

Osmolality is often confused with osmolarity. Osmolality is expressed as osmoles/kg of solvent and osmolarity as osmoles/litre of solution. Biological solutions are mainly water therefore the two terms are virtually identical.

Regulation of cell contents

Most cell membranes are permeable to water, but cells control the amount of water that enters. They do this by adjusting their osmolarity by regulating, directly and indirectly, the amount of solute within the cell. The principal solutes are Na^+, K^+ and Cl^-, but they also include proteins, organic phosphates (e.g. ATP) and other metabolic intermediates. Charged ions do not move freely across the cell membrane; they pass via channels and carrier proteins, but water follows along the osmotic gradient to maintain the same osmotic pressures inside and outside the cell.

If an animal cell is placed in a solution that is hypo-osmolar, water enters the cell until the osmotic pressure inside the cell is the same as that outside. This causes the cell to swell. The RBC is capable of the largest increase in volume (up to 67% of its original), because of its shape, but most cells can accommodate only small changes. In extreme cases, holes develop in the cell membrane and the cell loses its intracellular contents, or bursts. At an osmolarity of 150 mosmoles, about 50% of RBCs lyse. In hyperosmolar solutions, water passes from the cell to the surrounding medium and the cell shrinks.

The electrochemical gradient
Ions are charged and therefore, in addition to following their concentration gradients, their direction of movement is influenced by electrical gradients. The tendency of Na^+ to move to the inside of a cell is favoured both by the concentration gradient (Na^+ concentration is low) and by the electrical gradient (the inside of the cell is negatively charged which attracts the positively charged Na^+), therefore both the electrical and chemical (concentration) gradients are in the same direction. In contrast, K^+ tends to move out of the cell, down its concentration gradient, but is opposed by its electrical gradient because the outside of the cell is positive relative to the inside. The electrochemical gradient is the combination of these chemical (concentration) and electrical forces. The two may favour movement in the same direction or oppose each other.

Weak acids and bases
At body pH, organic acids and bases exist in ionized and non-ionized forms. The non-ionized form passes relatively easily through membranes and, once on the other side of the membrane, it may ionize, to give up an H^+ in the case of an acid, or to accept an H^+ in the case of a base. This ionization prevents diffusion back through the membrane and it remains 'trapped' on the other side. An example of this is the role of NH_3 in the control of urinary pH. NH_3, a weak base, diffuses from the cells into the lumen of the kidney tubule where it buffers an H^+ to become NH_4^+. Because NH_4^+ is highly charged, it is unable to diffuse back and is therefore excreted in the urine.

Movement of substances across membranes

Substances pass through cell membranes by passive or active movement. They may move through a membrane in one direction by a passive process and in the other direction by an active one.

Passive movement
Passive transport of a substance occurs down a concentration gradient by simple diffusion, facilitated diffusion, or osmosis, in the case of water, and does not involve the expenditure of energy. It usually results in a less concentrated state overall. Facilitated diffusion allows for faster transfer of solutes across membranes than simple diffusion, but the system can become saturated if all the binding sites on the proteins become occupied. Unlike simple diffusion, the process is also specific because it involves binding of specific solutes to specific sites on the proteins.

Cell membranes are lipid bilayers and are selectively permeable because they are permeable to nonpolar molecules, but not to highly polar or charged molecules (e.g. ions). Lipid-soluble (nonpolar) molecules cross cell membranes by diffusion (i.e. from an area of high concentration to an area of low concentration), though their rate of movement through the bilayer may be slowed compared with their movement across the aqueous phase on either side. The two principal factors that affect movement through the membrane are solubility in the bilayer and the size of the molecule. Thus, small lipid-soluble molecules diffuse the most easily and large polar ones with the greatest difficulty. The exception to this is water, which is polar but manages to cross membranes freely, possibly via 'water channels.' Small water-soluble molecules (e.g. urea, glycerol) also diffuse relatively freely throughout the intra- and extracellular fluid.

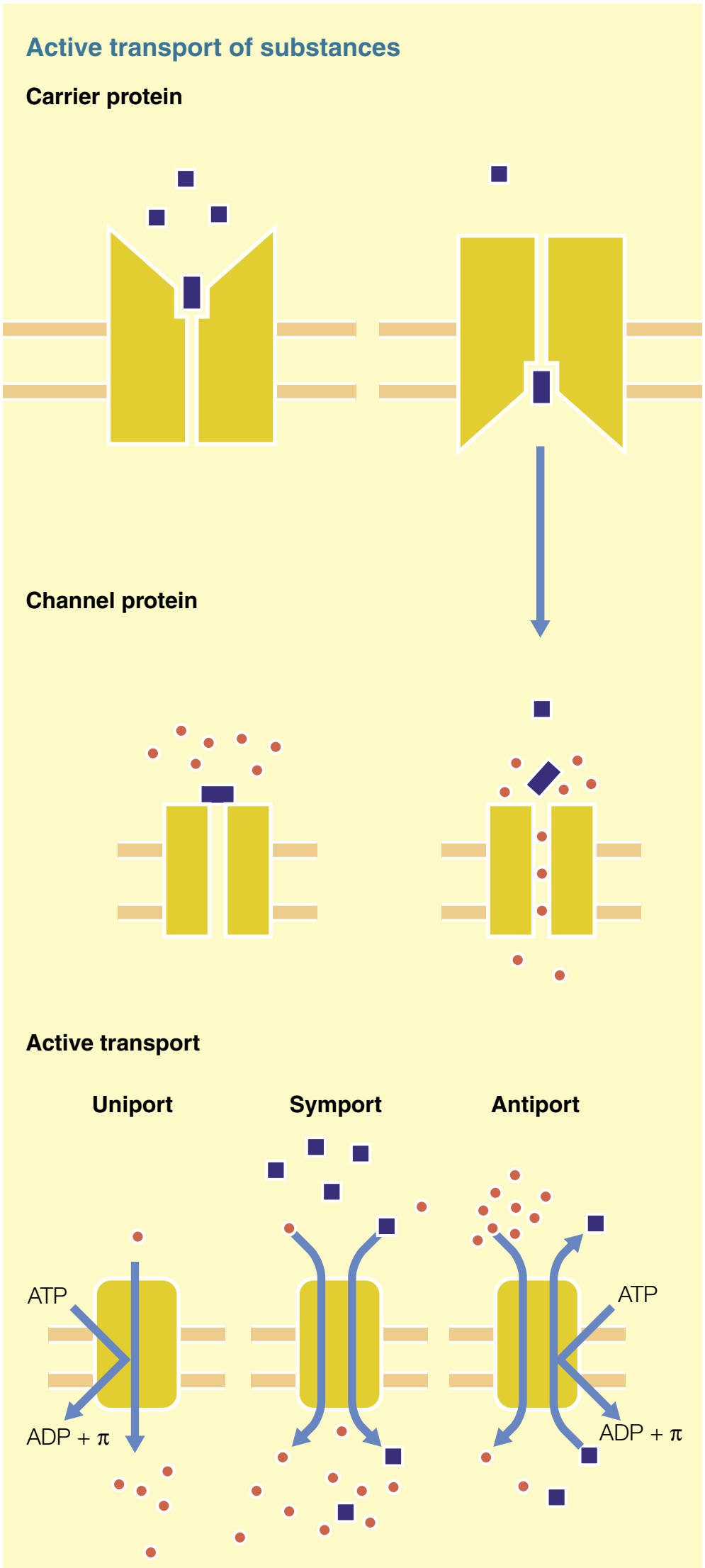
Carrier and channel proteins: strongly charged molecules (e.g. ions) and large water-soluble ones (e.g. amino acids, glucose) pass through membranes via specific carrier or channel proteins that span the bilayer by a process of facilitated diffusion (Figure 2). The intrinsic membrane proteins that act as carriers or channels move the solutes from one side of the membrane to the other and shield them from the lipid molecules. It is a passive process, following the electrochemical gradient, but differs from simple diffusion in a number of ways:

- it allows a high rate of transport
- it is saturable
- it is highly specific to the solute
- it can be blocked by competitive inhibitors.

Carrier proteins bind to a solute causing a conformational change in the protein. The solute then moves to the other side of the membrane where its concentration is low and it dissociates from the binding site. The protein reverts to its previous conformation and the process is repeated.

Channel proteins transfer ions from one side of the membrane to the other (more rapidly than carrier proteins do) and protect them from the surrounding lipid. This method of transport applies particularly to Na^+ and K^+, and the ions probably interact with charged groups in the channel, which quickens the transfer process. These channels are often held closed by 'gates' which open when certain voltages are detected in the surrounding membrane.

Active transport (Figure 2)
The movement of a solute across a membrane against a concentration gradient requires energy, usually in the form of ATP. When movement of the solute is coupled directly to an energy-yielding reaction, the process is known as primary active transport. When not coupled directly to an energy-yielding reaction, it is known as secondary active transport. Active transport generally results in a more concentrated state.



Molecules soluble in water move across membranes via carrier or channel proteins, either passively down their concentration gradient or against their concentration gradients. The latter movement involves the expenditure of energy (hydrolysis of ATP) either in the transport of a molecule (uniport), or the transport of two molecules in different directions (antiport). Symport usually exploits existing electrochemical gradients, but these are established by the expenditure of energy

Primary active transport: one type of ion can be transported singly across a membrane against its concentration gradient involving the expenditure of energy. The best known example of primary active transport is the Na^+/K^+-ATPase pump. Removal of a phosphate group from the ATP molecule provides energy to drive $3Na^+$ ions out of the cell and $2K^+$ ions into it, in both instances against the concentration gradient. Phosphorylation of the carrier protein is Na^+ dependent. This leads to a change in protein configuration which drives Na^+ out of the cell. The subsequent dephosphorylation triggered by the binding of K^+ allows the protein to return to its original configuration and moves the bound K into the cell.

Secondary active transport is energy dependent, but not coupled directly to the energy-producing reaction. A common example is a transport system driven by the energy stored in the electrochemical gradient of another solute, the gradient having been established by energy-consuming mechanisms. In animal cells, the solute is most commonly Na^+ moving intracellularly, the gradient having been established by the Na^+/K^+-ATPase pump.

Movement of solutes in the same direction as Na^+ is described as symport, coupled or co-transport. Movement in the opposite direction is known as antiport, exchange or counter transport. Na^+ binds to the protein carrier and this encourages binding of the solute even though the concentration may be low. A conformational change in the carrier then results in transport of the Na^+ and the solute through the membrane. With co-transport both Na^+ and solute move in the same direction, with exchange transport they move in opposite directions. The Na^+ then dissociates from the carrier because it is in a region of low Na^+ concentration and this causes the solute to dissociate from the transport protein, even though it is now in a region of higher concentration. Symport usually exploits ionic gradients, but counter transport may be linked to ATP hydrolysis.

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Pain, Spinal Cord and Senses

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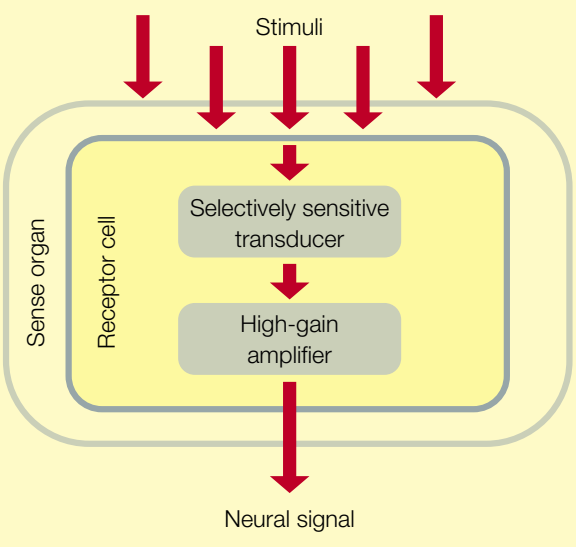
Pain

Pain is the perception of noxious stimulation by the CNS (Figure 1). Specific nociceptors encode noxious stimuli, but these are painful only if the CNS receives the information and reacts appropriately. If patients are given adequate levels of hypnotic agent and are therefore insensitive to noxious stimuli, or if they are given analgesics or local anaesthetics that block the transmission of nociceptor-sourced information, pain is not experienced even though the noxious stimulation is profound. Similarly, it is possible to induce states of intoxication or euphoria whereby noxious stimuli are perceived but are not interpreted as painful or of emotional importance. As a result, the threshold for a noxious stimulus to be perceived as painful depends on the individual and on the behavioural context of the stimulus. Since pain is a percept, it is also possible for the brain to be fooled into perceiving pain in the absence of nociception.

Typical receptor cell



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Surgical anaesthesia can be considered as chemically induced hypnosis in balance against the arousing effects of noxious stimulation on the CNS. Hypnotic anaesthetic agents lower cerebral metabolism, whereas ascending interneurons relaying the presence of noxious stimulation to the CNS potentially increase metabolic activity. By using appropriate analgesia, the threshold for perception of pain can be raised and therefore the level of hypnotic required to achieve a desired depth of anaesthesia can be reduced. It is difficult to assess the depth of analgesia accurately, and no commercial technique has been validated that measures the adequacy of analgesia.

Pain is generally classified depending on its duration and patient tolerance.
Acute – lasts for up to a few days and is mild or severe in magnitude. Nociceptive inut is presumed.

Sub acute – lasts a few days to months.

Recurrent acute – persistent nociceptive input from an underlying chronic process (e.g. arthritis).

Ongoing acute – uncontrolled cause with continuous nociceptive input.

Chronic – usually lasts more than 6 months. There is no peripheral nociceptive input. Pain can be enhanced by sensory input. Adequate patient coping.

Chronic intractable benign pain syndrome (CIBPS) – chronic pain with poor patient coping. Pain becomes the focus of the patient's attention. No peripheral nociceptive input.

Afferent nociceptive pathways – ascending spinal tracts

Spinothalamic tract is the most prominent ascending nociceptive pathway. It originates in both nociceptive-specific and wide dynamic range neurons in laminae I and V–VII of the dorsal horn, at which level it crosses the midline and ascends the anterolateral white matter to the thalamus on the contralateral side to the stimulus. As well as nociception, the corticospinal tract conveys information on temperature and crude touch. Electrical stimulation of the spinothalamic tract elicits pain.

Damage to the spinothalamic tract can lead to central pain. The ventroposterolateral thalamus receives input from the spinothalamic tract, and damage to it (Dejerine-Roussy syndrome) leads to spontaneous burning pain and dysaesthesia (abnormal sensation in regions where noxious stimuli are not normally painful).

Spinoreticular tract originates in laminae VII and VIII of the dorsal horn. Some axons form uncrossed projections to the reticular formation and thalamus.

Spinomesencephalic tract originates in laminae V and I and projects to the mesencephalic reticular formation, the periaqueductal grey area and other parts of the midbrain. There are also reciprocal connections to the limbic system, especially the amygdala, via the thalamus.

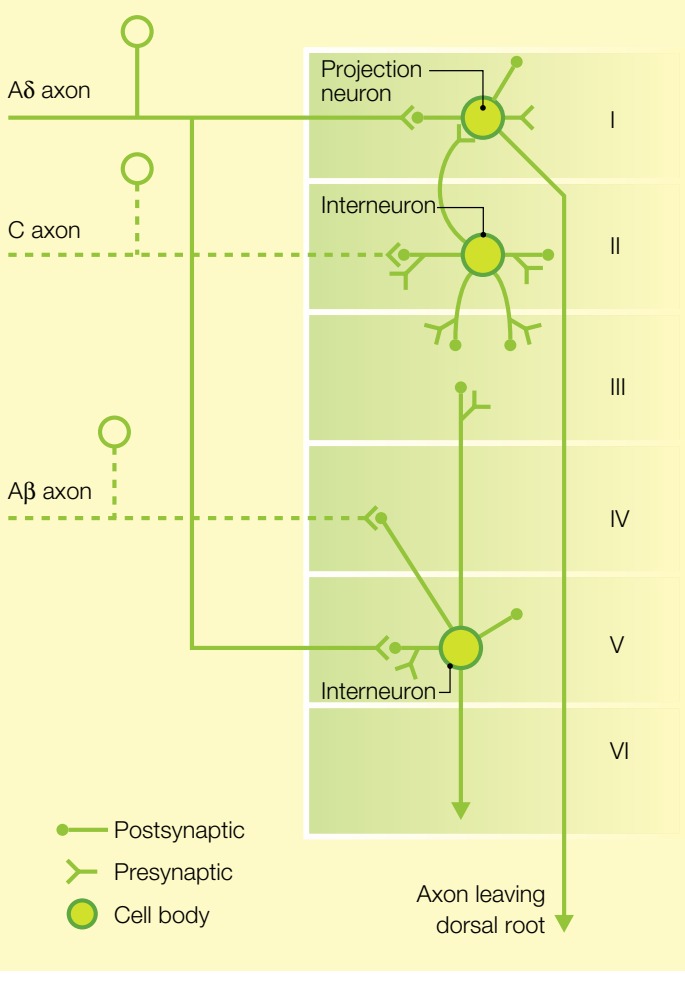
Cervicothalamic tract originates in laminae III and IV of the dorsal horn, projects to the lateral cervical nucleus, crosses the midline and ascends the median lemniscus to the midbrain and thalamus.

Spinohypothalamic tract originates in laminae I, V and VIII and projects to the supraspinal autonomic centres. It is implicated in cardiovascular control.

Dorsal horn

Without anaesthesia, the dorsal horn of the spinal cord is dominated by inhibitory activity (Figure 2). Light anaesthesia can cause disinhibition in the dorsal horn, altering the dynamic ranges of the neurons involved in nociception. Deep anaesthesia reduces the descending, neuromodulatory input into the dorsal horn from higher centres, and can lead to disinhibition of spinal reflexes. 'Industrially' (rather than pharmacologically) deep levels of general anaesthesia in animals lead to spontaneous movement, presumably by elimination of all spinal inhibition, so that reflexes in response to even the slightest noxious stimulus are not adequately damped.

Neurology of the dorsal horn



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Pain is not experienced in the spinal cord. The spinal cord receives nociceptive input and then gates and relays this on to higher centres where pain is perceived.

There are two types of nociceptor fibre (axon), both of which enter the dorsal horn. Fast Aδ fibres are thinly myelinated and conduct action potentials at 5–30 m/s. They are primarily responsible for the transmission of information regarding thermal and mechanical noxious stimuli. Slow C fibres are unmyelinated, and therefore conduct action potentials in the much slower range of 0.5–2.0 m/s. They are polymodal, transmitting information relating to a wide range of noxious stimuli. The nociceptive fibres bifurcate at the dorsal horn of the spinal cord, with Aδ fibres innervating laminae I and V, and C fibres innervating lamina II (Figure 3). Both Aδ and C fibres initiate the release of glutamate (causing fast synaptic potentials) and neuropeptides (e.g. substance P, causing slow synaptic potentials).

Types of fibres innervating laminae I–VIII

Lamina	Fibres	Significant function
I	Aδ	Nociceptive-specific neurons projecting to higher brain centres Wide dynamic range neurons responding to non-noxious and noxious mechanical stimuli Thermoreception
II	C fibres	Respond to noxious and non-noxious stimuli Interneurons
III	Aβ	Non-noxious stimuli, topographically mapped Thermoreception
IV	Aβ	Non-noxious stimuli, topographically mapped Low threshold mechanoreception Thermoreception
V	Aβ, Aδ, C	Nociceptors, local interneurons, visceral fibres Thermoreception
VI	Aα	Non-noxious proprioceptors (movement detectors)
VII	C	Bilateral polysynaptic nociceptors
VIII	C	Nociceptors

3

There are different populations of nociceptive (and related) neurons with cell bodies in the dorsal root. The laminae contain more than one type of cell, the borders of the laminae are not precise, and the inputs and responses of the neurons are not fixed.

Polymodal nociceptors respond to high intensity heat or cold, mechanical or chemical stimulation. They have slowly conducting (less than 1 m/s) unmyelinated C fibres.

Thermal nociceptors respond to temperatures greater than 45°C and less than 5°C. Mechanical nociceptors respond to heavy pressure on the skin. Both thermal and mechanical nociceptors have myelinated Aδ axons that are narrow in diameter and conduct action potentials at 5–30 m/s.

Free nerve endings in muscle encode noxious stimuli, and terminate in laminae I and V–VI. In the cornea, Aδ and C fibres encode mechanical stimuli, whereas C fibres encode thermal stimuli. In tooth pulp, Aδ fibres encode dentinal noxious stimuli and C fibres respond to external irritants.

Large diameter Aβ fibres are involved in the modulation of the nature of pain, even though the noxious stimuli actually stimulate receptors with C fibres. Temporary anoxia, as a result of prolonged inflation of a blood pressure cuff on the arm, results in the sensation of burning pain to stimuli that would normally be distinguished as individual pinpricks. This is because the Aβ fibres are more metabolically active than C fibres, and fail to conduct action potentials during such anoxia whereas the C fibres continue to function. The loss of Aβ fibres prevents proprioception and touch stimuli from being relayed to the dorsal column, so the perception of pain is distorted.

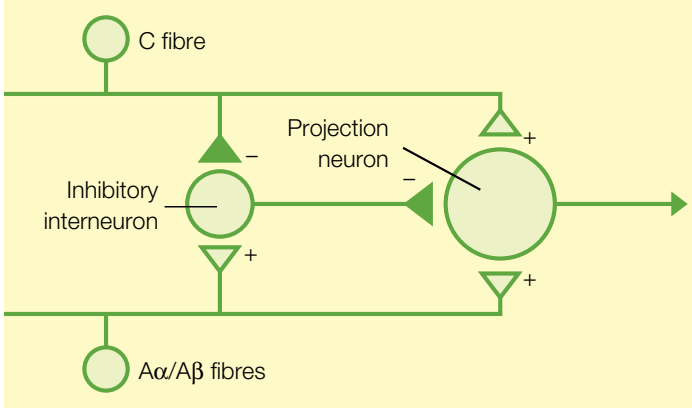
Central mechanisms

There is no central pain centre in the brain. However, functional imaging using positron emission tomography (PET) has demonstrated that emotional responses to a painful stimulus occur only with activation of the anterior cingulate cortex; lesions in the anterior cingulate reduce anxiety caused by pain. Areas S1 and the parietal operculum are important for judging the position and intensity of painful stimuli. The thalamus is vital for relaying information about noxious stimuli to these higher centres.

Neuromodulatory systems

Neuromodulation of the response to noxious stimuli at the level of the dorsal horn of the spinal cord is via descending monoaminergic neurons, originating in the raphe magnus nucleus of the medulla, and noradrenergic neurons, originating in the pons. Other, non-serotonergic interneurons in the medullary reticular formation probably also play a role in the descending neuromodulation of noxious response. The gate control hypothesis explains the modulation of nociception in the spinal cord (Figure 4). Important neurotransmitters in the dorsal horn are L-glutamate, adenosine triphosphate (ATP; causes fast depolarization), substance P (causes slow depolarization) and neurokinin A. Endogenous opiates (dynorphins and enkephalins) are found in the superficial dorsal horn. They may enhance or inhibit nociception; naloxone administered to the superficial layers of the dorsal horn can reduce the response to noxious stimuli, whereas naloxone in deeper layers can enhance the effect of nociceptors.

Modulation of nociception in the spinal cord by the gate control mechanism



The inhibitory interneuron is spontaneously active and would normally inhibit the projection interneuron, which transmits the nociceptive information to central regions that represent it as pain. Stimulation of Aα/Aβ fibres usually encoding the output from proprioceptors during movement or transcutaneous electrical nerve stimulation (TENS) results in excitation of the inhibitory interneuron which then blocks or 'gates' the input of slower nociceptive information from the C fibres

Visceral pain

Noxious visceral stimuli are conducted via both the sympathetic nerves leading to the spinal cord and the parasympathetic vagus nerves leading to the brainstem. The sympathetic nociceptive input ascends via the spinothalamic tract to the posterior thalamus. The parasympathetic nociceptive pathway is via the solitary nucleus of the medulla oblongata and on to the posterior thalamus and anterior cingulate. Functional imaging has shown that angina pectoris activates the hypothalamus, periaqueductal grey, thalamus and left anterior cingulate cortex.

The viscera have silent nociceptors, the activity of which is modulated by inflammation and chemical stimuli. Visceral afferents can continue to conduct noxious stimuli via the vagus nerves even in the presence of epidural or spinal blockade. The vagal nerves give a bilateral route straight into the medulla oblongata of the brainstem from organs such as the heart, stomach and lungs. 80% of vagal neurons are sensory, and most are slowly conducting C fibres. Vagal sensory input is associated with feelings of nausea. In addition, the burning sensation of tracheal intubation or use of a bronchial catheter can be abolished by blocking sensory fibres in the vagus nerve. Most of the sensory fibres of the vagus terminate in the nucleus tractus solitarius, which is rich in peptide neurotransmitters.

Sensitization and hyperexcitability

Sensitization occurs when, after repeated applications of a noxious stimulus, nearby nociceptors also start to transmit. This results from the presence of substances such as histamine, bradykinin and prostaglandins from the injured tissues. Aspirin is an effective analgesic because it blocks the function of the enzyme cyclooxygenase, thereby preventing the synthesis of prostaglandins. Central sensitization occurs in the dorsal horn after severe injury, whereby repeated C-fibre activity releases the excitatory neurotransmitter glutamate. Glutamate opens N-methyl-D-aspartate (NMDA) receptors and causes hyperexcitability in dorsal horn neurons, leading to hyperalgesia. Spontaneous pain and a lowered threshold for pain can both result from this wind-up of sensitivity. Phantom limb pain is an example of central sensitization, especially after amputation under general anaesthesia but with no spinal or local blockade, since the dorsal horn is still active and experiences the full nociceptive input of the amputation, leading to sensitization.

Neuropathic pain

Neuropathic pain is perceived after injury to nervous tissue, and is usually characterized as a burning or electric sensation. There are three specific classifications of pain that many have classified as 'neuropathic'.

Neuritis describes pain resulting from inflammation of a peripheral nerve. Inflammation of a nerve root is termed radiculoneuritis or radiculitis. Inflammation of the spinal cord is myelitis. The inflammation can result from a number of causes, including infection, nerve damage and toxins. Neuritis is usually acute. Treatments generally include rest and cooling of the affected region for the first few hours, followed by heat.

Neuralgia is centrally generated pain referred topographically to the periphery. An example is trigeminal neuralgia, in which repetitive, uncontrolled and abnormal firing of neurons in the trigeminal nucleus results in a referred pain.

Neuropathy: during neuropathy the axon or surrounding myelin sheath is damaged to such an extent that normal nerve conduction is disrupted or prevented. An example is seen in the last stages of shingles, after neuritis, when the sensory nerves have been permanently damaged. Transection of dorsal root nerves to block chronic pain can lead to anaesthesia dolorosa (pain without sensation) due to damage to the nerves. Diabetic neuropathy seldom results in pain, but can do if sensory fibres are damaged, which is more common in juvenile-onset diabetes.

Influence of therapy on nociceptive mechanisms

The gate control theory explains many mechanisms underlying therapeutic analgesia. Stimulation of fast fibres responsible for conveying non-nociceptive information 'close' neurological gates in the dorsal horn. Slow nociceptive afferents open these gates in the absence of non-nociceptive input. Vibration in the painful region activates fast proprioceptors that close the gates, preventing slower nociceptor input from reaching interneurons projecting to the brain.

Electrical stimulation of the brain, especially in the midbrain periaqueductal grey region, can induce profound analgesia. Stimulation in this region specifically reduces pain, while leaving the inputs from other sensory systems intact. This system works by stimulating descending interneurons that inhibit nociceptive neurons directly or via interneurons, in laminae I and V of the dorsal horn. The descending pathway projects from the periaqueductal grey region to the nucleus raphe magnus and other serotonergic nuclei, and then on to the dorsolateral funiculus and the dorsal horn. There are additional descending projections to the spinal cord from noradrenergic nuclei such as the locus ceruleus of the pons, and the nucleus paragigantocellularis.

Transcutaneous electrical nerve stimulation (TENS) has been used successfully as a treatment for pain. It is thought that it stimulates fast fibres that block the nociceptor input from being referred to higher centres.

Opioids

Opioid agents have the same central analgesic effect as electrical stimulation; morphine produces analgesia by activating the same descending pathways, and its effect is antagonized with injections of naloxone into the periaqueductal grey or nucleus raphe magnus. Transection of the descending pathways at the dorsal lateral funiculus also antagonizes stimulation and morphine-induced analgesia.

The three major classes of opiate receptor are μ, δ and κ. μ opiate receptors are found in high concentrations in the periaqueductal grey, the ventral medulla oblongata, and the superficial dorsal horn of the spinal cord. They are also widespread in the central and peripheral nervous system. Three endogenous opiates are known to bind to these receptors: enkephalins (leucine and methionine) bind to μ and δ receptors; dynorphin binds to the κ receptor; β-endorphin is primarily found in neurons of the hypothalamus that innervate the periaqueductal grey and noradrenergic nuclei of the brainstem. In addition to μ, δ and κ receptors, a nociceptin (QFQ/N1–17) receptor has also been identified, and is implicated in nociceptive, behavioural and physiological function.

Symptoms, other than analgesia, associated with the systemic use of opioids, such as constipation or respiratory depression can be explained by the presence of opiate receptors in the gut and medulla oblongata of the brainstem.

Spinal or epidural injection of opioids mimics the action of endogenous opiates and effectively closes the pain 'gates' so that nociceptive stimuli are not relayed via projection neurons to the CNS. Opioids decrease the duration of the action potential of nociceptors by influencing the calcium channels. This reduces the amount of neurotransmitter (e.g. glutamate and substance P) released at the synapses of the nociceptor. Opioids also hyperpolarize dorsal horn neurons by activating K^+ channels; opioids therefore reduce the amplitude of excitatory postsynaptic potentials.

Opioid receptors are also found on peripheral nerve terminals of skin, muscle and joints, but the source of endogenous opiates that target these receptors is unclear. Chromaffin cells of the adrenal medulla may be a source of these opiates, because they migrate to the source of injury during inflammation of tissue.

Spinal cord anatomy and blood supply

The adult spinal cord is about 50 cm long and occupies a volume of about 150 ml. The spinal cord extends to the second lumbar vertebra, below which the lower nerve roots extend. The anterior spinal artery supplies the ventral spinal cord and three spinal arteries supply the dorsal spinal cord. At its most rostral point, the anterior spinal artery is fed by the joining of two branches of the vertebral artery. Distally, segmental arteries of the aorta and iliac arteries feed the anterior and posterior spinal arteries via radicular arteries. The posterior spinal arteries are contiguous. The anterior spinal artery is not contiguous and depends on segmental supply, especially in the upper thoracic region. This anatomy leads to characteristic infarcts due to occlusion of the posterior spinal arteries affecting the territory of the anterior spinal artery. The anterior spinal artery produces sulcal arteries that enter left and right halves of the spinal cord alternately, leading to Brown-Séquard syndrome after infarct with characteristic ipsilateral weakness and contralateral loss of sensation to noxious stimuli and temperature. Damage to the corticospinal tracts alone leads to paraparesis or quadriparesis and loss of sensations of pain and temperature below the site of the lesion. If the dorsal columns are intact, proprioception and sensations of touch are maintained (Figure 5).

Effects of spinal cord section

Indicators of motor level lesions

Root	Major muscles	Reflex
Cervical 3–5	Diaphragm	
Cervical 5	Deltoid, biceps	Biceps
Cervical 7	Triceps, extensors of wrist and fingers	Triceps
Cervical 8	Interossei, abductor fifth finger	
Lumbar 2–4	Quadriceps	Knee jerk
Lumbar 5	Long extensors of great toe, anterior tibia	
Sacral 1	Plantar flexors, gastrocnemius	Ankle jerk

Indicators of sensory level lesions

Root	Sensory area
Cervical 4	Clavicle
Cervical 8	Fifth finger
Thoracic 4	Nipples
Thoracic 10	Umbilicus
Lumbar 1	Inguinal ligament
Lumbar 3	Anterior thigh
Lumbar 5	Big toe
Sacral 1	Lateral foot
Sacral 3–5	Perineum

Complete transection causes immediate trauma with the loss of voluntary movement and feeling below the level of the section. Bladder and bowel control is lost, but may become automatic after time. Normal tendon reflexes are absent as a result of spinal shock, which may recover over several weeks. Clonus (a rapid and repeated contraction of passively stretched muscle) is observed, as well as the Babinski sign, in which a pencil drawn from back to front over the plantar surface of the foot elicits an abnormal movement away from the direction of stimulus.

Partial transection – hemisection of the spinal cord (Brown-Séquard syndrome) causes ipsilateral loss of touch, vibration and positional sense and contralateral loss of noxious stimuli and temperature. Syringomyelia, in which cysts form in the central portion of the spinal cord, first affects nociception and temperature sensitivity, then when the cysts enlarge, touch and position sense are affected.

CSF

The choroid plexus generates about 700 ml of CSF per day. It travels in a predominantly one-way route from the ventricles, around the spinal cord, and into venous sinuses, and this removes metabolites from the CNS. The brain floats in CSF, reducing its weight *in situ* to about 50 g, and acting as a physical shock absorber against impact with the calvarium. The CSF allows peptide hormones to travel from the hypothalamus to other regions in the brain and the CNS. About 150 ml of CSF circulates in the brain and spinal cord.

CSF is usually clear and colourless and does not contain erythrocytes (Figure 6). Increased concentrations of leukocytes or protein make CSF look cloudy, and white cell counts above 4/mm^3 are abnormal. A bloody or yellow appearance (xanthochromia) occurs if the protein content exceeds 150 mg/dl or after a haemorrhage owing to the presence of bilirubin in the CSF. In multiple sclerosis, the γ-globulin content increases as a result of immunoglobin production within the CNS to comprise more than 13% of the total protein of CSF. Protein content greater than 500 mg/dl indicates a compressing lesion blocking the spinal subarachnoid space.

Comparison of typical CSF with serum

Component	CSF	Serum
Water (%)	99	93
Protein (ml/dl)	35	7000
Glucose (mg/dl)	60	90
Osmolarity (mOsm/litre)	295	295
Na^+ (meq/litre)	138	138
K^+ (meq/litre)	2.8	4.5
Ca^{2+} (meq/litre)	2.1	4.8
Mg^{2+} (meq/litre)	0.3	1.7
Cl^- (meq/litre)	119	102
pH	7.33	7.41

Source: Kandel E R, Schwartz J H, Jessell T M, eds. *Principles of Neural Science*. London: Elsevier, 2000.

CSF pressure can be measured by lumbar puncture from the lumbar subarachnoid space between the fourth and fifth lumbar vertebrae. Normal pressure is 65–195 mm H_2O or 5–15 mm Hg.

Senses

Sensory receptors

A typical sensory receptor cell consists of a selectively sensitive transducer and a high gain amplifier, contained within some form of structure to protect the receptor and amplify the stimulus. Sensory receptors are the interface between the environment (both external and internal) and the CNS. All that we see, hear, touch, smell and taste, along with our internal indications of balance and chemical environment, are represented as a result of a translation from energy into graded membrane potentials in sensory receptors.

The simplest receptors are free nerve endings responding to chemical agents. The most complex are involved in vision, where electromagnetic radiation is transduced into chemical electrical energy. In all sensory receptors, the greater the magnitude of an appropriate sensory stimulus, the greater the resultant amplitude of the receptor potential. Large excitatory receptor potentials result in a greater frequency of action potentials.

There are two main types of sensory receptor. Primary receptors generate action potentials within the receptor that propagate along axons into the CNS. An example is a stretch receptor within a muscle spindle. Secondary receptors generate graded receptor potentials that sum by reception of neurotransmitter by an interneuron. This causes some synaptic delay but allows for integration and modulation of the signal. Rods and cones in the retina are examples of secondary receptors.

Sensory receptors filter the environment into separate channels of information that can be perceived. For example, the concept of red, green and blue as individual colours is a perceptual classification of electromagnetic wavelengths. The fact that humans cannot see infra-red or ultra-violet radiation does not stop them from being useful visual wavelengths for other species.

The time taken to translate environmental stimuli from energy into perceived events is neither instantaneous nor consistent for different sensory modalities. The visual evoked potential (VEP) is the averaged electroencephalograph (EEG) response to thousands of visual stimuli. The first major peak of the VEP occurs 100 ms after a flash stimulus, and originates in the primary visual cortex (area V1) at the back of the brain. The primary visual cortex comprises different types of interneurons sensitive to the direction, thickness, width, velocity, colour and binocular disparity of everything seen. This means that everything seen is delayed by at least a tenth of a second from reality. Area V1 is only an early stage of visual processing, because the information from the retina and lateral geniculate nucleus contains raw, largely unprocessed visual information, and the completed cognitive response to a visual event occurs 300 ms after a stimulus. The auditory evoked potential (AEP) is faster than the VEP, indicating that sounds evoke a response in the primary auditory cortex about 40 ms after the stimulus. Resolving this difference in the temporal characteristics of different sensory inputs is a major task for the brain, which has to bind these varied virtual impressions together to make an internal projection of the world. Disorientation at recovery from anaesthesia, and with the use of hallucinogenic agents, can be partly explained by the partial breakdown of binding between these sensory inputs.

Visual system

Humans perceive colour because they have three different receptors in the retina (cones), peaking at 420 nm (blue), 531 nm (green) and 558 nm (red) wavelengths. Cones require more light to function than do rods, which are responsible for encoding light intensity. This explains why colour is not perceived at low light intensities; the colour is still reflected by objects, but is not perceived. Rods also exhibit more neural convergence in the retina, therefore they amplify the effect of available light at the cost of visual acuity, in contrast to the cones. The human retina is about two log units less sensitive to blue light than to red or green. Normal colour vision is trichromatic. About 5% of the male population exhibits congenital deuteranomaly, with an abnormality in the green cone pigment. 1.3% exhibit protanomaly, with abnormal red cone pigment, and 0.001% exhibit tritanomaly (blue cone pigment anomaly).

Increasing depth of anaesthesia progressively disrupts the visual system. It removes the ability of the visual cortex to process complicated visual information, including the texture of an object.

Auditory system

Auditory stimuli are encoded as a result of vibrations of frequency-tuned hair cells in the cochlea. The hair cells are paired and joined by a thin fibre that mechanically opens and closes ion channels in the hair cells as they move. The auditory information is relayed along the cochlear nerve and progressively through brainstem nuclei to the auditory cortices of the brain. Anaesthesia increases the time taken to process auditory information and reduces the magnitude of the AEP. Brainstem responses to auditory stimuli often remain during surgical levels of anaesthesia, meaning that patients can still potentially hear during surgery. Whether the auditory stimuli are perceived appropriately is unknown.

Other receptors

Temperature receptors are the simplest type of receptor in skin, being free nerve endings in the dermis and deeper epidermis. They adapt to stimuli slowly. Thinly myelinated Aδ fibres (1–5 µm in diameter, conducting at 5–30 m/s) encode cooling or pricking noxious stimuli. Unmyelinated C fibres (0.2–2 µm in diameter, conducting at 0.5–2 m/s) encode warming, burning and itching stimuli. If high temperatures damage the free nerve endings, they can release bradykinin, which results in a sticking or jabbing pain.

Mechanoreceptors function by distorting the cell membrane pulling an ion gating protein against an anchoring site within the neuron, such as a more rigid part of the cytoskeleton. The distortion affects the bias of the opening and closing frequency of the ion gate; stretch receptors can be activated or deactivated by distortion, and can be specifically permeable to potassium, calcium, sodium or chloride ions. Receptors such as the carotid sinus or hair cells in the ear can transduce structural distortion using such stretch mechanism. Cell swelling due to changes in osmolarity can also trigger stretch-activated or stretch- inactivated channels.

Osmoreceptor cell bodies are located in the hypothalamus, with axons leading to the pituitary. Osmoreceptors encode changes in the osmolarity of blood, and secrete the hormones oxytocin and vasopressin to modulate plasma osmolarity.

Olfactory receptors initiate a second messenger cascade, that eventually opens cyclic nucleotide-gated ion channels and depolarizes the olfactory cell membrane, and can elicit action potentials when enough channels are opened. ◆

FURTHER READING

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The Pancreas

Garry Tan

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The pancreas weighs 70–100 g, yet secretes 1000 g of pancreatic fluid daily. Most cells in the pancreas have an exocrine function, manufacturing digestive enzymes. A small proportion of pancreatic cells (about 1 million) are aggregated into small clusters (tens of cells to several thousand cells) and are scattered throughout the exocrine cells. These aggregations, the islets of Langerhans, contain at least four different cell types (Figure 1) which are densely innervated with autonomic and peptidergic nerves. Despite accounting for only 2% of the mass of the pancreas, the islets receive 10% of the pancreatic blood flow.

Pancreatic islet cell secretion

Cell type	Proportion of islets cells	Peptides secreted	Anatomical distribution
α	25%	Glucagon (GLP-1, GLP-2)	Within islets throughout the pancreas with a preference for pancreatic tail and body
β	60–70%	Insulin, c-peptide (islet amyloid peptide)	Within islets throughout the pancreas
δ	5–15%	Somatostatin 12 and 14	Within islets throughout the pancreas
PP	2%	Pancreatic polypeptide polypeptide (and small amounts of gastrin)	Within islets throughout the pancreas with a preference for posterior portion of the head Also found in acini

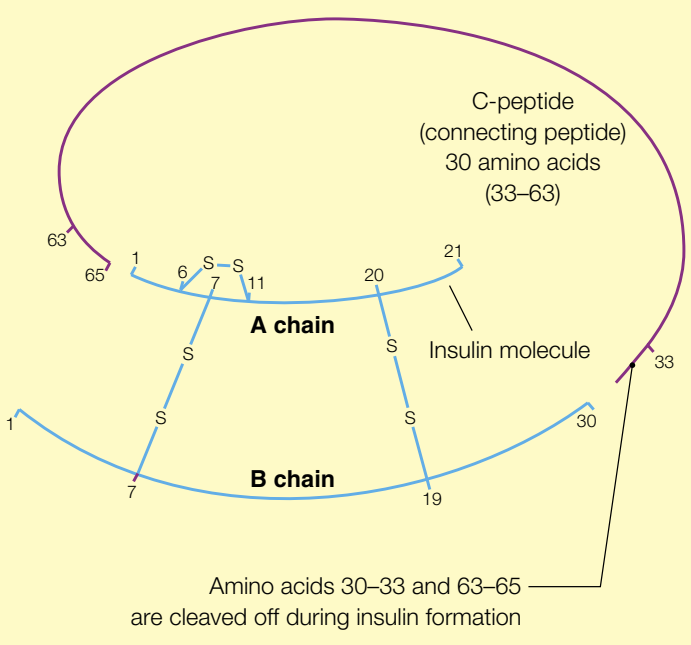
1

Endocrine pancreas

Insulin and c-peptide

Insulin is a polypeptide consisting of two peptide chains, A and B, linked by two disulphide bridges (Figure 2). It is synthesized as preproinsulin, a precursor of insulin. Preproinsulin is cleaved in the endoplasmic reticulum to form proinsulin which is itself cleaved in the Golgi apparatus, to form insulin and c-peptide. These are stored in granules in the β-cell cytoplasm to await secretion. Glucose is one of a number of stimuli that can cause β-cell degranulation and insulin release. In order for glucose to do this, it must first be metabolized; glucose enters the β-cell via the GLUT-2 glucose transporter and is phosphorylated by the enzyme glucokinase (this is the rate-limiting step of islet glucose use). The resulting glucose-6-phosphate undergoes glycolysis to produce ATP. The ATP-sensitive K^+ channels in the cell membrane close, causing membrane depolarization. This causes a calcium influx into the cell as calcium channels open. This leads to granule exocytosis and insulin (and c-peptide) release. Insulin and c-peptide are released into the circulation in equimolar amounts. Insulin circulates as unbound monomers, in contrast to its state before release from the secretory granule, when it forms insulin hexamers around a core of two zinc molecules (pharmaceutical preparations of insulin are based on crystalline zinc insulin).

Insulin



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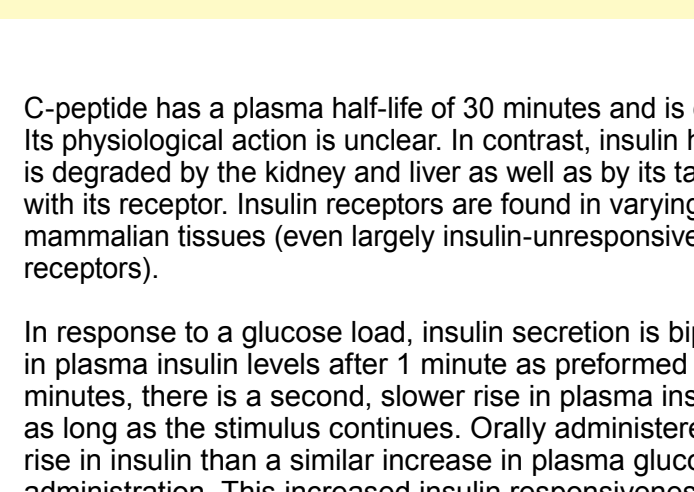
C-peptide has a plasma half-life of 30 minutes and is excreted unchanged by the kidneys. Its physiological action is unclear. In contrast, insulin has a half-life of 4 minutes and is degraded by the kidney and liver as well as by its target cells where it is internalized with its receptor. Insulin receptors are found in varying concentrations on virtually all mammalian tissues (even largely insulin-unresponsive red blood cells possess about 70 receptors).

In response to a glucose load, insulin secretion is biphasic: there is a sharp peak in plasma insulin levels after 1 minute as preformed insulin is released. After 5–10 minutes, there is a second, slower rise in plasma insulin levels which continues for as long as the stimulus continues. Orally administered glucose induces a greater rise in insulin than a similar increase in plasma glucose achieved by intravenous administration. This increased insulin responsiveness is partly due to the production of glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP) which also act as insulin secretagogues (stimulators of insulin secretion). Amino acids are insulin secretagogues and act synergistically with glucose. The levels of ketoacids found in fasting can also promote insulin secretion. Factors affecting insulin release are shown in Figure 3.

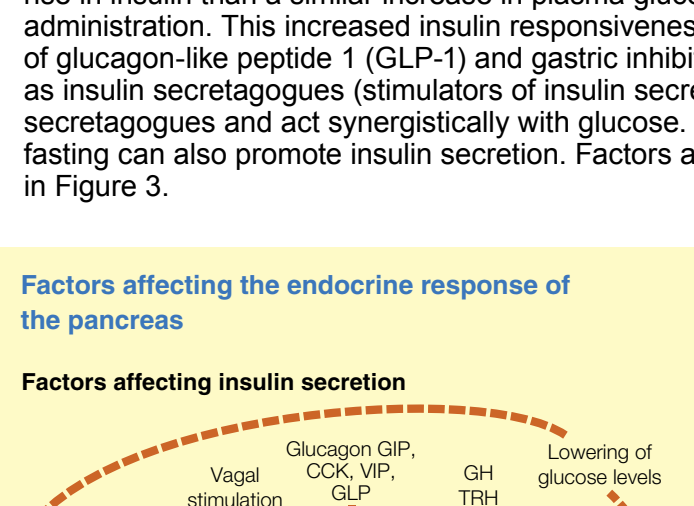
Factors affecting the endocrine response of the pancreas

Factors affecting insulin secretion

Factors affecting glucagon secretion



Factors affecting somatostatin secretion



ACTH, adrenocorticotrophic hormone; CCK, cholecystokinin; GH, growth hormone; GLP-1, glucagon-like peptide 1; GIP, gastrointestinal peptide; NEFA, non-esterified fatty acids; TRH, thyroid releasing hormone; VIP, vasoactive intestinal peptide

3

After binding to its receptor at the cell surface, insulin causes rapid shifts in the fluxes in various metabolic pathways by the activation or deactivation of enzymes at critical steps. It also leads to alterations in gene expression (e.g. inducing glucokinase gene expression) thus reinforcing the metabolic shifts.

Insulin promotes the storage of excess nutrients while inhibiting mobilization of endogenous substrates. It is required for the entry of glucose into most cells, particularly muscle (skeletal and cardiac) cells. The brain and red blood cells are exceptions in which glucose diffuses down a steep concentration gradient into these cells. Insulin also stimulates glycogen formation from glucose in muscle and liver while simultaneously inhibiting glycogen breakdown in the liver. This produces a reduction in the intracellular concentration of glucose in hepatocytes. Glucose diffuses into hepatocytes down this gradient through the GLUT-2 transporter. In contrast, insulin actively enhances glucose uptake into myocytes and adipocytes by inducing GLUT-4 expression (another specialized plasma membrane glucose protein transporter – the only one to be induced by insulin).

In adipose tissue, insulin inhibits mobilization of intracellular triglycerides by uppressing hormone-sensitive lipase activity. Because of this, circulating non-esterified fatty acid (or free fatty acid) levels fall. The resulting fall in their delivery to the liver causes a decrease in their β-oxidation and hence a decrease in the production of ketone bodies.

Other effects of insulin include an anabolic effect on protein metabolism and the promotion of potassium, phosphate and magnesium uptake into muscle cells. The renal tubular reabsorption of potassium, phosphate and sodium is increased. The insulins of different animals differ slightly in their amino acid sequence but have identical biological actions.

Glucagon

Glucagon is a 29 amino acid peptide produced from proglucagon in α-cells. Proglucagon is also synthesized in the gut where it is processed differently to produce GLP-1. The factors affecting glucagon secretion are shown in Figure 3; the stimulating and suppressing factors interact. For example, the suppression of glucagon production by high glucose concentrations is potentiated in the presence of insulin. Despite this, plasma glucagon levels vary less than plasma insulin levels.

Glucagon promotes mobilization rather than storage of fuels, particularly glucose, maintaining normoglycaemia in the presence of an increased glucose demand. Glucagon binds to a hepatic membrane receptor and prompts a cascade of intracellular events involving cAMP as a second messenger, to activate or to deactivate a number of enzyme kinases or phosphatases. The net result is a rapid increase in glucose production from glycogen breakdown, in tandem with a decrease in glycogen synthesis from glucose. Similarly, hepatic gluconeogenesis (e.g. from lactate, pyruvate, amino acids such as alanine) is increased while glycolysis is decreased. Glucagon also diverts incoming non-esterified fatty acids from triglyceride synthesis to β-oxidation, leading to ketogenesis. Hepatic cholesterol synthesis is also suppressed as hepatic hydroxymethylglutaryl CoA reductase is inhibited by glucagon.

Other actions of glucagon include activation of myocardial adenyl cyclase, increasing the cardiac output. It also causes natriuresis by inhibiting renal tubular resorption. In adipose tissue, glucagon also increases hormone-sensitive lipase activity.

Somatostatin
Somatostatin is produced as prosomatostatin which is processed to produce a 14 amino-acid peptide variety of somatostatin (SS14). Prosomatostatin is also produced in intestinal cells but is processed differently to form a 28 amino-acid product (SS28). Within the islets, SS14 is a potent inhibitor of insulin, glucagon and pancreatic polypeptide secretion. SS28 decreases gastric, duodenal and gall bladder motility and gastrointestinal secretions, thus enabling nutrient input to be co-ordinated with substrate disposal.

Islet amyloid peptide
Islet amyloid peptide (amylin) is a 37 amino-acid peptide. It is regulated in a similar fashion to insulin. It accumulates in β cells with age and its accumulation is further increased in type II diabetes mellitus. Its physiological role is unclear.

Pancreatic polypeptide
Pancreatic polypeptide is a 36 amino-acid peptide secreted in response to feeding or hypoglycaemia. It is regulated by the autonomic nervous system. Its physiological role is unclear.

Coordination of insulin and glucagon action
The pancreatic endocrine products act in concert to regulate the metabolism of glucose, non-esterified fatty acids, amino acids and other substrates (Figure 4). As insulin and glucagon usually have antagonistic effects, the direction of substrate fluxes through the metabolic pathways is partly determined by the insulin:glucagon ratio. The usual molar ratio is 2:1, but it changes to 1:2 when mobilization of endogenous substrates is required, such as during fasting or prolonged exercise. The change in the ratio is caused by a simultaneous decrease in insulin secretion and an increase in glucagon secretion, promoting glycogenolysis and gluconeogenesis in the liver and lipolysis in adipose tissue, as well as increasing the flux of non-esterified fatty acids to the liver for β-oxidation.

Effects of insulin and glucagon on metabolism

	Insulin	Glucagon
Liver		
Glycogen synthesis	+	–
Glycogenolysis	–	+
Gluconeogenesis	–	+
Glycolysis	+	–
De novo lipogenesis	+	–
Non-esterified fatty acid oxidation	–	+
Protein catabolism	–	+
Muscle		
Glycogen synthesis	+	
Glycogenolysis	–	
Glucose uptake	+	
Protein synthesis from amino acids	+	
Adipose tissue		
Glucose uptake	+	+
Lipolysis	–	

In the postprandial state, the insulin:glucagon ratio can rise to more than 10:1, primarily because of increased insulin secretion. This ensures increased glucose uptake along with oxidation and storage of glucose as glycogen in muscle and liver. Adipose tissue lipolysis by hormone-sensitive lipase is suppressed; postprandially non-esterified fatty acids are not required.

The endocrine activity of the pancreas is regulated by a variety of factors as well as glucose (Figure 3). For example, while parasympathetic activity stimulates insulin and glucagon secretion, sympathetic activity increases glucagon but decreases insulin secretion. The response of the pancreas depends on the predominating influence. For example, in minor injury, the glucose levels are raised and the insulin levels elevated appropriately. In contrast, in a more serious injury, when there is marked sympathetic activation and the circulating adrenaline levels are elevated, the insulin secretion is not as high as might be expected for that degree of hyperglycaemia.

Exocrine pancreas

The secretory units of the exocrine part of the pancreas are groups of cells, known as acini, surrounding the ends of small ducts. These ducts feed into a centrally located pancreatic duct which drains into the hepatic duct and from there into the duodenum. The acinar cells secrete a fluid rich in digestive enzymes, which can digest proteins, carbohydrates, nucleic acids and fat. In general, these digestive enzymes are secreted as proenzymes. The epithelial cells lining the ducts secrete water and bicarbonate ions. This alkaline pancreatic juice (pH 8) neutralizes the hydrochloric acid from the stomach and provides the optimal conditions for the digestive enzymes to function. The pancreatic juice contains the highly active pancreatic amylase which digests starch and glycogen in the small intestine to di- and tri-saccharides.

Proteins are cleaved to smaller peptides by trypsin and chymotrypsin. Trypsin is the most abundant protease secreted. Carboxypolypeptidase further divides the peptide fragments into their constituent amino acids. Pancreatic proteases are secreted in an inactive form and are activated in the duodenum. Enterokinase, a membrane-bound intestinal enzyme activates trypsinogen to its active form, trypsin. Trypsin activates procarboxypolypeptidase and chymotrypsinogen. To prevent pancreatic autodigestion, the acinar cells also produce ‘trypsin inhibitor’. This prevents activation of trypsinogen in the secretory cells and in the ducts of the pancreas.

Protein and carbohydrate breakdown occur in various parts of the gastrointestinal tract. In contrast, fat digestion occurs only in the small intestine as the pancreas is the only source of intestinal lipase (pancreatic lipase). Pancreatic amylase and lipase are secreted in their active forms.

DNA and RNA are hydrolysed to their nucleotide monomers by pancreatic nucleases.

Pancreatic exocrine secretion is regulated by a number of factors that are part of the response to food of the gastrointestinal tract. Acid from the stomach causes S cells in the duodenal and upper jejunal mucosa to release secretin which causes the secretion of pancreatic fluid and bicarbonate. Secretin causes virtually no pancreatic enzyme secretion.

Stimuli such as long-chain fatty acids and peptides in the duodenum cause the release of cholecystokinin from the I cells of the duodenum and upper jejunal mucosa. Cholecystokinin stimulates the acinar cells of the pancreas to increase digestive enzyme secretion.

Both secretin and cholecystokinin pass from the upper gastrointestinal tract to the pancreas by the blood stream.

Vagal stimulation (and acetylcholine secretion by the enteric nervous system) causes the pancreas to secrete digestive enzymes (though few reach the gastrointestinal tract because vagal stimulation causes the pancreatic fluid secretion to ‘wash’ the enzymes along the pancreatic duct). Vagal stimulation can occur during the cephalic phase or as a result of the presence of food in the stomach.

It is important to emphasize that these stimuli of pancreatic secretion usually occur in concert and exert a multiplicative effect on one another. The response of the pancreas to

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Physiology of Ageing

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The processes that underlie the changes of biological ageing affect all tissues, organs and systems to some extent. As a general rule, functions most critical for survival exhibit the least marked changes, whereas systems that are less critical may show marked changes (Figure 1). Ageing processes alone are benign and seldom threaten life. Of more concern are the interactions between ageing changes and co-morbid factors, which may not be immediately apparent. This contribution focuses on the systems of most relevance for a practising anaesthetist.

The newer drugs available for anaesthesia and effective physiological monitoring, make anaesthesia extremely safe for older people, provided they are medically stable at the start of the procedure. Greater threats to homeostasis derive from the nature of the surgical procedure, the abilities of the surgeon and the quality of postoperative care and monitoring.

The World Health Organization classifies those aged 65–75 years as 'young elderly', those aged 75–85 years as old, and those over the age of 85 years as the 'oldest old'. As a rule, the young elderly are physiologically similar to younger age groups and most changes of clinical relevance occur in those aged over 75 years.

Some ageing changes expressed as a percentage of young adult values

Little change

- Body temperature
- Body fluid pH
- Resting heart rate
- Pa_{O_2}

60–70% change

- Maximum heart rate
- V_{O_2} max
- Resting cardiac output
- Renal blood flow
- Urine-concentrating capacity

1

Cardiovascular system

The ECG is a sensitive screening tool for heart disease in older people. Prevalence rates of 5–20% have been reported; the highest rate occurring in the oldest men, and the lowest in the youngest women. Most abnormalities suggest underlying coronary artery disease. Atrial fibrillation is the most common dysrhythmia, and occurs in 1–5% of old people. Hypertension is common in older people, and the prevalence is 20–25% at the age of 70 years. The prevalence of valvular heart disease in the general elderly population is uncertain, but it is the third most common cause of heart failure (after ischaemic heart disease and hypertension).

The ability of the myocardium to generate force does not decline with ageing, though both contraction and relaxation are prolonged by 15–20%. Healthy older people have ejection fractions of 50–75%. The changes in contractility caused by ageing are related to cellular changes in the excitation–contraction coupling mechanism, and may be an adaptation to sustain contractility in the face of an increasing afterload.

Afterload increases modestly with age, in association with a decreasing arterial compliance. Thus, systolic blood pressure and pulse pressure tend to increase with age. Diastolic pressure also tends to increase, but to a lesser extent. The left ventricle reactively hypertrophies to reduce the wall stress imposed by the elevated afterload. Decreased ventricular compliance and impaired diastolic relaxation reduce early diastolic filling (a passive phenomenon) and old people depend on late filling, mainly from atrial contraction. Thus, they tolerate rapid heart rates from any cause poorly, and atrial tachydysrhythmias particularly poorly.

Responsiveness to β-adrenergic stimulation declines with age (as a result of decreased receptor numbers and function), despite age-related increases in circulating catecholamine concentrations. However, responses to α-adrenoreceptor activation are unimpaired. Thus, the ability to increase cardiac output by increasing heart rate is attenuated, and the old become more reliant on the Starling mechanism. Even with relatively mild circulating blood volume reduction, cardiac output can fall precipitously in some older people, and therefore is to be avoided.

Respiratory system

Changes in respiratory function are caused by ageing and external factors. In some populations, overt respiratory diseases are common.

Alveolar surface area is reduced by loss of alveolar septa and disruption of alveolar walls. Static elastic recoil falls, resulting in an increase in lung compliance. However, this is offset by reductions in chest wall compliance and chest mobility and, in some, kyphoscoliosis. Thus, there is no overall change in total lung capacity but there is a fall in respiratory system compliance, which increases the work of breathing. Several studies have shown age-related reductions in peak expiratory flow rate, forced expiratory volume in 1 second and forced vital capacity, even after adjusting for loss of height, reduced muscular effort and the change in lung compliance.

Changes in lung ventilation and perfusion with age show that compensatory mechanisms operate. Closing volume increases with age as a result of the loss of elastic recoil, with reduced lower lobe ventilation. Physiological dead space increases and greater ventilation–perfusion mismatch occurs. This is partly compensated for by increased upper lobe blood flow, but overall, diffusion capacity falls. The Pa_{O_2} is about 9 kPa in those aged 70–80 years.

Reductions in ventilatory drive have been reported, but other age-related changes could explain the fall in ventilation for any given level of ventilatory drive. Even measurements of mouth occlusion pressures (which avoid the limitations of volume measurements) show conflicting results. The precise effects of ageing on ventilatory control, including the regulation of breathing during sleep, have yet to be determined.

Reduced respiratory sensation has been reported in older individuals, which may have clinical implications for the awareness of the severity of asthma attacks. Small studies have reported a reduced ability to detect added elastic and resistive loads, but studies with hypercapnia suggest increased respiratory sensation. As the perception appears stimulus-specific, it suggests that central processing mechanisms are preserved.

Kidney

The reserve capacity of renal function far exceeds the usual demands of young people and the decline in function with ageing adequately meets needs under normal circumstances, though it may be challenged by a variety of stressors or deteriorations in other systems. In the young, the kidneys compensate for all but the most incompetent fluid regimens, but this is not the case in many older people.

The changes observed in the elderly may represent an accumulation of toxic insults as much as the effects of ageing per se. The interactions between changes in multiple systems is well demonstrated in the ageing kidney, which is subject to simultaneous changes in the nervous, cardiovascular and endocrine systems. Also, any disorder modifying renal blood flow (e.g. hypertension, atherosclerosis) will manifest as renal dysfunction.

Both renal plasma flow and glomerular filtration rate (GFR) decline with age in many people. Plasma creatinine is not a reliable indicator of GFR in the old because owing to a fall in muscle mass with age, reduced GFR is often unaccompanied by a rise in plasma creatinine. Acid–base balance is maintained in an unstressed state, but the old have a reduced ability to excrete an acid load, possibly because of defective tubular secretion of ammonium ions.

Concentration of urine in response to water deprivation is impaired in the elderly, possibly because of a reduced number of nephrons to deal with an increased solute load, or the increased perfusion of medullary glomeruli producing medullary washout. The response to water loading is also impaired, but the underlying mechanisms are unclear. Studies with water loading have demonstrated both normal and reduced vasopressin responses, and salt loading has demonstrated normal and exaggerated vasopressin responses. Renal salt conservation on a low salt diet is markedly delayed. The sensation of thirst, despite marked elevations in osmolality, is impaired through uncertain mechanisms.

CNS

The effects of ageing on the CNS are numerous. Major changes include progressive loss of neurons in the grey matter and in major neurotransmitter synthesizing areas. There is modest white matter atrophy and increased CSF volume. The modest reductions in blood flow in the brain seem to be related to reduced metabolic demand rather than to the vasculature per se.

The activities of several neurotransmitter systems are reduced (e.g. adrenergic, noradrenergic, dopaminergic, cholinergic) but not the serotoninergic system. The number, density and binding affinity of cell surface receptors for dopaminergic, β-adrenergic and serotoninergic agonists are also reduced.

Touch and pain thresholds tend to rise with advancing age. However, afferent pain stimuli undergo marked central processing in the spinal cord and thalamus, therefore it should not be assumed that pain perception and the need for analgesia are reduced in the old.

Drug effects: the pharmacokinetics and pharmacodynamics of almost all drugs used in anaesthesia change with ageing, leading to a lower dose requirement, though inter-individual variation is marked. The old are sensitive to drugs with anticholinergic properties, which often explains postoperative delirium. Delayed recovery from anaesthesia is not uncommon with traditional barbiturates and narcotics, probably explained by age-related pharmacokinetic changes. This problem has reduced with the increasing use of agents such as althesin, propofol and desflurane, the kinetics of which are less vulnerable to ageing changes.

Peripheral and autonomic nervous systems

Between young adulthood and the age of 80 years, there is a progressive decline in motor and sensory nerve conduction velocities of about 40%. Conduction velocity in long spinal tracts is well maintained until late middle age but declines rapidly thereafter.

There is also a progressive loss of cell bodies in the spinal cord, which is a major determinant of muscle fibre loss and an increased size of motor units. There are subtle changes at motor end plates as well as an increase in extrajunctional receptors. These extrajunctional cholinergic receptors have a reduced affinity for agonist and respond more slowly after agonist binding. Overall, the dose requirement for competitive non-depolarizing neuromuscular blockers tends to increase with ageing.

The sensitivity of the baroreflex declines rapidly in early adult life, and then more slowly into advancing age. The so-called carotid sinus syndrome (which is common in old age) probably has little to do with true baroreflex sensitivity. The baroreflex is intimately affected by chemoreceptors in the carotid body and in the medulla. Old people do not readily demonstrate tachycardia in response to hypoxaemia, hypercapnia and respiratory acidosis.

Principles of Control Mechanisms

James Waterhouse

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Man, like all other living organisms, is involved in a continuous struggle to survive not only the rigours and vicissitudes of the environment, but also the biochemical and physiological consequences of any activities. For example, ambient temperature changes, as does the drying effect of wind speed and humidity; there are changes in the provision of energy for metabolism following eating or fasting; and there are changes in the distribution and amount of blood required by different tissues during exercise – followed by other physiological changes such as temperature, water content and pH.

Enzyme-mediated processes work only within a restricted range of pH, temperature and ion concentration, and it therefore becomes necessary to preserve the internal environment despite the surroundings. This was recognized about 150 years ago by Claude Bernard and, about 70 years ago, Cannon introduced the term 'homeostasis' to describe this principle.

Variation between and within individuals

If any biochemical or physiological variable is measured on several occasions in the same individual, it is found to vary. These changes can arise from differences in the environment and from an individual's recent activities. For these reasons, it is necessary to standardize the conditions before a measurement is taken. For some variables, the previous effects of lifestyle and the environment take a long time to wear off (e.g. the increase in haematocrit that follows training at altitude) while for others, there is a regular and reproducible daily change in value due to the activities of a 'body clock' (e.g. the blood level of cortisol).

When more than one healthy individual is studied inter-individual variations are found. It then becomes important to determine if a particular individual falls within the normal range associated with health. A normal value is one that falls inside a range that encompasses 95%, or some other proportion, of the population.

Even if homeostatic control processes are operating on the variable being controlled, it continues to show changes, but they are within a narrower range than would exist without such control. For example, whether people are asleep or exercising, core body temperature does not normally move outside a range of 35–40°C even though they might be in an environment that is hotter or much cooler than this range. Homeostatic processes therefore limit the range shown by a variable and control its mean value.

Spontaneous corrections of some changes

Many changes that normally occur in the body tend to correct automatically without the need to invoke special control mechanisms. If systems in equilibrium are disturbed, changes occur spontaneously to minimize the disturbance.

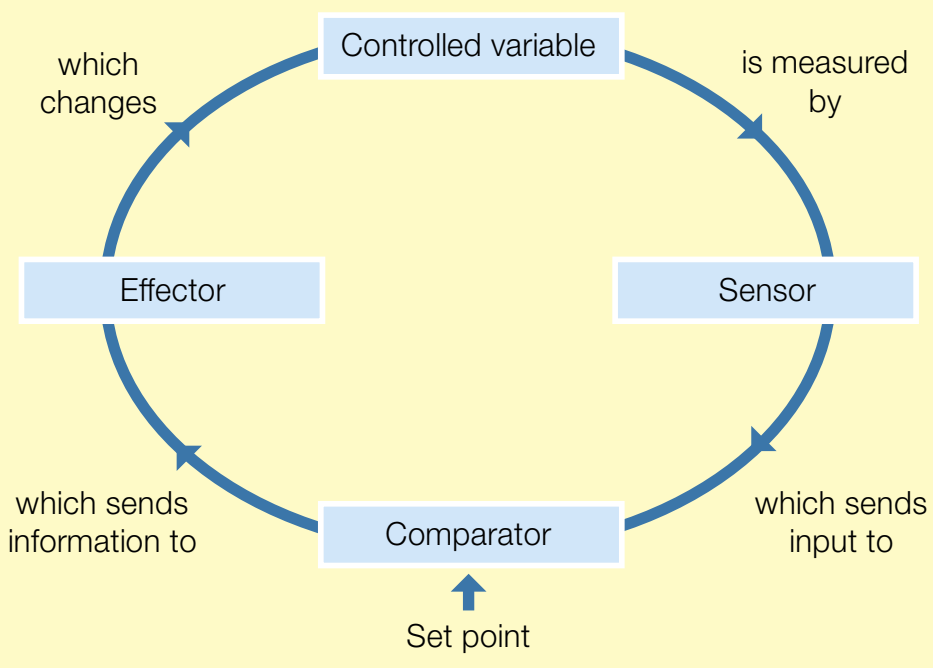
- Consider the delivery of oxygen from the RBC to an active tissue, a process that normally shows a dynamic equilibrium between its different stages. Increased oxygen use by the tissue lowers the concentration of oxygen in the tissue, and this causes oxygen to diffuse more quickly down the increased concentration gradient between the RBC and the tissue; in this way, more oxygen is delivered to the active tissue. Such changes reduce the concentration of oxygen inside the RBC, so upsetting the original equilibrium that existed between free oxygen, reduced haemoglobin and oxyhaemoglobin in the cell; therefore, more oxyhaemoglobin breaks down, so reducing the fall of free oxygen. In such a dynamic system, any initial disturbance results in further changes throughout the system that reduce the initial disturbance.
- Enzymes greatly speed up the rate of attainment of equilibrium in biochemical systems. The kinetics of enzyme activity are such that the rate at which the enzyme-mediated reaction occurs increases if the amount of substrate increases.
- The rate at which sodium is pumped out across the cell membrane is increased if the concentration of sodium ions in the intracellular fluid increases.
- The rate at which a reaction takes place (in order to regain equilibrium) can be considered as a function of the amount of disequilibrium present at that moment. If blood urea rises above normal then more will be filtered by the kidneys and, because urea moves passively, more will be lost in the urine; the greater the rise of blood urea above normal, the greater the rise of urea excretion in the urine above normal.

These examples illustrate that there are widespread mechanisms by which changes away from an equilibrium position can be reversed without the need for special biological reflexes. However, there would be serious problems if these were the only mechanisms involved. One difficulty arises because there would be no control over what the equilibrium would be. On a hot day, for example, the body would equilibrate at a value that was too high for optimal enzyme activity, and on a cold day at too low a value. Also, after a meal, the whole body would equilibrate with glucose levels that were too high, and during fasting the equilibrium value would fall progressively. There is therefore a need for mechanisms that can control a variable at a value determined by physiological and biochemical considerations rather than one influenced by the surrounding environment. The second difficulty with such mechanisms is that, as equilibrium is approached, the response becomes progressively less; deviations from the equilibrium value can be corrected only slowly. Therefore, although the above mechanisms are widespread and important, there must also be mechanisms for controlling the organism independently of the environment and for correcting any errors more quickly. These control mechanisms involve feedback loops.

Feedback loops

The principle of feedback control is widely used in engineering (from which much of the terminology is derived), and is often illustrated by reference to the temperature of a thermostatically controlled water bath. In this system, the temperature of the water in the bath (the controlled variable) is continuously monitored by a thermometer (the sensor), which sends a signal to a comparator (Figure 1). As its name suggests, the comparator compares the signal from the sensor with a pre-set value (the set point). If the signal from the sensor falls below this pre-set value (the temperature of the water has fallen), the comparator sends a signal to switch on a heater (the effector or controller). As a result, the water temperature rises and the original disturbance is corrected. The sequence of events is called a feedback loop, because it is initiated by a change (in water temperature) and results in another change (to the water temperature). There are negative and positive feedback loops.

Feedback loop



Negative feedback loops are the backbone of homeostasis. In negative feedback (Figure 1), the initial disturbance initiates changes that negate the original effect. If the initial disturbance in Figure 1 had been a rise in water temperature, a negative feedback loop would have initiated a cooling process. The action of a negative feedback loop is to stabilize the controlled variable.

Positive feedback produces changes in the same direction as the initial disturbance. This accentuation of the disturbance acts as a further stimulus to change brought about by the loop. The end result is an increasing change that is limited only by the maximum values that can be achieved by the components of the loop, or by the initiation of some opposing mechanism once a threshold has been reached. There are few examples of positive feedback in human physiology, but they are important.

- Oxytocin release is promoted by the pressure of the fetus on the cervix; this hormone promotes uterine contraction thus increasing the stimulus for oxytocin secretion. The end-point is the expulsion of the fetus from the uterus.
- Many gut enzymes are secreted in an inactive form. A small amount of breakdown of this inactive enzyme in the gut produces an active form which, among other actions, promotes breakdown of more of the inactive form into the active one; this process is known as autocatalysis.
- At the onset of inspiration, a group of neurons begin to fire, this promotes activity of the inspiratory muscles and inhibits the firing of expiratory neurons. This activity of the inspiratory neurons also promotes their own firing rate and that of other inspiratory neurons. The result is that, once started, inspiration rapidly takes over from expiration (the same system exists for expiratory neurons and the process of expiration).
- During the rising phase of the nerve action potential, sodium influx across the nerve membrane increases and this causes a depolarization of the cell membrane. In turn, this causes the voltage-gated sodium channels to begin to open, thus increasing sodium influx and a further opening of the gates. This 'explosive' process causes the sodium channels to open quickly – the permeability of the cell membrane to sodium increases over a thousand-fold in under 1 millisecond.

Types of feedback mechanism

In the example of the water bath, the heater was either on or off, with no intermediate state; such systems are described as discontinuous. They are less common in physiological control systems where many processes show continuous or tonic activity.

The above examples of positive feedback can be considered as discontinuous systems, with an action potential, expulsion of the fetus, respiratory neuron activity and enzyme activity not being required all the time, but being brought into action when necessary. When called into action, they must work quickly and effectively (this is where positive feedback is so valuable) and the term 'all-or-none', which is applied to the action potential, could also be applied to the other situations.

Discontinous systems in biology can also show negative feedback, but they seem to be more of an 'emergency' system.

- The clasp-knife reflex is initiated by Golgi tendon organs when the tension in muscles and tendons threatens to become damagingly high. The receptors have a high threshold (they are ineffective in normal movements), but when they do become effective, they inhibit the muscle contraction, so relieving the tension and acting as part of a negative feedback loop.
- Sweating is used when the heat load on the body is too high for it to be controlled by changes in cutaneous vascular tone alone.

Set point

The set point is the value towards which the feedback loop regulates the controlled variable. The set point in a discontinuous negative feedback system is the threshold at which the system is turned on (e.g. the tension in the Golgi tendon organs or the core temperature when sweating starts).

The concept of a set point cannot be applied so easily to a positive feedback system. However, positive feedback mechanisms are initiated when, for example, sodium influx across the nerve membrane is sufficient to cause the voltage-gated sodium channels to begin to open or when the neuro-physiological state that causes inspiratory (or expiratory) neurons to begin to fire is reached.

The set point of a continuous negative feedback system is an important concept, and requires the comparator and set point elements of Figure 1 to be replaced by an integrator. This component of the loop is normally found in the CNS and can be an assemblage of structures. Its role is to integrate the inputs from the various sensors and then to send a signal to the effector systems. Figure 2 shows how the set point can be determined.

The set point exists when the two parts of the feedback loop balance each other. If the value of the controlled variable differs from this set point, then the two arms are not in equilibrium and the feedback loop will initiate changes that continue until this equilibrium is re-established.

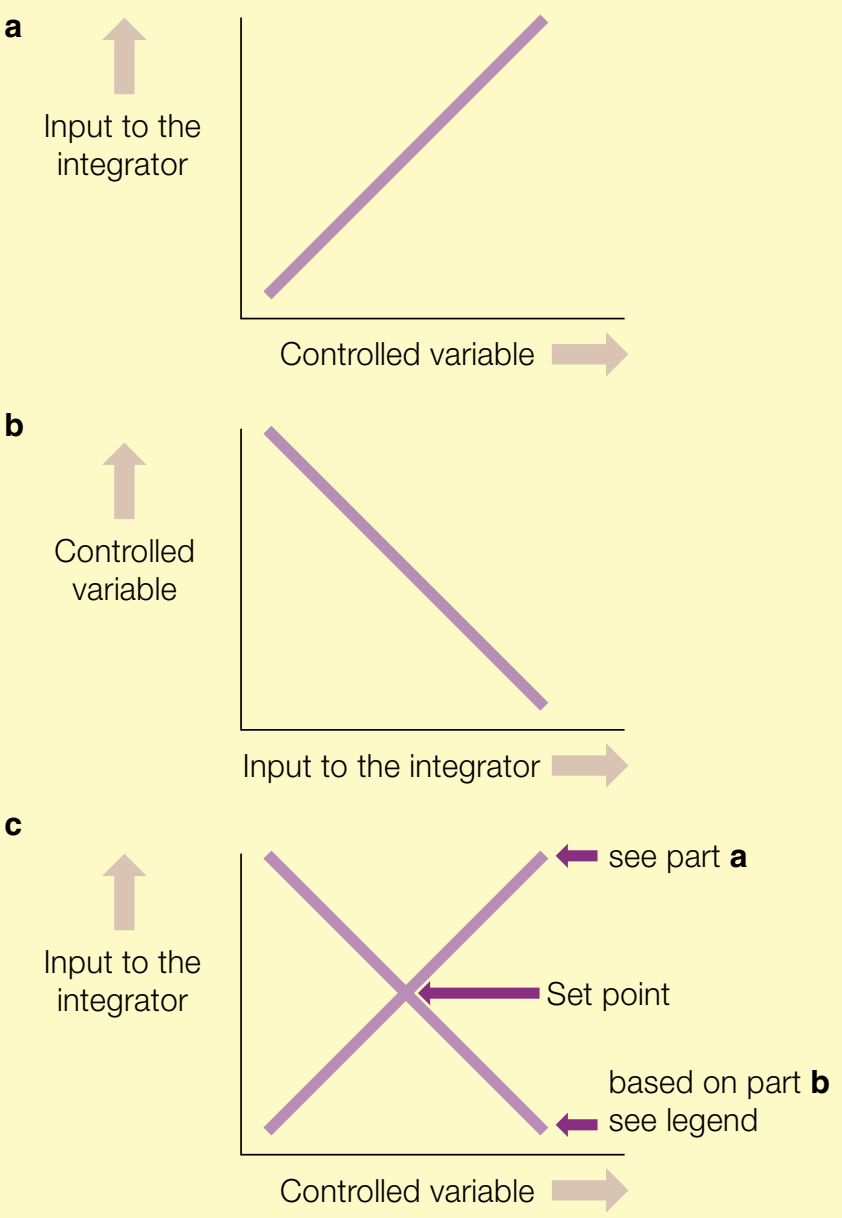
The crossover point (Figure 2) can be altered by changes to the gradient or intercept of either line; biologically, this means by changes in the properties of the sensor, the central integrator and/or the effector mechanisms. It can become (see later) the mechanism by which alterations to the controlled variable are brought about both in health and in physiological disorder.

Oscillation

Even though a variable is controlled by a negative feedback mechanism, its value is not constant, and it oscillates (though this does not mean that it is caused by an oscillator) within a band of values. It is desirable that these deviations from the set point, often referred to as 'errors', should be as small as possible. There are three main causes of oscillation in negative feedback systems.

The 'store' of the variable being controlled: in the control of body water, if the store of water is large, then any inbalance between intake and output will produce only a small proportional change in the overall store, its value will move away from the set point comparatively slowly, and there will be more time to correct the error. By contrast, with a smaller store, the proportional change and the consequent rate of movement of the controlled variable away from the set point will be more rapid, with less time available to correct the error before it becomes life-threatening. This would pose a problem to babies.

Determining the set point



a Part of the feedback loop shows a direct relationship between the value of the controlled variable and the input to the integrator. **b** Because it is a negative feedback loop, the other part of the loop (which starts with the input to the integrator and ends with the changes to the controlled variable produced by the effector systems) shows an inverse relationship. **c** Since the two parts of the loop work are connected and have the same elements (controlled variable and input to the integrator), this can be represented by combining the graphs. The graph of **b** has been reflected and rotated clockwise by 90° before superimposition on **a**. The cross-over point is the set point of the loop

2

Sensitivity of the components of the feedback loop: the feedback loop relies for its operation on a sensor that can measure any change in the controlled variable, and integrator and effector mechanisms that can readily respond. If the sensitivity of any component of the loop were too low, then the error would have to become large before compensatory changes were initiated. Problems can arise in babies (in whom many mechanisms are not fully developed), and in old people (in whom mechanisms are deteriorating).

To increase the sensitivity of the feedback loop to error might seem a good solution, particularly since the initial deviation of a controlled variable from the set point is small; with an increased sensitivity, it might be argued, small errors would be dealt with more rapidly. To an extent this is correct, but too high a sensitivity of a feedback loop can also cause oscillation. The oscillation arises because a small error initiates too large a correction response, and so the error becomes one in the opposite direction; this, in turn, initiates a correction in the opposite direction, which also causes the controlled variable to overshoot, and so on.

Delay in the response to an error can be illustrated by attempts to take a shower. Supposing that the water is too cold, the dial controlling the water temperature is turned towards hot. Because there is a delay between doing this and the warm water coming out of the shower, the dial is turned too far towards hot; eventually the water becomes too hot. There is then a tendency to turn the dial too far towards cold, and after a delay, the water is once again too cold, and the cycle begins again. Some computer games require movements of a joystick to track a moving target; if there is a delay between moving the joystick and producing a movement, it can become difficult to perform the task successfully, because there is a tendency to over-correct any error and initiate oscillation around the target.

Neural feedback loops, such as the stretch reflex in muscles, tend to suffer less from this cause of oscillation, because the delay in the feedback loop is small. In hormonal feedback loops, oscillation due to the slower timing of a response is more likely. This is not only due to the time it takes for the secretion by a gland to build up to a sufficient concentration in the whole of the extracellular fluid, but also because, after a reduction of hormone secretion, it takes time for the hormone that has been released to be removed by metabolism.

Minimizing problems

Many of the above problems are minimized in healthy adults. Some of the mechanisms involved are described below.

Multiple and opposing systems: a variable is seldom controlled by a single feedback loop; instead, there are generally several loops acting in parallel, sometimes in opposite directions and with different time courses. The short-term control of blood pressure is through the interaction of loops involving the sympathetic and parasympathetic nervous systems. They tend to have opposite effects on blood pressure, and also act at several sites (heart, arterioles and venules) and by more than one mechanism (inotropic and chronotropic effects on the heart). The longer-term control of blood pressure involves several hormones that modify salt and water balance. Several hormones are involved in the control of metabolism; between them they promote the metabolism or storage of glucose, or its production from carbohydrate stores or non-carbohydrate sources, and the storage of fatty acid in adipose tissue or its mobilization from this tissue in preparation for its metabolism.

Dynamic sensitivity of sensors: the problem that an error in a feedback loop is initially small can be overcome if the sensor shows dynamic as well as static sensitivity. Dynamic sensitivity is sensitivity to the rate of change of the variable, and it differs from static sensitivity, which measures the actual value of the variable. When an error first arises, even though it is small, the rate at which it is changing need not be small. A sensor with dynamic sensitivity can send a large signal to the integrator as soon as an error appears. Many sensors show dynamic sensitivity, including the baroreceptors and the stretch-receptors in muscles.

Disturbance detectors: so far we have considered sensors that are an integral part of the feedback loop insofar as they are responsible for directly measuring the controlled variable; they are sometimes called ‘error detectors’. However, another type of sensor is found called a ‘disturbance detector’. Even though such a sensor is not a direct part of the feedback loop (and so would not appear in Figure 1), it sends information to the loop, generally to the integrator. Its effect is to give warning of changes that will, in due course, alter the controlled variable.

- A well-known example is in thermoregulation where the error sensors are in the bloodstream (and measure hypothalamic temperature), but the disturbance detectors are in the skin (the cutaneous thermoreceptors). As a result of inputs to the hypothalamus from the disturbance detectors, sweating starts as soon as an individual is placed in a hot environment, and shivering as soon as he is in a cold one.
- Another example is the release of gut hormones that affect metabolism, which occurs soon after eating a meal but before most of the food has been absorbed.

In both the above examples, the disturbance detector enables the feedback loop to initiate changes before the disturbance has produced an ‘error’ in the controlled variable.

- A third example is the sensation of thirst. We feel thirsty because of dehydration and the raised osmotic pressure of the blood acts on osmoreceptors in the hypothalamus. Several effects are produced including the sensation of thirst and secretion of antidiuretic hormone (ADH), which reduces further water loss by the kidneys. After drinking about the amount of water required to correct the osmotic pressure of the blood, the sensation of thirst is abolished, even though the water has not been absorbed and the osmotic pressure of the blood is still raised. The inhibition to drink comes from volume receptors in the stomach and from other inputs originating from the mouth and oesophagus; these can be considered to be acting collectively as a disturbance detector which indicates that, after absorption of the water, the osmotic pressure will have been corrected.

Using feedback mechanisms to produce a controlled change

The set point or equilibrium value of the controlled variable in a negative feedback system can be controlled by altering the properties of its components (Figure 2). One case where this is normally done is in the performance of a controlled movement; the power for the movement comes from the α-motor units, but control comes from a modification of discharge of γ-efferents. The γ-efferents act on the muscle spindles to change their dynamic and static sensitivities. As a result, a new equilibrium point (crossover point in Figure 2) is achieved, and this causes the controlled contraction of the muscle to take up a new length. Similarly, the sensitivity of the chemoreceptors in the carotid body and aortic arch might be changed in exercise, so that ventilation can be increased without marked changes in the partial pressure of carbon dioxide and oxygen in the blood. Also, changes in the sensitivity of the integration component of a feedback loop during sleep, and circadian changes due to the body clock, can both result in changes in the set point of several variables (e.g. blood pressure, core temperature).

Changes in the sensitivity of some sensors can occur. For example, the declining elasticity of blood vessels with ageing, particularly those in the carotid sinus, can result in a decreased distension of this structure caused by the blood ejected at systole. This alters the sensitivity of this component of the feedback loop controlling blood pressure, and might contribute to the increase in blood pressure commonly found with ageing.

Interaction between neural and humoral control mechanisms

Humorally mediated reflexes are slower than, but not inferior to, neurally mediated reflexes; they play different roles. Consider the case of the changes in cardiac output that take place during exercise. Initially, the changes are mediated by neural influences on the heart and the vasculature. However, to maintain a high rate of firing of the sympathetic nervous system would be uneconomical from the viewpoint of the metabolic energy required by the sodium–potassium exchange pumps in the cell membrane of the nerve cells. The secretion of catecholamines by the adrenal medulla, itself brought about by sympathetic discharge, can provide an alternative way of maintaining stimulation of the cardiovascular system; it has the added benefit that, as a blood-borne hormone, it can exert its effects throughout the body. In this way, there can be an increase in blood flow to the vasculature of the skeletal muscles, a decrease in blood flow to the gut and kidneys, and a dilatation of the airways depending on whether the tissue contains mainly α- or β-adrenoreceptors.

Similarly, at the start of a meal, the secretion of saliva needs to be immediate, and is neurally-mediated by the parasympathetic nervous system. As the food passes through the stomach and into the small intestine, the secretory processes (which now do not need to be initiated rapidly but need to be sustained for longer periods) are influenced more by hormonal activation.

In homeostasis, slightly different roles are played by the neurally and humorally mediated reflexes, as can be illustrated by the control of arterial blood pressure. In the short term, it is controlled by the neurally mediated baroreceptor reflexes acting via both branches of the autonomic nervous sytem. In the longer term, it is regulated by the hormonal control of the body’s water balance (by ADH) and sodium content (atrial natriuretic peptide and the renin–angiotensin–aldosterone axis).

It would be wrong to consider that neurally and humorally controlled systems tend to be separate, because of their different time courses; they act in parallel. One example is that of the thyroid gland and thermoregulation. Even though thermoregulation is achieved by a series of neurally mediated feedback loops, they act against a background of basal metabolism controlled by thyroid hormones. In cooler weather, there is an increase in secretions from the thyroid gland and these raise metabolic rate. In this way, it becomes less difficult for the thermoregulatory mechanisms to conserve heat.

This combination of fast-acting, neurally controlled and the slower-acting, hormonally controlled mechanisms requires some point of interaction so that the total response can be integrated. This interaction can be the result of innervation of an endocrine gland by the sympathetic nervous system, as with the islets of Langerhans and the adrenal medulla. In the case of the effects of stress on the release of oxytocin and ADH by the posterior pituitary, it is the fact that this part of the pituitary (the neurohypophysis) is composed of neurons.

However, the interaction between the neural and hormonal systems is most elaborate in hormones that come from the non-neural tissue of the anterior pituitary gland. That there is an interaction is established from the interaction between the thyroid gland and thermoregulation (see above), and from the disruption of the menstrual cycle caused by stress, to give two examples.

There are no neural connections to the anterior pituitary gland, but rather a humoral pathway through which releasing factors can travel from the hypothalamus via a portal system. The control of hormone release that occurs through a feedback loop – between a trophic hormone from the anterior pituitary gland, the endocrine gland and the hormone it secretes, and feedback of this hormone on to the anterior pituitary gland – can be modified by the effects of the releasing factors.

The secretion of these releasing factors is controlled by, among other factors, activity in the CNS. The effect of the releasing factor can be considered to be some form of disturbance detector and/or some mechanism for altering the sensitivity of one component of the feedback loop that exists between the pituitary gland and the target gland; whatever description is applied, there is a neuroendocrine integration that benefits the individual.

Protective Mechanisms of the Body

Peter J Wood

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The body is constantly exposed to environmental microorganisms (pathogens) that have the potential to infect and cause disease. Most pathogens have to enter the body to cause infection though a few (e.g. papilloma viruses, *Vibrio cholerae*) can cause disease without technically entering the body. Even pathogens that do not enter the body must be able to survive on the skin or a mucosal surface.

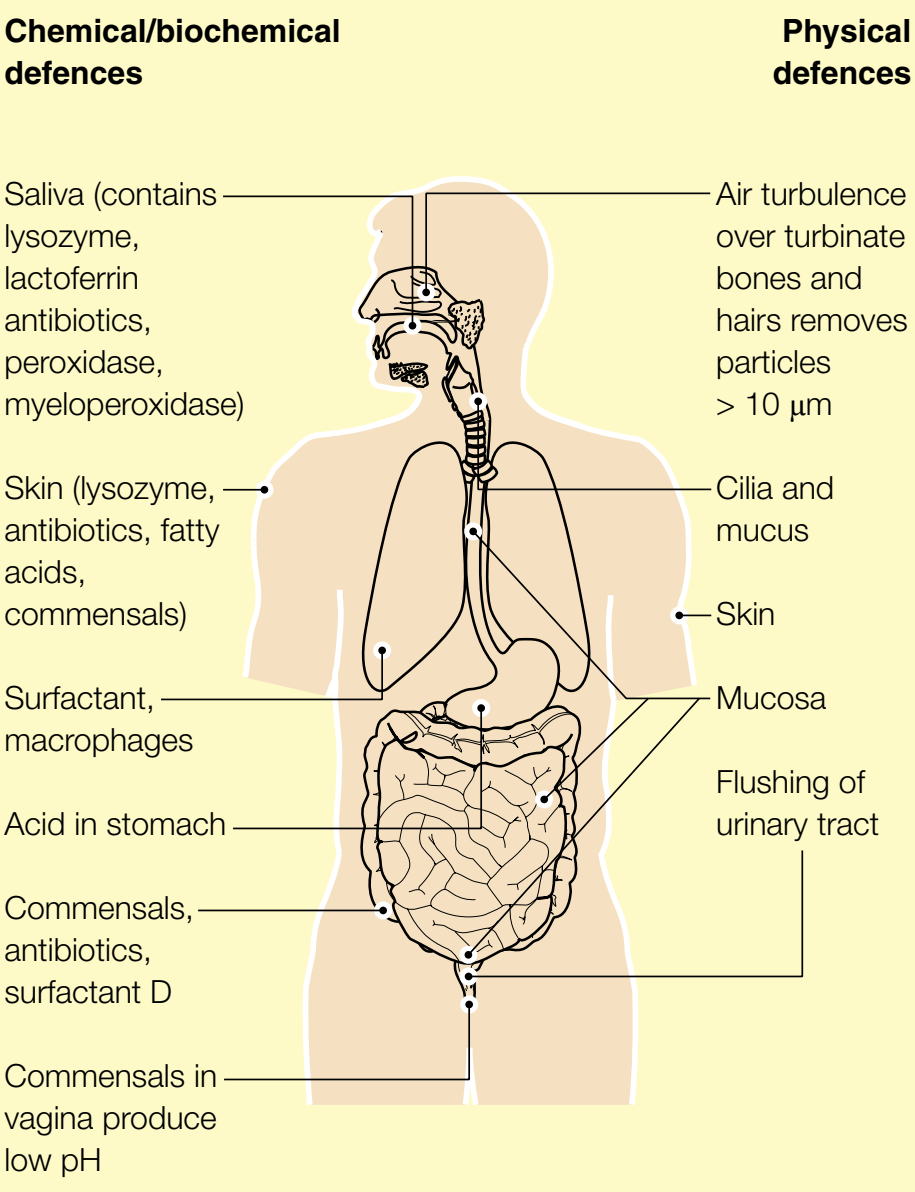
Individuals possess a number of physical, chemical and biochemical defence mechanisms designed to prevent infectious pathogens from gaining entry into the organism (Figure 1). They do this by physically preventing the entry of pathogens into the body, killing pathogens that are on the body surface, or inhibiting the replication of pathogens on the body surface.

Our understanding of protective mechanisms has undergone radical change in the past decade. Far from being primarily a physical barrier with a few fairly unsophisticated chemical and biochemical adjuncts to provide extra protection against bacteria, families of protective molecules are present in mucosal and skin secretions, which provide powerful defences against other types of pathogens, including viruses, fungi, yeast and protozoan and helminth parasites.

The relative importance of the physical, chemical and biochemical defences of the body is difficult to establish but is demonstrated by the following:

- damage to skin leads to increased risk of infection
- overuse of wide-spectrum antibiotics can result in elimination of commensal organisms and increased risk of infection
- use of alkaline douches that neutralize vaginal pH leads to increased susceptibility to infection.

Physical, chemical and biochemical defence mechanisms



1

Physical defence mechanisms

The outer layers of the body that interface with the environment are the skin and the mucosal surfaces of the gastrointestinal, respiratory and genitourinary tracts. Physical defence mechanisms consist of:

- physical barriers (the skin and mucosa)
- cilia (hair-like structures that line the respiratory tract)
- mucus (a viscous high molecular weight secretion).

Skin

The outer layer of the skin consists of dead cell layers containing keratin and lipid. This provides a relatively strong physical barrier compared with mucosal surfaces. Protection is also provided by the constant shedding of dead skin, which carries with it infectious organisms attached to the skin. Commensal organisms on the skin compete with pathogens for environmental niches and therefore limit occupation by pathogens. The most common commensal organisms are bacteria (e.g. *Staphylococcus epidermis*, *Staph. aureus*) and yeast (e.g. *Candida*).

The balance between commensal organisms and surface antimicrobial agents (e.g. lysozyme) is complex. Many commensal organisms are opportunistic pathogens and have the potential to cause disease. The mucosal surfaces and skin hold these potential pathogens in check, but if the balance is upset the commensal organism can cause disease (e.g. *Haemophilus influenzae* causes pneumonia if lung defences are compromised through damage).

Few pathogens can penetrate intact skin; those that can are usually parasites (e.g. schistosomal cercaria). Damage to the skin can allow the entry of pathogens. Mild abrasions may allow the entry of aerobic pathogens (e.g. *Staphylococcus*, *Streptococcus*), while deeper wounds, especially those involving crushing of tissue, provide an anaerobic environment suitable for pathogens such as *Clostridium* spp.

Mucosa

The role of mucosa is more complicated than that of skin because of the specialized nature of different mucosa. To enable it to fulfil its absorptive role much of the intestinal mucosa is a simple stratified epithelium. The respiratory epithelium is exposed to large volumes of potentially contaminated air and the alveoli must enable efficient gaseous exchange. Therefore, mucosa does not provide as strong a physical barrier as skin and is more vulnerable to infection. Many pathogens can enter the body through intact mucosal sites (Figure 2). However, the mucosae provide some physical protection in that the continuous growth and shedding of mucosal cells can remove pathogens in the same way as skin. Like skin, many mucosal surfaces harbour commensals that compete with pathogens for space and nutrients; the most extreme example of this is the intestine where the density of commensal organisms can reach a level of more than 10^{10} organisms per gram of tissue. Some mucosae, such as those of the lower respiratory tract and bladder are normally sterile.

Mucus, secreted by goblet cells, provides a physical trap for pathogens and other particles and contains many substances with antibacterial properties. Mucus consists primarily of mucins, which are macro-molecules of 200–2000 kDa with a peptide backbone and extensive O-linked carbohydrates. As the first stage of infection, most potential pathogens have to bind to mucins through interaction with the carbohydrate component; however, commensal microorganisms compete with pathogens for the mucin carbohydrate binding sites and thus provide protection.

Mucus is continually secreted on to the surface of mucosa, which produces a flow of mucus away from the epithelial surface, carrying microbial and other particles with it. The mucus is further propelled to the opening of the mucosal tract by peristalsis in the intestine or by the beating motion of the cilia in the respiratory tract which propels the mucus towards the throat where it is expelled or swallowed. This so-called respiratory elevator plays an important role in keeping the lower respiratory tract sterile and particle-free. Another specialized physical trap present in the alveoli is provided by pulmonary macrophages, which are able to phagocytose microorganisms and other particles that enter the lower respiratory tract; they may also secrete biochemical defence molecules.

Mucosal sites of entry for pathogens

Pathogen	Disease	Mucosal site of entry
Rhinovirus	Common cold	Nasal epithelium
Influenza virus	Influenza	Upper respiratory tract
Bordatella pertussis	Whooping cough	Lower respiratory tract
Salmonella spp.	Food poisoning	Small intestine
Entamoeba histolytica	Dysentery	Colon
Escherichia coli (some strains)	Urinary infection	Bladder, ureter
Neisseria gonorrhoeae	Gonorrhoea	Vagina, urethra

2

Chemical defence mechanisms

Various chemicals produced in the body kill pathogens or inhibit their growth. Hydrochloric acid in the stomach maintains a pH of 1–2, which is lethal for many bacteria. Sweat and sebaceous secretions contain lactic acid and fatty acids, some produced by commensal bacteria, that provide a pH of 5–6 on the skin and have antibacterial properties. Commensal bacteria in the vagina produce lactic and propionic acid from glycogen secreted by vaginal epithelial cells. The resulting pH of about 5 is acidic enough to inhibit the growth of other bacteria.

Biochemical defence mechanisms

It has been known for many years that secretions of the skin and mucosa contain biochemical agents that have antimicrobial properties. Recently, the discovery of animal and human antibiotic proteins and peptides has increased knowledge about the molecules that provide protection.

Lysozyme, lactoferrin and myeloperoxidase

Lysozyme is a powerful antibacterial agent found in sweat, tears and mucosal secretions. It is able to break down the peptidoglycan component of bacterial cell walls (Figure 3). Because the peptidoglycan component of Gram-positive bacteria is prominent and accessible, they are susceptible to lysozyme. However, in combination with lactoferrin, an iron-binding protein, lysozyme can also kill a number of Gram-negative bacteria. Lactoferrin is also thought to provide antibacterial action by binding iron, which reduces the iron level to below that required for bacterial growth.

Myeloperoxidase is usually found in the granules of neutrophils and macrophages and participates in the killing of phagocytosed microbes. It is also found in lower concentrations in mucosal secretions, where it may have antimicrobial activity. Myeloperoxidase catalyses the production of hypochlorous acid from hydrogen peroxide.

Hypochlorous acid is a strong oxidizing agent capable of killing many microbes. In the presence of chloride, hypochlorous acid can form chlorine, which also has microbicidal properties.

Animal antibiotics

Over 500 animal antibiotic proteins and peptides (peptides are defined as having fewer than 100 amino acids) have been discovered. They can be divided into α- and β-defensins, cathelicidins and peptides derived from other functional proteins. The defensins were originally identified as microbicidal peptides in the granules of neutrophils but they have now been found in secretions of mucosa and skin. Cathelicidins have conserved N-terminal prosequences homologous to cysteine protease inhibitors. They were originally identified as insect antibacterial peptides, but are also present in mucosal secretions. The final type of peptide antibiotic is that derived from other proteins; for instance an antimicrobial peptide derived from the histone H1 has been identified in the ileum.

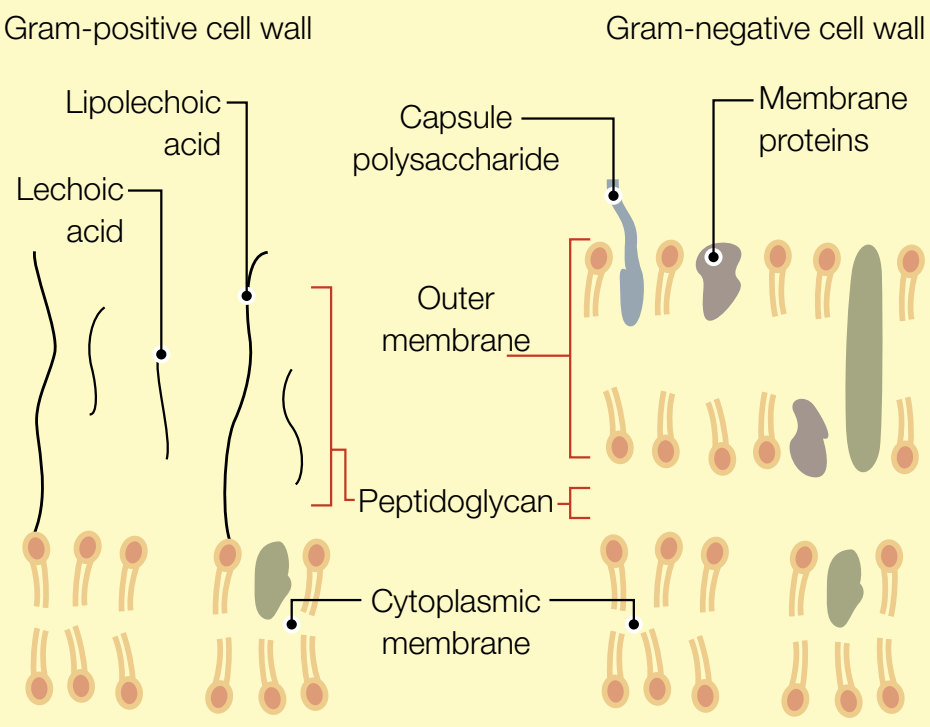
Each individual makes and secretes tens of different peptide antibiotics. The antibiotics have a wide spectrum of antimicrobial activity and are able to kill all types of bacteria, viruses, fungi, yeast and protozoan and helminth parasites.

Originally, it was thought that epithelial leucocytes were the source of mucosal antibiotics but it is now becoming clear that epithelial cells at many sites are capable of synthesizing and secreting these molecules. In the ileum, Paneth cells secrete defensins, cathelicidins, lysozyme and phospholipase A_2, another enzyme that is able to break down the lipid component of bacterial cell walls. Enterocytes secrete the H1 histone-derived peptide antibiotic, and goblet cells secrete mucus. All epithelial cell types in the ileum contribute to the production of antimicrobial factors (Figure 4).

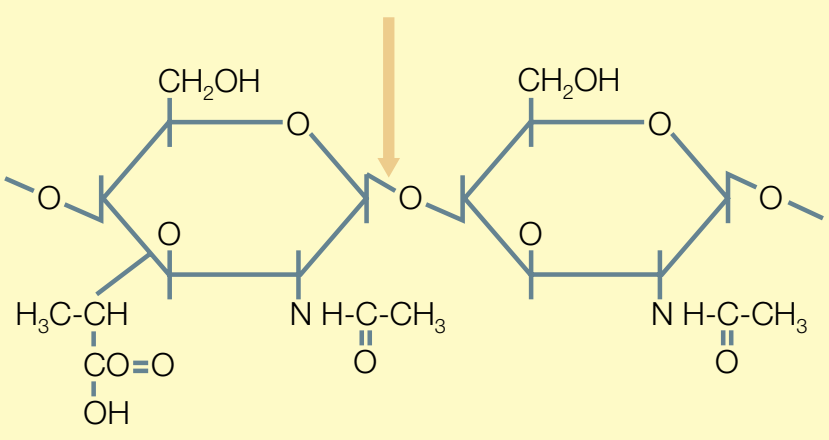
The action of these antibiotics is best understood with respect to the killing of bacteria. Most of the antibiotics are cationic in nature and therefore interact with the anionic components of prokaryotic organisms, fungi or enveloped viruses. The most common mechanism of killing is by insertion of the antibiotic into the bacterial cell membrane leading to loss of ion balance. Other killing mechanisms include disruption of bacterial enzyme metabolism and interference with biosynthetic pathways. One interesting recent observation is that the microbicidal activity of some of these antibiotics is inhibited at the high salt concentrations present in the mucous secretions of individuals with cystic fibrosis and this may contribute to the increased susceptibility to infection seen in these patients.

Action of lysozome

Bacterial cell wall



Basic building block of peptidoglycan

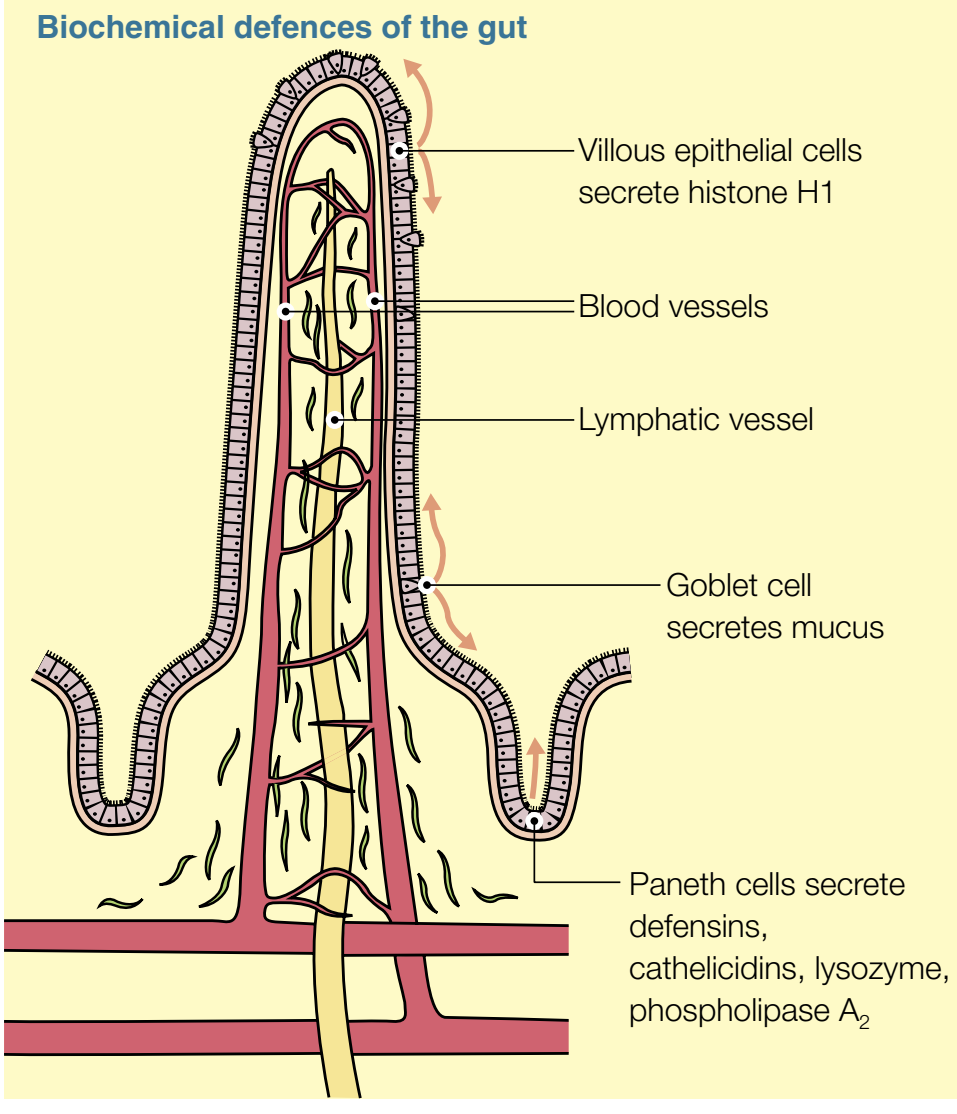


Lysozyme breaks this bond thus breaking down the peptidoglycan layer in the bacterial cell wall

N-acetylmuramic acid N-acetylglucosamine

3

Biochemical defences of the gut



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Collectins

The collectins provide biochemical protection at mucosal surfaces. They include the serum protein, mannose-binding protein, and the A and D lung surfactants. Collectins are calcium-dependent lectins (C-type lectins) that bind sugar residues on microbial surfaces. They can act as opsonins and promote the phagocytosis of microbes and may also have more direct antimicrobial activity. Although originally identified as lung secretory products, surfactant D has also been found in the gastrointestinal tract.

These biochemical defence molecules are made constitutively and therefore provide pre-existing protection against infection. However, many of them are inducible and their levels increase substantially on exposure to appropriate microorganisms.

FURTHER READING

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Starvation, Exercise, Injury and Obesity

Iain Campbell

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Energy is derived from oxidation of the macronutrients, carbohydrate, fat and protein (see **PHYSIOLOGY**). Glucose is an immediate source of energy, fat represents the long-term energy store and protein normally supplies about 10–15% of the body's energy needs. Protein, however, forms the structure of the body and any net loss of protein is accompanied by a deterioration in function. The normal interrelationships between these macromolecules, and their control, mostly by the hormones glucagon and insulin, is described in **PHYSIOLOGY**. This contribution describes the modifications to metabolism that occur in a number of abnormal situations, namely starvation, exercise, trauma and obesity. These conditions represent a stress to the system; trauma and exercise in terms of matching supply to demand; starvation in terms of stretching out limited resources to meet continuing demand; and obesity results from a mismatch of the two. Trauma is also often accompanied by an element of undernutrition because part of the metabolic response is a decline in appetite and food intake.

Starvation

Starvation is an absence or inadequacy of exogenous energy (and protein) intake. It may be partial or complete and the body survives wholly, or in part, on its endogenous stores.

A number of integrated biochemical and physiological changes have evolved in response to starvation. They contribute to a reduction in energy requirements, a preservation of protein (lean tissue) mass and the maintenance of a continuing supply of glucose to those tissues that are obligatory users, mainly the nervous system, but also RBCs and the renal medulla. RBCs and the renal medulla obtain their energy by glycolysis, but the nervous system, initially at least, can obtain energy only from glucose oxidation. Energy expenditure is reduced and protein oxidation diminishes. In normal circumstances, lean body mass is relatively constant, but there is a continuous turnover of protein (synthesis and breakdown to amino acids, some of which are oxidized) as tissues are continually renewed and replaced. In a stable state, nitrogen excretion equals nitrogen (protein) intake, but in starvation intake is absent. Protein oxidation is decreased, but there is an inevitable continuing loss, albeit at a reduced rate, which results in a steady decline in lean tissue mass, and thus in function.

The responses to starvation are behavioural and biochemical. The behavioural response is a decrease in spontaneous activity. Responses to environmental stimuli are diminished; unnecessary movement is eliminated. At the extreme, the organism may respond only if survival is threatened. Some biochemical pathways disappear (glycogenolysis). Minor pathways (gluconeogenesis) achieve major importance, at least transiently, and others that are normally only minimally active (ketogenesis) become extremely important. Temporally, the response to starvation can be described in three phases; glycogenolytic, gluconeogenic and ketogenic (Figure 1).

Phases of starvation

Glycogenolysis
- Stimulated by the decline in insulin and the rise in glucagon
- Liver and muscle glycogen stores exhausted within 24–48 hours

Gluconeogenesis
- Synthesis of glucose from amino acids, glycerol and lactate
- Stimulated by decrease in insulin and rise in glucagon
- Increases over first few days then declines

Ketogenesis
- Tissues (including CNS) adapt, at least in part, to using ketones instead of glucose
- Ketones synthesized from fatty acids by liver
- Stimulated by low insulin

Glycogenolysis
When food intake stops, blood glucose levels decline. Insulin decreases and glucagon rises; it is this reciprocal relationship that normally keeps blood glucose concentrations stable. The stimulus, and the response, is secondary to the change in the glucose levels, but may be partly mediated by the autonomic nervous system (α stimulation inhibits and β stimulation stimulates both insulin and glucagon secretion). Liver glycogen stores are mobilized via glucagon and the activation of liver phosphorylase enzymes. Hepatic glycogen is broken down to glucose-6-phosphate, which is converted to glucose and released into the bloodstream. The liver, which weighs about 1.0–1.5 kg, stores about 50–120 g of glycogen. Muscle is a much larger tissue mass than liver, comprising 40% of body weight or about 25 kg, and holds about 350–400 g of glycogen. This does not, however, contribute to blood glucose directly. Glycolysis occurs, but when the muscles are relatively inactive, the resulting pyruvate is converted to lactate which passes into the circulation and to the liver where, as a gluconeogenic precursor, it is converted to glucose for export into the general circulation. This cycle of glucose to lactate in peripheral tissue, and to glucose in the liver, is known as the Cori cycle.

Gluconeogenesis
Body glycogen stores last only 24 hours (48 hours at most) but the brain requires glucose at a rate of about 100–120 g/day. Initially, this comes from amino acids derived from protein breakdown. The release of amino acids from peripheral tissue is stimulated by the decline in insulin concentration and the concomitant rise in glucagon. Amino acids are converted to glucose by the liver, and to a lesser extent by the kidney. Not all amino acids, however, are glucogenic and 1.75 g of protein has to be broken down to provide 1 g of glucose. If the brain requires 100–120 g of glucose/day and no other adaptation took place, this would result in a daily loss of over 200 g of protein, and a rapid depletion in lean body mass.

Gluconeogenesis increases to a maximum at about 48 hours then decreases over the next 1–2 weeks as keto-adaptation takes place (see below). This may be reflected in a transient rise in urinary nitrogen excretion over days 2–4 until, with full adaptation to starvation, it settles down to about 4–6 g/day. Normal 24-hour urinary nitrogen excretion on a mixed diet is about 11–12 g/day. Gluconeogenesis declines because peripheral tissues adapt to the use of ketones and because of a decrease in metabolic rate (see below). About 50% of the amino acids are released from peripheral tissue as alanine or glutamine. Alanine is the principal gluconeogenic precursor for the liver, and glutamine for the kidney. They are released in larger quantities than occur in peripheral tissue. Alanine is the corresponding amino acid to pyruvate, the principal product of glycolysis, and glutamine the corresponding amino acid to α-ketoglutarate, a constituent of the Krebs', or citric acid cycle. Transamination of these substances (pyruvate and α-ketoglutarate) occurs in peripheral tissues, the amino group being donated by one or other of the branched chain amino acids (valine, leucine and isoleucine), the carbon skeletons of which can then be oxidized. The branched chain amino acids are metabolized only in peripheral tissue; they cannot be used by the liver.

Cortisol is the hormone that normally induces proteolysis, but in starvation, cortisol changes follow no consistent pattern and it seems to have no specific role. The breakdown of protein is due largely to the reduction in the insulin:glucagon ratio and most of it comes from muscle. In the early stages, gluconeogenic amino acids may come from rapidly turning over tissue pools, such as the lining of the gastrointestinal tract, but in the long term, the major protein 'store' is skeletal muscle. It is the largest protein mass in the body and is ultimately the main source of gluconeogenic precursors. This is accompanied by muscle wasting and weakness. Muscle weakness occurs surprisingly early in starvation, but is probably a result more of glycogen depletion than of protein loss.

The other principal gluconeogenic precursor, in addition to lactate and the amino acids, is glycerol. This is a three-carbon alcohol and a major constituent of triglyceride, the form in which most of the fat in the body is stored (see **PHYSIOLOGY**). As the adapatation to starvation takes place, triglyceride is broken down in to its constituents of glycerol and free fatty acids (lipolysis), and the glycerol moiety is transported to the liver where it is converted to glucose. The energy supply for the metabolic activity of the liver comes from fat. The energy for the synthesis of glucose in the liver, from these precursors, is thus derived from the major energy store.

Ketogenesis
Ketogenesis is the final adaptive process that allows the body to function for a prolonged period without food intake. Many of the tissues, including muscle (and the myocardium) adapt to using fatty acids as their energy source. Fatty acids arriving at the liver are normally esterified to triglyceride, a process stimulated by insulin. In the presence of low insulin concentrations, however, fatty acids are converted to ketone bodies (aceto-acetate and β-hydroxybutyrate) and, in many tissues, these substances are oxidized instead of glucose. This includes the brain, which is able to derive two-thirds of its metabolic requirements from ketone oxidation, thus sparing up to 80 g of glucose/day. In the nervous system, there is no alteration (decline) in metabolic demand. Circulating concentrations of ketone bodies increase from their usual level of less than 0.2 mmol/litre up to 6–7 mmol/litre. The glucose requirement of RBCs and the renal medulla remain, but they produce lactate, which is recycled to glucose as described above.

Hormonal changes
Most hormonal changes result from the decline in insulin and the rise in blood glucagon concentrations. This combination has both glycogenolytic and lipolytic effects, which increase free fatty acid concentrations and the rise in glucagon promotes gluconeogenesis. Tri-iodothyronine (T3) levels decrease and there is a rise in reverse T3. This is not only associated with a fall in metabolic rate, but the fall in T3 may have a protein-sparing effect. Sympathetic activity is reduced in starvation. In long-term starvation, difficulties may be experienced with, for example, the control of blood pressure and postural hypotension, as well as with thermoregulation because one of the body's defences against cold stress is sympathetic activation.

Metabolic rate
The metabolic rate decreases in starvation, to some extent out of proportion to the weight loss. In absolute terms, energy expenditure decreases by about 40%. When corrected for the decrease in body weight and expressed per kg body weight or per m^2 of body surface area the figure is nearer 15–20%. There are a number of probable causes; the decrease in sympathetic nervous activity, the decline in T3 and a relatively greater loss of metabolically more active tissue, such as the lining of the gastrointestinal tract and the liver. Although active in terms of gluconeogenic and ketogenic activity, the liver is no longer involved in the daily processes of digestion and assimilation.

Energy value of weight loss
It is a common observation of slimmers that weight loss on a low-energy diet is initially quite rapid and then slows until continuing weight loss is extremely difficult to achieve. Early weight loss is due largely to loss of lean tissue with its high water content and a relatively low energy density of 1000–2000 kcal/kg. As the fast continues and the body adapts to using mostly fat, the energy density of the weight loss increases until, in an established fully adapted fast, it is virtually only adipose tissue being metabolized. The energy density of the weight loss in prolonged starvation is about 7000–8000 kcal/kg.

Duration of starvation
Although there are instances of very obese individuals surviving without food for a year, death normally occurs at 60–70 days. Survival is essentially for as long as the fat stores last. When they run out, the body protein is oxidized for fuel and there is a 'premortal' rise in urinary nitrogen excretion. In practice, when the body has lost about half its muscle, the individual becomes too weak to cough and clear his lungs, and pneumonia ensues.

Exercise

The basal or resting metabolic rate as described in *Anaesthesia and Intensive Care Medicine* **2:3:** 115 is the energy expended in maintaining the processes of life in the resting state. Exercise is part of the body's interaction with its environment (Figure 2). The energy expended during exercise may be up to 20 times the basal metabolic rate and can be quantified in multiples of basal expenditure (MET from metabolic rate). Thus, resting awake and fasted would be 1 MET, sleeping would be 0.9 MET, walking at 5 km/hour 3.5 MET, jogging 10–12 MET and marathon running 18–20 MET.

Exercise can be classified as isometric or isotonic, and as aerobic or anaerobic. In isometric exercise, muscles contract against a resistance, but do not shorten (or lengthen) as opposed to isotonic exercise where muscles shorten (and lengthen) and move joints. In the performance of exercise against a resistance, many forms of 'isotonic' exercise have an isometric element. In aerobic exercise, the supply of oxygen keeps pace with the rate of fuel utilization (e.g. jogging). With anaerobic exercise, the rate of fuel utilization exceeds the oxygen supply; for example a fast sprint or any form of isometric exercise where the strength of the muscle contraction tends to cut off the blood (and oxygen) supply.

The body is about 25% efficient. Thus, in performing external work, 75% of the energy expended is released as heat. Although the energy comes ultimately from the oxidation of carbohydrate, fat and protein, the immediate supply is from the hydrolysis of adenosine triphosphate (ATP). There is enough ATP in skeletal muscle to support a maximal effort for a few seconds but, as this is used up quickly, it requires replenishing. The inorganic phosphate for replenishment comes immediately from phosphocreatine, present in muscle in concentrations about four times that of ATP. The use of these 'phosphagens' (ATP and creatine phosphate) allows time for the longer term mechanisms of energy supply (glycogen breakdown and glycolysis) to come into play. There is an immediate increase in flux through the glycolytic pathway of up to 1000-fold. The substrate driving this process is glucose-6-phosphate, which is released from glycogen stores in the muscle by glycogen phosphorylase, as well as by an increase in the sensitivity of various of the enzymes involved in glycolysis. Glycogen phosphorylase is activated by the increase in sarcoplasmic Ca^{2+} concentrations that occurs with the onset of exercise (driven in turn by the CNS via the motor nerves; Figure 2). Inorganic phosphate, the co-substrate for glycogen phosphorylase, comes from the ATP hydrolysed during muscle contraction and from phosphocreatine. With the onset of exercise the rate of glycolysis exceeds the supply of oxygen until the necessary cardiovascular adjustments take place (i.e. cardiac output increases) and lactate accumulates. Thus, the onset of muscle contraction and the supply of energy substrate are closely interrelated.

Skeletal muscle broadly consists of two types of fibre. Slow twitch or type I oxidative fibres tend to be red, rich in mitochondria and myoglobin and obtain their energy by aerobic mechanisms. Characteristically, they are found in the postural muscles of the back. Fast twitch, type II or glycolytic fibres contract rapidly and obtain their energy supply via anaerobic glycolytic mechanisms. Characteristically, they are found in the small muscles of the hand, though in practice most muscles in the body are made up of roughly equal proportions of fast and slow twitch fibres.

Intensity of exercise relative to the individual's capability is quantified in terms of the maximal oxygen uptake achievable (VO_2max). VO_2max is normally limited by cardiovascular rather than respiratory or metabolic factors. Low intensity exercise (involving a VO_2 at a relatively low percentage of VO_2max) is associated with greater fat oxidation than carbohydrate. As the intensity of the exercise increases, so a greater percentage of the energy expended is obtained from the oxidation of carbohydrate until the so-called 'anaerobic threshold' is reached, usually at about 50–70% of VO_2max. Oxygen delivery can then no longer support energy requirements and lactic acid accumulates. This is evident as an increase in the volume of carbon dioxide relative to the volume of oxygen and thus a rise in the respiratory exchange ratio. The contribution of fat oxidation to energy expenditure at 100% VO_2max does not usually exceed 60%.

Energy supplies come predominantly from muscle glycogen stores, but also from fat stored in muscle. The contribution of circulating substrates (glucose from liver glycogen and free fatty acids from adipose tissue) is relatively small compared with the muscle glycogen and fat stores. Some energy comes from gluconeogenesis, particularly from the recycling of lactate, but this is limited by the visceral (hepatic) vasoconstriction seen as part of the cardiovascular response to exercise (see *Anaesthesia and Intensive Care Medicine* **2:3:** 115). Endurance capacity (i.e. time to exhaustion) is related directly to the size of the muscle glycogen stores.

As an individual gets fitter (i.e. VO_2max increases), the contribution of fat to substrate oxidized at a given VO_2 increases. The fitter individual (with a higher VO_2max) is also better able to tolerate higher levels of lactic acid accumulation than the less fit. The ability to store glycogen and fat in muscle also increases with improving fitness.

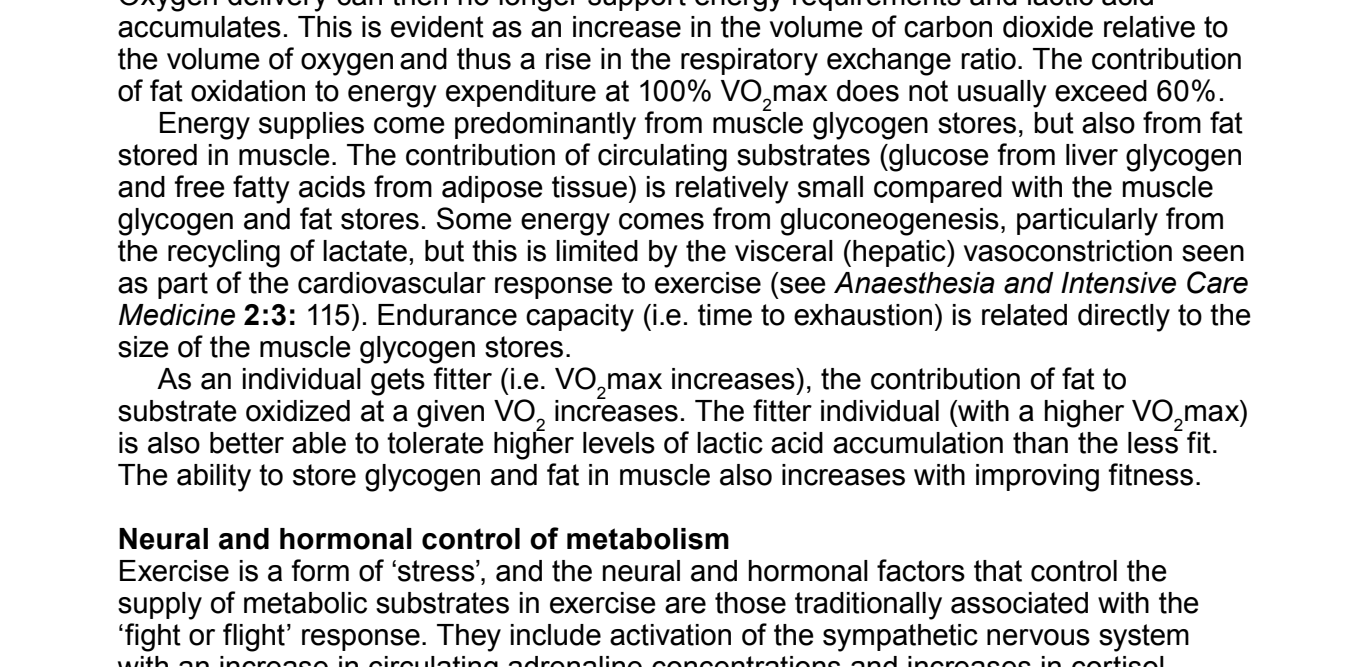
Neural and hormonal control of metabolism

Exercise is a form of 'stress', and the neural and hormonal factors that control the supply of metabolic substrates in exercise are those traditionally associated with the 'fight or flight' response. They include activation of the sympathetic nervous system with an increase in circulating adrenaline concentrations and increases in cortisol and glucagon. As discussed above, skeletal muscle contraction stimulates glycogen breakdown, but sympathetic activation mediated via adrenaline does the same and, with anticipation, may even start before the exercise. Glucose is mobilized from liver glycogen and free fatty acids are released from adipose tissue stores secondary to sympathetically mediated lipolysis. Sympathetic stimulation can either inhibit (α effect) or stimulate (β effect) insulin secretion but, in these circumstances, the inhibitory effect predominates and circulating insulin concentrations fall. There is a reciprocal rise in glucagon. Growth hormone and cortisol are both stimulated, and rise more gradually over the first 30–60 minutes of a bout of exercise.

Sympathetic stimulation also stimulates the cardiovascular system with increases in cardiac output and blood supply to the muscles. There is a fall in pH as lactic acid accumulates and carbon dioxide production increases; these promote vasodilatation and stimulate ventilation. However, the major stimulus to glycogen mobilization in muscle is muscle contraction; the role of the sympathetic system is comparatively minor.

Sympathetic activation stimulates lipolysis, but extreme sympathetic activation also results in vasoconstriction of the blood vessels supplying adipose tissue and this can limit the rise in free fatty acid levels, some of which may remain within the adipose tissue and may become re-esterified. This limits the extent to which fat can be used as a fuel at the highest exercise intensities. Typically, when the exercise stops, free fatty acid concentrations rise as vasodilatation occurs in the fat depots and the fatty acids are flushed into the circulation.

Metabolic features of exercise



2

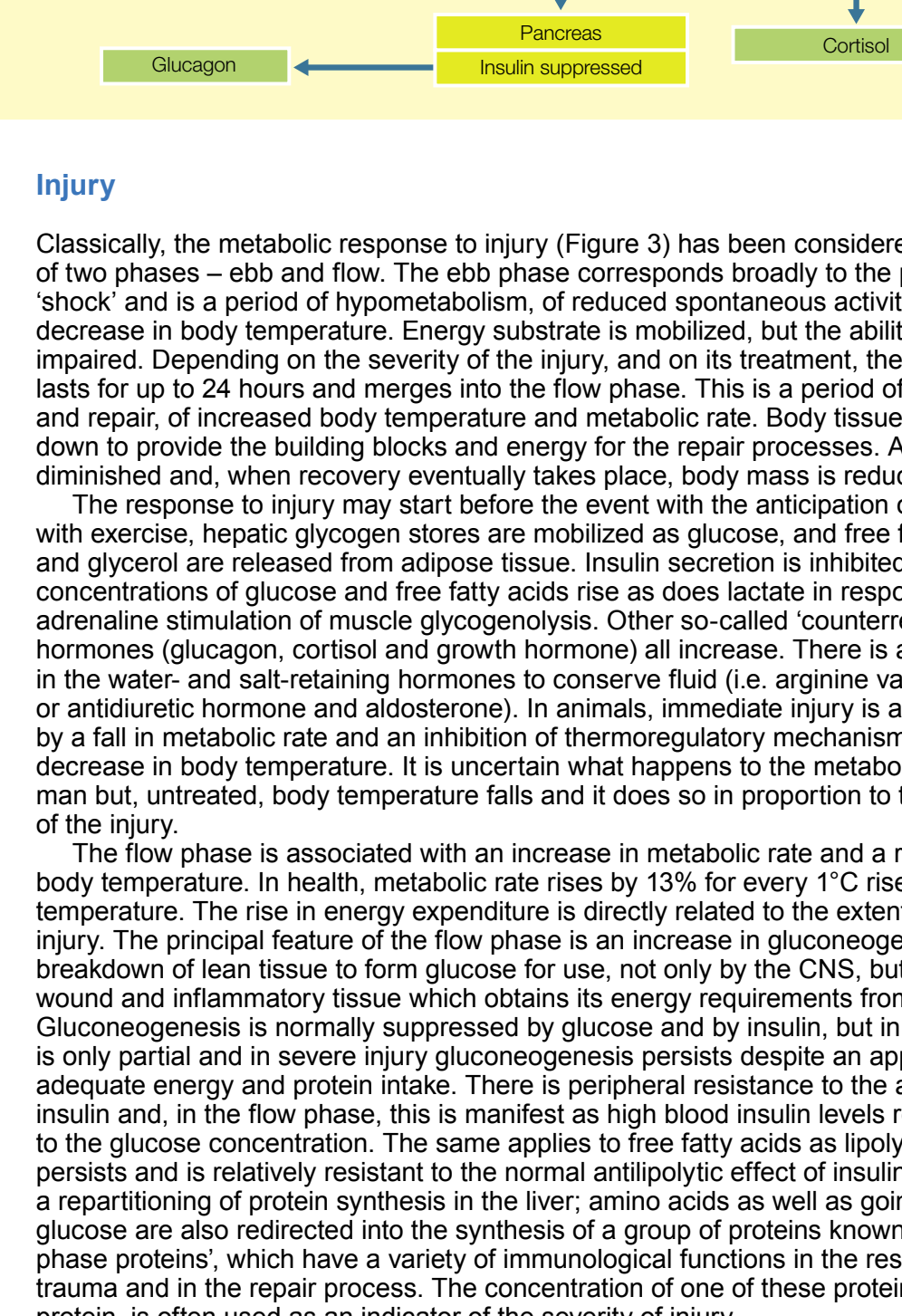
Injury

Classically, the metabolic response to injury (Figure 3) has been considered to consist of two phases – ebb and flow. The ebb phase corresponds broadly to the period of 'shock' and is a period of hypometabolism, of reduced spontaneous activity and a decrease in body temperature. Energy substrate is mobilized, but the ability to use it is impaired. Depending on the severity of the injury, and on its treatment, the ebb phase lasts for up to 24 hours and merges into the flow phase. This is a period of regeneration and repair, of increased body temperature and metabolic rate. Body tissue is broken down to provide the building blocks and energy for the repair processes. Appetite is diminished and, when recovery eventually takes place, body mass is reduced.

The response to injury may start before the event with the anticipation of stress. As with exercise, hepatic glycogen stores are mobilized as glucose, and free fatty acids and glycerol are released from adipose tissue. Insulin secretion is inhibited. Circulating concentrations of glucose and free fatty acids rise as does lactate in response to adrenaline stimulation of muscle glycogenolysis. Other so-called 'counterregulatory' hormones (glucagon, cortisol and growth hormone) all increase. There is also a rise in the water- and salt-retaining hormones to conserve fluid (i.e. arginine vasopressin or antidiuretic hormone and aldosterone). In animals, immediate injury is accompanied by a fall in metabolic rate and an inhibition of thermoregulatory mechanisms with a decrease in body temperature. It is uncertain what happens to the metabolic rate in man but, untreated, body temperature falls and it does so in proportion to the severity of the injury.

The flow phase is associated with an increase in metabolic rate and a rise in body temperature. In health, metabolic rate rises by 13% for every 1°C rise in temperature. The rise in energy expenditure is directly related to the extent of the injury. The principal feature of the flow phase is an increase in gluconeogenesis with breakdown of lean tissue to form glucose for use, not only by the CNS, but also for wound and inflammatory tissue which obtains its energy requirements from glycolysis. Gluconeogenesis is normally suppressed by glucose and by insulin, but in injury this is only partial and in severe injury gluconeogenesis persists despite an apparently adequate energy and protein intake. There is peripheral resistance to the action of insulin and, in the flow phase, this is manifest as high blood insulin levels relative to the glucose concentration. The same applies to free fatty acids as lipolysis also persists and is relatively resistant to the normal antilipolytic effect of insulin. There is a repartitioning of protein synthesis in the liver; amino acids as well as going to form glucose are also redirected into the synthesis of a group of proteins known as 'acute phase proteins', which have a variety of immunological functions in the response to trauma and in the repair process. The concentration of one of these proteins, C-reactive protein, is often used as an indicator of the severity of injury.

Metabolic response to major trauma over 24 hours



3

Obesity

Obesity is the result of a long-term imbalance between energy intake and energy expenditure. The precise mechanisms (i.e. excessive intake or reduced expenditure) have been elusive, because of the problems of making the measurements. A fat gain of 20 kg over 10 years denotes an imbalance of energy intake over expenditure of about 50 kcal/day; techniques to measure this difference between these two parameters do not exist. There are a number of complex techniques for measuring adiposity, none of which are entirely satisfactory, and which are beyond the scope of the present discussion. The simplest measure of excess weight is, however, the body mass index, which is weight divided by height^2 (kg/m^2). The normal range is 18–25, 25–30 is described as overweight, above 30 as obese and above 40 kg/m^2 as morbidly obese. Obesity is associated with an increased incidence of other pathologies, such as hypertension, diabetes, coronary artery disease, cancer and osteoarthritis, as well as respiratory impairment. Obesity is a restrictive respiratory defect and obese individuals are hypoxaemic to a degree proportional to the severity of the obesity.

Opinion as to the cause of the obesity is coming down on the side of a dysregulation of intake rather than expenditure. In hibernating rodents, there is evidence that weight can be controlled by thermogenic mechanisms involving the sympathetic nervous system and brown adipose tissue similar to that seen in response to cold, but this does not appear to apply in man. Increased sympathetic activity increases metabolic rate (i.e. cardiovascular stimulation, glycogenolysis, free fatty acid/triglyceride cycling), but it is not a mechanism for weight control. In the last few years, a peptide hormone called leptin has been identified as being produced by adipose tissue. Circulating levels correlate with adipose tissue mass and it suppresses appetite. It has been suggested that obesity represents a leptin-resistant state, perhaps with reduced levels of leptin transport into the CSF.

The nature of the excess intake is largely fat, which is taken up directly into adipose tissue stores. In man, there is little conversion of excess carbohydrate intake into fat. Carbohydrate does, however, stimulate insulin secretion and this is a potent antilipolytic, suppressing fat mobilization and utilization. Likewise, alcohol significantly suppresses fat oxidation; it is an energy-rich poison (7 kcal/g) that is oxidized preferentially to either fat or carbohydrate.

The characteristic metabolic features of obesity are a propensity to metabolize fat rather than carbohydrate and a degree of insulin resistance that improves with weight loss. The extent to which fat is metabolized relative to carbohydrate is a function of circulating fatty acid concentrations and insulin (stimulated by glucose ingestion), which is antilipolytic. High rates of fat oxidation inhibit pyruvate dehydrogenase and this in turn inhibits glycolysis. This results in a high circulating level of glucose, which stimulates insulin secretion. The obese individual has chronically high fatty acid levels and so is insulin resistant because of this inhibitory effect on carbohydrate metabolism. This results in increased triglyceride synthesis and impaired glucose utilization in peripheral tissue, particularly muscle. This whole scenario predisposes to hypertension, peripheral and coronary vascular disease, and diabetes.

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Thyroid and Parathyroid Hormones and Calcium Homeostasis

Adrian Heald

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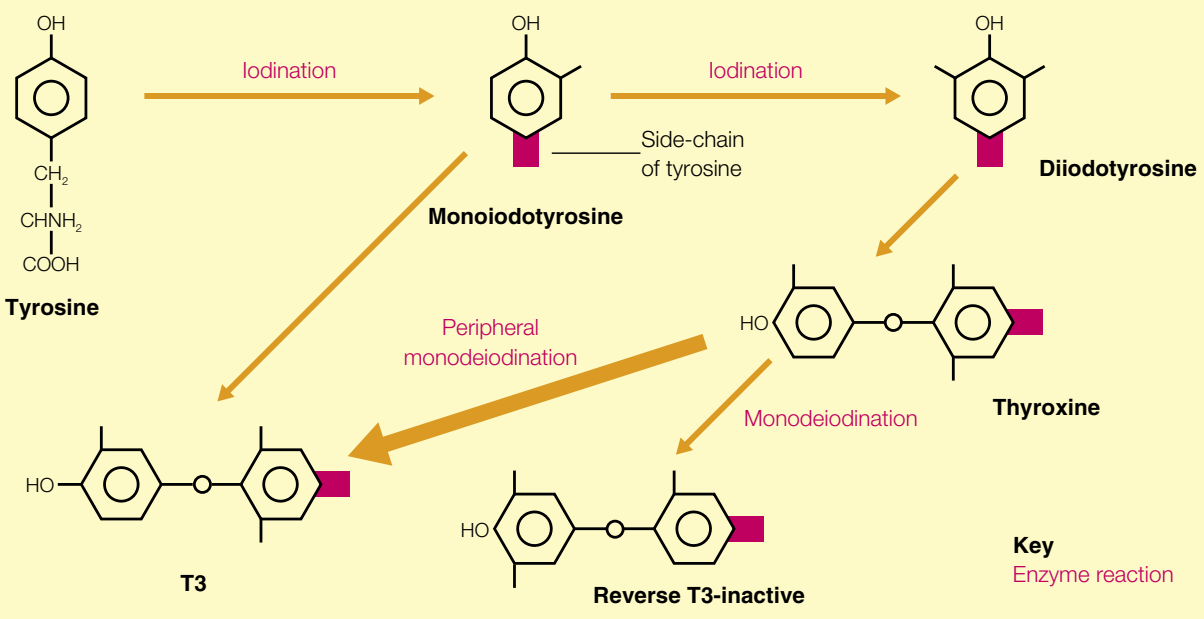
Thyroid hormones

Thyroid gland: thyroid hormone synthesis requires iodide. Iodide is oxidized by thyroid peroxidase and stored as iodinated thyroglobulin within the thyroid follicular cell where it is incorporated into tyrosine residues. Thyroglobulin is the main precursor of thyroid hormones. The bioactive iodothyronines are tri-iodothyronine (T3) and thyroxine (T4). Three or four T4 molecules are present per molecule of human thyroglobulin. Thyroglobulin is synthesized in the thyroid follicular cell (Figure 1) and extruded into the follicular luminal colloid where it is stored. Secretion of T4 and T3 (very little T3 is secreted) occurs following proteolytic cleavage of thyroglobulin in the thyroid follicular cell. This process is activated by thyroid stimulating hormone (TSH).

Thyroid hormones in the circulation: various proteins bind T4 and T3 in the circulation but 75% is by thyroxine-binding globulin. About 0.04% of T4 and 0.4% of T3 circulate in the unbound state. The biologically active thyroid hormone is T3. This is produced by peripheral monodeiodination (Figure 1) of T4. Reverse T3 is also produced by monodeiodination of T4. The half-life of T4 is 6.7 days, a reflection of the extent to which T4 is protein bound. Conversely T3 is rapidly cleared from the plasma with a half-life of 0.75 days. Circulating thyroid hormone levels negatively regulate TSH secretion by a classical biofeedback loop on the hypothalamus and pituitary gland.

Thyroid hormone biosynthesis



1

Thyroid hormone action is via a nuclear receptor. Thyroid hormone receptors belong to a family of nuclear receptors that include glucocorticoid, mineralocorticoid, oestrogen and vitamin D receptors. Multiple thyroid hormone receptor isoforms are produced by alternative splicing during trans-cription. The interaction of thyroid hormones with the nuclear receptor stimulates calorigenesis (resulting in increased oxygen consumption), protein synthesis, and carbohydrate and lipid metabolism.

Hyperthyroidism (thyrotoxicosis)
The prevalence of hyperthyroidism is about 20/1000 women and 2/1000 men. Cardinal features are restlessness, heat intolerance, excessive sweating, weight loss despite increased appetite, loose motions and disturbance of the menstrual cycle and may include features of Graves' disease, namely goitre, ophthalmopathy and occasionally pre-tibial myxoedema. Typically circulating T4 and T3 concentrations are raised but occasionally there is elevation of T3 alone (T3 toxicosis).

Graves' disease is the most common cause of hyperthyroidism. The patient is typically female and aged 20–40 years. It is characterized by a diffusely enlarged thyroid gland, ophthal-mopathy and hyperthyroidism. There is a strong familial predisposition. It is associated with several major histocompatibility (HLA) antigens. There is lymphocytic infiltration of the thyroid gland. Pathogenesis is determined by the presence of antibodies (usually of the IgG1 subclass) to the thyroid follicular cell surface membrane TSH receptor.

Toxic multinodular goitre usually occurs in an older individual associated with an existing multinodular goitre. Thyroid gland overactivity is usually less marked than in patients with Graves' disease.

Solitary toxic adenoma is an uncommon cause of hyper-thyroidism. The diagnosis may be confirmed by radionuclide scanning which demonstrates localization of radioisotope to the nodule with suppression of uptake by the surrounding normal thyroid.

Thyroiditis (de Quervain's thyroiditis) is thought to be viral in aetiology and often follows an upper respiratory infection. Presentation is with pain in the thyroid gland, often with fever. Follicular destruction in the thyroid gland leads to leakage of preformed hormone with development of hyperthyroidism. Erythrocyte sedimentation rate (ESR) is high in association with the acute inflammation.

Antithyroid drugs and other treatment: carbimazole and propylthiouracil inhibit oxidation of iodide by H_2O_2 and organification by incorporation into the tyrosine residues of thyroglobulin. Additionally propylthiouracil inhibits the conversion of T4 to T3 in the periphery. Management of thyrotoxicosis is by titration, block or replacement whereby endogenous thyroid hormone secretion is suppressed and the patient maintained on exogenous T4. This regimen is unsuitable in pregnancy because thyroxine does not cross the placenta.

β-blockers (usually propanolol) relieve the peripheral manifestations of hyperthyroidism and are often used in conjunction with antithyroid drugs for symptom relief.

When the patient has been rendered euthyroid, other treatment options are subtotal thyroidectomy and radioactive iodine treatment using the isotope I^{131}. There is a significant long-term consequence of hypothyroidism after treatment with I^{131}. Some patients require more than one dose of radioactive iodine.

Hypothyroidism
Hypothyroidism is usually a result of primary thyroid disease (primary hypothyroidism) rather than reduced TSH secretion from the anterior pituitary gland. Common features include fatigue, lethargy, mental slowness, weight gain, facial puffiness, constipation, delayed relaxation phase of deep tendon reflexes, intolerance of cold, and dry skin. In areas where iodine intake is adequate, the most common cause is autoimmune lymphocytic thyroiditis. This is painless and may occur with enlargement of the thyroid (Hashimoto's disease) or with no goitre (atrophic thyroiditis). Treatment is usually with thyroxine though tri-iodothyronine can be used. In patients with known coronary artery disease, thyroxine must be started at a low dose (25 μg/day) and the dose increased cautiously.

Parathyroid hormones and calcium homeostasis

The concentration of calcium is maintained in a narrow range, varying by less than 5% despite large calcium fluxes across bone, kidney, gut and other tissues. 99% of calcium and 88% of phosphate is found in bone. About 50% of plasma calcium is ionized. The extent to which calcium is protein bound is pH dependent. Alkalosis, induced for example by hyperventilation, results in a decrease in ionized calcium (but no change in total plasma calcium) and symptoms of hypocalcaemia, typically paraesthesiae. The amount of calcium in the extracellular fluid is principally determined by parathormone, calcitriol (1,25-dihydroxyvitamin D_3) and calcitonin.

Parathormone (PTH)
PTH is a single polypeptide chain containing 84 amino acids. Only the first 32–34 amino acids from the amino-terminal end are responsible for biological activity. It is synthesized as a prohormone in the rough endoplasmic reticulum of the chief cells of the parathyroid glands. The major stimulus to secretion is a fall in the plasma ionized calcium concentration. Chronic hypomagnesaemia results in impaired PTH release and consequent hypocalcaemia. Actions of PTH are:

- to increase renal tubular resorption of calcium and decreased tubular resorption of phosphate (causing an increase in plasma calcium and a decrease in plasma phosphate)
- to decrease proximal tubular resorption of bicarbonate (causing an increased excretion of bicarbonate and hyperchloraemic acidosis)
- to stimulate the 1α-hydroxylase enzyme in kidney, responsible for the formation of 1,25-dihydroxyvitamin-D_3 (calcitriol) from 25-hydroxyvitamin-D_3 (calcifidiol)
- to increase the number and activity of osteoclasts causing increased bone resorption
- to decrease proximal tubular resorption of sodium and increased amino-acid excretion.

Calcitonin
Calcitonin is a peptide containing 32 amino acid residues. It is secreted by the parafollicular cells (C-cells) of the parathyroid. The salmon form of calcitonin resembles human calcitonin more than that of other mammals. This has led to therapeutic uses in humans, for example in the treatment of Paget's disease and osteoporosis. Secretion of calcitonin is stimulated by an increase in serum concentration of calcium. Its actions are opposite to those of PTH (e.g. it inhibits osteoclast numbers and activity) it also inhibits the secretion of several gastrointestinal hormones (e.g. gastrin and cholecystokinin).

Vitamin D
Vitamin D_3 (fat soluble) is derived from the diet and from the skin by ultraviolet irradiation of 7-dehydroxycholesterol. Further conversions are in the liver to 25-hydroxyvitamin-D_3 (calcifidiol) which is the main circulating vitamin D metabolite. The concentration of this in serum is highest in late summer and lowest in late winter. Conversions also occur in the kidney (also placenta and decidua) to 1,25-dihydroxyvitamin-D_3 (calcitriol), 24,25-dihydroxyvitamin-D_3 and 25,26-dihydroxyvitamin-D_3. Failure of the process is implicated in the pathogenesis of vitamin D resistance in renal failure. The actions of 1,25-dihydroxyvitamin-D_3 (calcitriol) are to increase the intestinal absorption of calcium and phosphate and to increase the resorption of bone mineral and matrix. Weakness of skeletal muscles, particularly limb girdles, is a feature of vitamin D deficiency.

Hyperparathyroidism
Primary hyperparathyroidism is usually caused by a single parathyroid adenoma of the chief cells of the parathyroid gland. Occasionally it is caused by diffuse hyperplasia or multiple adenomata. Presentation is with symptoms of hypercalcaemia including thirst, fatigue, constipation and renal calculi. Diagnosis is by demonstration of a raised plasma calcium concentration in the face of a normal or raised plasma PTH level. Treatment is by surgical removal of the parathyroid adenoma.

Secondary hyperparathyroidism is caused by prolonged hypocalcaemia, for example in chronic renal failure or
vitamin D deficiency. This results in increased secretion of PTH and hyperplasia of the parathyroid glands. There may be associated osteomalacia. Treatment involves normalization of plasma calcium, often using 1α-hyroxylated derivatives of vitamin D.

Tertiary hyperparathyroidism describes patients with longstanding secondary hyperparathyroidism who develop autonomous parathyroid gland function and hypercalcaemia. The problem is most commonly seen after renal trans-plantation but may occur in patients with longstanding malabsorption or chronic renal failure. Treatment is by parathyroidectomy and appropriate management of the cause.

Pseudohyperparathyroidism involves synthesis of PTH-like substances by tumours, particularly of the lung. Presentation is with biochemical abnormalities similar to those seen in primary hyperparathyroidism.

Hypoparathyroidism
Hypoparathyroidism results in hypocalcaemia and hyper-phosphataemia secondary to defective secretion or action of PTH. It causes paraesthesiae, carpopedal spasm and abdominal cramps, sometimes with irritability and emotional lability or with epilepsy. It most commonly results from parathyroid, thyroid or laryngeal surgery. It has a familial form and a sporadic form associated with autoimmune spectrum disorder and monoliasis.

Pseudohypoparathyroidism results from resistance of one or more target tissues to the actions of PTH. Circulating levels of PTH are high and are suppressed by giving a calcium infusion. There is an association with several somatic abnormalities including short stature, round face and shortening of the metacarpal and metatarsal bones. Resistance to PTH may be partial or complete. There may be other associated endocrine abnormalities, for example TSH deficiency leading to hypo-thyroidism and diabetes mellitus.

In pseudopseudohypoparathyroidism the somatic features of seudohypoparathyroidism are present but plasma concen-trations of calcium and phosphate are normal. PTH levels are usually normal but may be raised. ◆

Physiology: Cardiac

Anaesthesia
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The Electrocardiogram

Emrys Kirkman

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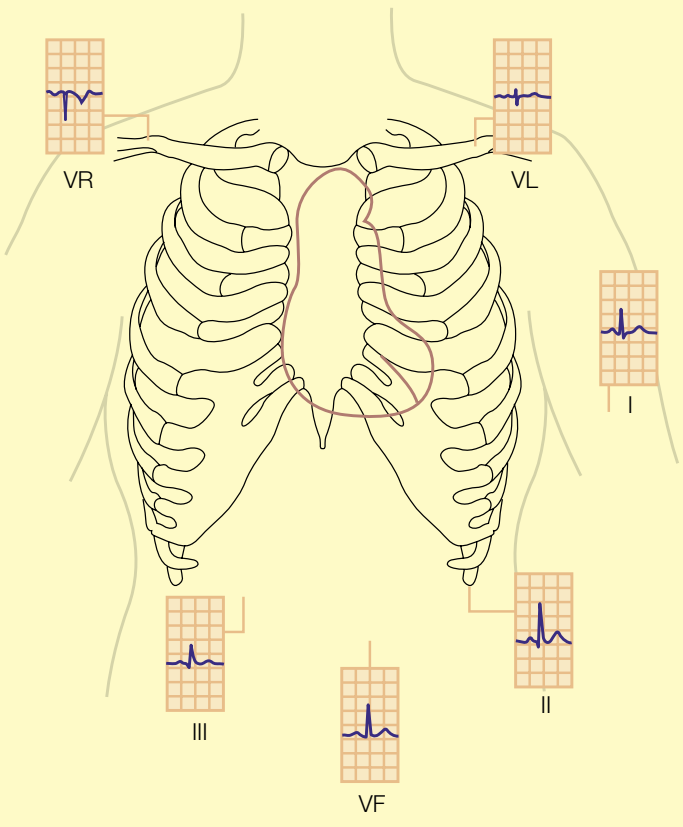
A large number of cardiac muscle fibres become activated synchronously and generate sufficient electrical disturbance to be recorded at the body's surface: this forms the basis of the electrocardiogram (ECG). An examination of the ECG reveals detail of the pathways along which electrical activity travels in the heart. The ECG does not represent the electrical activity of any single fibre, but the combined activity of all the muscle fibres at any one instant.

Electrical views of the heart

Twelve ECG 'leads' are usually recorded. It is important not to confuse an ECG 'lead' with the 'wires' connected to the electrodes used to make the recording. In ECG terms, 'lead' refers to an electrical view of the heart.

Standard leads: there are six standard leads (I, II, III, VR, VF, VL) which view the heart in the vertical plane (e.g. lead II looks at the left lateral surface of the heart from about the left hip, while VR looks at the heart from the right shoulder). The detail of the other views are given in Figure 1. A further six leads (V_1, V_2, V_3, V_4, V_5, V_6) view the heart in the horizontal plane (Figure 2).

Normal ECG from the standard leads



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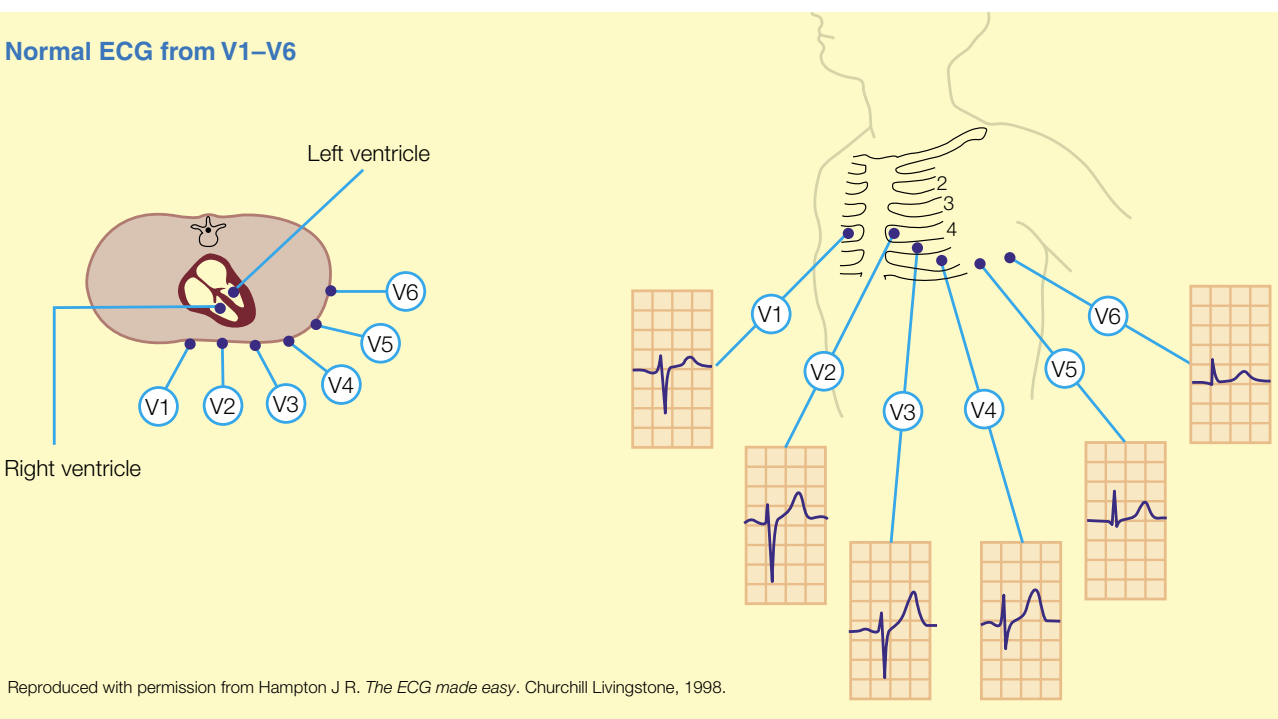
1

Normal ECG from V1–V6



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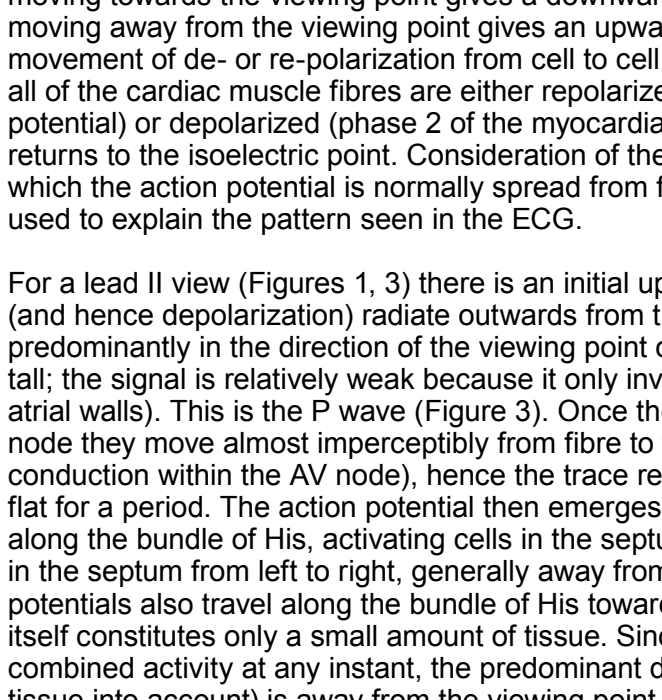
2

The differential amplifiers used to record the ECG are configured such that if a wave of depolarization moves towards the viewing point there is an upward deflection away from an isoelectric starting point. Depolarization moving away from the viewing point gives a downward deflection below the isoelectric point. Conversely, repolarization moving towards the viewing point gives a downward deflection and repolarization moving away from the viewing point gives an upward deflection. When there is no movement of de- or re-polarization from cell to cell with respect to the viewing point (i.e. all of the cardiac muscle fibres are either repolarized (phase 4 of the myocardial action potential) or depolarized (phase 2 of the myocardial action potential)) then the trace returns to the isoelectric point. Consideration of these rules and the pathway along which the action potential is normally spread from fibre to fibre through the heart can be used to explain the pattern seen in the ECG.

For a lead II view (Figures 1, 3) there is an initial upward deflection as action potentials (and hence depolarization) radiate outwards from the SA node across the atria, predominantly in the direction of the viewing point on the left hip. The wave is not very tall; the signal is relatively weak because it only involves a small amount of tissue (thin atrial walls). This is the P wave (Figure 3). Once the action potentials invade the AV node they move almost imperceptibly from fibre to fibre through the AV node (slow conduction within the AV node), hence the trace returns to the isoelectric line and is flat for a period. The action potential then emerges from the AV node and proceeds along the bundle of His, activating cells in the septum. This causes activity to spread in the septum from left to right, generally away from the viewing point. Although action potentials also travel along the bundle of His towards the apex of the heart, the bundle itself constitutes only a small amount of tissue. Since the trace is influenced by the combined activity at any instant, the predominant direction of activity (taking quantity of tissue into account) is away from the viewing point, giving the small downward Q wave. The next major event is the activation of the bulk of the ventricular myocardium, from the endocardial to the epicardial surface: activity in a large amount of tissue moves from cell to cell towards the viewing point. This gives the large upward R wave. Finally, the few muscle fibres at the base of the heart are depolarized giving a small downward S wave. At this point, all the ventricular muscle fibres are depolarized and are on the shoulder (phase 2) of the cardiac muscle action potential (see pages 274 and 277). Thus, there is no wave of depolarization moving with respect to the viewing point, so the trace returns to the isoelectric line. Finally, after 200–300 ms the myocardial fibres repolarize (phase 3 of the myocardial action potential). However, those of the epicardial surface of the heart have a shorter duration action potential (nearer 200 ms) than those of the endocardial surface (nearer 300 ms), so that the wave of repolarization moves away from the viewing point giving a final upward wave, the T wave (Figure 3). Atrial repolarization occurs coincident with ventricular depolarization and, because of the greater amount of tissue involved in the ventricles, the wave produced by the atrial repolarization is lost in the QRS complex. The normal durations of the waves and intervals between them are given in Figure 3. If the viewing point is transferred to the right shoulder (lead VR) then essentially a mirror image is seen (Figure 1) with the bulk of the myocardial depolarization moving away from the viewing points with a predominant large downward wave in the QRS complex.

Waves of a typical lead II ECG showing mean (range) for relevant intervals and durations



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3

In summary, the P wave represents atrial depolarization, the QRS complex in its entirety represents ventricular depolarization and the T wave represents ventricular repolarization.

V_1–V_6: these leads view the heart in the horizontal plane (Figure 2). V_1 andV_2 view the heart from the right and V_5 and V_6 from the left, with V_3 and V_4 in between. Because the septal depolarization arises before ventricular depolarization, and occurs from left to right, initial parts of the ventricular depolarization are shown by an upward deflection in V_1 and V_2 but downward deflections in V_5 and V_6 (Figure 2). Thereafter, the main mass of ventricular tissue is depolarized. However, since there is a much greater mass in the left ventricle, during ventricular depolarization the predominant movement is away from V_1 and V_2 giving a downward deflection and towards V_5 and V_6 giving an upward deflection in these views (Figure 2).

Convention for naming waves: the waves of the ECG are labelled P, Q, R, S and T (with an additional U wave sometimes visible). If the first deflection after a P wave (if it exists) is downward it is called a Q wave. An upward deflection is called an R wave, whether or not it is preceded by a downward wave. A deflection below the isoelectric line after an R wave is called an S wave, whether or not a Q wave has been seen.

Ectopic foci and conduction problems

It is beyond the scope of this article to discuss any ECG abnormalities in detail, but a few examples are given. It should be stressed that a single abnormality in a few leads can be the result of a range of problems, and that the entire picture from all leads and other clinical signs must be integrated.

Ectopic foci can develop in the atria or ventricles. They lead to an abnormal sequence of spread of the action potentials from fibre to fibre through the heart, and hence abnormalities of the ECG.

Atrial ectopic foci can give rise to abnormally shaped P waves (e.g. inverted P waves in lead II). Furthermore, since the focus may be much closer to the AV node, the P–R interval may be abnormally short. However, the spread of the action potentials should be essentially normal from the AV node onwards, and the QRS complex should be normal. Conversely, a ventricular ectopic focus gives rise to an abnormally shaped QRS complex, which is not preceded by a P wave. The shape of the abnormality occurs because of the altered sequence of fibres along which the myocardial action potential travels within the ventricles. The QRS complex is much wider (occurs over a greater period of time) because the spread of the action potentials does not make proper use of the fast conduction system.

In some circumstances, the myocardial action potential is prolonged, which in turn prolongs the QT interval. Long QT syndrome is a recognized condition associated with sudden death and often associated with ventricular arrhythmias and fibrillation. The problem is that during the repolarization of the ventricles the heart is in a critical state, termed the vulnerable period. At this time (which corresponds to the rising phase of the T wave of the ECG) some of the ventricular myocytes have repolarized while others have incompletely repolarized or are still depolarized. Under these circumstances an ectopic beat can establish a re-entry and a circus of action potentials leading to fibrillation.

Conduction problems in the AV node can be indicated by a prolonged P–R interval. If all of the P waves result in a QRS complex this is referred to as a first-degree heart block. In other instances some, but not all, P waves result in a QRS complex: this is second-degree heart block. In more extreme circumstances there is complete block at the AV node and no P wave results in a QRS complex. This is third-degree heart block and in this case ventricular beating is driven by an alternative ventricular pacemaker. In this latter circumstance there may be regular P waves and regular QRS complexes, but they occur at different rates.

Sinus arrhythmia

Examination of the ECG in the normal individual reveals that the heart rate is often not steady at rest: the R–R interval becomes progressively increased during expiration and shortened during inspiration. This rhythmical fluctuation in heart rate in phase with respiration is called sinus arrhythmia. It reflects resting vagal tone to the heart: during inspiration the vagus nerve is inhibited as a consequence of activity in medullary inspiratory neurons and because of inhibition from an afferent pathway originating in pulmonary stretch receptors. On expiration the inhibition is lost and vagal activity increases, leading to a bradycardia. The degree of sinus arrhythmia in part depends on the level of resting vagal tone. If this is high, there is considerable scope for inhibition during inspiration, while if resting vagal activity is low, there is little scope for inhibition during inspiration and sinus arrhythmia is weak or absent. Sinus arrhythmia can therefore be used as a test of vagal activity. It is reduced by anxiety, a decline in cardiovascular fitness and pathological states affecting the vagus nerve, therefore care must be taken when interpreting the results. ◆

Electromechanical Coupling and Regulation of Force of Cardiac Contraction

Emrys Kirkman

Emrys Kirkman is Senior Lecturer in Physiology at the University of Durham, UK. He has a PhD from Manchester University and has worked at the MRC Trauma Group, Manchester. He also holds an honorary Senior Lectureship in the Academic Division of James Cook University Hospital, Cleveland. His research interests include trauma-induced changes in cardiovascular control mechanisms, the underlying central nervous pathways and the resulting alterations in haemodynamics and oxygen transport.

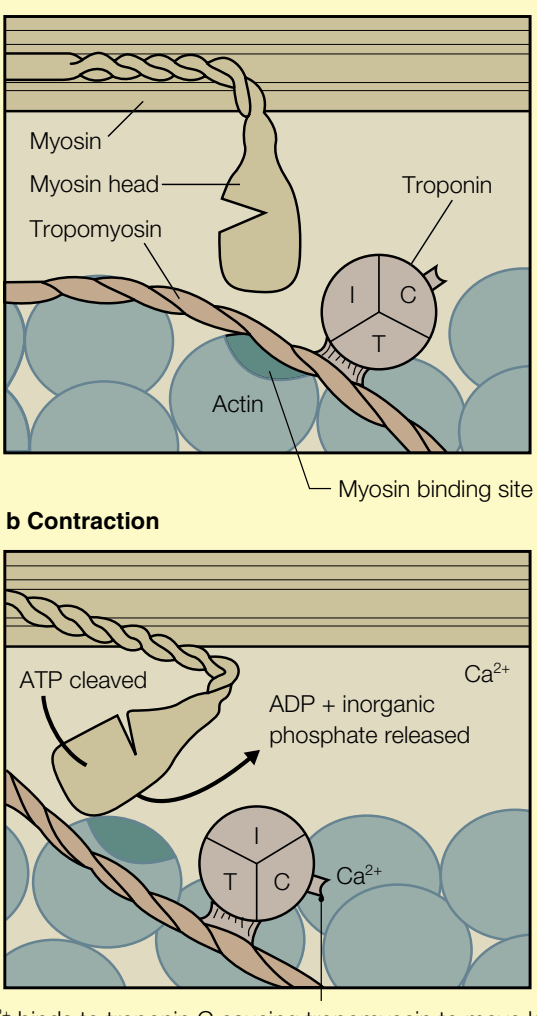
Cardiac muscle fibres, like skeletal muscle fibres, are divided into sarcomeres, the basic unit of contraction. The contractile elements include actin, myosin, tropomyosin and troponin. The myosin molecules are arranged into thick filaments while the actin molecules form the basis of the thin filaments. The troponin and tropomyosin are attached to the thin filaments as in skeletal muscle. In contrast to fast skeletal muscle fibres, which need to produce repetitive mechanical action only for short periods before resting, and hence can accrue an oxygen debt, cardiac muscle fibres need to perform repetitive activity for long periods (a lifetime) without rest. Consequently, cardiac muscle fibres are much more dependent on the utilization of oxygen and have an abundance of mitochondria, with rapid oxidation of substrates and formation of ATP, needed for mechanical contraction.

The myocardium is well supplied with capillaries, and diffusion distances between blood and cardiac muscle fibres are relatively short. In addition, the fibres have a well-defined transverse or T-tubule system. These are deep invaginations of the cell membrane, which connect with longitudinally running axial tubules that constitute an extensive network of 'intracellular' tubules whose lumen is continuous with the interstitium. Thus, the intracellular organelles (e.g. the mitochondria) are positioned close to structures that contain interstitial fluid, with short diffusion distances between the two. This arrangement is prevalent in the force-producing fibres of the ventricles, but less well developed in atrial cells. The T-tubules also come into close approximation with other organelles, such as the sarcoplasmic reticulum, which serves as an important reservoir of the calcium ions needed for part of the contractile process. This system of T-tubules plays an important part in electromechanical coupling, the process by which the action potential in the muscle fibre membrane leads to activation of the actin-myosin contractile mechanism and mechanical shortening.

Molecular mechanisms of contraction

The molecular mechanism of contraction in cardiac muscle is similar to that seen in skeletal muscle. In essence, the thick filaments are made up of myosin molecules, which are long chains grouped together to form the axis of the thick filaments, from which protrude globular heads: two heads for each tail of a myosin molecule. These myosin molecules interdigitate with the thin filaments. Each thick filament is surrounded by six thin filaments in a hexagonal structure, while each thin filament is surrounded by three thick filaments. The thin filaments are made up of two chains of actin molecules, which are twisted round each other to form a long structure with a longitudinal helical groove between the two strands (Figure 1). Positioned along this groove are the rod-shaped tropomyosin molecules, onto which are attached troponin molecules. The part of the troponin molecule attached to tropomyosin is called troponin T. A separate region of troponin (troponin I) also binds to actin.

Arrangement of thick and thin filaments during relaxation and contraction

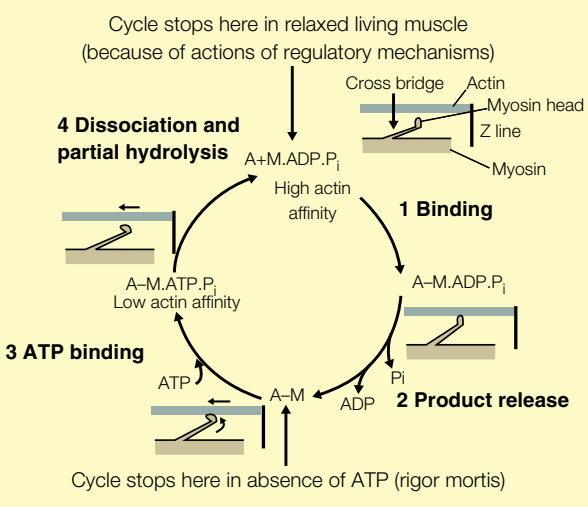


Ca^{2+} binds to troponin C causing tropomyosin to move laterally revealing the myosin binding site on the actin molecule

1

The contractile cycle has four steps (Figure 2). The process is repeated over and over again during contraction. The force of contraction partly depends on the number of myosin heads simultaneously binding and cycling in this way. In the relaxed state, the process does not occur because the sites at which the myosin head binds onto the actin are blocked by tropomyosin (Figure 1). The entire process of contraction is initiated by Ca^{2+} which binds to a region of the troponin molecule (troponin C) weakening the binding of troponin I onto actin and allowing a conformational change, whereby tropomyosin moves laterally and uncovers the myosin binding site on the actin molecule. The elevation of intracellular free Ca^{2+} concentration is initiated by the action potential.

The four steps of muscle contraction



1 An energized myosin head, onto which is bound ADP and phosphate and which has high affinity for a binding site on the actin molecule, binds to the actin molecule
2 Once binding has been achieved, the myosin head releases the ADP and Pi (inorganic phosphate) and energy from a cleaved ATP molecule (origin of the ADP and phosphate). Because of this the myosin head, previously at 90° to the actin molecule, assumes a new conformation at 45° to the actin molecule, pulling the actin over the myosin towards the centre of the sarcomere and shortening the muscle fibre
3 Further ATP is now able to bind to the myosin, reducing its affinity for actin and therefore the myosin head detaches
4 ATP is split to produce ADP and phosphate (still bound to the myosin molecule) again energizing the myosin molecule. The orientation of the head returns to 90 with respect to the actin filaments and the affinity of myosin for actin is increased, leading back to step 1

2

Cardiac action potentials and intracellular Ca^{2+}

The ionic basis of the cardiac action potential is discussed elsewhere.

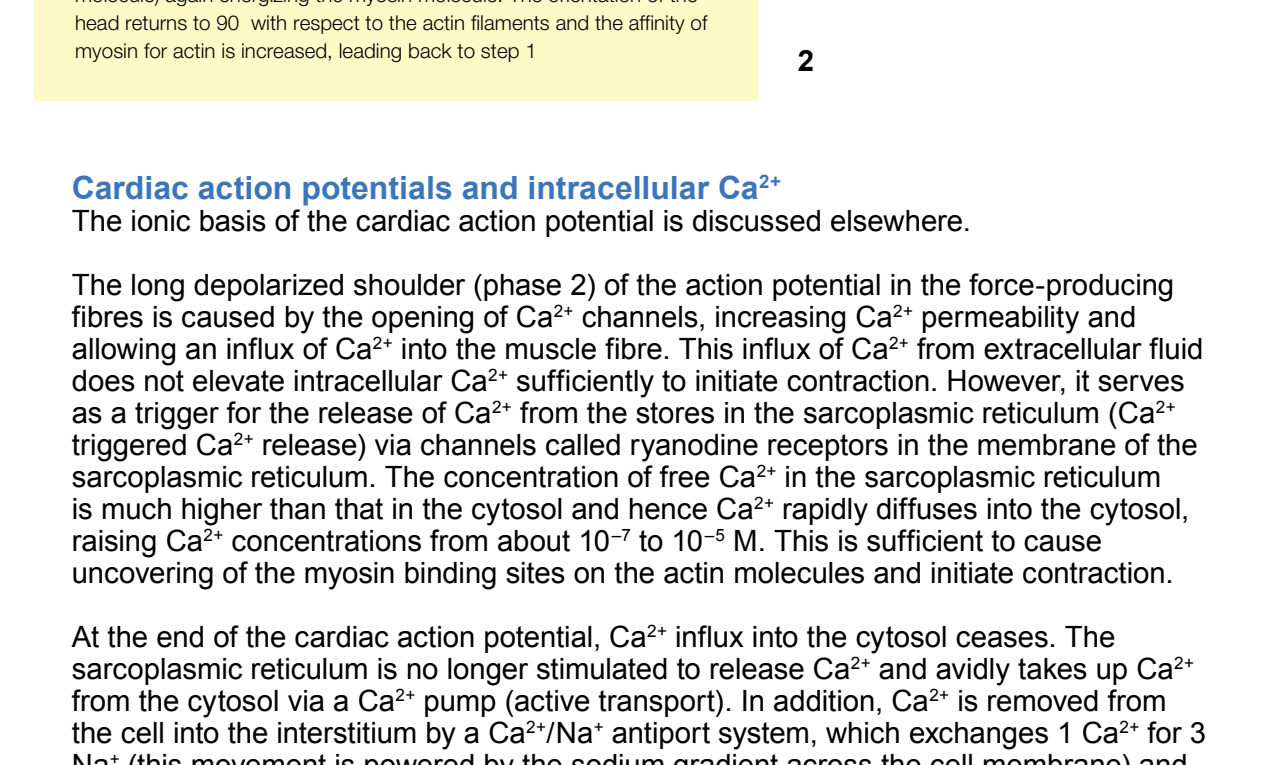
The long depolarized shoulder (phase 2) of the action potential in the force-producing fibres is caused by the opening of Ca^{2+} channels, increasing Ca^{2+} permeability and allowing an influx of Ca^{2+} into the muscle fibre. This influx of Ca^{2+} from extracellular fluid does not elevate intracellular Ca^{2+} sufficiently to initiate contraction. However, it serves as a trigger for the release of Ca^{2+} from the stores in the sarcoplasmic reticulum (Ca^{2+} triggered Ca^{2+} release) via channels called ryanodine receptors in the membrane of the sarcoplasmic reticulum. The concentration of free Ca^{2+} in the sarcoplasmic reticulum is much higher than that in the cytosol and hence Ca^{2+} rapidly diffuses into the cytosol, raising Ca^{2+} concentrations from about 10^{-7} to 10^{-5} M. This is sufficient to cause uncovering of the myosin binding sites on the actin molecules and initiate contraction.

At the end of the cardiac action potential, Ca^{2+} influx into the cytosol ceases. The sarcoplasmic reticulum is no longer stimulated to release Ca^{2+} and avidly takes up Ca^{2+} from the cytosol via a Ca^{2+} pump (active transport). In addition, Ca^{2+} is removed from the cell into the interstitium by a Ca^{2+}/Na^{+} antiport system, which exchanges 1 Ca^{2+} for 3 Na^{+} (this movement is powered by the sodium gradient across the cell membrane) and by active transport of Ca^{2+}. By these means, intracellular (cytosolic) Ca^{2+} concentrations fall rapidly and the myosin binding site on the actin molecule is again blocked by tropomyosin leading to relaxation of the fibre.

Autonomic regulation of force of contraction

Only the sympathetic division of the autonomic nervous system has a significant direct effect on the force of myocardial contraction, because the parasympathetic system provides little innervation of the ventricles. Adrenaline and noradrenaline released from the sympathetic system both activate the G-protein-coupled β_1-adrenoceptors in the cell membrane, which raises the intracellular levels of cAMP. This leads to phosphorylation of the Ca^{2+} L-type channels by a cAMP-dependent protein kinase, which facilitates opening of the channels and leads to influx of Ca^{2+} into the cell (Figure 3). Consequently, a greater number of cross- bridges form and a more forceful contraction occurs. In addition to accelerating contraction, activation of β_1-adrenoceptors also accelerates relaxation. This is because cAMP protein kinase also phosphorylates phospholamban, which enhances Ca^{2+} reuptake into the sarcoplasmic reticulum, and phosphorylates troponin I, which inhibits Ca^{2+} binding to troponin C, thus facilitating relaxation.

Movement of calcium during excitation–contraction coupling in cardiac muscle and the positive inotropic effect of catecholamines



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Any process that elevates the cytoplasmic concentration of Ca^{2+} increases the force of contraction. Cardiac glycosides achieve this by an indirect mechanism: they reduce the activity of Na^{+}-K^{+} ATPase in the cell membrane (Figure 2). Consequently, intracellular Na^{+} levels rise, leading to a reduction in the transmembrane Na^{+} concentration gradient. This reduces the driving force for Na^{+}-Ca^{2+} exchange and leads to a reduced extrusion of Ca^{2+}. The resulting elevation in intracellular Ca^{2+} increases the force of contraction. ◆

Initiation and Regulation of the Heartbeat

Emrys Kirkman

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The heart has all the components necessary to initiate and maintain a regular heartbeat, without the need for external influence. Thus, a transplanted heart without nervous connection, or a heart completely removed from the body, if adequately perfused with oxygen, beats rhythmically. In the normal intact body, the function of the nervous and humoral regulation is to modulate the activity of the heart, though some aspects of modulation are intrinsic properties of cardiac muscle.

Origin of the heartbeat: pacemaker cells

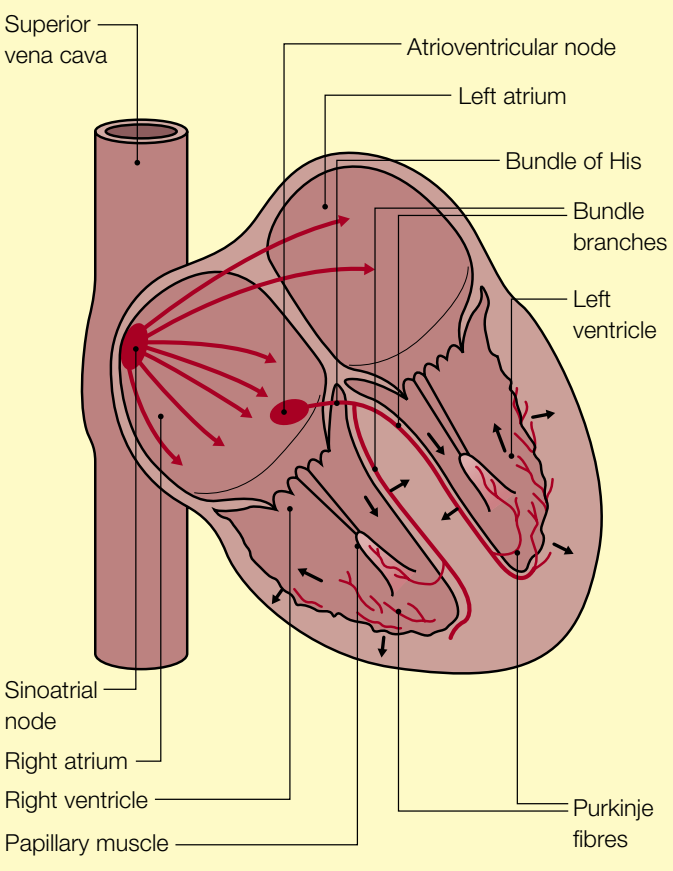
Cardiac muscle fibres can be grouped broadly into three main functional categories:

- pacemakers, which initiate the heartbeat by spontaneously generating action potentials
- conducting fibres, which spread the action potentials throughout the heart in an ordered manner to ensure efficient pumping
- myocardial fibres (most fibres) which produce the force needed to pump blood round the body.

Some of the conducting fibres are also capable of generating action potentials spontaneously, though they do not do so under normal circumstances. The force-producing (myocardial) fibres are normally incapable of spontaneous action potential generation, although under abnormal conditions (e.g. following a period of ischaemia) they may acquire the property and cause problems such as arrhythmias.

The two main groups of pacemaker cells in the heart are found in the sinoatrial (SA) and atrioventricular (AV) nodes (Figure 1). Normally, those of the SA node dominate and the rate and rhythm of the heart is dictated by that of the SA node. However, if the SA node fails, or electrical conduction between the atria and ventricles is blocked, then the AV node pacemaker cells assume control and pace the heart. If the AV node fails, other pacemakers lower in the hierarchy can assume the role of heartbeat generation, though the spread of the heartbeat may be grossly abnormal.

The pacemaker and conduction system



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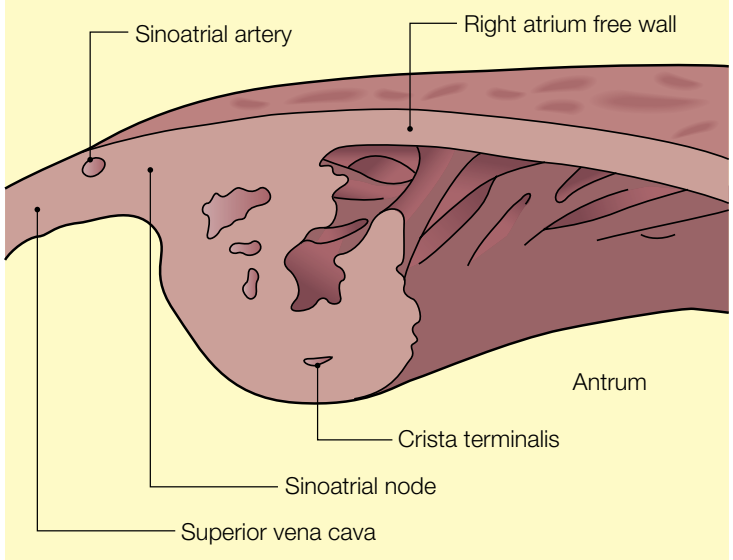
In the human heart, the SA node lies in the groove where the superior vena cava joins the right atrium (Figure 2). The SA node contains two histologically distinct fibres types:

- small round cells with few organelles and contractile proteins
- longer elongated cells, which look intermediate between the small round cells and the atrial force-producing cells.

Location of the sinoatrial node



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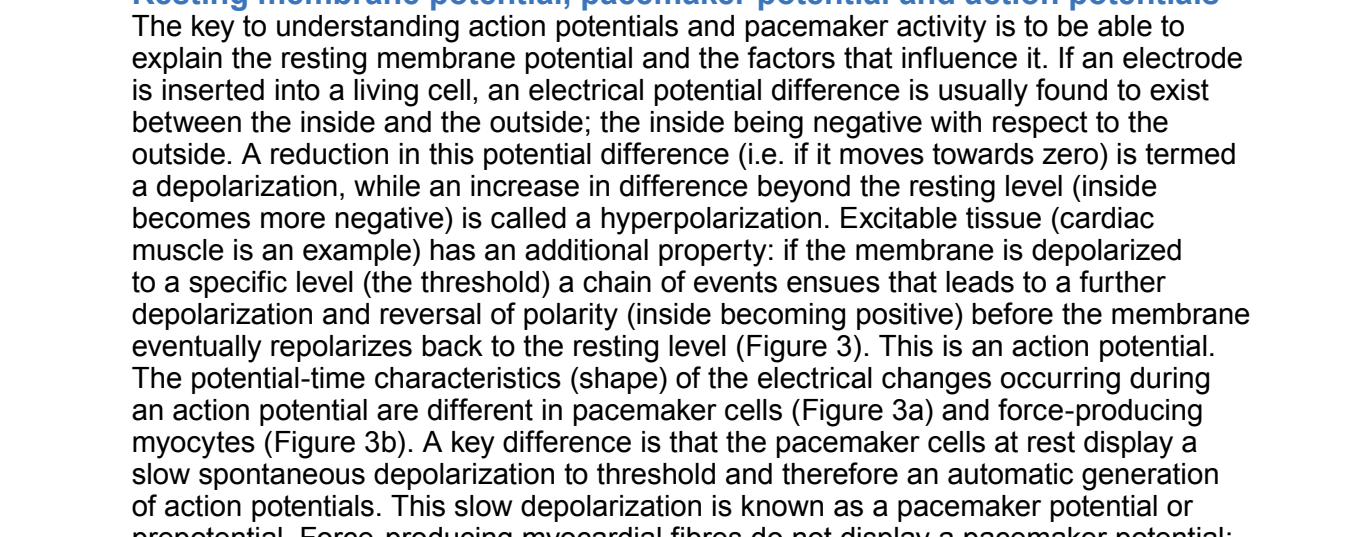
The small round cells are thought to be the pacemakers. Detailed mapping of the atrial surface reveals that there are two to three sites of automaticity within 1–2 cm of the SA node. It is suggested that these sites, together with the SA node, act as the normal atrial pacemaker complex. At times, all of the loci may produce action potentials simultaneously, while at other times the primary focus of activity shifts from one group to another, depending on the prevailing level of autonomic activity.

Resting membrane potential, pacemaker potential and action potentials

The key to understanding action potentials and pacemaker activity is to be able to explain the resting membrane potential and the factors that influence it. If an electrode is inserted into a living cell, an electrical potential difference is usually found to exist between the inside and the outside; the inside being negative with respect to the outside. A reduction in this potential difference (i.e. if it moves towards zero) is termed a depolarization, while an increase in difference beyond the resting level (inside becomes more negative) is called a hyperpolarization. Excitable tissue (cardiac muscle is an example) has an additional property: if the membrane is depolarized to a specific level (the threshold) a chain of events ensues that leads to a further depolarization and reversal of polarity (inside becoming positive) before the membrane eventually repolarizes back to the resting level (Figure 3). This is an action potential. The potential-time characteristics (shape) of the electrical changes occurring during an action potential are different in pacemaker cells (Figure 3a) and force-producing myocytes (Figure 3b). A key difference is that the pacemaker cells at rest display a slow spontaneous depolarization to threshold and therefore an automatic generation of action potentials. This slow depolarization is known as a pacemaker potential or prepotential. Force-producing myocardial fibres do not display a pacemaker potential; their resting membrane potential is stable and they require an external stimulus, normally a depolarization from a neighbouring cell, to attain threshold and generate an action potential.

Transmembrane potential changes and currents associated with action potentials



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Resting membrane potential

The origin of the resting membrane potential is the chemical concentration gradients of ions across the cell membrane and the selective permeability of the membrane to these ions. With regard to pacemaker activity, the two main ions are potassium (K^+) and calcium (Ca^{2+}), together with some contribution from sodium (Na^+). The K^+ concentration is much higher inside the cells, while that of Ca^{2+} and Na^+ is much higher outside (Figure 4). These ions cross the membrane via channels, which display varying degrees of selectivity for particular ions.

K^+ diffuses out of the cell down its concentration gradient. The amount diffusing, as a proportion of the total amount present, is minuscule. However, the movement of the positive ions against a resistance generates a potential difference, with the inside of the cell becoming negative. This electrical gradient opposes the movement of K^+ out of the cell, the negative interior attracting the positive K^+ ions. A state of equilibrium is therefore obtained when the electrical gradient is exactly equal and opposite to the chemical gradient. This is the electrochemical equilibrium, and potential difference attained at this point is referred to as the equilibrium potential for that particular ion. In the case of Ca^{2+} and Na^+ the chemical concentration gradient is such that these diffuse into the cell (Figure 4). Thus, the electrochemical equilibria for these ions has the inside of the cell positive (Figure 4). It is possible to calculate the equilibrium potential for any ion, given the concentrations of the ions on either side of the cell membrane, using the Nernst equation. For a positive ion at equilibrium in an environment at 37°C:

$$E_{ion} = -61.5 \log_{10}([Ion^+]_i/[Ion^+]_o)$$

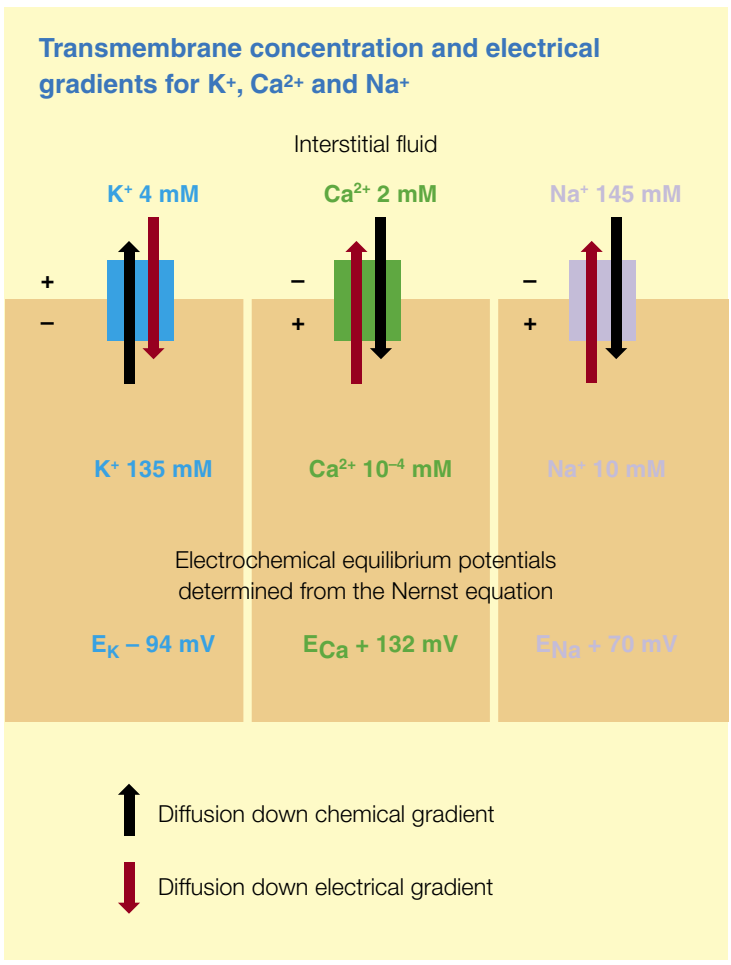
where E_{ion} is equilibrium potential for the ion, $[Ion^+]_i$ is the concentration of the ion inside the cell and $[Ion^+]_o$, is the concentration of the ion outside the cell.

For a typical cardiac muscle fibre cell the equilibrium potential for K^+, Ca^{2+} and Na^+ is shown in Figure 4. Given that each of these ions is attempting to 'drive' the membrane potential to their respective equilibrium potentials, what determines the membrane potential at any given instant? To answer this we must discuss the relative permeability of the membrane to these ions.

Consider an extreme example in which the membrane was permeable only to K^+. Under these circumstances, Ca^{2+} and Na^+ could not diffuse across the membrane and could not influence its electrical potential. Under 'resting' conditions, the membrane potential is closer to E_K (the equilibrium potential for potassium) than it is to E_{Ca} or E_{Na} because the membrane is more permeable to K^+. The resting membrane potential is influenced by the transmembrane chemical concentration difference of a number of ions and the relative permeability of membrane to these ions. This allows us to explain the pacemaker potential and the action potential in the pacemaker cells.

SA node cells: pacemaker and action potentials

The pacemaker and the action potential are brought about by a change in the relative permeability of the membrane to a range of ions, the most important of which are K^+ and Ca^{2+}, with some contribution from Na^+. This change in membrane permeability occurs because a number of membrane channels for these ions are 'gated' (they can be open and functional, or closed and prevent passage of the ion). The state of some ion channels (open or closed) is dictated by the membrane potential (i.e. they are voltage-gated).



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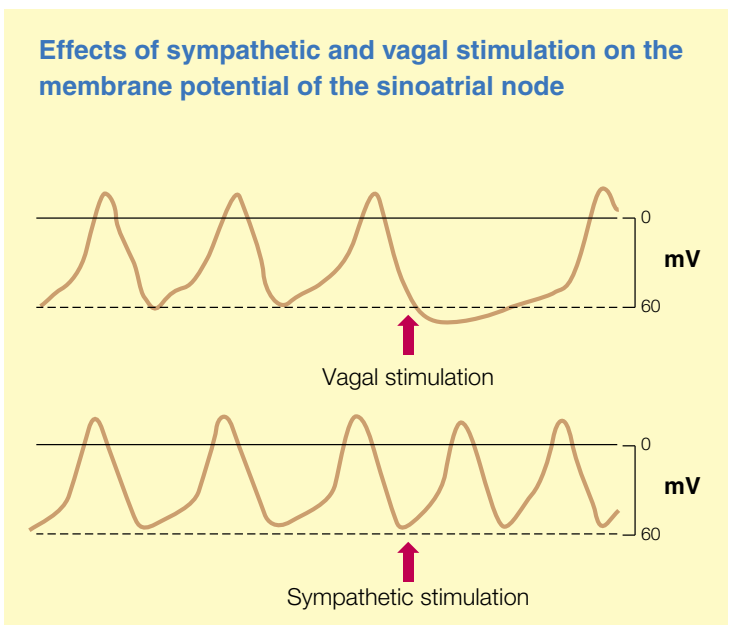
At the start of the prepotential, the permeability to K^+ is high, therefore there is an outward movement of K^+ (producing an outward current called i_K) while the permeability to Ca^{2+} is low. The depolarization that constitutes the pacemaker potential is due to a change in at least three ionic currents:

- an inward current i_f
- an inward calcium current i_{Ca}
- an outward potassium current i_K.

The inward current i_f is mediated mainly by Na^+ entry via specific sodium channels. This inward current became activated (channels opened) during the repolarization phase of the previous action potential, as the membrane potential became more negative than –50 mV. The more negative the membrane potential becomes during the repolarization, the greater the magnitude of this inward current. This inward current serves to depolarize the membrane. The effects of this inward current on membrane potential are opposed by the outward currents due to K^+ (i_K). However, the outward (hyperpolarizing) i_K progressively diminishes and this diminution of a hyperpolarizing current contributes to the depolarization that is the prepotential. As the membrane becomes depolarized beyond about –55 mV, a group of voltage-gated Ca^{2+} channels called T-channels (T for transient because they stay open only for a short while) begin to open, thus increasing membrane permeability to Ca^{2+} and leading to an additional inward current, this time to Ca^{2+} (i_{Ca}), which completes the depolarization to threshold. As threshold is approached, a further group of voltage-gated Ca^{2+} channels called L-channels (L for long-lasting) open, producing a dramatic increase in Ca^{2+} permeability and hence a rapid depolarization, which constitutes the upstroke of the action potential. Then, the L-channels begin to close and the i_K channels open, leading to a repolarization of the cell membrane and the end of the action potential, ready for the whole cycle to begin again. The relationship between the currents of the membrane potential are summarized in Figure 3a.

Autonomic alterations in heart rate

Although nervous impulses are not needed to initiate the heartbeat, activity in the autonomic nervous system can profoundly alter the frequency of action potential formation in the SA node. Vagal stimulation reduces the frequency of spontaneous action potential formation (Figure 5) and induces a bradycardia, while sympathoactivation increases the frequency of action potential formation and gives a tachycardia (Figure 5).



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Vagal stimulation causes a hyperpolarization and a reduction in the slope of the pacemaker potential (Figure 5) because acetylcholine released from the vagal nerve terminals activates cholinergic M_2-receptors in the SA node cell membrane. This is an example of a G protein-coupled receptor. Binding of the ligand (acetylcholine) to the M_2-receptor causes the $\beta\gamma$ subunits of the G protein to facilitate opening of a specialized group of K channels in the SA node cell membrane. This increases the permeability to K and causes an inward K current (i_{KACh}) which:

- hyperpolarizes the cell
- counters the decay in K permeability produced by closure of the K channels discussed above and reduces the slope of the prepotential
- in addition, the particular G protein attached to the M_2-receptor leads to a fall in intracellular cAMP which in turn slows the opening of the Ca^{2+} channels, further reducing the slope of the prepotential.

In contrast, noradrenaline and adrenaline both increase the slope of the prepotential (Figure 5) because they activate β_1-adrenoceptors. The β_1-adrenoceptor is another example of a G protein-coupled receptor. However, in this case, the specific G protein coupled to the receptor leads to an increase in intracellular cAMP and facilitates the opening of Ca^{2+} channels.

The right vagus and sympathetic nerves predominantly affect the SA node, and the left predominantly affects the AV node, therefore right-side stimulation has a greater effect on heart rate while left-side stimulation predominantly affects AV conduction. The left vagus slows AV conduction and sympathetic stimulation shortens conduction time and refractoriness. ◆

Mechanical Events and the Pressure–Volume Relationships

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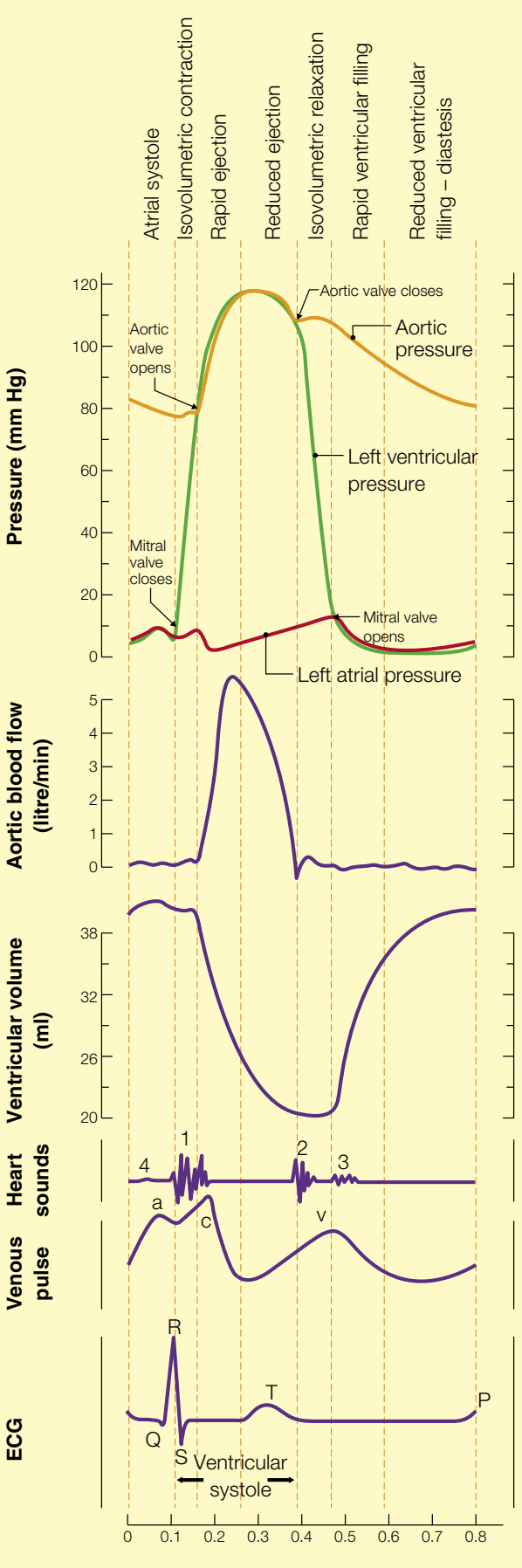
The depolarization phases in the cardiac muscle fibres spread throughout the myocardium. In a single fibre, conduction starts just after depolarization and lasts until just after repolarization is complete. The atria contract, completing the filling of the ventricles and thus enhancing their action. In the absence of effective atrial contraction (e.g. atrial fibrillation) cardiac output is decreased on average by 15%.

During diastole, when cardiac muscle is relaxed, blood returns to the heart and passes through the atrioventricular (AV) valves into the ventricles. The semilunar valves, between the ven-tricles and the arteries, are closed as arterial pressure exceeds ventricular pressure (Figure 1). Under normal circumstances, 70% of ventricular filling occurs by late diastole.

Pressure and volume in the left ventricle, systemic artery and veins, heart sounds and ECG



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Immediately after the P wave of the ECG, the atrial muscle fibres contract giving atrial systole. This helps to push a final amount of blood towards the ventricles. Although there are no valves between the atria and the veins, only small amounts of blood regurgitate into the veins because atrial contraction tends to narrow the orifices between the atria and the superior and inferior venae cavae and the pulmonary veins. In addition, the inertia of blood flowing towards the heart tends to keep the blood within it. The small regurgitation of blood that does occur into the veins gives rise to the 'a' wave of the venous pulse (Figure 1). Thereafter the action potentials sweep through the ventricles (giving rise to the QRS complex) causing ventricular contraction and ventricular systole. During the first phase of ventricular systole, the overall muscle fibre length is not shortened. This is because as the filaments slide, tension is generated in the elastic elements of the walls of the ventricles, which raises pressure in the ventricles above that in the atria. This causes closure of the AV valves (and generation of the first heart sound). However, ventricular pressure is initially below arterial pressure and therefore the semilunar valves remained closed. Thereafter, pressure increases rapidly within the ventricles and, as there is no change in volume, this is termed the isovolumetric phase of ventricular systole (Figure 1). As ventricular pressure continues to rise it eventually exceeds arterial pressure (at about 10.8 kPa (80 mm Hg) in the left and 1.3 kPa (10 mm Hg) in the right ventricle) and blood is ejected rapidly into the arteries so that there is a large and rapid decrease in ventricular volume, accelerating blood flow into the arteries and increasing arterial pressure. This period of rapid ejection accounts for about the first third of ejection time and culminates in the attainment of the peak arterial and ventricular pressures (about 16 kPa (120 mm Hg) and 3.3 kPa (25 mm Hg), respectively in the left ventricle/aorta and right ventricle/pulmonary artery (Figure 1), though there is considerable normal variation between and within individuals. Thereafter, there is a further period of reduced ejection as blood continues to be ejected into the arteries. However, during this phase, blood flow decelerates as potential energy stored in the elastic wall of the arteries reverses the pressure gradient and arterial pressure exceeds ventricular pressure (Figure 1). Despite this reversed pressure gradient, flow continues into the arteries because of its momentum. However, pressure in the arteries falls in this phase because the run-off of blood into the tissues exceeds the amount of blood entering the arteries from the ventricles.

In a normal heart, immediately before ventricular systole, the ventricles contain about 130 ml blood (end-diastolic ventricular volume, EDV). During the entire ventricular ejection phase, about 70–90 ml blood is ejected from each ventricle (stroke volume, SV), leaving about 50 ml of blood in the ventricles (end-systolic ventricular volume, ESV). Ejection fraction (SV/EDV) is thus about 65%. The rapid increase in arterial pressure causes the arteries in some places to impact with the wall of adjacent veins. This, together with a pushing of the tricuspid valves towards the atria in early systole, contributes to the second venous pressure wave of the cardiac cycle: the c wave (Figure 1).

About 50 ms after the end of the myocardial action potential the fibres begin to relax (during and immediately after the T wave of the ECG); this is ventricular diastole. The rapid reduction in ventricular pressure results in it falling quickly below the arterial pressure and the threatened regurgitation of blood from the arteries towards the ventricles causes the semilunar valves to snap shut, giving rise to the second heart sound and the dicrotic notch, evident on the arterial pressure waveform. Pressure within the arteries is now kept higher than ventricular pressure because of the elastic recoil of elements of the arterial wall, which were stretched during systole.

During the first phase of ventricular diastole both semilunar and AV valves are closed. Therefore the rapidly falling pressure is not accompanied by a change in volume and this phase is called isovolumetric relaxation. Thereafter, ventricular pressure falls below atrial pressure and the AV valves open. Initially, blood flow into the ventricles is rapid, giving a sharp rise in intraventricular volume (Figure 1), and a fall in venous pressure (which had previously been increasing as blood was unable to flow from the atria through the closed interventricular valves). This sharp fall in venous pressure produces the third venous pressure pulse of the cardiac cycle: the v wave (Figure 1).

Following the rapid filling phase, blood continues to flow into the ventricles during the remainder of diastole, but now at a reduced rate. This phase is termed diastesis, at the end of which, ventricular filling is about 70% complete before the whole cycle is initiated again by atrial systole immediately after the next P wave of the ECG.

It should be evident from this description that atrial contraction is not essential for ventricular filling, which occurs even in atrial fibrillation. At lower heart rates, atrial contraction is even less important because ventricular filling is essentially complete by the end of diastesis. However, as heart rate increases there is a much more marked reduction in diastolic that in systolic time. Thus, atrial systole becomes increasingly important for ventricular filling during tachycardia.

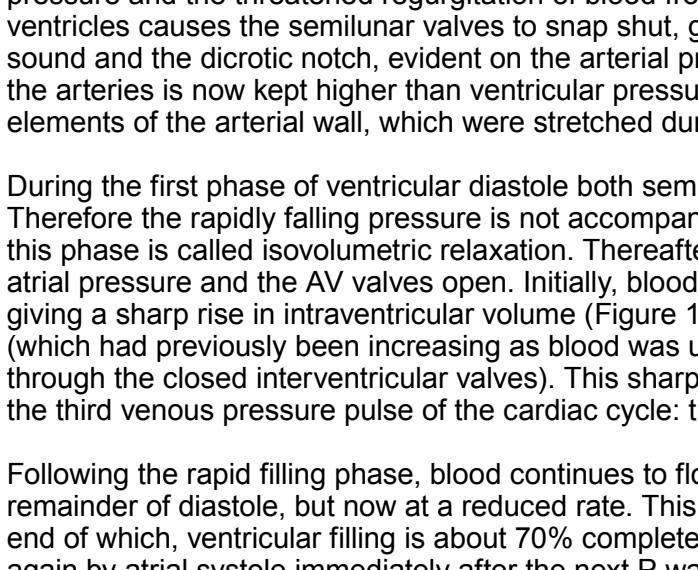
Regulation of cardiac contraction

The two main mechanisms important for regulating the force of cardiac contraction and stroke volume are those that are intrinsic to cardiac muscle and those that are mediated by nervous and hormonal control of the heart.

Intrinsic mechanisms: the Frank–Starling mechanism

A relationship exists between the maximal force a muscle fibre can produce and its length immediately before contraction (preload). This was first described for cardiac muscle by Frank in 1895. He showed that over a limited range of preloads, increasing preload can increase force of contraction. This idea was refined by Starling in a series of studies published in 1914, which showed that an increase in right atrial pressure led to increased force of ventricular contraction and thus stroke volume. This can be represented graphically (Figure 2) as a relationship between end-diastolic volume (which dictates the length of the ventricular muscle fibres just before systole) and an index of cardiac muscle force of contraction: in practice this is taken as either stroke volume or stroke work.

Starling curves and the effects of haemorrhage and exercise



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Normal cardiac function is represented by a point on the upward slope of this relationship (Figure 2). Thus, if venous return and end-diastolic volume increase (increased preload) the heart responds by producing a more forceful contraction to eject the excess blood. This is an important safety feature, which also matches the output from each side of the heart. Thus, if one side of a heart ejects more blood than the other, there is an increased venous return to the second side and, by the Frank–Starling mechanism, an increase in the output of the second side to match the first.

The Frank–Starling mechanism also helps the heart to respond to changes in afterload (arterial blood pressure or vascular resistance). An increase in the force against which the heart has to pump, leads initially to a reduction in the amount of blood ejected. As a consequence, more blood is left in the heart at the end of systole. When the venous return is added to this, the end-diastolic volume for the next beat is increased and the heart produces a more forceful contraction. Thus, over a few beats, stroke volume can be returned to the original level despite an increase in afterload, albeit at the cost of increased preload.

The mechanisms underlying the Frank–Starling relationship include a variation in the total number of cross-bridges that can be formed. There is an 'optimal' length of muscle fibre at which the maximal number of cross-bridges can be formed, beyond which the number of cross-bridges is reduced. In addition, stretching cardiac muscle increases the sensitivity of the contractile mechanism to Ca^{2+}.

An increase in heart rate can also increase the force of contraction independent of changes in preload. If preload and afterload are maintained constant (experimentally), then an increase in heart rate leads to an increased force of contraction (the Treppe phenomenon). The mechanism underlying this effect is an elevation in intracellular Ca^{2+} concentration for two reasons: there are more depolarizations (action potentials) per unit time (with Ca^{2+} moving in with ejection potential) and there is an increase in the inward Ca^{2+} current per action potential. *In vivo*, this effect is offset by the reduction in diastolic filling time (which accompanies a tachycardia) and, as a consequence, a reduction in preload if the increase in heart rate is sufficiently great.

Extrinsic regulation

The most important extrinsic regulator in normal physiology is the sympathetic nervous system. Activation of cardiac β_1-adrenoceptors by catecholamines increases the myocardial force of contraction. This is achieved by increasing the concentration of cytosolic Ca^{2+} during each beat and results in the Starling curve being displaced upwards and leftwards (Figure 2). This means that for a given filling pressure, cardiac output is increased, and for a decreased filling pressure, cardiac output is maintained. This increase in force of contraction without the need for an increase in resting (end-diastolic) muscle fibre length is termed a positive inotropic effect. Other hormones (e.g. insulin, glucagon) also have positive inotropic effects, though they are not thought to play a part in normal cardiac regulation. Conversely, some agents (e.g. inhalational anaesthetics) have a negative inotropic effect (moving the Starling curve downwards and to the right, Figure 2).

The term inotropic effect is sometimes used interchangeably with the term contractility, which a number of authors take as a 'measure of the performance of the heart at a defined preload and afterload'. Because of the need to eliminate the effects of alterations in preload, afterload and heart rate, measuring inotropic effect in practice is difficult. In an experimental setting, one index of contractility is obtained from the contour of individual ventricular pressure curves. Stimulation of the sympathetic nerves to the heart produces a more forceful contraction, resulting in a rapid rise in pressure, while a depressed heart shows the opposite effect. This can be quantified by measuring the maximum rate of rise of ventricular pressure (dP/dt max) during the beat. Such measurements are difficult to make in practice. Clinically, an indication of inotropic state is taken from the initial velocity of blood flow in the ascending aorta or cardiac ejection fraction. All of these can be influenced by confounding factors (e.g. heart rate) which means that in clinical practice they are only a rough guide.

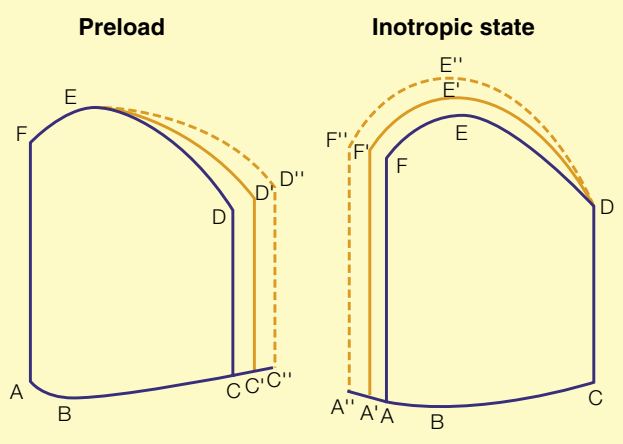
Pressure–volume loops

By directly relating changes in intracardiac pressure to volume, and eliminating the time element, pressure–volume loops can provide additional insight into cardiac function. The effects of altering preload and inotropic state on pressure–volume loops are summarized in Figure 3.

For each pressure–volume loop, A–C represents diastolic filling (ventricular pressure falls despite inflow of blood between A and B because of the progressive relaxation of ventricular muscle). Thereafter C–D represents the phase of isovolumetric contraction (pressure rises but there is no reduction in volume) until the semilunar valves open at D. Ventricular ejection occurs from D to F (D–E represents the period of rapid ejection where the greatest volume of blood is ejected and pressure continues to rise in the ventricle). E–F represents the reduced ejection phase with ventricular pressure falling. The volume of blood ejected between D and F is the stroke volume. After F the pressure in the ventricles falls rapidly and the semilunar valves close as the heart enters diastole. F–A therefore represents isovolumetric relaxation before the AV valves open at A and blood flows once again into the ventricles.

With increasing venous return and preload (Figure 3) end- diastolic volume becomes progressively larger A–C, C' and C'', respectively. However, because of the Frank–Starling mechanism there is a greater stroke volume (D, D' and D''–F, respectively). By contrast, a positive inotropic effect produces a greater force of contraction and hence greater pressure development (E–E'') and emptying of the ventricle (D to F–F'') and reduced residual volume A–A''.

Effects of increases in preload and inotropic state on the pressure–volume relationships of the left ventricle during a complete cardiac cycle



See text for explanation

These pressure–volume loops from successive heart rates can be used to assess the inotropic state of the heart *in vivo* without the need to maintain preload and afterload strictly constant. However, they require a high degree of invasive monitoring and are not applicable to routine clinical practice.

Control of cardiac output

In vivo, many intrinsic and extrinsic factors operate simultaneously. This can be exemplified by considering the response to haemorrhage and exercise.

Haemorrhage

The initial consequences of blood loss is a reduction in venous return and therefore in end-diastolic volume. This, by the Frank–Starling mechanism, leads to a reduction in cardiac stroke volume (Figure 2). Consequently, there is a reduction in arterial pulse pressure, which in turn leads to unloading of the baroreceptors. This causes a reflex increase in sympathetic drive to the heart and an inhibition of vagal efferent activity to the heart. The increased sympathetic drive to the ventricles produces a positive inotropic effect which limits the fall in stroke volume (Figure 2). In addition, the tachycardia resulting from vagal inhibition and sympatho-activation helps to limit the fall in cardiac output (cardiac output = stroke volume x heart rate). However, a severe tachycardia would be counter-productive because it would diminish diastolic filling time and preload, especially when venous return is impaired. This is perhaps one reason why heart rate does not rise to high levels during simple blood loss: as simple haemorrhage becomes severe, a second reflex supersedes the baroreceptor reflex causing a bradycardia, which can paradoxically improve cardiac output because stroke volume may increase as a result of improved diastolic filling.

Exercise

During exercise an initial anticipatory increase in sympathetic drive to the ventricles provides a positive inotropic effect and an increase in stroke volume. This is reinforced once exercise begins as venous return and consequently preload is enhanced because of activity of the skeletal muscle pump. A much larger tachycardia can be tolerated in this instance because venous return is enhanced rather than diminished as is the case during blood loss. ◆

FURTHER READING for CARDIAC PHYSIOLOGY

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Myocardial Action Potential

Emrys Kirkman

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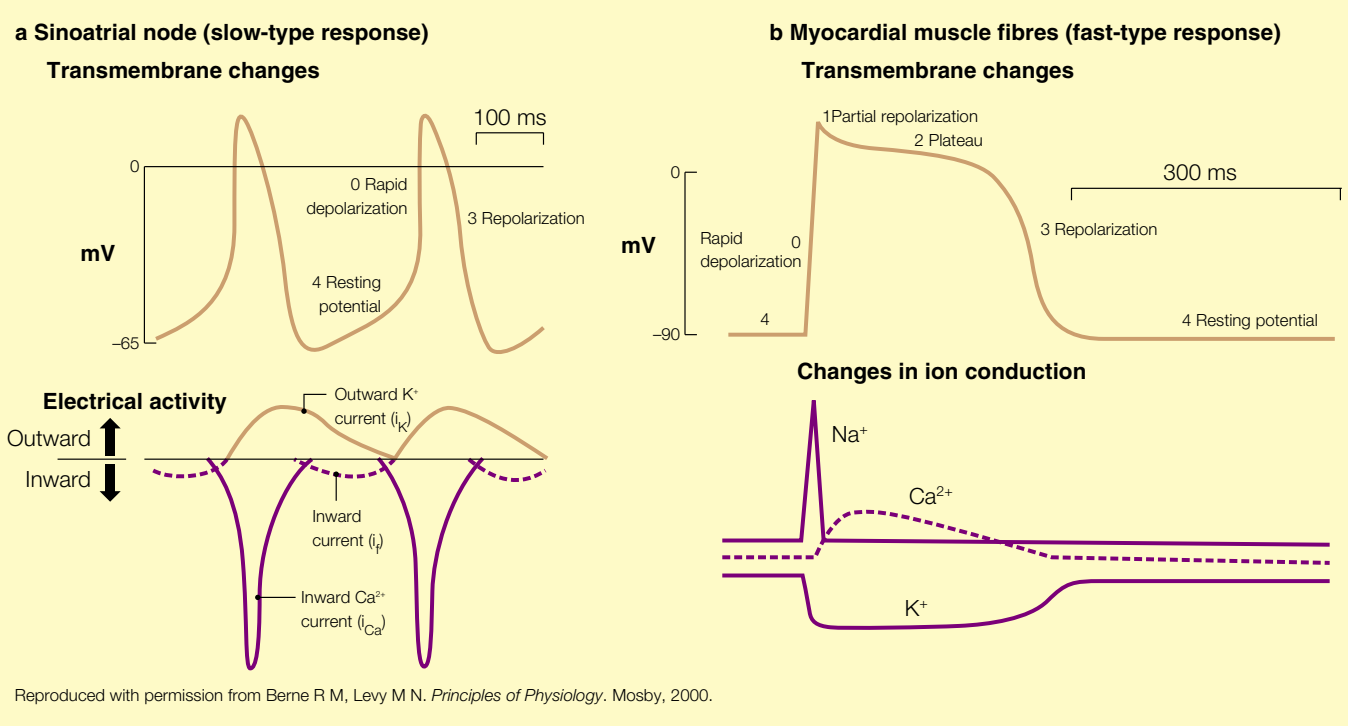
A recording of membrane potential during an action potential in a myocardial (force-producing) fibre shows a different profile from that in the pacemaker cells. The resting membrane potential in myocardial fibres is constant and considerably more negative (Figure 1b). Once the cells have been depolarized to threshold by an external stimulus (normally spread of activity from a neighbouring fibre) the overshoot of the action potential is much steeper than that seen in the pacemaker cells. It is followed by a partial repolarization and a long shoulder (with the inside of the cell positive) before the membrane repolarizes to its resting level (Figure 1b).

Transmembrane potential changes and currents associated with action potentials



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The rapid upstroke is produced by the opening of voltage-gated fast sodium channels. These channels have two gates called the 'm' or activation and 'h' or inactivation gates. At the resting membrane potential the m gate is closed (the channel does not allow passage of Na^+) and the h gate is open. When the membrane is depolarized towards threshold some of the channels respond by opening the m gate enclosing the h gates. However, the important difference between the m and h gates is that the m gates open rapidly (within 0.1–0.2 ms) while the h gates close relatively slowly (over 1 ms). Thus, for a period, the channels open as the m gates have opened and h gates have not yet closed, thus allowing passage of Na^+. As a consequence, membrane permeability to Na^+ increases. Because the sodium equilibrium potential E_{Na} is markedly positive this depolarizes the membrane further, causing more sodium channels to be opened and generating a positive feedback or regenerative process, giving a very fast depolarization and overshoot of membrane potential. This is short-lived because the h gates close and inactivate the channel. The membrane permeability to Na^+ falls and the fibre begins to repolarize (Figure 1b). In addition, in some myocardial cells, there is a transient increase in K permeability during this phase, which augments this partial repolarization.

Unlike skeletal muscle, and most nerves, the early repolarization described above is only partial because of a slightly delayed increase in permeability to Ca^{2+}. The two main groups of calcium channels important here are both voltage gated and are described in relation to heart rate elsewhere. The T-channels begin to open when the membrane potential has depolarized to about –70 mV and are followed by the L-channels which begin to open when the membrane is depolarized to –10 mV. These allow Ca^{2+} to move down its electrochemical gradient into the cell and thus maintain the depolarized state. The Ca^{2+} channels do not contribute to the upward stroke of the action potential because they take much longer to open than the fast Na channels. However, by the time the fast Na channels have become inactivated these Ca^{2+} channels are open, giving a long shoulder to the myocardial action potential, during which substantial amounts of Ca^{2+} enter the cell (this is important in initiating mechanical contraction). Although the activation of T-channels is short-lived, that of L-channels is long lived, hence the long shoulder of the myocardial action potential. The L-channels can be blocked by a number of calcium channel blocking agents (e.g. verapamil, nifedipine, diltiazem).

During the shoulder of the action potential, the Ca channels begin to close. Towards the end of the shoulder, one group of K channels is activated. They began to open at membrane potentials that prevailed towards the end of the initial upstroke of the myocardial action potential. However, they open slowly and it is not until the end of the shoulder of the action potential that they produce an increase in membrane permeability to K and hasten the process of repolarization (Figure 1). This repolarization causes the closure of the remaining Ca channels (contributing further to the repolarization). The importance of the K current in bringing about repolarization is emphasized by the finding that genetic defects that result in blockade of some of the K channels are associated with delayed repolarization.

During repolarization, increasing numbers of fast Na channels (which were inactivated by closure of the h gates at the end of the initial fast up-stroke of the action potential) begin to reset by closure of the m and opening of the h gates. Although the Na channels are still closed, the importance of this event is that they are returned to the original state ready to be activated during the next action potential.

As a consequence of these changes, the muscle fibre is absolutely refractory (unable to produce a second action potential) while most of the fast Na channels are inactivated and the Ca channels have not completed their cycle. The absolute refractory period is from the start of the upsweep of action potential until halfway through the main repolarization. For a further period, the fibre is relatively refractory (can produce an action potential but only with a stronger than usual stimulus) until the resting membrane potential has been regained. Since the duration of action potential (200–300 ms) is longer (the time required to obtain the peak mechanical event) the cardiac muscle fibre cannot be tetanized. This is an important safety feature, because tetanic contraction would preclude the heart's repeated pumping action.

The numbering of the phases of the membrane potential changes within the action potential are shown diagrammatically elsewhere. Phase 0 is much steeper in the myocardial fibres because it is carried by Na^+ entering through fast-opening Na channels, while it is less steep in the sinoatrial (SA) and atrioventricular (AV) node pacemaker cells, which do not have fast Na channels, and rely on the slower opening Ca channels.

AV node and Purkinje fibres

The mechanisms underlying spontaneous generation of action potential in the AV node are probably similar to those in the SA node. The Purkinje fibres are also capable of producing action potentials spontaneously, though it is thought that Ca is not involved and that the process is determined by the shift in balance between the outward K current (i_K) and the inward current (i_f), mediated by Na^+.

Spread of the heartbeat from the SA node

The action potential from the SA node travels along each muscle fibre, in the same way action potentials travel along nerve fibres, until it comes to a junction with the next muscle cell. The neighbouring force-producing atrial muscle fibre is then depolarized to threshold by local currents flowing via low-electrical resistance gap junctions between cells.

In the heart, muscle cells are joined by intercalated discs, which incorporate gap junctions. They are sites of low electrical resistance and facilitate the movement of local currents between cells. They are made up of conexons, which are hexagonal structures made up of six polypeptide chains surrounding a central channel about 1.6–2.0 nm wide which connect with the cytosol of the adjacent cell. Thus, when one cell is depolarized, giving an action potential, the potential difference between the two cells causes local currents to flow into its neighbour, depolarizing the second cell to threshold and triggering an action potential in it. These gap junctions are predominantly found between cells that are in contact with one another longitudinally, and are sparse between cells that lie side by side. The action potential therefore travels in a direction parallel to the long axis of the muscle fibres and spreads radially over the surface of the right atrium away from the SA node at rate of about 1 m/s (Figure 1).

Tracts of specialized conducting muscle fibres rapidly transmit the action potentials from the SA node to the left atrium. These consist of the anterior interatrial myocardial band and the middle and posterior bands, which consist of a mixture of ordinary myocardial and specialized conducting cells. Although action potentials can spread throughout the atria in this manner, they cannot pass directly from the atria to the ventricles because there are no low electrical resistance pathways between these two structures, except at the AV node. Action potential conduction through the AV node is relatively slow, resulting in a delay before the action potential is passed on to the bundle of His (a group of specialized conducting muscle fibres that rapidly transmit the action potential towards the apex of the heart).

The bundle of His originates in the AV node as a single bundle of muscle fibres running subendocardially for about 1 cm along the interventricular septum. The bundle divides into a right and left branch. The right branch is essentially a continuation of the original bundle while the left, thicker, branch arises at right angles to the original, perforates the interventricular septum and runs down the left subendocardial surface of the septum. The left branch splits again into a thick branch that runs posteriorly and a thinner anterior branch. Finally, all of these branches divide into complex networks of conducting Purkinje fibres, which ramify over the subendocardial surface of both ventricles. The Purkinje fibres have a larger diameter and are able to conduct action potentials faster than any other tissue within the heart (1–4 m/s).

Action potentials from the AV node travel down the bundle of His towards the apex of the heart, generating action potentials in the cells of the interventricular septum. These action potentials sweep from left to right through the septum (Figure 2). In addition, the fibres of the papillary muscles are depolarized to threshold. Once the action potentials reach the Purkinje fibres (via the bundle of His) there is rapid conduction over the entire subendocardial surface of the ventricles. The wave of excitation then spreads at a slower rate (0.3–0.4 m/s) through the thickness of the wall of the ventricles towards the epicardial surface (Figure 2). The apical and central epicardial regions tend to be depolarized first, while the last portions of the ventricles to be excited are the posterior basal epicardial regions (Figure 2).

Fast versus slow response action potentials

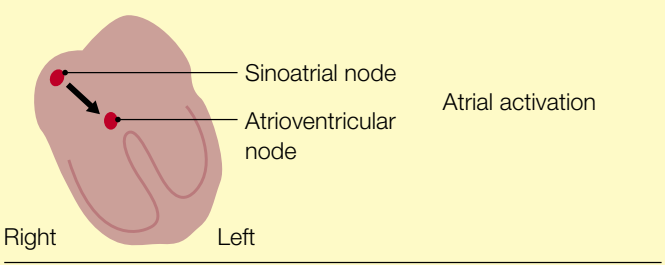
The velocity of transmission of action potentials from fibre to fibre is influenced by the shape (voltage-time profile) of the action potential. Figure 1 shows the two basic shapes of cardiac action potential: the pacemaker-type from the SA and AV nodes and the myocardial type from the other fibres. The former is termed a slow response action potential and the latter is called a fast response. Notable differences in the fast response action potential include a greater resting membrane potential, more rapid depolarization and greater overshoot during the action potential. All of these influence how quickly the action potential is transmitted from one fibre to the next. A greater potential difference between two fibres causes a more rapid depolarization in the next fibre in the chain to threshold and a more rapid transmission. This is why transmission is slow through the AV node, but more rapid elsewhere. Fast response fibres may be converted to slow response after a period of ischaemia, and such changes may predispose to arrhythmias.

The spread of depolarization and action potentials through the heart, starting at the SA node, has a number of important implications. These include effects on other cardiac pacemaker regions and the generation of electrical disturbances, which can be recorded at the body surface as an electrocardiogram.

Hierarchy of cardiac pacemakers

Several regions in the heart have intrinsic pacemaker activity. However, the SA node normally predominates because it has the highest intrinsic rate. Thus, an action potential originating in the SA node is delivered to the other pacemaker cells before they reach the threshold of their own accord. However, if an ectopic focus developed pacemaker activity at a higher rate, the heart rate would be dictated by the fastest pacemaker focus and the pacemaker cells of the SA node would become suppressed by a process known as overdrive suppression. The mechanism underlying this phenomenon is thought to involve the Na^+-K^+ ATPase (sodium–potassium) pump. Although only a relatively small number of Na^+ enter and K^+ leave the cell with each action potential, after repeated action potentials a significant quantity of ions have moved. The Na^+-K^+ ATPase restores the chemical gradients for these ions. Therefore, after the period of stimulation at high frequency the activity of the Na^+-K^+ ATPase is increased. This transports an unequal number of Na^+ and K^+ ions: 3 Na^+ are extruded for every 2 K^+ pumped into the cell. Therefore, there is a net movement of positive charge outwards. Consequently, activity of Na^+-K^+ ATPase tends to hyperpolarize the membrane and make it less likely to depolarize spontaneously to threshold. If the SA node has been driven at a high rate by an ectopic focus it takes some time to regain its own intrinsic rhythm once the ectopic focus ceases activity – this is known as the sinus node recovery time. In the case of sick sinus syndrome, the sinus node recovery time is prolonged and the asystole, because of the delay before the SA node regains its automaticity, can lead to syncope.

Normal spread of electrical activity in the heart



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Ectopic foci

Under normal conditions the heartbeat originates from the SA node and spreads in an ordered sequence to the remainder of the heart. Each cardiac muscle fibre produces only one action potential in response to stimulation by a neighbouring cell. However, it is possible for an alternative area of the heart to develop automaticity because of a change in the properties of the muscle fibres. Recent studies have shown that an important area for the development of ectopic foci leading to atrial fibrillation are the pulmonary veins.

Triggered activity

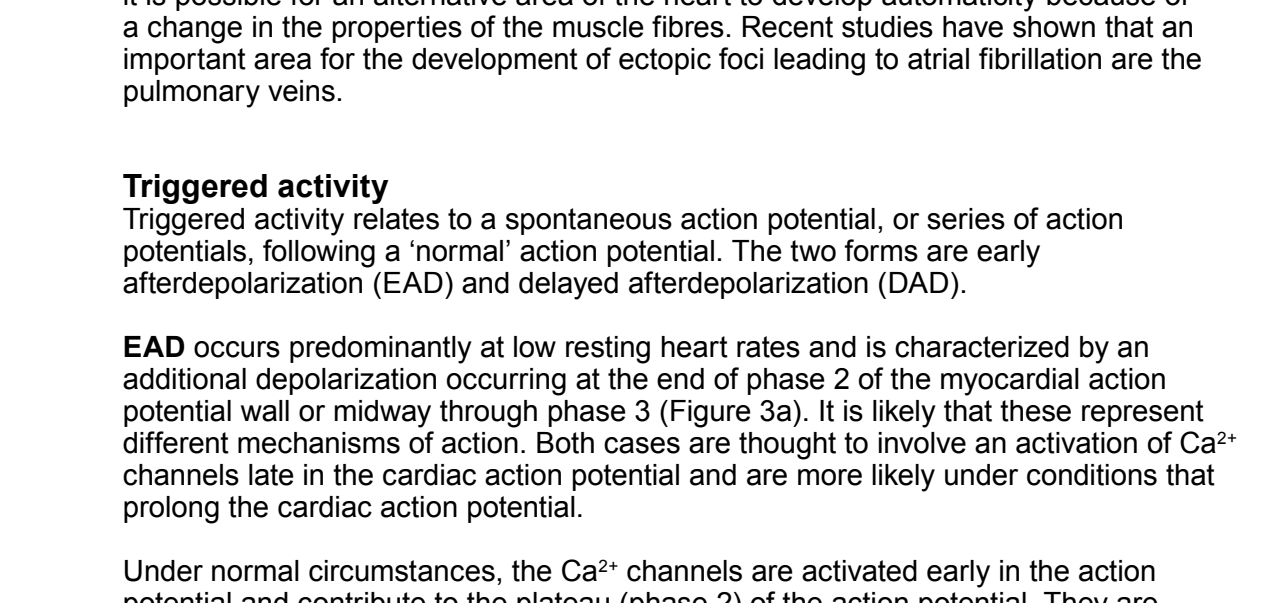
Triggered activity relates to a spontaneous action potential, or series of action potentials, following a 'normal' action potential. The two forms are early afterdepolarization (EAD) and delayed afterdepolarization (DAD).

EAD occurs predominantly at low resting heart rates and is characterized by an additional depolarization occurring at the end of phase 2 of the myocardial action potential wall or midway through phase 3 (Figure 3a). It is likely that these represent different mechanisms of action. Both cases are thought to involve an activation of Ca^{2+} channels late in the cardiac action potential and are more likely under conditions that prolong the cardiac action potential.

Under normal circumstances, the Ca^{2+} channels are activated early in the action potential and contribute to the plateau (phase 2) of the action potential. They are inactivated at the end of phase 2 and during phase 3. However, if the cardiac action potential is sufficiently prolonged, some of these Ca^{2+} channels can become reset and then re-activated, allowing a further inward Ca^{2+} current, causing a second depolarization of the membrane and additional action potentials. It is thought that the L-type Ca^{2+} channels may be responsible for the EADs that occur towards the end of phase 2, while the T-channels, which can be activated only at membrane potentials significantly below the plateau level, may be responsible for the EAD occurring midway through phase 3.

DAD involves an afterdepolarization during phase 4 of the cardiac action potential (Figure 3b) and is more likely at higher heart rates. As the cardiac muscle fibre is stimulated at increasingly higher rates an afterdepolarization becomes apparent in phase 4. At higher stimulation rates this becomes more pronounced and depolarizes the fibre to threshold, thus producing a spontaneous action potential followed by further afterdepolarization. At even higher stimulation rates, successive spontaneous action potentials produce afterdepolarizations to threshold, giving volleys of spontaneous action potentials and hence a potential ectopic focus in the heart. The mechanisms underlying this phenomenon are thought to involve intracellular Ca^{2+} levels, and the appearance of DAD is a feature of the toxic effects of drugs (e.g. cardiac glycosides, which raise intracellular Ca^{2+} levels). It is thought that the elevated levels of intracellular Ca^{2+} cause the opening of membrane channels, which allow the inward movement of positive ions including Na^{+}. In addition, it is known that the elevated intracellular Ca^{2+} levels stimulate Na^{+}/Ca^{2+} exchange across the cell membrane. This is electrogenic, because 3 Na^{+} enter the cell for every Ca^{2+} expelled, producing a net inward movement of positive charge and a depolarization.

Potential-time profile from a myocardial fibre during an action potential



Progressive development of DADs and related action potentials as the frequency of stimulation increases (tachycardia)

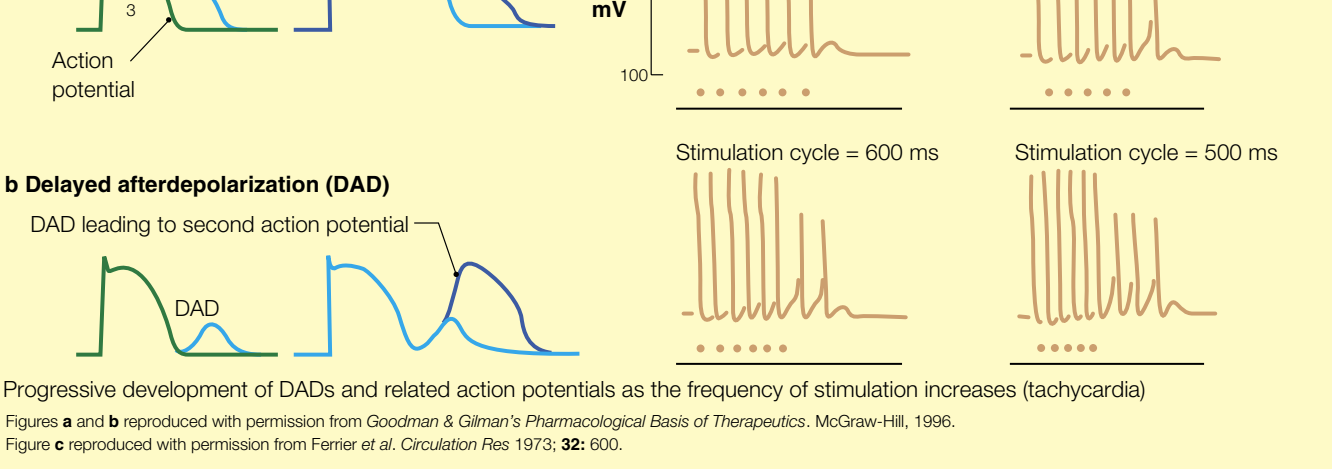
Figures **a** and **b** reproduced with permission from *Goodman & Gilman's Pharmacological Basis of Therapeutics*. McGraw-Hill, 1996.
Figure **c** reproduced with permission from Ferrier *et al*. *Circulation Res* 1973; **32:** 600.

Re-entry

Re-entry is a feature of a series of muscle fibres in contrast to triggered activity which is the property of individual muscle cells. In re-entry, activity generated by single cardiac impulse (SA node depolarization) re-invades part of the heart through which it has previously passed, thereby causing further action potentials. This is termed ordered when the activity traverses a fixed anatomical pathway or random when the pathway is constantly changing. A good example of random re-entry is fibrillation.

Consider a chain of muscle fibres along which the cardiac action potential spreads. In a number of areas in the heart, bundles split into two branches (left and right), and action potentials spread simultaneously through both branches (Figure 4a). When the action potential encounters a connecting branch, the action potential becomes extinguished within it, because the action potentials travelling leftwards from the right branch and rightwards from the left branch encounter fibres that are absolutely refractory (Figure 4a). If a bidirectional conduction block develops in either the left or the right branch then the connecting branch ensures that the action potential is spread to parts of the heart beyond the block (Figure 4b). However, under some circumstances the block can be unidirectional (i.e. the blocked area may not allow passage of action potentials in the normal direction, but allows transmission with difficulty in a retrograde direction). If transmission through this damaged area is also slowed, action potentials may traverse the region and re-invade part of the heart where the cells have gone beyond their refractory period, giving rise to a circus of action potentials that repeatedly traverse the circuit (Figure 4c). The necessary conditions for re-entry therefore include an unidirectional block in one part of the loop and a delay in conduction through this part so that action potentials can re-invade earlier parts of the loop that have gone beyond their refractory period.

The role of unidirectional block in re-entry



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Under some circumstances, the conduction is in aberrant anatomical pathways (e.g. the additional conduction fibres between the atria and ventricles responsible for Wolff–Parkinson–White syndrome). In this case, the normal AV nodal pathway constitutes the slow pathway while the abnormal extra fibres constitute the fast pathway. Under other circumstances, conduction through a region of the heart that has been modified because of damage (e.g. ischaemia where groups of fibres have become converted from the fast type to the slow type) slows conduction rates and generates the necessary conditions for re-entry. ◆

Physiology: Kidney

Anaesthesia
and intensive care medicine
on CD-ROM

Function of the Nephron and the Formation of Urine

John C Atherton

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Every day, about 160–180 litres of plasma are filtered (assuming glomerular filtration rate (GFR) is 120–140 ml/min) at the renal glomerular capillaries and delivered to the proximal tubules (see page 226, Figure 1). The composition of this ultrafiltrate is identical to that of plasma except that it is virtually protein free. If body fluid volume and composition are to be maintained, this fluid must undergo considerable changes in volume and composition by reabsorption and secretion as it passes along the nephron.

Movement of solutes across any membrane can occur by passive or active transport.

Proximal convoluted tubule

Bulk reabsorption of the filtered load occurs at the proximal convoluted tubule. Over 65% of the solutes and water filtered are reabsorbed (Figure 1); the exceptions are urea (about 50%) and Mg^{2+} (about 20%). Na^+-K^+ ATPase in the basolateral membrane maintains a low intracellular Na^+ concentration which provides the driving force for Na^+ movement into the cell across the apical membrane.

Reabsorption (% filtered load) of solutes and water in different parts of the nephron

	Proximal tubule	Loop of Henle	Distal tubule	Collecting duct
Glucose	99–100	0	0	0
Amino acids	99–100	0	0	0
Na^+	65–70	20–25	3–5	3–5
K^+	70–80	10–15	Secretion	20–30
Mg^{2+}	15–20	60–65	3–5	3–5
Ca^{2+}	65–70	20–25	5–8	1–2
Cl^-	65–70	20–25	5–10	3–5
HCO_3^-	75–85	10–15	3–5	0–5
Urea	45–50	Secretion	0	45–50
Water	65–70	15–23	0	5–10

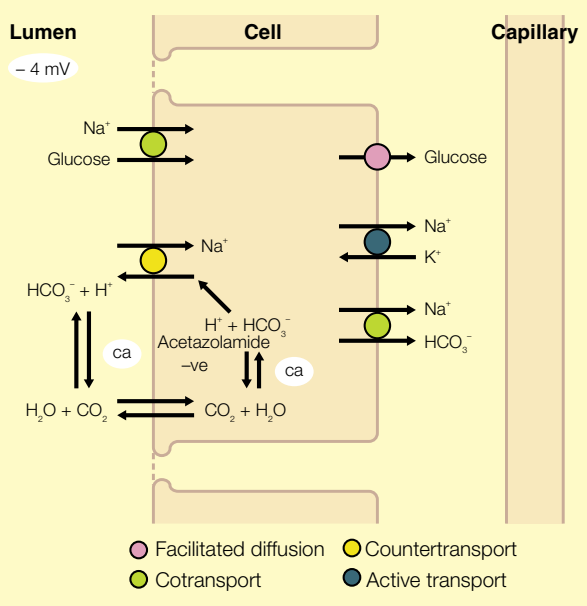
Values are given in percentages. For urea and K^+ the amounts secreted are variable. Urea secretion depends primarily on the medullary interstitial fluid urea concentration and could represent up to 50% of the filtered load.
K^+ secretion is influenced by many factors (see text) and can be equivalent to 20–180% of the filtered load

1

Changes in the tubular fluid to plasma concentration ratios for different solutes along the proximal tubule indicate that there is asymmetry in solute transport. In the early part of the tubule (Figure 2) there is preferential reabsorption of HCO_3^-, PO_4^{2-}, glucose and amino acids, whereas significant Cl^- reabsorption occurs in the second half (Figure 3). The Na^+ concentration ratio does not change along the proximal tubule, therefore there is no asymmetry in Na^+ reabsorption. Reabsorption is by transcellular (66%) and paracellular (33%) pathways.

Early proximal tubule (Figure 2) – Na^+ is reabsorbed on the cotransporters for glucose, amino acids and PO_4^{2-}. The sodium-glucose transporter (SGLT2) is a protein, the amino acid sequence of which is known. Following the combination of two Na^+ ions, the glucose transporter undergoes a conformational change that enhances its affinity for glucose. Reorientation of the transport protein within the apical membrane exposes the glucose and Na^+ binding sites to the cytoplasm, and glucose and Na^+ leave the protein. Passive glucose exit from the cell is facilitated by the presence of glucose transporters (GLUT1 and GLUT2) in the basolateral membrane. Another important entry step for Na^+ across the apical membrane is the Na^+-H^+ countertransporter, which probably accounts for about 60% of transcellular movement. Secreted H^+ combines with filtered HCO_3^-; the CO_2 so formed (carbonic anhydrase is found in the brush border) is in equilibrium with intracellular pCO_2, which is hydrated to form H^+ and HCO_3^-. H^+ is recycled and HCO_3^- leaves the cell via a basolateral Na^+-HCO_3^- cotransporter. The Na^+-H^+ countertransporter can secrete NH_4^+ by replacing the H^+.

Na^+, glucose and HCO_3^- reabsorption across an early proximal tubule cell



Glucose reabsorption is coupled to Na^+ reabsorption across the apical membrane via a SGLT2 transport protein. Glucose moves across the basolateral membrane by facilitated diffusion (GLUT2 transporter). Intracellular hydration of CO_2 is catalysed by carbonic anhydrase (ca), a reaction that is inhibited by diuretics (e.g. acetazolamide)

2

Late proximal tubule – transcellular Na^+ reabsorption is linked to Cl^--anion exchange mechanisms as well as H^+ secretion. The anion countertransport mechanism (Figure 3) is HCO_3^--Cl^- but this can apply to Cl^- and other anions (e.g. hydroxyl, sulphate, formate, oxalate). Secreted H^+ in exchange for Na^+ combines with secreted HCO_3^- to form CO_2 and H_2O. CO_2 diffuses into the cell where it is hydrated and, in the presence of carbonic anhydrase, forms H^+ and HCO_3^-. H^+ and HCO_3^- are recycled; Cl^- (exchanged for HCO_3^-) and Na^+ leave across the basolateral membrane. Cl^- reabsorption in the proximal tubule is not restricted to this mechanism. Preferential HCO_3^- reabsorption in the early part of the tubule leads to an increase in tubular fluid Cl^- concentration (120–140 mmol/litre) providing a concentration gradient sufficient to promote paracellular Cl^- reabsorption against an adverse transepithelial potential difference (4 mV, lumen positive; Figure 3). Water is also reabsorbed through the paracellular route and some Cl^- and Na^+ dissolved in it will be reabsorbed; a process known as solvent drag.

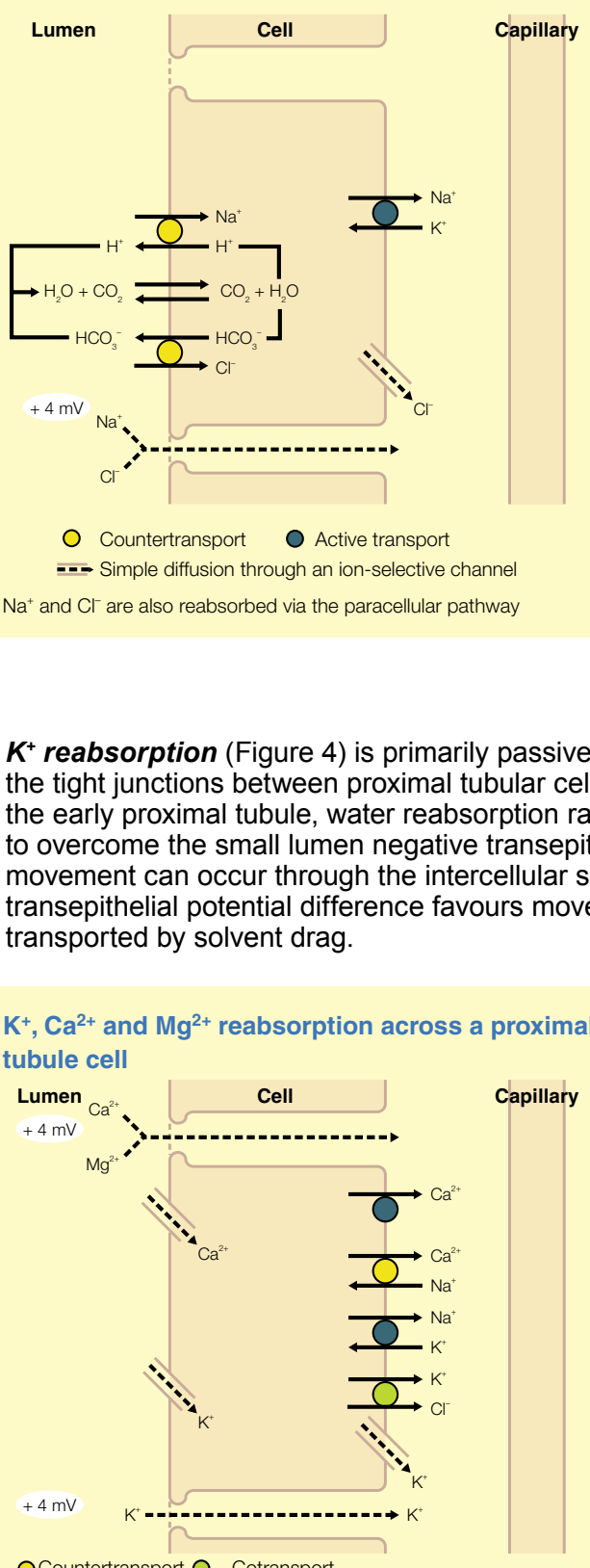
Na^+ and Cl^- reabsorption across a late proximal tubule cell

Na^+ and Cl^- are also reabsorbed via the paracellular pathway

3

K^+ reabsorption (Figure 4) is primarily passive through the paracellular route because the tight junctions between proximal tubular cells are relatively permeable to K^+. In the early proximal tubule, water reabsorption raises the K^+ concentration sufficiently to overcome the small lumen negative transepithelial potential difference, so that movement can occur through the intercellular spaces. In the late proximal tubule, the transepithelial potential difference favours movement through this route. K^+ is also transported by solvent drag.

K^+, Ca^{2+} and Mg^{2+} reabsorption across a proximal tubule cell



Paracellular movement of these cations probably accounts for most reabsorption

4

Ca^{2+} reabsorption occurs through transcellular and paracellular (80%) routes. Reabsorption is by solvent drag along the length of the proximal tubule with a favourable transepithelial potential difference in the second half of the tubule. The transcellular component includes passive entry down a steep electrochemical gradient through Ca^{2+} channels in the apical membrane and exit by a Ca^{2+}-ATPase and/or Ca^{2+}-Na^+ countertransporter.

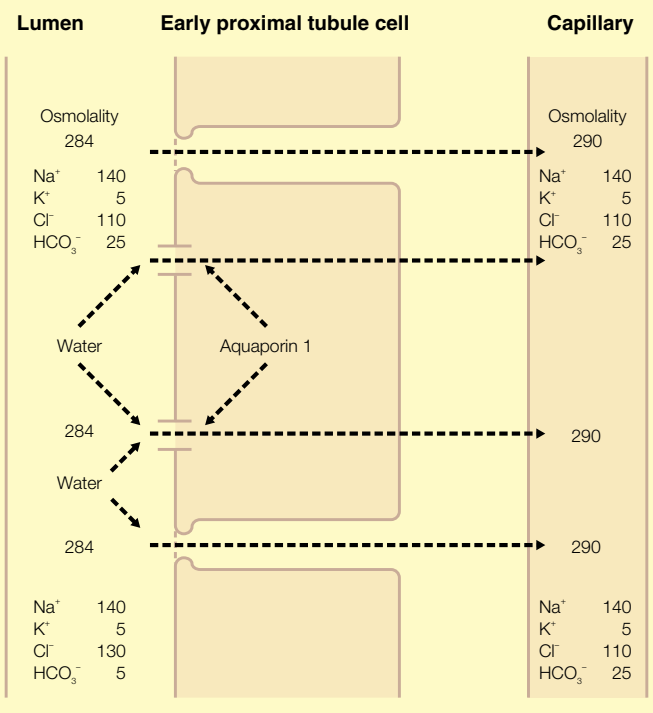
Mg^{2+} reabsorption in the proximal tubule is only 15–20% of the filtered load. Cells have a low permeability to Mg^{2+} and transporters for it have not been isolated in the proximal tubule, therefore paracellular reabsorption in the second half of the tubule probably occurs.

Water reabsorption (Figure 5) is passive and requires an osmotic gradient. Tubular fluid osmolality is about 6 mosmole/kg H_2O lower than that of the surrounding interstitial fluid. This small difference is sufficient (apical and basolateral membranes and tight junctions are highly permeable to water) to account for large amounts of water movement through paracellular and transcellular routes. The effectiveness of the osmotic gradient also depends on the solutes involved. If the difference in osmolality were due solely to the presence of a permeant solute, the gradient would be less effective than if the solute was impermeant (i.e. the composition of the fluid on each side of the membrane is important). The preferential reabsorption of HCO_3^- in the early proximal tubule results in a tubular fluid in the later parts with higher Cl^- and lower HCO_3^- concentrations than interstitial fluid. Since HCO_3^- has a higher reflection coefficient than Cl^-, the effective driving force for water reabsorption is greater in the late proximal tubule. As in other parts of the nephron, transcellular water movement is thought to occur through channel integral proteins (aquaporins). Aquaporin 1 is a 28 kDa protein found in the proximal tubule.

Loop of Henle

The loop of Henle can be divided into three different anatomical components, which exhibit different transport and permeability characteristics (see page 226, Figure 1). The thin descending limb is relatively impermeable to most solutes but has high permeability to water; 15–25% of the filtered fluid is reabsorbed through water channels (aquaporin 1). The thin ascending limb is impermeable to water but is permeable to Na^+. The thick ascending limb is relatively impermeable to water but has a high reabsorptive capacity; about 20–25% of filtered Na^+, Cl^-, K^+ and Ca^{2+} are reabsorbed and about 60% of filtered Mg^{2+}. HCO_3^- escaping reabsorption in the proximal tubules is also reabsorbed by a mechanism similar to that in the proximal tubule.

Transcellular (aquaporin 1) and paracellular water reabsorption in the proximal tubule

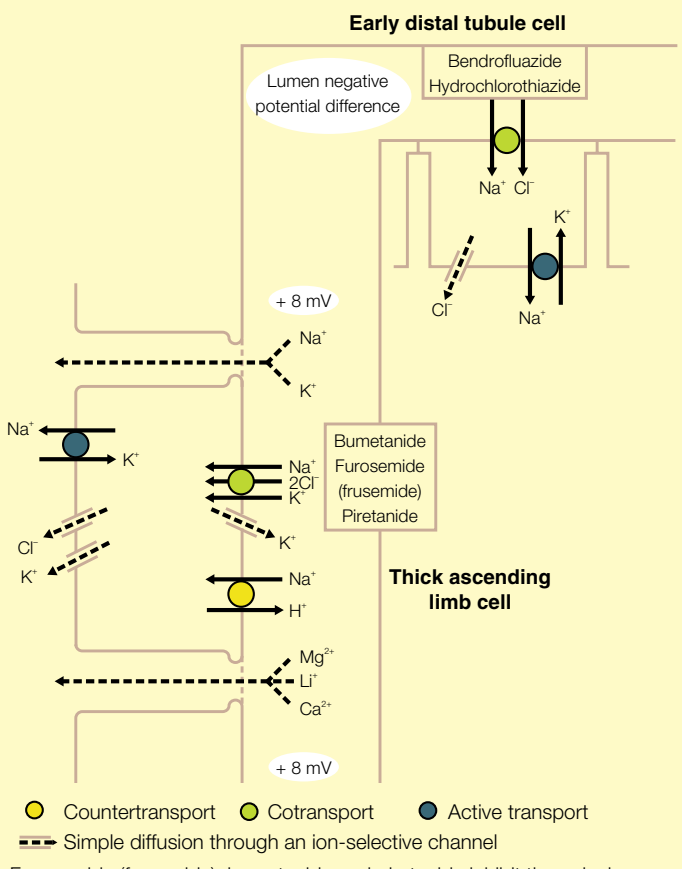


Note the small osmotic gradient across the proximal tubule. Preferential reabsorption of HCO_3^- in early proximal tubule cells results in an increase in the effective osmotic gradient promoting water reabsorption across late proximal tubule cells

5

The primary component of reabsorption is the Na^+-K^+ ATPase in the basolateral membrane (Figure 6). By keeping the intracellular Na^+ concentration low, this maintains a favourable electrochemical gradient for Na^+ entry into the cell across the apical membrane via either a Na^+-H^+ countertransporter (for HCO_3^- reabsorption) or a protein carrier capable of transporting Na^+, K^+ and $2Cl^-$ ions (the Na^+-K^+-$2Cl^-$ cotransporter is quantitatively more important). Exit from the cell across the basolateral membrane of the thick ascending limb is via Na^+-K^+ ATPase for Na^+ and ion-specific channels for K^+ and Cl^-. Some of the K^+ returns to the tubular fluid via apical K^+ channels. The result of these ion movements is the generation of a transepithelial potential difference (about 8 mV lumen positive) that drives reabsorption of many cations through the paracellular pathway. Na^+ movement is transcellular (50%) and paracellular (50%). Most Ca^{2+}, Mg^{2+} and perhaps Li^+ reabsorption occurs via the paracellular route, though some transcellular movement of Ca^{2+} and Mg^{2+} has been suggested. Ca^{2+} transcellular movement is via mechanisms similar to those described for the proximal tubule. Mg^{2+} movement could be via basolateral Mg^{2+} ATPase and Na^+-Mg^{2+} countertransport. NH_4^+ secreted by the proximal tubule can replace K^+ on the triple cotransporter.

Reabsorption of ions across the thick ascending limb of the loop of Henle and early distal tubule



Furosemide (frusemide), bumetanide and piretanide inhibit the apical membrane Na^+:K^+:$2Cl^-$ cotransporter in thick ascending limb cells. Thiazide diuretics (e.g. bendrofluazide, hydrochlorothiazide) inhibit the apical membrane Na^+-Cl^- cotransporters in early distal tubule cells

6

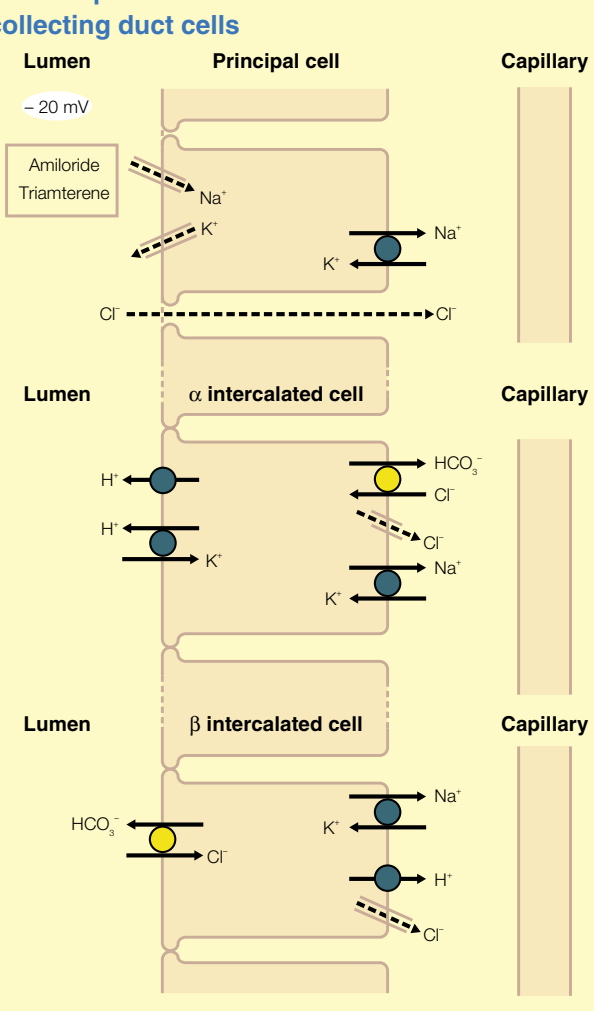
Distal tubule and collecting duct

Transport activity in the final segments of the nephron accounts for 5–10% of the reabsorption of filtered Na^+, Cl^-, Ca^{2+}, Mg^{2+} and water. Urinary excretion of K^+ is normally determined by passive secretion but when dietary K^+ intake is low, active reabsorption occurs. Urinary pH is controlled by H^+ secretion and HCO_3^- reabsorption. The distal tubule is impermeable to water whereas the collecting duct exhibits a variable permeability to water controlled by antidiuretic hormone (ADH).

As in other nephron segments the key transport mechanism is the activity of Na^+-K^+ ATPase in the basolateral membrane of the cells to maintain a low intracellular Na^+ concentration. In cells of the early distal tubule, entry across the apical membrane is via a Na^+-Cl^- cotransporter and exit is via the Na^+-K^+ ATPase and a Cl^- channel (Figure 6). About 60% of the amino acid sequence of the cotransporter is similar to the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb.

Principal cells make up 60% of the cells of the collecting duct. Na^+ movement across apical membranes of principal cells (Figure 7) is by passive diffusion down an electrochemical gradient through Na^+ channels. Na^+ exits the cell via the Na^+-K^+ ATPase in the basolateral membrane. The large transepithelial potential difference (lumen negative) generated by Na^+ movement is probably sufficient to drive Cl^- reabsorption through the paracellular pathway. Passive secretion of K^+ through apical K^+ channels is driven by the steep chemical gradient (maintained by basolateral membrane Na^+-K^+ ATPase) that is sufficient to overcome the adverse transmembrane electrical gradient (cell negative). Water movement is through water channels in the apical (aquaporin 2) and basolateral (aquaporins 3 and 4) membranes.

Reabsorption of ions across cortical and medullary collecting duct cells



Amiloride and triamterene inhibit Na^+ movement through the Na^+ selective channel

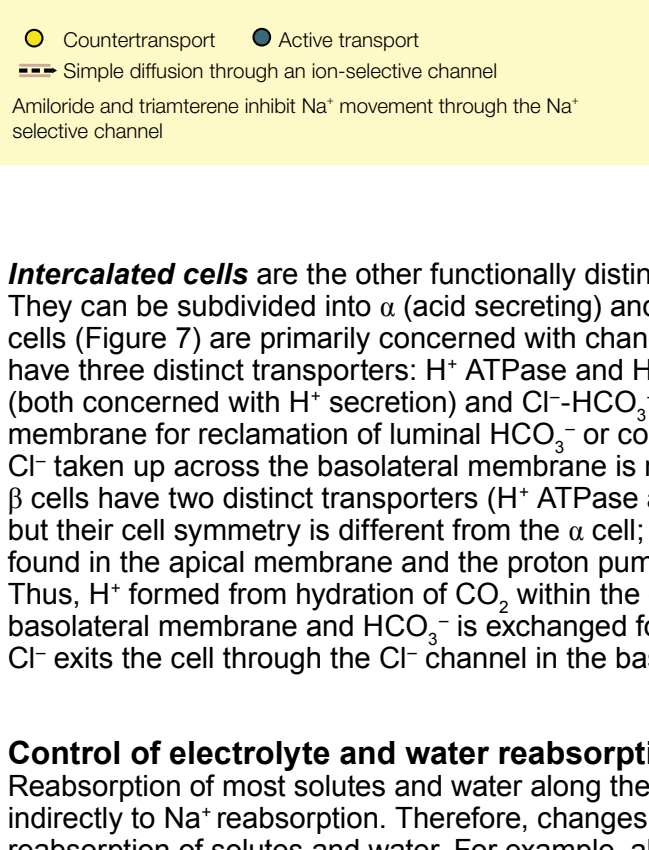
7

Intercalated cells are the other functionally distinct types of cell in the collecting duct. They can be subdivided into α (acid secreting) and β (base secreting) cells. Intercalated cells (Figure 7) are primarily concerned with changes in acid–base status. The α cells have three distinct transporters: H^+ ATPase and H^+-K^+ ATPase in the apical membrane (both concerned with H^+ secretion) and Cl^--HCO_3^- countertransporter in the basolateral membrane for reclamation of luminal HCO_3^- or conservation of newly formed HCO_3^-. Cl^- taken up across the basolateral membrane is recycled through Cl^- channels. The β cells have two distinct transporters (H^+ ATPase and Cl^--HCO_3^- countertransporter) but their cell symmetry is different from the α cell; the anion countertransporter is found in the apical membrane and the proton pump in the basolateral membrane. Thus, H^+ formed from hydration of CO_2 within the cell is actively transported across the basolateral membrane and HCO_3^- is exchanged for Cl^- across the apical membrane. Cl^- exits the cell through the Cl^- channel in the basolateral membrane.

Control of electrolyte and water reabsorption along the nephron

Reabsorption of most solutes and water along the nephron is coupled directly or indirectly to Na^+ reabsorption. Therefore, changes in Na^+ reabsorption cause changes in reabsorption of solutes and water. For example, altered transcellular Na^+ reabsorption in the thick ascending limb modifies paracellular movement of other cations in the same part of the nephron and influences water reabsorption in the descending limb of the loop of Henle and the collecting duct through changes in medullary interstitial fluid osmolality and in the cortical collecting duct through changes in the tubular fluid osmolality. Starling forces also contribute to the control of salt and water movement in leaky transporting epithelia (e.g. proximal tubule). The control mechanisms in different parts of the nephron are summarized in Figure 8.

Reabsorption in different parts of the nephron



8

Proximal tubule – for many years, it was thought that reabsorption at the proximal tubule was load-dependent with a constant fraction of the filtered load being reabsorbed (i.e. glomerular–tubular balance). This simplistic view is incomplete. Na^+ reabsorption is enhanced by angiotensin II and catecholamines released from the renal sympathetic nerve endings (noradrenaline (norepinephrine)) and adrenal medulla (adrenaline (epinephrine)) and reduced by dopamine (released from renal dopaminergic nerves or produced in proximal tubule cells). Parathormone decreases Na^+ reabsorption in the proximal tubule. Reports that atrial natriuretic peptide (ANP) had a direct inhibitory effect on Na^+ reabsorption lack evidence, though the effect could be mediated by inhibition of renin release or an increase in dopamine release.

Thick ascending limb – Na^+ reabsorption in the thick ascending limb is also load-dependent: increasing the load, increases reabsorption. However, other mechanisms affect transcellular and paracellular movement. Renal sympathetic nerve stimulation (catecholamine release) increases reabsorption. Glucagon, parathormone and ADH increase Na^+ reabsorption. The mechanism for this hormonal control, at least for ADH is by basolateral Cl^- channel phosphorylation, increased Cl^- reabsorption and, as a consequence, enhanced activity of the Na^+-K^+-$2Cl^-$ cotransporter. Aldosterone may increase Na^+ reabsorption in the thick ascending limb but the mechanism is unknown. Ca^{2+} reabsorption in the thick ascending limb is controlled by the parathyroid hormones parathormone and calcitonin; parathormone has the greater effect.

Alterations in intratubular flow rate and apical K^+ channel activity affect the lumen positive transepithelial potential difference and therefore paracellular movement. Decreasing flow causes the lumen positive potential difference earlier in the thick ascending limb and decreasing the activity of the K^+ channel (intracellular acidity, NH_4^+, ATP) decreases the lumen positive potential difference.

The distal tubule and collecting duct is where the composition of tubular fluid is finely tuned for the maintenance of body fluid volume and composition. Renal sympathetic nerve activity is involved in Na^+ reabsorption. The Na^+-retaining properties of aldosterone are manifest in the cortical collecting duct; increasing intracellular protein synthesis and insertion of additional transmembrane proteins enhance Na^+ reabsorption and K^+ excretion. There are compelling arguments to consider that the primary physiological action of aldosterone is for K^+ secretion. In conditions of avid salt retention, the natriuretic effects of many distal-acting diuretics are minimal, suggesting that avid salt retention has occurred at sites proximal to the action of the diuretic, and a major stimulus to aldosterone secretion is raised plasma K^+ concentration. Perhaps changes in Na^+ reabsorption are a consequence of aldosterone-induced changes in K^+ secretion.

The natriuretic action of ANP is mediated (as is that of urodilatin) by reducing apical membrane Na^+ permeability in medullary collecting ducts. Urodilatin has a more powerful natriuretic action than ANP, presumably because it gains access to the apical membrane through secretion at the distal tubules rather that at the glomerulus as does ANP, and therefore it is not subject to degradation by proximal tubule brush border endopeptidases. Both ANP and urodilatin inhibit ADH-stimulated water reabsorption in the collecting duct. This might be a direct effect on the transport process or simply reflect inhibition of Na^+ reabsorption reducing the osmotic gradient promoting water movement.

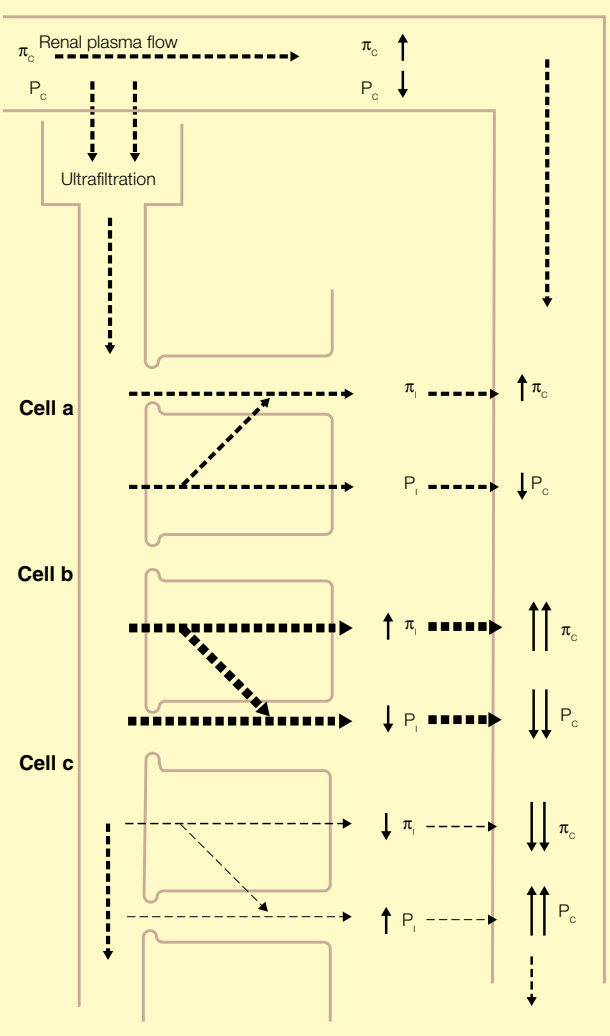
Mechanisms (in addition to aldosterone) that control K^+ secretion include tubular flow rate, Na^+ delivery to more distal nephron sites, ADH and acid–base balance. Excreted K^+ is primarily determined by K^+ secretion in the distal nephron. Increases in either or both tubular flow rate and the amount of Na^+ delivered to Na^+ channels in the principal cells lead to enhanced distal nephron K^+ secretion. Increasing the amount of Na^+ presented to Na^+ channels results in an increase in Na^+ reabsorption, a more lumen negative transepithelial potential difference and, therefore, more K^+ secretion through K^+ channels. Cl^- reabsorption through the paracellular pathway also increases. ADH increases the Na^+ permeability of principal cells, decreases the cell negative apical membrane potential difference and, therefore, favours K^+ secretion. Acidosis and alkalosis, decrease and increase K^+ secretion, respectively, by altering the permeability of the apical membrane to K^+. Alkalosis increases apical membrane permeability thereby enhancing K^+ secretion and excretion; acidosis has the opposite effect. Differences in the response to acidosis depend on whether the acidosis is acute or chronic. Chronic acidosis favours K^+ excretion, presumably because the delivery of fluid from the proximal tubule is increased (proximal tubule Na^+-K^+ ATPase activity is reduced) as are Na^+ load and fluid flow rate to the principal cells, both of which favour K^+ secretion and override the effect of acidosis on K^+ channel permeability.

Calcitonin and calcitriol (a metabolite of vitamin D produced in proximal tubule cells) enhance Ca^{2+} reabsorption at the distal tubules and cortical collecting ducts. These effects appear in-dependent of Na^+ reabsorption because following administration of diuretics (amiloride or bendrofluazide) that reduce Na^+ reabsorption, Ca^{2+} excretion decreases.

Water reabsorption in most nephron segments is a consequence of solute movement and water permeability, the exceptions being the water-impermeable thick ascending limb and distal tubules. Collecting ducts are also impermeable to water except in the presence of ADH, which increases water permeability. This occurs by ADH-induced insertion of water channels in the apical membrane.

Starling forces operating across the peritubular capillaries are important in the control of salt and water reabsorption (Figure 9). The balance of forces operating across the capillary wall influences fluid uptake into the capillary. Uptake of fluid promoted by colloid osmotic pressure (π_c) and interstitial fluid pressure (P_I) is opposed by hydrostatic pressure in the capillaries (P_c) and colloid osmotic pressure in the interstitial fluid (π_I) (Figure 9, cell a). Changes in the uptake of fluid modify reabsorption by increasing or decreasing P_I and hence net fluid movement through the paracellular pathway. For example, assuming RPF is unchanged and GFR increases (i.e. filtration fraction is increased), net fluid uptake into the capillaries is enhanced because P_c decreases and π_c increases (Figure 9, cell b). Back flux into the tubule via the paracellular pathway is reduced. The converse occurs if GFR falls (constant RPF), P_c increases and π_c decreases. The overall effect is reduced uptake into the peritubular capillaries, an increase in P_I and an increase in back flux into the tubule (Figure 9, cell c).

Effect of peritubular Starling forces on transcellular and paracellular reabsorption across the proximal tubule



P_I and P_c are the hydrostatic pressures in the interstitial fluid and peritubular capillary plasma, respectively. π_I and π_c are colloid osmotic pressure in interstitial fluid and peritubular plasma, respectively.

Cell a represents reabsorption when GFR and ECF volume are normal. Cell b represents increased reabsorption when GFR is increased (or reduced ECF volume; see page 241). Cell c represents decreased reabsorption when GFR is reduced (or expanded ECF volume; see page 240)

Diuretics – mechanisms of action

Most diuretics act by inhibition of Na^+ transport at different parts of the nephron, leading to increases in Na^+ and water excretion. Carbonic anhydrase inhibitors (e.g. acetazolamide) reduce Na^+ reabsorption by reducing H^+ secretion and cause modest changes in urine flow. Bumetanide, furosemide (frusemide) and piretanide exert powerful but short lasting natriuretic and diuretic effects by inhibition of the Na^+-K^+-Cl^- cotransporter in the water impermeable thick ascending limb and by binding the concomitant reductions in medullary interstitial fluid osmolality and transtubular osmotic gradient in cortical collecting ducts. Cotransporter inhibition also leads to lowering the lumen positive, transepithelial potentail difference and a reduction in paracellular cation reabsorption. Thiazide diuretic inhibition of Na^+-Cl^- cotransporters in early distal tubules reduces Na^+ reabsorption and the transtubular osmotic gradient in the distal tubule. Some (e.g. bendrofluazide, hydrochlorothiazide) are specific to this cotransporter whereas others (e.g. chlorothiazide) also inhibit carbonic anhydrase activity. The unwanted hypokalaemic effects of many diuretics can be avoided by co-administration of K^+ sparing diuretics (e.g. amiloride and triamterene, which block Na^+ channels in principal cells; and the aldosterone antagonists such as spironolactone). ◆

Micturition

Christopher Fry

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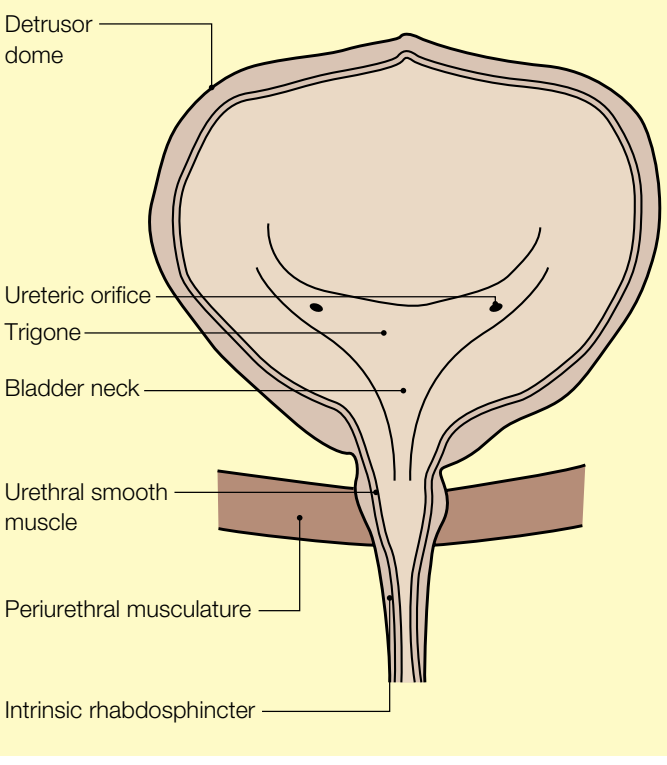
The bladder has a dual function. For most of the time it is a compliant muscular organ that stores up to 1 litre of urine. It is therefore important that the intravesical pressure is less than that of the upper tract to allow filling. Its second function is to facilitate controlled voiding and for this purpose a sufficient intravesical pressure must be generated to overcome the resistance of the outflow tract.

Lower urinary tract

Figure 1 shows the components of the lower urinary tract. Figure 2 shows the three layers of the bladder dome: a trans-itional epithelium facing the lumen with an underlying submucosal layer containing sensory nerves and blood vessels; a detrusor smooth muscle layer; and an adventitial layer. Towards the base of the bladder the ureters open into the lumen and the triangular region thus formed, with the bladder neck as the apex, is the trigone. Towards the bladder neck and urethra the muscle bundles become smaller with more connective tissue. The bladder neck forms a proximal sphincter mechanism, but there is no readily identifiable anatomical structure. In the male, the prostate merges with the neck to form an additional sphincter, mainly to prevent retrograde ejaculation.

Lower urinary tract



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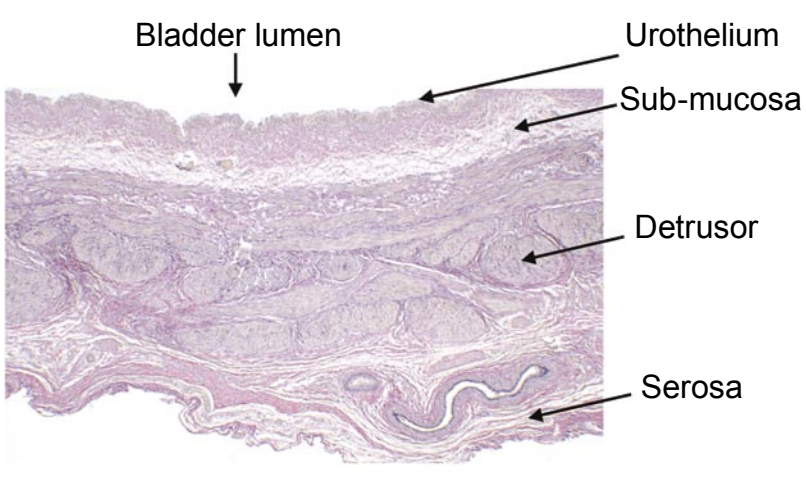


2 Three-layered structure of the bladder wall.

Further down the urethra is a distinct distal sphincter mechanism consisting of an inner layer of smooth muscle, a layer of skeletal muscle (the intrinsic rhabdosphincter) and a pubo-urethral sling of skeletal muscle especially effective in the male. The intrinsic rhabdosphincter is probably the most important component; it forms a horseshoe-like structure round the urethra, which kinks the tract when it is contracted and reduces flow. The lower urinary tract lies within a number of supporting structures.

Nervous control of the bladder

Efferent innervation: the lower urinary tract receives a dual autonomic innervation; a parasympathetic supply from S2–S4 and a sympathetic supply from T10–L2. Preganglionic parasympathetic fibres run as the nervi erigentes and synapse at ganglia in the pelvic plexus which lie in the adventitia round the bladder base and in the bladder wall. Postganglionic fibres thus act as a motor supply to the bladder and urethra.

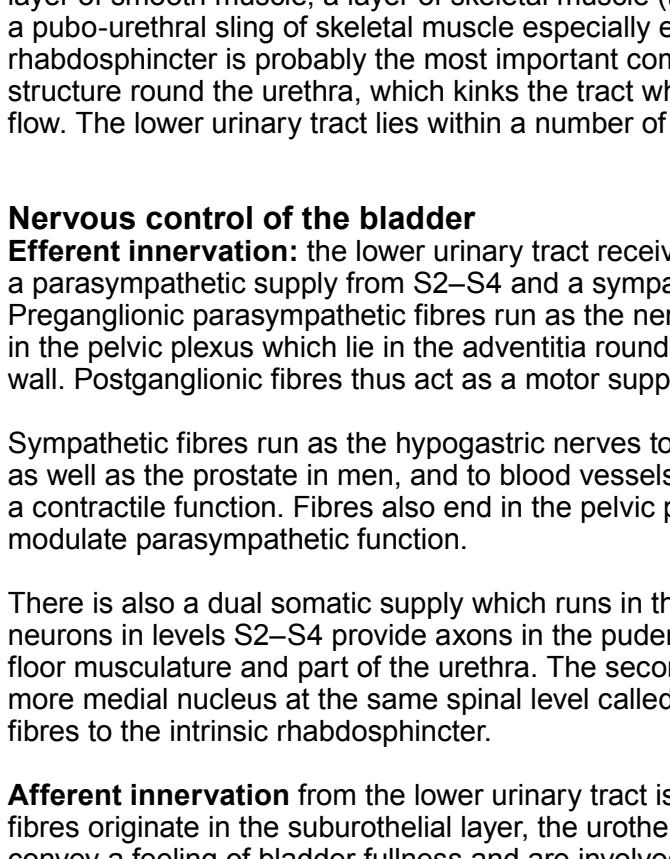
Sympathetic fibres run as the hypogastric nerves to the trigone and bladder base, as well as the prostate in men, and to blood vessels in the bladder, where they effect a contractile function. Fibres also end in the pelvic plexus ganglia where they can modulate parasympathetic function.

There is also a dual somatic supply which runs in the nervi erigentes. Typical motor neurons in levels S2–S4 provide axons in the pudendal nerve to innervate the pelvic floor musculature and part of the urethra. The second component arises from a distinct, more medial nucleus at the same spinal level called Onuf's nucleus. This provides fibres to the intrinsic rhabdosphincter.

Afferent innervation from the lower urinary tract is less well understood. Afferent fibres originate in the suburothelial layer, the urothelium and detrusor layers. They convey a feeling of bladder fullness and are involved in micturition reflexes. The transduction mechanism between bladder filling and afferent excitation was assumed to be mediated by stretch receptors in the suburothelial layer, a hypothesis marred only by the inability to identify such receptors convincingly. More recently, it has been proposed that the urothelium releases chemical mediators such as ATP when stretched, and it is these that initiate afferent activity. The afferent fibres are myelinated (A-δ), but unmyelinated C-fibres are also present, which may respond to more extreme conditions and contribute to pathological reflexes (see below).

Afferent fibres also originate from the trigone and urethral wall and run in the sympathetic hypogastric nerves and pudendal nerves, respectively. They respond to greater degrees of bladder fullness and convey varying levels of urgency to void. Efferent and afferent innervation is shown in Figure 3.

Innervation of the lower urinary tract



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Micturition and co-ordination of efferent activity

Micturition requires that the lower urinary tract undergoes two co-ordinated processes: reduction of bladder outflow resistance and an increase of bladder vesical pressure. Normal micturition is impossible if these two processes do not occur together. Although afferent and efferent fibres form spinal connections, a simple spinal reflex is insufficient to explain this co-ordinated process and control from higher nervous centres is required.

Most afferent fibres make synaptic connections with ascending fibres that travel in lateral tracts. It is thought that these tracts project to the periaqueductal grey, which controls a region of the rostral pons (the micturition centre). Other fibres travel to areas in the cerebral cortex (the paracentral lobule) that control the pelvic floor musculature and to the medial pre-optic area. The latter projects directly to the pontine micturition centre to co-ordinate different 'pelvic' functions including micturition, defecation and coitus. Fibres that project to the frontal cortex allow social and conscious control over micturition.

The micturition centre is thought to act as a final common pathway and controls the co-ordinated voiding process involving bladder outlet relaxation and detrusor contraction. Descending fibres reduce motor neuron activity to the intrinsic rhabdosphincter by acting on inhibitory sacral interneurons using glycine and γ-aminobutyric acid (GABA) as transmitters. In addition, other fibres to the urethral smooth muscle may be activated to relax this tissue, possibly by the release of a relaxing neurotransmitter (e.g. nitric oxide). Descending fibres also activate parasympathetic fibres that cause the detrusor smooth muscle to contract. This reciprocal innervation theory remains to be proved but represents a reasonable hypothesis.

The role of sympathetic fibres in this process is less clear. In the lower urinary tract, sympathetic innervation is most dense to the trigone and bladder neck and a decrease of activity would relax both these components and assist in the reduction of outlet resistance.

This co-ordinated process of outlet relaxation and detrusor contraction can be seen in Figure 4 which shows the pressures recorded in the urethra and bladder during filling and voiding. During filling, bladder pressure remains fairly constant despite the large increase in volume and there is a small, but definite, rise of urethral pressure. Voiding is characterized by an initial fall of urethral pressure followed almost immediately by a rise of detrusor pressure.

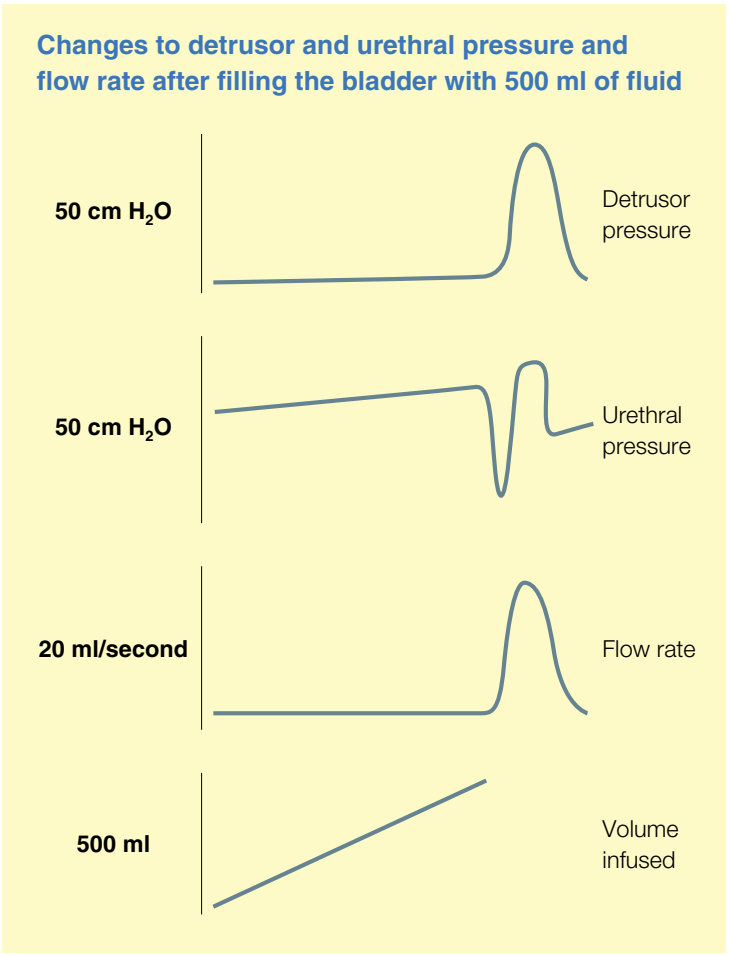
Bladder filling

The tissues that comprise the bladder wall are fairly compliant. They show a remarkable ability to realign themselves when subjected to strain, thus dissipating stress within the tissue (stress relaxation). Whether there is active relaxation of detrusor smooth muscle is more contentious and there is no unequivocal evidence. However, different gating mechanisms may attenuate parasympathetic efferent activity during filling: these include sympathetic inhibition on the pelvic plexuses and a gating of afferent information, such that low threshold activity does not break through to activate a micturition reflex.

The rise of urethral pressure may be a spinal reflex from local afferents that either excite parasympathetic fibres and/or inhibit relaxatory nitrergic efferents.

Smooth muscle function in the lower urinary tract

The end target of efferent nerves is largely the muscular layers in the wall of the urinary tract. In the normally functioning bladder wall, detrusor is under the exclusive control of cholinergic fibres. Parasympathetic fibres release acetylcholine that binds to muscarinic M3 receptors, which elicits a transient rise of intra-cellular calcium via the intermediate generation of the second messenger inositol trisphosphate. In some bladder pathologies (and in most animals, except old-world primates) a second excitatory transmitter, ATP, is involved which increases the intracellular calcium by depolarizing the cell membrane and eliciting calcium influx through calcium channels. The importance of muscarinic receptors in mediating detrusor contraction is the basis of most of the therapeutic control of bladder overactivity.



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In the trigone and bladder neck, sympathetic activation via α-adrenoreceptor activation plays an important role, alongside muscarinic activation, in regulating contractile activity. This tissue tends to show more spontaneous activity, suggesting that there is more tone in this region of the bladder wall, which may help to preserve a functional proximal sphincter.

Urethral smooth muscle offers a more complex target for efferent fibres as both contractile cholinergic and sympathetic fibres, as well as relaxatory nitrergic fibres have been demonstrated. The balance of efferent activity that maintains urethral tone in filling and relaxation in voiding remains to be elucidated. Nitric oxide relaxes smooth muscle by generating another intracellular second messenger, cyclic GMP, which reduces the proportion of the contractile protein myosin that is in a state to generate contractile force.

Disorders of micturition

Urinary incontinence occurs when bladder intravesical pressure exceeds intraurethral pressure. Thus, incontinence may arise from abnormally high and uncontrolled bladder pressure or abnormally low urethral pressure. The International Continence Society divides the causes into three broad classes: bladder overactivity; bladder underactivity; and underactive sphincter activity. These classifications are not mutually exclusive and patients often exhibit several pathologies.

Bladder overactivity can result from a neurological deficit (hyperreflexia); low bladder compliance or an overactive detrusor activity (idiopathic detrusor instability). Hyperreflexia results from numerous causes that may reduce inhibitory control from the pontine or higher centres or result in the development of abnormal spinal reflexes, a result of disease or injury to the sacral or sub-sacral cord. Attempts have been made to correlate reduced bladder compliance, as observed during urodynamics, with changes in the degree of fibrosis and collagen content and subtype in the bladder wall. A myogenic component to bladder overactivity has been advanced as the cause of idiopathic detrusor instability whereby the detrusor smooth muscle undergoes abnormal and uncontrolled contractions. The causes of such activity remain unclear and are the subject of research.

Bladder underactivity may also cause incontinence particularly in patients with bladder outflow obstruction. There is a retention of urine such that physical intravesical pressures are raised until they are large enough to overcome the increased outflow resistance and result in ‘overflow’ incontinence. This situation may also arise from neuropathies of bladder sensation and from the more infrequent condition of poor detrusor contractility.

Underactive sphincter: in men, sphincter injury following radical (and less commonly transurethral) prostatectomy, radical surgery for pelvic cancer or pelvic trauma commonly results in incontinence. In women, stress incontinence can result from a number of factors that affect smooth and skeletal muscle tone, the pelvic floor musculature and the relative ability of abdominal pressure changes to affect intravesical and intraurethral pressure. ◆

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Regulation of Fluid and Electrolyte Balance

John C Atherton

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The kidneys match renal excretion to intake of water and electrolytes to regulate the osmolality and volume of body fluids. Deficits of water or electrolytes can be compensated for by increases in intake and retention, whereas excesses are compensated for by increases in urinary excretion. It is usually considered that regulation of water excretion determines osmolality, and regulation of electrolyte excretion (principally NaCl) determines fluid volume, however, regulation of water excretion influences fluid volume and osmolality. For example, an increase in osmolality, through excessive sweating or diarrhoea, triggers water retaining and fluid intake mechanisms such as antidiuretic hormone (ADH) release or thirst to return osmolality to normal and restore body fluid volume.

An increase in dietary NaCl that is sufficient to increase plasma osmolality, activates fluid retaining and intake mechanisms and expansion of volume, but the expansion is restricted to the extracellular fluid (ECF) volume. These simple examples show that NaCl, water intake and the regulation of urinary output determine the osmolality and volume of body fluids. The kidneys are the main route for the excretion of salt and water and have an important role in the control of body fluid osmolality and ECF volume.

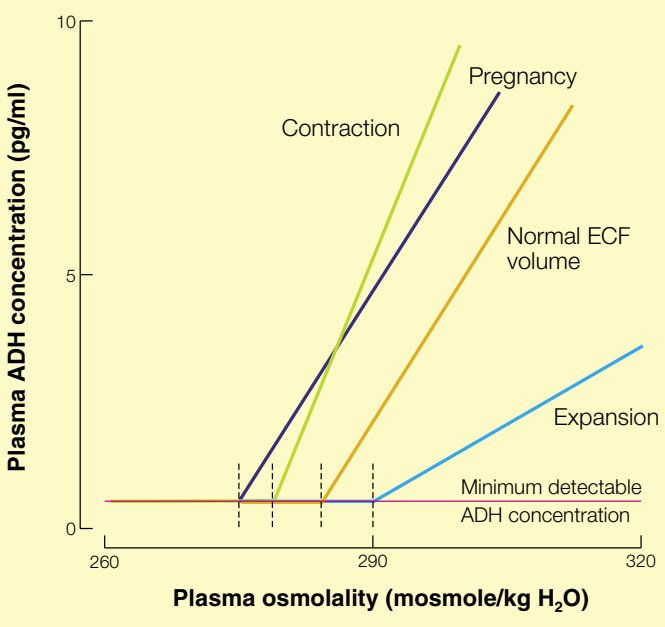
Water balance

Antidiuretic hormone (ADH)

ADH (arginine vasopressin) is a 9-amino acid peptide hormone, synthesized in the magnocellular neurons in the supra-optic and paraventricular nuclei in the anterior hypothalamus, as a 166-amino acid polypeptide. It passes by axoplasmic flow along the hypothalamohypophyseal tract to the posterior pituitary. During its passage along the nerve tract the molecule is cleaved, before storage in secretory granules, as free arginine vasopressin, neurophysin II and glycopeptide.

The main stimuli to ADH secretion are changes in effective plasma osmolality and circulating blood volume. Osmoreceptors in the anterolateral hypothalamus detect changes in effective osmolality to regulate ADH secretion; the set point (osmotic threshold) is 285 mosmole/kg H_2O. Effective osmolality is determined by the extent to which the contributory solute crosses the cell membrane. If cell entry is restricted, the solute (e.g. NaCl) causes cellular dehydration (i.e. it has an effective osmotic effect), whereas solutes (e.g. urea) that readily gain cellular access are less effective in causing cellular dehydration. An increase in effective osmolality of only 1% above the osmotic threshold causes a dramatic and rapid increase in plasma ADH concentration. At plasma osmolality below the osmotic threshold, ADH secretion is minimal (Figure 1).

Effect of ECF volume expansion and contraction on the relationship between plasma osmolality and plasma ADH concentration



The osmotic threshold (---) for antidiuretic hormone (ADH) secretion varies with the state of expansion. In pregnancy the osmotic threshold is reduced by about 10 mosmole/kg H_2O. The osmotic thresholds for the stimulation of thirst are also altered at the different extracellular fluid (ECF) volume expansions (including pregnancy)

1

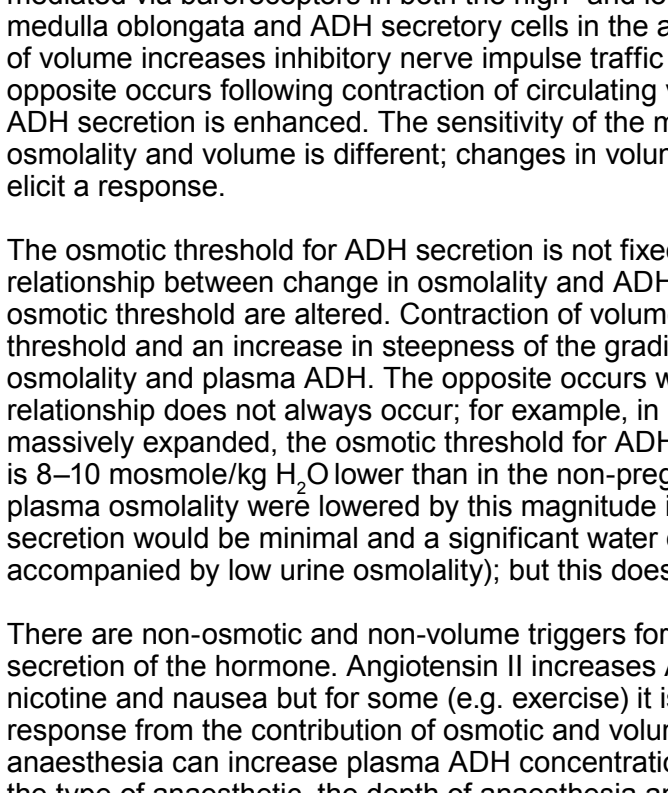
The effects of circulating blood volume and pressure on ADH secretion are reflexly mediated via baroreceptors in both the high- and low-pressure sides of the circulation, medulla oblongata and ADH secretory cells in the anterior hypothalamus. Expansion of volume increases inhibitory nerve impulse traffic and reduces ADH secretion. The opposite occurs following contraction of circulating volume (e.g. haemorrhage) when ADH secretion is enhanced. The sensitivity of the mechanisms for ADH secretion to osmolality and volume is different; changes in volume of about 10% are required to elicit a response.

The osmotic threshold for ADH secretion is not fixed. If ECF volume is altered, the relationship between change in osmolality and ADH secretion (Figure 1) and the osmotic threshold are altered. Contraction of volume is associated with a lower osmotic threshold and an increase in steepness of the gradient for the relationship between osmolality and plasma ADH. The opposite occurs when volume is expanded. This relationship does not always occur; for example, in pregnancy, when ECF volume is massively expanded, the osmotic threshold for ADH secretion (and for thirst sensation) is 8–10 mosmole/kg H_2O lower than in the non-pregnant condition (Figure 1). If plasma osmolality were lowered by this magnitude in the non-pregnant condition, ADH secretion would be minimal and a significant water diuresis manifest (high urine flow accompanied by low urine osmolality); but this does not occur in pregnancy.

There are non-osmotic and non-volume triggers for ADH secretion, but few reduce secretion of the hormone. Angiotensin II increases ADH secretion as does exercise, nicotine and nausea but for some (e.g. exercise) it is difficult to disassociate the response from the contribution of osmotic and volume triggers. Surgery and anaesthesia can increase plasma ADH concentrations; the response is related to the type of anaesthetic, the depth of anaesthesia and the type and extent of surgical intervention. Alcohol inhibits ADH secretion, as does atrial natriuretic peptide (ANP), though this could be ECF volume-mediated.

ADH increases the water permeability of principal cells in the cortical and medullary collecting ducts of the kidney. ADH delivered to the peritubular environment binds to V_2 receptors on the basolateral membrane (Figure 2). This receptor is a member of a family of G-protein-coupled receptor groups (7 membrane- spanning domains) that, once ADH is bound, increases the formation of intracellular cyclic adenosine monophosphate (cAMP) by activation of the enzyme adenylyl cyclase. The increase in cAMP activates another enzyme, phosphokinase A that phosphorylates preformed, inactive water channels (aquaporin 2 channels close to the apical membrane) and this results in their insertion in the apical membrane. Exit of water through the basolateral membrane is facilitated by the presence of aquaporins 3 and 4. When ADH is removed from the receptor, aquaporin 2 water channels resume their original position inside the cell. The rapid insertion of these channels enables rapid and precise changes in the water permeability of the apical membrane of the principal cells and hence corresponding changes in water reabsorption.

Cellular action of antidiuretic hormone (ADH) to increase water reabsorption in a collecting duct principal cell



2

Another action of ADH is to increase urea permeability in medullary collecting ducts but not in late distal tubule or cortical collecting ducts.

The effects of ADH on water and urea reabsorption would be relatively ineffective in the absence of a difference in osmolality or urea concentration across the tubular epithelium favouring their passive movement. That such a gradient exists across cortical collecting ducts for water is a function of the loop of Henle. For urea, establishment of the gradient across medullary collecting ducts depends on the differential effects of the hormone on water and urea permeability in cortical collecting ducts.

Thirst

Changes in ADH secretion are vital to water conservation but are insufficient to maintain water balance. Hypo-osmotic fluid loss (e.g. sweating, diarrhoea) causing dehydration cannot be corrected through increased renal water retention alone. There is always an obligatory water loss to excrete solute (300–400 ml/day) and the kidneys cannot produce water. Thirst centres, located in the anterolateral hypothalamus, respond to changes in plasma osmolality and circulating blood volume. An increase in effective osmolality (e.g. increased NaCl intake) and a decrease in volume (e.g. haemorrhage) elicit the sensation of thirst, but the sensitivity of the mechanism to each stimulus is different. The response to changes in osmolality is initiated by a small (1–2%) increase, whereas a much larger change in circulating volume (8–10%) is required. Changes in volume appear to sensitize the thirst response to changes in osmolality, thus for any given decrease in volume, the thirst response is elicited at lower plasma osmolality (Figure 1).

Angiotensin II exerts a powerful dypsogenic effect via the hypothalamic nuclei; this might be the effective stimulus to thirst in response to changes in circulating blood volume. Blockade of angiotensin II inhibits the response to hypovolaemia, but not completely, suggesting that baroreceptor reflex responses might contribute. Prolactin has also been implicated. Dryness of the pharyngeal mucous membranes elicits the sensation of thirst through nerve reflexes.

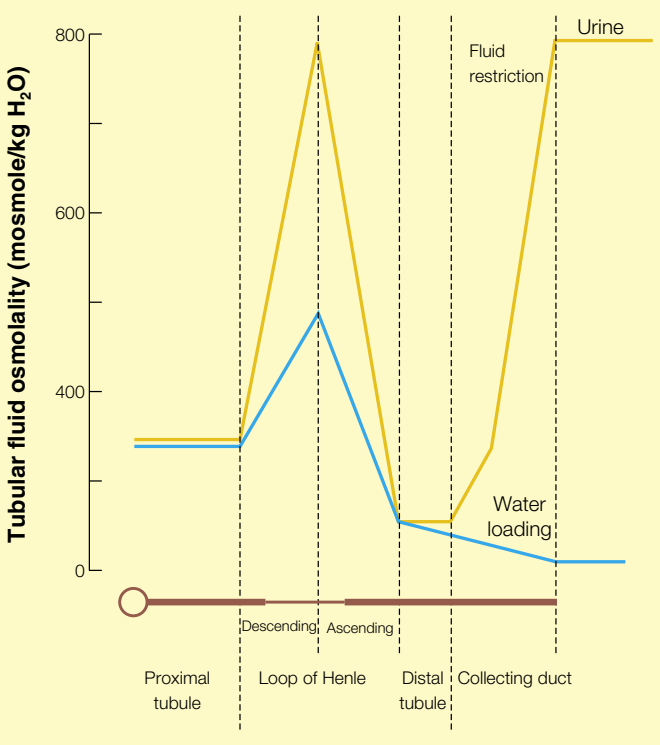
Whatever the stimuli to thirst, corrections in water balance (deficits or excesses) depend on the integrated hypothalamic responses of altered ADH secretion and the sensation of thirst to changes in volume and osmolality of body fluids.

Elaboration of concentrated urine

The osmolality of tubular fluid changes as it moves along the nephron from glomerulus to the terminal part of the collecting duct (Figure 3). Osmolality of fluid leaving the proximal tubule is slightly lower than that of plasma. The descending limb of the loop of Henle is permeable to water, therefore the tubular fluid equilibrates with the increasingly hyperosmotic medullary interstitial fluid such that at the bottom of the loop, deep within the medulla, the osmolality is similar to the maximum osmolality of interstitial tissue fluid at that level in the kidney. As fluid traverses the water-impermeable ascending limb, solute is reabsorbed without water and the tubular fluid becomes increasingly hypo-osmotic to the surrounding interstitial fluid. This occurs along the length of the limb, to such an extent that tubular fluid arriving at the early distal tubule is hypo-osmotic to cortical interstitial fluid. If ADH is present, osmotic equilibration occurs between cortical collecting duct fluid and cortical interstitial fluid. Fluid descends the collecting duct and, if ADH is present, osmotic equilibration occurs with the increasing hyper-osmotic medullary interstitial fluid. Final urine osmolality (maximum 1200–1400 mosmole/kg H_2O) is similar to that of interstitial fluid as tubular fluid leaves the medulla.

This emphasizes another important consequence of the action of ADH on cortical collecting duct water permeability. It reduces the volume flow (ml/min) to medullary collecting ducts, thus avoiding the major dilution of medullary interstitial fluid osmolality that would otherwise occur. Maximum achievable urine osmolality would be reduced. For example, if the glomerular filtration rate (GFR) is 120 ml/min and 85% of the filtrate is reabsorbed before the distal tubule, 18 ml/min fluid with an osmolality about 100 mosmole/kg H_2O would be delivered to the cortical collecting duct. In the presence of ADH, fluid leaving will have equilibrated with cortical interstitial fluid (about 300 mosmole/kg H_2O), thus only 6 ml/min would enter the medullary collecting duct. In the absence of ADH this would increase to 18 ml/min and tubular fluid osmolality would be lower.

Changes in tubular fluid osmolality along the nephron during water restriction and water loading



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Urine osmolality in humans loaded with water (15–25 ml/kg body weight) to suppress endogenous ADH secretion (water diuresis) can be as low as 30–35 mosmole/kg H_2O. In these conditions, medullary interstitial fluid osmolality is lower and osmotic equilibration across cortical and medullary collecting ducts does not occur (Figure 3). Volume flow to collecting ducts is high and final urine osmolality reflects the hypo-osmolality of fluid leaving the loop of Henle and the extent of electrolyte reabsorption without water in these nephron segments. The absolute (but not fractional) amount of water reabsorbed across collecting ducts is greater in the absence of ADH than when ADH is present. This contributes to the lower medullary interstitial fluid osmolality and would decrease urine flow, but the effect on urine osmolality would not be great because of high volume flow to collecting ducts.

The two reasons why urine with high osmolality can be elaborated are the existence of a hyperosmotic medullary interstitial fluid and the action of ADH on the water permeability of the collecting ducts, which facilitates osmotic equilibration between tubular fluid and the surrounding interstitial fluid.

Countercurrent multiplication mechanism in the loop of Henle

The basic operation of this countercurrent multiplication mechanism is widely known, but some of the fine detail needs to be resolved. It involves two simple steps:

- movement of solute without water out of the ascending limb of the loop of Henle
- flow in opposite directions in ascending and descending limbs of the loop of Henle.

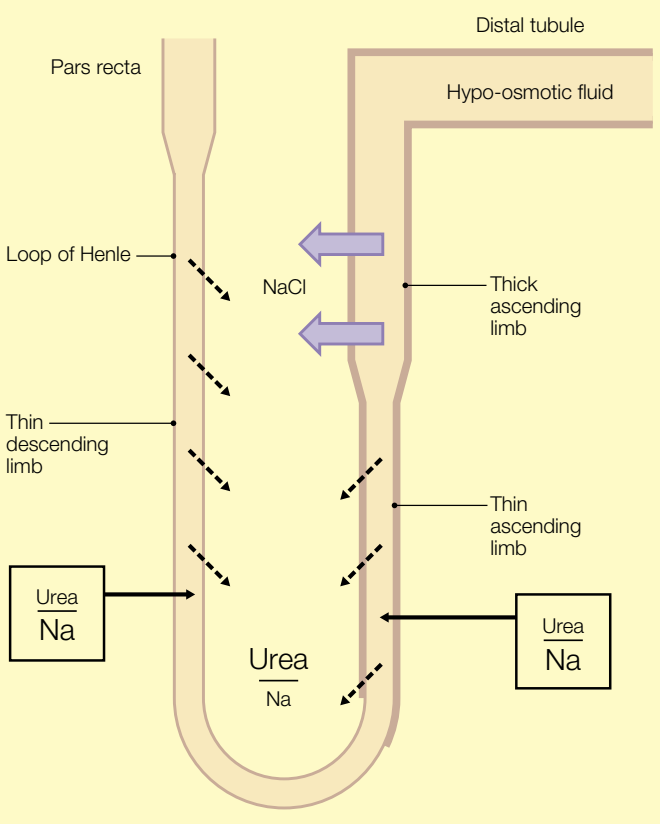
The consequence of the first step is that for any level between the limbs of the loop there is osmotic concentration of fluid in the descending limb (and medullary interstitial fluid) by solute addition to and/or water removal from the descending limb. The second step multiplies this single osmotic effect.

Given that these two steps are operative, it follows that there will be an axial gradient of hyperosmolality within the medulla, with the highest values being at the medullary tip. The steepness of the gradient generated depends on the length of the loop relative to kidney size. In normal antidiuretic conditions, major contributions to this gradient are NaCl (about 45%) and urea (about 45%) with smaller contributions from K^+ and NH_4^+ and their attendant anions. In diuretic conditions, medullary interstitial fluid osmolality is lower but still hyperosmotic. The reduction is a consequence of almost complete dissipation of the urea concentration gradient with smaller contributions from changes in concentrations of NaCl and other electrolytes.

The single osmotic effect in the thick ascending loop of Henle is active reabsorption of Na^+ accompanied by Cl^- but without water into medullary interstitial fluid (Figure 4). If this were the only transport process involved, the osmotic gradient generated would not be continuous from the corticomedullary boundary to the tip of the medulla. The maximum value would be detected at the level of the thick ascending limb and would determine the NaCl concentration at the tip of the medulla by passive transverse movement through the interstitial fluid. The main problem is the failure to demonstrate active Na^+ transport in the thin ascending limb. However, the single osmotic effect in the thin ascending limb may be passive Na^+ movement down a concentration gradient, the magnitude of which is determined by the contribution of urea to the hyperosmotic environment. The greater the contribution of urea, the steeper the gradient favouring passive Na^+ movement, and descending limb fluid being concentrated principally by fluid abstraction rather than solute addition – this limb appears to have limited permeability to Na^+ and urea.

Fluid delivered to the ascending limb has a higher Na^+ concentration than medullary interstitial fluid, thereby facilitating passive Na^+ reabsorption. The single osmotic effect occurs at all levels of the ascending limb, therefore multiplication of this effect generates an increasing Na^+ concentration gradient from the corticomedullary boundary to the tip of the medulla. Although these mechanisms focus on Na^+ movement accompanied by Cl^- as the single osmotic effect, any electrolyte reabsorbed from the ascending limb contributes to the effect of countercurrent multiplication. For example, corticomedullary concentration gradients for K^+ and NH_4^+ are presumably a consequence of their reabsorption by Na^+-K^+-$2Cl^-$ transporters in the thick ascending limb apical membranes and concentration in descending limb fluid.

Components of the countercurrent multiplication system in the loop of Henle



The ratio of urea:Na^+ represents their relative contributions to fluid (tubular and interstitial) fluid osmolality. Fluid in the descending limb is progressively concentrated by passive water abstraction, resulting in the delivery of fluid with a higher Na^+ concentration than in medullary interstitial fluid to the ascending limb

Key: ◂- - - passive water or sodium reabsorption, ⇦ active transport

4

Countercurrent exchange mechanism in the vasa recta capillaries

The arrangement of the capillaries in tissues other than renal medullary tissue is such that any interstitial fluid hyperosmolality generated would soon be dissipated. In the renal medulla the vasa recta capillaries form parallel hairpin loops that enable them to function as countercurrent exchangers. Since all capillaries are freely permeable to solutes and water, plasma entering the medulla in descending limbs is encountering regions of higher osmolality; osmotic equilibration occurs by water loss and solute addition. This continues along the length of the descending limb so that plasma at the hairpin bend is quite viscous (due to the concentration of proteins) and is at an osmolality similar to the hyperosmotic surroundings. The reverse occurs as plasma moves along the ascending limbs to leave the medulla; water enters from and solutes leave the capillaries to the hypo-osmotic interstitial fluid and plasma protein concentration decreases. The net effect is that water entry into the medullary tissue is restricted by short-circuiting across the bases of vasa recta capillaries from descending to ascending limbs whereas solutes move in the opposite direction and are retained in medullary tissue. It follows that volume flow of plasma decreases down the descending limb and increases up the ascending limb. This lower flow rate in the medulla is essential to allow osmotic exchange. A possible ADH-induced constriction of medullary vessels would reduce vasa recta blood flow and contribute to the efficiency of countercurrent exchange.

If plasma flow rate increases, the time for osmotic exchange reduces, more plasma water enters and more solutes leave the medulla with the results that medullary interstitial fluid osmolality decreases, less water is reabsorbed from the medullary collecting ducts, and less concentrated urine of increased volume is excreted. There is a limit to the effect of decreasing flow on medullary hyperosmolality. If blood flow is reduced to the extent that there is insufficient oxygen delivery to active transport sites, especially in the thick ascending limb, tubular transport is impaired, as is the generation of medullary interstitial fluid hyperosmolality.

Control of Na^+ excretion and ECF volume

Under normal conditions, the kidneys maintain ECF volume relatively constant by matching Na^+ excretion to dietary Na^+ intake. However, if changes in dietary Na^+ intake are not accompanied by changes in Na^+ excretion the osmotic stimulus is altered to increase or decrease water retention with a corresponding increase or decrease in ECF volume. Correction for changes in ECF volume could be effected by changes in Na^+ excretion through changes in the filtered load and/or reabsorption of Na^+.

ECF volume may be compromised by changes in Na^+ balance. If Na^+ excretion increases, an equivalent change in water excretion ensues and ECF volume contracts. Even small changes in Na^+ excretion produce a significant effect. For example, for a small increase in Na^+ excretion from 1% to 4% of the filtered load, the additional Na^+ loss will be about 700 mmole/day (GFR and plasma Na^+ are, respectively, 0.12 litre/min and 140 mmole/litre). If this were iso-osmotic salt loss, an additional 5 litre of ECF volume would be excreted.

ECF volume consists of extravascular and intravascular fluid components.
The circulating intravascular volume component is the important trigger for the compensatory mechanisms because it should reflect volume, pressure and flow within the circulatory system. In health, there is a direct correlation between ECF volume and vascular volume perfusing tissues but there are conditions in which this correlation does not apply. For this reason the effective circulating volume is used to describe the variable that triggers compensatory mechanisms.

Changes in effective circulating volume are detected by volume (stretch) receptors in the low-pressure (atrial and pulmonary receptors) and high-pressure (aortic arch and carotid sinus receptors) sides of the circulation. Low-pressure receptors transmit inhibitory nerve impulses via the vagus nerve to the tractus solitarius nucleus in the medulla oblongata, as do high-pressure receptors via afferent nerve fibres in the vagus and glossopharyngeal nerves. Efferent nerve activity from this nucleus modifies ADH secretion and sympathetic nerve activity. The renal juxtaglomerular apparatus in renal afferent and efferent arterioles is another high-pressure receptor sensing hydrostatic pressure.

Renal control of Na^+ and water reabsorption

Reabsorption of Na^+ and water at different nephron segments is discussed elsewhere.

Renal sympathetic nerve activity mediates its effect in three ways.

- Stimulation of α-adrenergic receptors on vascular smooth muscle of afferent and efferent arterioles to reduce GFR (afferent arteriole constriction appears to be the dominant effect and glomerular hydrostatic pressure is reduced).
- β-adrenergic stimulation of juxtaglomerular cells to stimulate renin secretion.
- α-adrenergic stimulation of Na^+ reabsorption at most nephron segments with the quantitatively important effect on proximal convoluted tubules.

Renin–angiotensin–aldosterone: stimuli to renin secretion include β-adrenergic stimulation of juxtaglomerular cells, reduced perfusion pressure in afferent arterioles and reduction in Na^+ load arriving at macula densa cells in distal convoluted tubules. Renin is a proteolytic enzyme that cleaves angiotensinogen (an α-globulin produced in the liver) to form the decapeptide angiotensin I. Angiotensin I has no known physiological function. However, further cleavage results in the formation of the octapeptide angiotensin II by angiotensin-converting enzyme found on the surface of vascular endothelial cells in pulmonary and renal capillaries.

Angiotensin II has at least five actions important in the regulation of ECF volume:

- as a powerful vasoconstrictor it affects afferent and efferent arterioles to decrease GFR and increases blood pressure through its systemic vascular action
- proximal tubule reabsorption of Na^+ and water is increased
- ADH release is increased with effects on water reabsorption
- thirst sensation is enhanced
- secretion of the mineralocorticosteroid hormone, aldosterone from the zona glomerulosa of the adrenal cortex is increased.

Aldosterone increases Na^+ reabsorption from principal cells in cortical collecting ducts by increasing the synthesis of proteins that increase the number of Na^+ selective protein channels in the apical membrane, increase the number of active Na^+ pumps (Na^+-K^+ ATPase) in the basolateral membrane or increase the available ATP as energy source for the Na^+ pumps.

Atrial natriuretic peptide is a hormone produced in atrial myocytes in response to expansion of circulating volume (increased atrial stretch, increased atrial pressure). Its actions are, in general, opposite to those of the renin–angiotensin–aldosterone axis. They include relaxation of afferent arteriolar smooth muscle to increase GFR and Na^+ reabsorption inhibition, either directly by blocking Na^+ selective channels in apical membranes of inner medullary collecting duct cells, or by decreasing renin secretion and hence the Na^+-retaining actions of angiotensin II and aldosterone.

Challenges to effective circulating volume

Small changes in GFR (e.g. changes in posture or exercise) lead to large changes in filtered load that could cause excessive urinary Na^+ (hence water) loss and a significant contraction of volume. For example, an increase in GFR of only 3% increases the filtered load by over 700 mmole/day, which, if not compensated for, leads to loss of about 5 litres ECF volume. That this does not happen is primarily a direct consequence of glomerulotubular balance and autoregulation of GFR. These compensatory mechanisms maintain the Na^+ load delivered to the nephron distal to the proximal tubule, particularly those sited in the late distal tubule and collecting duct.

Autoregulation of GFR ensures that changes in GFR in the face of changes in perfusion pressure and renal blood flow are of short duration. Glomerular–tubular balance is the balance between the filtered load and proximal tubule reabsorption. A constant fraction (about 70%) of the filtered load is reabsorbed in the face of changes in GFR thereby minimizing changes in the amount delivered to the loop of Henle. The mechanisms responsible focus on changes in Starling forces operating across peritubular capillaries and their effect on reabsorption. If GFR increases and RPF is unchanged (afferent arteriole dilatation, efferent arteriole constriction), filtration fraction increases, as would plasma colloid osmotic pressure (π_C), but peritubular capillary pressure (P_C) decreases. Net fluid uptake into the capillaries is enhanced as filtration fraction increases.

Load dependency of reabsorption in the thick ascending limb and distal tubule also contribute to constancy of Na^+ delivery to the collecting duct. This is necessary to avoid swamping aldosterone-sensitive Na^+-retaining mechanisms in this part of the nephron, thereby avoiding excessive loss of Na^+ and water.

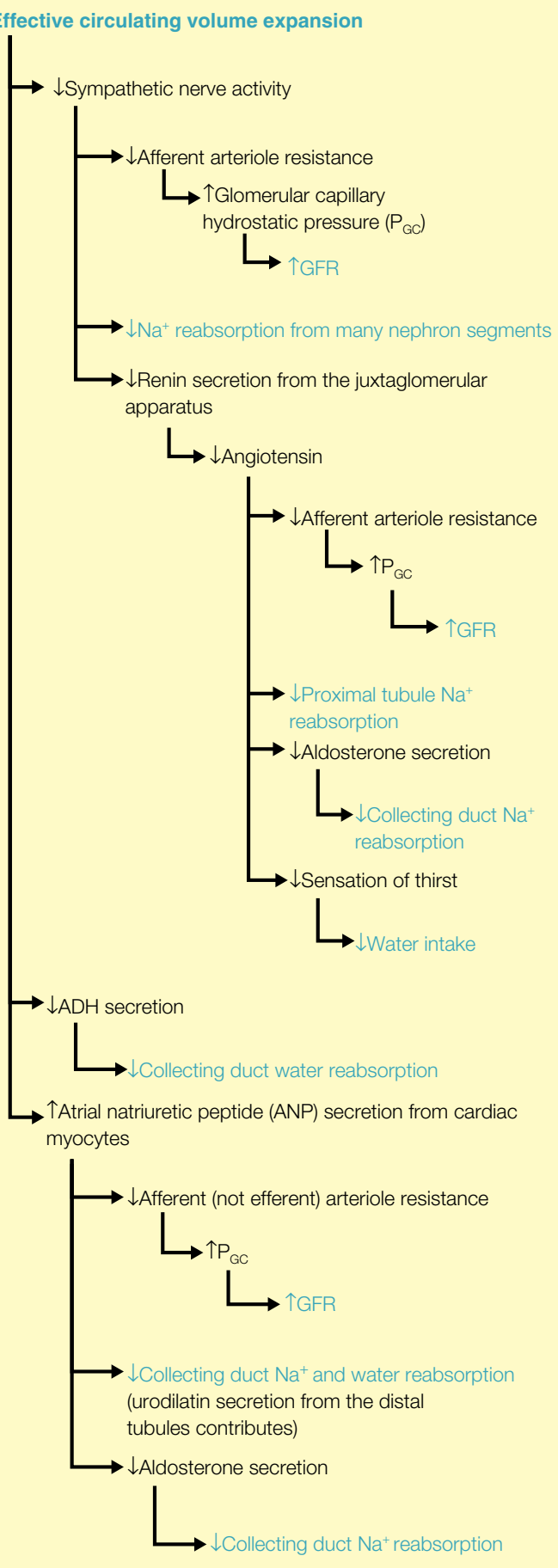
Renal response to ECF volume expansion and contraction

The mechanisms that compensate for changes in ECF volume are illustrated in Figures 5 and 6. In addition to these compensatory mechanisms, volume expansion dilutes plasma proteins and increases hydrostatic pressure in glomerular capillaries. Both contribute to the increase in GFR and to changes in the peritubular capillary environment, which has a direct effect on proximal tubule Na^+ and water reabsorption. Therefore, there is an increase in P_C (due also to a volume expansion-induced increase in venous pressure) and a decrease in π_C with the result that proximal tubule reabsorption is reduced. In contrast, volume contraction is accompanied by decreased hydrostatic pressure in the glomerular capillaries (and decreased venous pressure), which is transmitted to the peritubular capillaries with the effect that fluid uptake from the interstitial fluid (reduction in P_C) is increased and proximal tubule reabsorption is stimulated.

The paradox highlighted here is that volume-induced changes in GFR are accompanied by altered proximal tubular reabsorption that is opposite to changes accompanying spontaneous changes in GFR. Thus, during volume expansion, GFR is increased but proximal tubule reabsorption is decreased; for spontaneous increases in GFR, proximal tubule reabsorption is enhanced. The converse applies to volume contraction. The reasons for these differences are obscure, but it appears that volume expansion or contraction overrides mechanisms responsible for glomerular–tubular balance and autoregulation of GFR.

The overall effect of volume expansion is an increase in GFR and filtered load accompanied by reduced Na^+ and water reabsorption from almost all parts of the nephron with the result that fractional Na^+ and water excretion increase and volume is restored to normal. For volume contraction, reductions in GFR and filtered load are associated with enhanced Na^+ and water reabsorption from almost all parts of the nephron to the extent that Na^+ is almost absent from the urine. These changes, plus any associated increases in fluid intake, restore the volume.

Compensatory mechanisms for extracellular fluid (ECF) volume expansion



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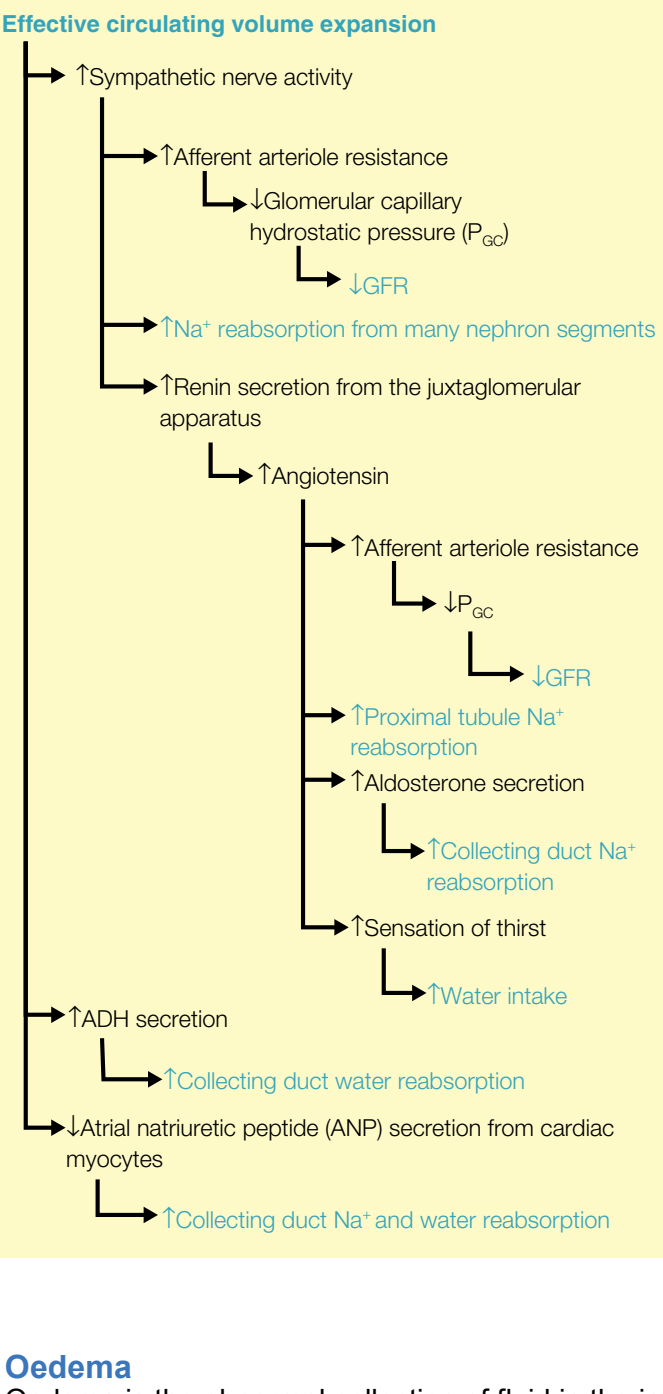
Compensatory mechanisms for extracellular fluid (ECF) volume contraction



6

Oedema

Oedema is the abnormal collection of fluid in the interstitial fluid. Changes in Starling forces operating across capillary walls are responsible. Net movement of fluid = $K_f((P_C - P_I) - (\pi_C - \pi_I))$, where: K_f is the ultrafiltration coefficient; P and π are hydrostatic pressure and colloid osmotic pressure, respectively, in the capillaries (C) and interstitium (I). Any clinical condition that leads to an increase in K_f and/or P_C or a decrease in π_C leads to accumulation of fluid in the interstitial space.

Changes in Starling forces alone are responsible for localized oedema. For example, in deep vein thrombosis increased P_C occurs as a result of restriction of venous outflow. In inflammatory responses, P_C and K_f are increased. Generalized oedema is associated with a more complicated pathogenesis arising from liver malfunction, cardiac insufficiency or abnormal renal function and includes significant contribution from excessive renal Na^+ and water retention as well as changes in Starling forces.

In liver failure and abnormal loss of protein in the urine (nephrotic syndrome) plasma protein concentration declines (decreased π_C) with a continuous loss of fluid to the interstitial space. This loss is self-limiting because as fluid accumulates, an increase in P_I and a decrease in P_C occur to the point where there is no further fluid loss. Total ECF volume does not change, but loss of fluid from the vascular compartment (about 2–3 litres before it is clinically detectable) is such that cardiac output and blood pressure decrease to the point where compensatory changes are initiated in an attempt to restore circulating volume (decreased GFR and increased Na^+ and water retention by the mechanisms described above). This additional renal Na^+ and water retention contributes to the oedema by this positive feedback loop.

Cardiac insufficiency leading to increased venous pressure (hence increased P_C) in either or both the systemic or pulmonary circulation causes systemic or pulmonary oedema. If the cardiac insufficiency is such that cardiac output and blood pressure are reduced, renal compensatory mechanisms are triggered (retention of Na^+ and water). In terms of total ECF volume this is a false signal; total vascular volume might be unchanged but the true signal (effective circulating volume) is reduced. The additional Na^+ and water retention contribute to the oedema, but if untreated, contribute to cardiac insufficiency.

Treatment of generalized oedema can be dietary and/or by prevention of Na^+ and water retention. Reduction in dietary Na^+ limits the amount of Na^+ and water that can be retained and therefore limits the oedema. Diuretic-induced inhibition of Na^+ reabsorptive mechanisms limits retention by increasing Na^+ and water loss. ◆

FURTHER READING

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Renal Blood Flow, Glomerular Filtration and Plasma Clearance

John C Atherton

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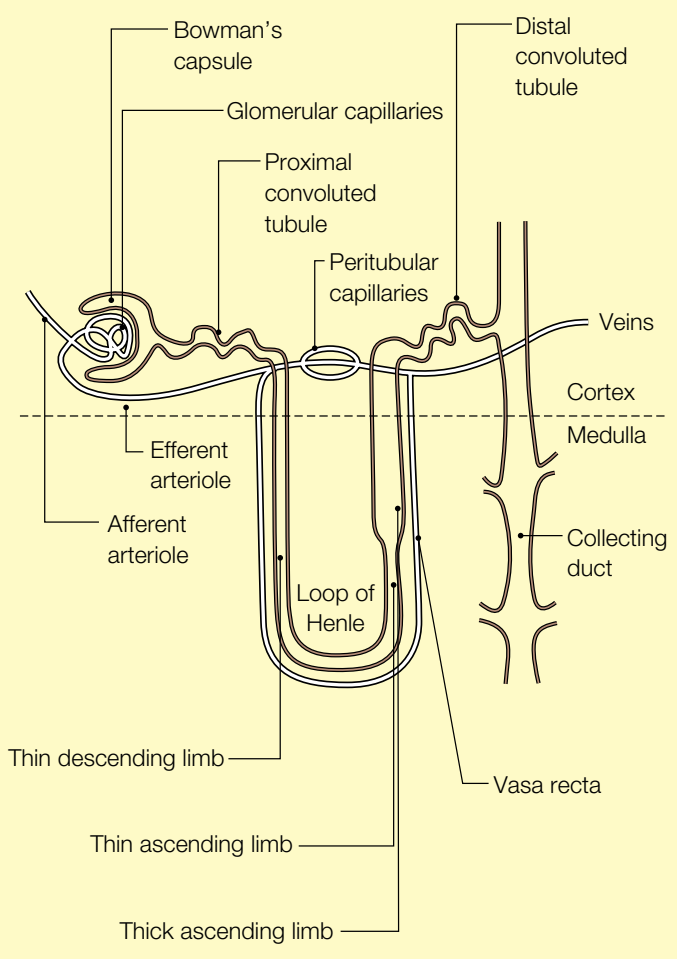
Normal functioning of the kidneys to subserve homeostasis and excretion of metabolic waste products depends on: an adequate blood supply; production of an ultrafiltrate of plasma; and the ability to modify the composition of the filtrate through reabsorption from and secretion into the tubule.

About 25% of cardiac output (> 1 litre/min) is directed to the kidneys, but the distribution is not uniform. Almost 100% supplies the cortex, through the glomerular capillaries and peritubular capillaries that surround the proximal and distal convoluted tubules (Figure 1). Only about 10% enters the medulla, of which less than 3% reaches the inner medulla. Renal plasma flow is 600–650 ml/min of which 100–140 ml/min is filtered (glomerular filtration rate (GFR)) across the glomerular capillary wall into Bowman's space. The magnitude and selectivity of the filtration process is possible because of the arrangement of the capillaries within Bowman's space, the structure of the capillary wall, and the visceral epithelial layer (podocytes) of Bowman's capsule with which it is in intimate contact (Figure 2a).

The three main barriers (Figure 2b) to filtration are: the fenestrated capillary endothelium with pores (diameter 70 nm) that acts as a gross filter preventing the passage of blood cells; the basement membrane consisting of a porous matrix of extracellular proteins; and an epithelial layer with podocytes and foot-like processes (pedicels) that surround the glomerular capillaries. Thin membranous sheets containing pores (4 nm by 14 nm) span the gaps (filtration slits, width 25–60 nm) between the pedicels.

The nephron and its blood supply



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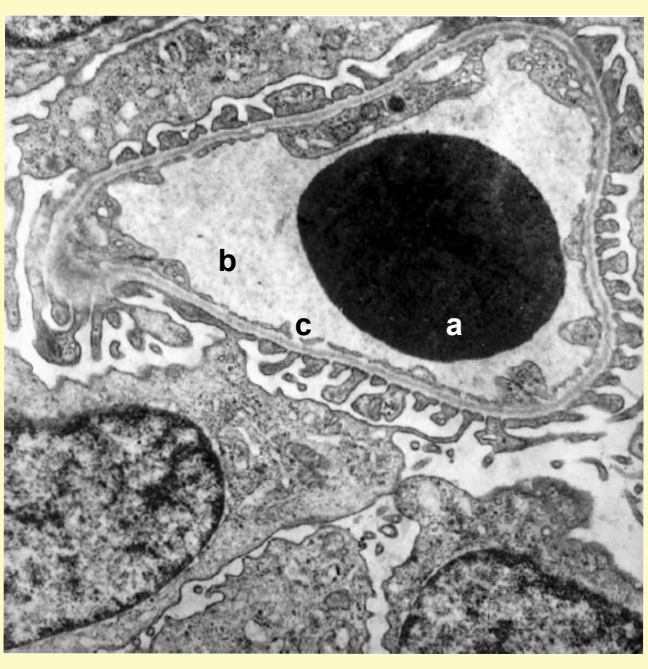
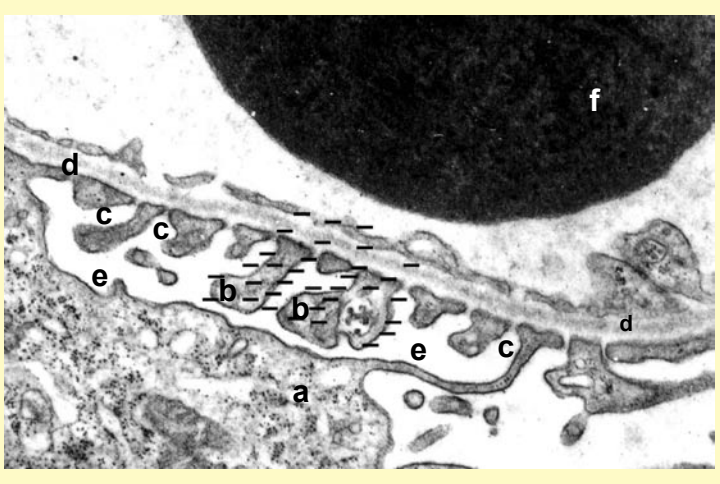


2a Electron micrograph (x 24,000) through a glomerular capillary and surrounding podocytes
a red blood cell; **b** capillary lumen;
c endothelial cells.



2b Area of fenestrated glomerular capillary wall (x 70,000)
a podocyte
b pedicels
c filtration slits
d basement membrane
e Bowman's space
f red blood cell.
Negative charges on the pedicels, basement membrane and endothelial cells are indicated by bars.

The passage of large molecules is limited, but haemoglobin (molecular diameter 6.5 nm) and some small plasma proteins (e.g. albumin; molecular diameter about 7 nm) can pass through the filtration barrier, albeit in small amounts. However, electrostatic charge is as important as the size and shape of the molecule. In general, neutral molecules with a molecular diameter less than 4 nm are freely filtered, but molecules (irrespective of charge) with diameters exceeding 8 nm are not filtered. Between 4 and 8 nm diameter the extent of filtration depends on size and charge. This can be explained by the presence of negatively charged glycoproteins on the filtration barriers (Figure 2b). Thus, for molecules of similar size but opposite charge, cationic molecules pass more readily through the barrier; but negatively charged plasma proteins with molecular diameters less than 8 nm do not pass easily.

Mesangial cells found between capillaries within the glomerular tuft have at least three important functions in the filtration process. They exhibit contractile properties, thereby influencing the surface area over which ultrafiltration occurs. They have a structural role in the glomerular tuft and can secrete extracellular matrix. They are actively phagocytic, preventing accumulation within the extracellular matrix of macromolecules that have escaped through the basement membrane of the capillaries (i.e. they keep the filter clean). They also secrete prostaglandins and cytokines that may enhance the inflammatory response to invasion of the extracellular matrix by immune complexes (the basement membrane surrounds only part of the glomerular capillaries).

Forces involved in ultrafiltration

Forces involved in the formation of an ultrafiltrate of plasma are the Starling forces operating across the glomerular capillary wall (Figure 3). Forces that promote fluid movement out of the glomerular capillary are hydrostatic pressure in the glomerular capillary (P_{GC}) and colloid osmotic pressure in Bowman's space (π_{BS}). The forces that oppose fluid movement from the glomerular capillary are colloid osmotic pressure (π_{GC}) and intrarenal pressure (mainly hydrostatic pressure in Bowman's space (P_{BS})). Thus, net ultrafiltration pressure can be represented as $(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})$. However, since large protein molecules do not traverse the glomerular capillary wall, π_{BS} can be discounted. Hence, net ultrafiltration pressure and fluid movement out of the capillary (GFR) equal $P_{GC} - (P_{BS} + \pi_{GC})$ and $K_f (P_{GC} - (P_{BS} + \pi_{GC}))$, respectively, where K_f is the ultrafiltration coefficient that takes account of the surface area of the glomerular capillary as well as the permeability per unit of surface area.

At the afferent arteriolar end of the capillary, net ultrafiltration pressure is about 10–15 mm Hg. The ensuing fluid movement without significant protein movement results in a rise in π_{GC}; net ultrafiltration pressure is reduced. Fluid moves out of the capillary until the forces promoting and opposing fluid movement from the capillary are equal. At this point (ultrafiltration pressure equilibrium) fluid movement from the capillary ceases. It is thought that this equilibrium is reached in some species (e.g. rat) but not in others (e.g. humans).

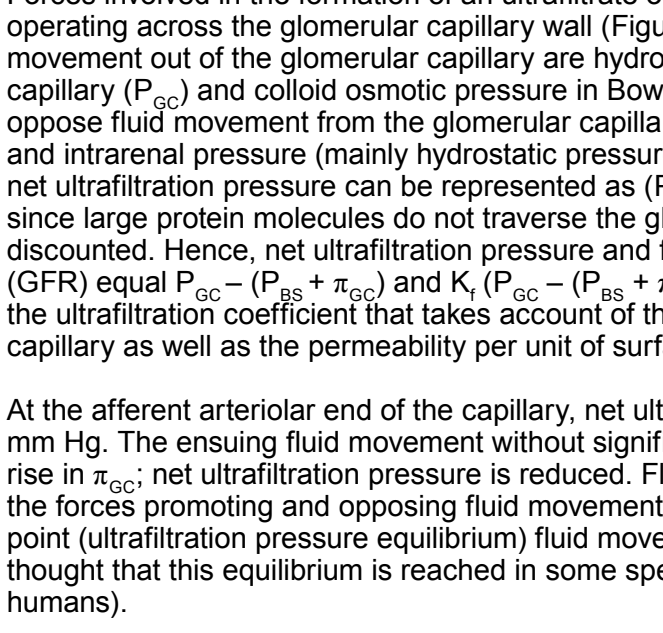
The relationship between these forces operating across a glomerular capillary is different from a systemic capillary. Hydrostatic pressure declines along the length of the systemic capillary and there is no difference between the colloid osmotic pressure at the arterial and venous ends of the capillary. Fluid moves out of the capillary at the arteriolar end into the capillary at the venous end; fluid always moves out of the glomerular capillary. The reason for this difference is primarily because the glomerular capillary is in series with the afferent and efferent arterioles; the balance of vascular resistances is such that only a small decline in hydrostatic pressure occurs along the length of the glomerular capillary.

Factors influencing GFR

Changes in GFR can be mediated by changes in K_f and/or changes in the Starling forces.

Renal plasma flow (RPF) is also an important determinant of GFR. The arrangement of the glomerular capillaries, in series between two sets of arterioles, the resistances of which can be changed independently, means that it is possible to produce changes in GFR that are both in parallel to and divergent from changes in RPF (Figure 4). As flow along the glomerular capillary increases, the difference between P_{GC} and π_{GC} does not decrease at the same rate as at lower flow (Figure 3); the increase in π_{GC} is smaller and therefore net ultrafiltration pressure is greater at all points along the capillary; ultrafiltration pressure disequilibrium at the efferent arteriolar end of the capillary is greater. The opposite changes occur if both afferent and efferent arterioles constrict.

Starling forces and ultrafiltration along a glomerular capillary



P_{GC} and P_{BS}, hydrostatic pressure in glomerular capillary and Bowman's space, respectively; π_{GC}, colloid osmotic pressure on glomerular capillary plasma

3

Effect of changing renal arteriole resistance

Afferent arteriole resistance	Efferent arteriole resistance	Renal plasma flow	Glomerular capillary pressure	Glomerular filtration rate
Decreased	Unchanged	↑	↑	↑
Unchanged	Decreased	↑	↓	↓
Unchanged	Increased	↓	↑	↑
Increased	Unchanged	↓	↓	↓
Decreased	Decreased	↑	↔	↑
Increased	Increased	↓	↔	↓

Changes in sympathetic nerve activity – renal nerves and the adrenal medulla affect afferent and efferent arteriolar resistance by α-adrenoceptor-mediated vasoconstriction, mainly on the afferent arteriole. Moderate stimulation lowers RPF without an equivalent change in GFR, suggesting that vasoconstriction of the efferent arteriole is the predominant effect. More intense stimulation of renal sympathetic nerves (e.g. following severe haemorrhage) dramatically reduces RPF and GFR, suggesting powerful and equivalent changes in resistance in afferent and efferent arterioles.

Angiotensin II – the effects of this vasoconstrictor depend on the plasma concentration; efferent arterioles are more sensitive than afferent arterioles. At low concentrations any reduction in RPF may not be accompanied by an equivalent change in GFR whereas at high concentrations both RPF and GFR are lower.

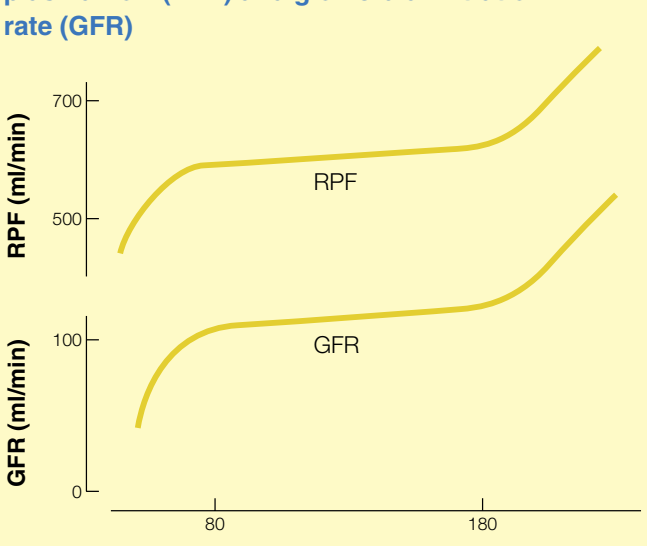
The endothelial cells lining the renal arterioles produce a number of autacoids that have important vasodilator or vasoconstrictor actions. Endothelin has powerful vasoconstrictor effects on the afferent and efferent arterioles, which reduces RPF and GFR. These cells may also have angiotensin-converting enzyme on their cell surface thereby converting angiotensin I, produced systemically or locally, to angiotensin II. Nitric oxide, released from endothelial cells, has significant vasodilator effects causing increases in RPF and GFR. Prostaglandins (PGE_2, PGI_2) produced locally, vasodilate afferent and efferent arterioles to increase RPF (not GFR), but their effects are manifest only during intense sympathetic nerve vasoconstrictor activity. Their primary role is to modulate the powerful vasoconstriction and therefore to protect the kidney from renal ischaemia.

Other hormones are implicated in the control of RPF and GFR in pathophysiological conditions but their role in normal regulation has yet to be defined. Examples are direct vasodilator (dopamine, atrial natriuretic peptide) or vasoconstrictor (adenosine) effects on afferent and/or efferent arterioles or in-direct effects via the release of nitric oxide from the endothelial cells (bradykinin, ATP, histamine).

Mesangial cells may also be involved in the regulation of RPF and GFR; their contractile elements respond to autacoids in a similar way to arteriolar smooth muscle cells. They might influence GFR by controlling flow through glomerular capillaries and by affecting the surface area available for ultrafiltration (an important determinant of K_f).

Autoregulation (Figure 5) – kidneys regulate blood flow by adjusting vascular resistance to changes in perfusion pressure (blood pressure): renal blood flow = perfusion pressure/renal vascular resistance. Within 80–200 mm Hg, increments in blood pressure are not accompanied by significant changes in RPF or GFR. The myogenic feedback mechanism ensures that when blood pressure rises the ensuing stretching of muscle instigates contraction of the muscle and RPF and GFR are relatively constant. The tubuloglomerular feedback mechanism depends on the macula densa sensing tubular flow (or some function of changing flow such as changing sodium load). This sensing mechanism initiates a sequence of events leading to altered afferent arteriolar resistance. If GFR increases, flow past the macula densa increases, the afferent arteriole constricts and RPF and GFR decrease. The converse occurs when GFR declines. This maintains constancy of the filtered load delivered to the reabsorptive sites.

Relationship between renal arterial pressure, renal plasma flow (RPF) and glomerular filtration rate (GFR)



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Renal clearance measurements

Renal clearance of a solute (C_x) is defined as the volume of plasma passing through the kidneys from which all the solute has been removed and excreted in the urine in unit time. Thus $C_xP_x = U_xV$, where: C_x is clearance of solute x, U_x and P_x are the urinary and plasma concentrations of x; and V is urine flow rate. Hence $C_x = U_xV/P_x$.

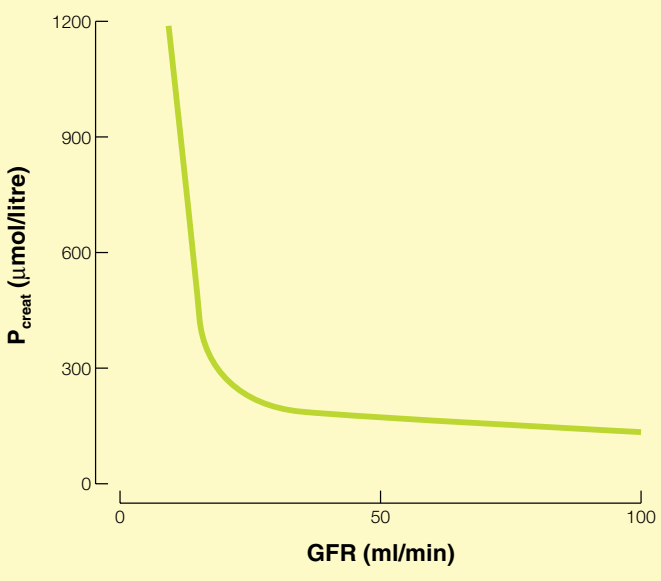
Measuring RPF: to apply this principle to measurement of RPF it is essential to identify a solute that is completely removed from the plasma as it flows through the kidney (i.e. it is filtered and secreted to the extent that the renal venous concentration of the solute is zero) and it is not metabolized in the kidney. The amount delivered to the kidney equals the amount excreted ($RPF.P_x = U_xV$). Such a solute is p-aminohippuric acid (PAH) but it is not endogenous and has to be administered. The kidney excretes this organic acid by ultrafiltration and by a proximal tubular anion secretory mechanism that can actively transport up to a maximum amount per minute (i.e. it can be saturated). When the plasma concentration increases, the amount delivered to the transport sites increases, the transport maximum may be exceeded and renal venous plasma concentration will not be zero. Use of C_{PAH} to measure RPF will not be valid in these circumstances unless both systemic plasma and renal venous PAH concentrations are measured. It is important, therefore, that the secretory transport mechanism is not saturated.

RPF is calculated as $C_{PAH} = U_{PAH}V/P_{PAH}$. However, even at low plasma PAH concentrations, a small amount of PAH escapes secretion because some of the tissues perfused do not possess PAH secretory mechanisms. Measurement of C_{PAH} is referred to as the effective renal plasma flow (ERPF) – plasma flow through renal tissues that effectively remove PAH from the plasma passing through. This assumption underestimates the RPF by about 10%.

Measuring GFR: to apply this principle to measurement of GFR it is essential to identify a solute that is freely filtered and excreted unchanged. Thus, amount filtered = amount excreted ($GFR.P_x = U_xV$). Such a solute is inulin; a polysaccharide of fructose that is not endogenous so has to be administered. GFR is calculated as $C_{inulin} = U_{inulin}V/P_{inulin}$. Inulin has to be administered intravenously over several hours to achieve steady-state plasma concentrations before accurate measurements of GFR can be obtained. For this reason, endogenous plasma creatinine (derived from the muscle protein creatine) and 24-hour urinary creatinine measurements are used instead but they have the disadvantage that some creatinine is secreted by organic cation secretory mechanisms in the proximal tubule. It is usually claimed that this overestimate of GFR is 'balanced' by the error in measuring plasma creatinine that is high owing to the presence of non-specific chromogens. Some data indicate that creatinine clearance can overestimate GFR by 10–30% suggesting that tubular secretion might make a more significant contribution to excreted creatinine.

Plasma creatinine concentration alone is used to assess kidney function in the clinical setting. This might detect significant changes in GFR, but small changes could pass unnoticed. Creatinine production is relatively constant and must equal excreted creatinine if plasma creatinine is to remain constant (i.e. creatinine production = $GFR.P_{creat} = U_{creat}V$). If GFR decreases, a transient decrease in $U_{creat}V$ occurs and P_{creat} increases until equality of production and output is re-established at the lower GFR. Therefore, with a continual chronic reduction in GFR, plasma creatinine concentration increases exponentially (i.e. an initial small reduction in GFR produces only a small increase in plasma creatinine concentration). Only when there is a relatively large reduction in GFR will plasma creatinine increase dramatically (Figure 6).

Hyperbolic relationship between glomerular filtration rate (GFR) and plasma creatinine concentration (P_{creat})



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Renal clearance is not restricted to measurement of GFR, RPF and filtration fraction (GFR/RPF). Renal clearances of any solute can be measured and, when compared with GFR, its handling by the kidney can be assessed. For example, if the clearance of a solute is less than C_{inulin} there has been net reabsorption of the solute whereas if the clearance is greater than C_{inulin} there has been net secretion.

Proximal and distal nephron function can be estimated using clearances of lithium and free water (C_{H2O}, calculated as $V–C_{osm}$), respectively, but neither is entirely satisfactory. When proximal tubule reabsorption is altered, $C_{lithium}$, a marker of fluid delivery from the proximal tubule, changes in the predicted direction. However, this underestimates fluid delivery because some lithium (12–15%) is reabsorbed in the loop of Henle. C_{H2O} (measured during a maximal water diuresis when ADH secretion is suppressed) is used to estimate Na^+ reabsorption in the water impermeable ascending limb of the loop of Henle and early distal tubule. However, because significant reabsorption of this 'freed water' occurs in the collecting duct even in the absence of ADH, C_{H2O} provides an underestimate of Na^+ absorption. ◆

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Role of the Kidney in Acid–Base Balance

John C Atherton

John C Atherton is Senior Lecturer in Physiology at Manchester University. He graduated from Newcastle upon Tyne and gained his PhD at Manchester. His research interests focus on renal physiology with particular interest in urinary concentrating mechanisms, renal function in pregnancy and assessment of nephron function.

The main problem encountered in the homeostatic control of plasma pH within the narrow range 7.38–7.42 is to preserve the alkaline environment in the face of the production of large quantities of volatile acid (15–20 mmol/day as CO_2) and non-volatile acid (about 50 mmol/day) from the metabolism of fats and certain proteins. Defence is achieved through the operation of three basic mechanisms.

- Physicochemical buffering by extracellular and intracellular buffer systems is instantaneous but only limits the fall in pH.
- Respiratory compensation is rapid (minutes) and operates via the control of plasma pCO_2 through changes in alveolar ventilation and subsequent evolution of the volatile acid CO_2. Plasma pH is returned towards the normal values but acid–base status cannot be corrected completely.
- Renal compensation is slower (hours or days) and operates via the control of plasma bicarbonate through changes in the renal secretion of H^+ and the reabsorption and production of bicarbonate. Acid–base status can be corrected completely. This article focuses on these renal mechanisms of controlling acid–base balance.

Reabsorption of filtered HCO_3^- is described elsewhere. The rate of HCO_3^- reabsorption is influenced by glomerular filtration rate (GFR), extracellular fluid (ECF) volume, arterial pCO_2 and a variety of hormones.

Increasing GFR leads to an increase in the filtered load and an increase in total HCO_3^- reabsorption (but not fractional reabsorption). The opposite occurs when GFR is reduced. Glomerulo-tubular balance links filtered load and reabsorption; this protects body buffer stores against spontaneous changes in GFR.

Changes in ECF volume influence HCO_3^- reabsorption in the proximal tubule in the same way as Na^+ reabsorption is affected. ECF volume expansion decreases reabsorption and contraction increases reabsorption. The close linking of HCO_3^- and Na^+ reabsorption via the Na^+-H^+ exchanger in the apical membrane of early proximal tubule cells (accounting for most HCO_3^- reabsorption) provides a mechanism for the association between volume-induced changes in Na^+ and HCO_3^- reabsorption. This also increases the possibility of the involvement of other factors that modify transcellular Na^+ reabsorption (via Na^+-H^+ exchange) in the proximal tubule (and in other nephron segments) in controlling HCO_3^- reabsorption. Thus, altered catecholamines, increased sympathetic nerve activity and angiotensin II, which increase Na^+ reabsorption, and parathormone, dopamine and atrial natriuretic peptide (ANP), which decrease Na^+ reabsorption in the proximal tubule, have corresponding effects on HCO_3^- reabsorption.

pCO_2 – there is an association between chronic changes in pCO_2 and HCO_3^- reabsorption. Raised pCO_2 following prolonged hypoventilation leads to an increase in HCO_3^- reabsorption
in almost all nephron segments, whereas during chronic hyperventilation HCO_3^- reabsorption is reduced. The possible mechanisms responsible include changes in the filtered load and a direct effect on the active pumps for H^+ secretion. During prolonged hypoventilation, plasma HCO_3^- concentration and therefore filtered load increase; HCO_3^- reabsorption increases. Opposite changes (decreased plasma HCO_3^- concentration and HCO_3^- reabsorption) occur in prolonged hyperventilation. Acute changes in pCO_2 are not accompanied by these changes because only small changes in plasma HCO_3^- concentration (hence filtered load) occur. Intracellular acidosis, resulting from chronic increases in pCO_2, increases the steepness of the transmembrane gradient favouring H^+ secretion, and is also thought to cause insertion of more H^+ transport proteins (H^+-ATPase and perhaps H^+-K^+ exchangers) in the apical cell membranes of renal tubular cells, especially intercalated cells in the collecting duct. Both changes favour HCO_3^- reabsorption.

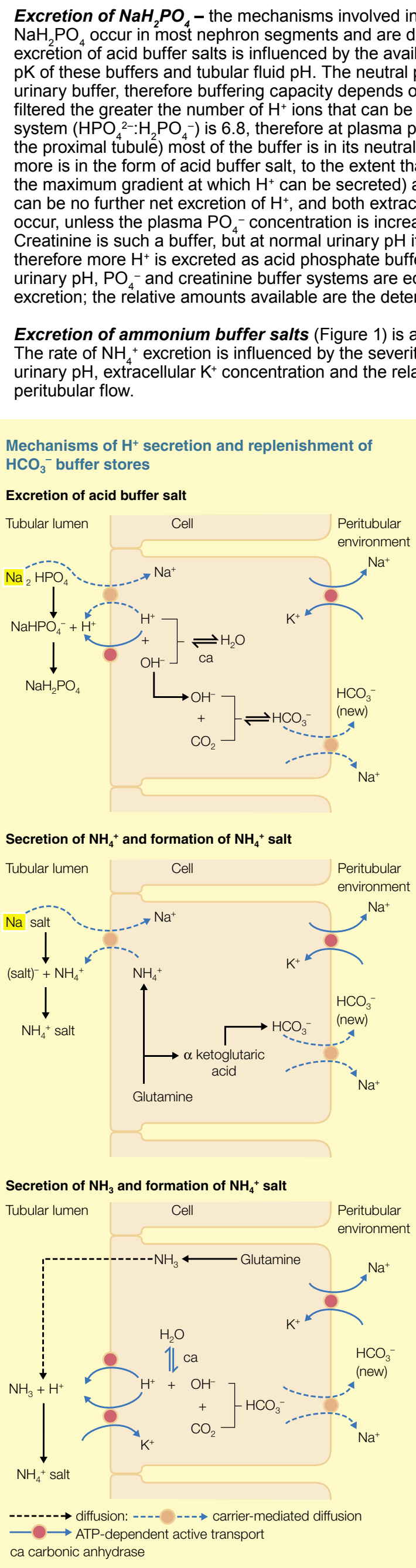
Aldosterone may have a physiological role in HCO_3^- homeostasis. Chronic acidosis raises plasma K^+ concentration and stimulates aldosterone secretion. Aldosterone increases H^+ secretion by collecting duct cells directly and indirectly. The direct effects relate to stimulation of secretion by Na^+-H^+ countertransport in principal cells and by H^+-ATPase in intercalated cells, presumably by increasing the number of protein transporters in the apical membranes. Indirectly, aldosterone increases the negative potential difference in the lumen thereby reducing the electrochemical gradient against which active H^+ secretion occurs.

Production of HCO_3^-: the secretion of H^+ as described above does not lead to net excretion because the CO_2 formed within the tubular lumen is returned to the cell, where more H^+ is formed and then secreted. However, H^+ can be excreted either as neutral ammonium salts (e.g. $(NH_4)_2SO_4$) or as acid buffer salts (NaH_2PO_4). Both these routes for H^+ excretion lead to the formation of one new HCO_3^- for every H^+ secreted.

Excretion of NaH_2PO_4 **–** the mechanisms involved in the formation and excretion of NaH_2PO_4 occur in most nephron segments and are described elsewhere. The rate of excretion of acid buffer salts is influenced by the availability of the urinary buffers, the pK of these buffers and tubular fluid pH. The neutral phosphate buffer salt is the main urinary buffer, therefore buffering capacity depends on its availability; the more that is filtered the greater the number of H^+ ions that can be excreted. The pK of this buffer system (HPO_4^{2-}:$H_2PO_4^-$) is 6.8, therefore at plasma pH (i.e. pH of the fluid as it enters the proximal tubule) most of the buffer is in its neutral form. As tubular fluid pH declines, more is in the form of acid buffer salt, to the extent that at pH 4.4 (minimum urinary pH, the maximum gradient at which H^+ can be secreted) all will be acid buffer salt. There can be no further net excretion of H^+, and both extracellular and intracellular acidosis occur, unless the plasma PO_4^- concentration is increased or other buffers are available. Creatinine is such a buffer, but at normal urinary pH it is less effective (pK = 4.97), therefore more H^+ is excreted as acid phosphate buffer than with creatinine. At minimal urinary pH, PO_4^- and creatinine buffer systems are equally effective for H^+ excretion; the relative amounts available are the determining factor.

Excretion of ammonium buffer salts (Figure 1) is also described in detail elsewhere. The rate of NH_4^+ excretion is influenced by the severity and duration of the acidosis, urinary pH, extracellular K^+ concentration and the relative rates of tubular and peritubular flow.

Mechanisms of H^+ secretion and replenishment of HCO_3^- buffer stores



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It was reported over 50 years ago that for a given urinary pH, total NH_3 excretion (NH_3+NH_4^+) is higher in prolonged acidosis than in normal acid–base balance. The mechanism appears to be increased NH_4^+ secretion in proximal tubules arising from intracellular pH-induced stimulation of the enzymes involved in the metabolism of glutamine. Stimulation of new enzyme would increase metabolism of glutamine and hence produce more NH_4^+ available for secretion. Chronic alkalosis has the opposite effect.

There is an inverse relationship between urinary pH and total NH_3 excretion; as pH declines, total NH_3 excretion increases. The pK (9.2) of the NH_3:NH_4^+ urinary buffer system is far removed from normal acid urinary pH; total NH_3 is almost exclusively in the NH_4^+ form. Therefore, the relationship between pH and total NH_3 excretion must result from increased NH_3 diffusion into collecting duct lumen with immediate conversion to NH_4^+ at acid pH of luminal fluid. Thus, the gradient favouring passive diffusion of NH_3 into the lumen is maintained and the increase in total NH_3 excretion is a consequence of increased non-ionic diffusion and trapping of the impenetrable ionic form (NH_4^+) in the tubular lumen.

Changes in extracellular K^+ concentration influence NH_4^+ excretion; hyperkalaemia inhibits NH_4^+ excretion; hypokalaemia has the opposite effect. The mechanism responsible is uncertain but may relate to extracellular K^+-induced changes in intracellular pH. Thus, increased exchange of K^+ and H^+ in hyperkalaemia raises intracellular pH, reduces glutamine metabolism and decreases NH_4^+ production and secretion. Hypokalaemia decreases intracellular pH and, therefore, increases NH_4^+ excretion.

NH_3 is lipophilic, therefore any NH_3 produced in renal tubular cells can diffuse into the luminal fluid or peritubular capillary plasma: net movement is determined by relative flow rate and the pH of tubular fluid and plasma. Since the peritubular capillary plasma flow rate is higher (at least five times higher in the cortex) than tubular flow, the more rapid removal in plasma favours movement of NH_3 into the capillary and none appears in the urine. This does not normally occur because of the acid tubular fluid pH, which favours secretion into the tubule. If tubular fluid is more alkaline than peritubular capillary plasma (e.g. following intravenous administration of $NaHCO_3$ in the partial treatment of phenobarbital poisoning or acetylsalicylate overdose) NH_3 formation is reduced and almost all of it moves into the peritubular capillary plasma. Urinary NH_3 excretion is then minimal.◆

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Physiology: Liver

Anaesthesia
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Liver: Functional Anatomy and Blood Supply

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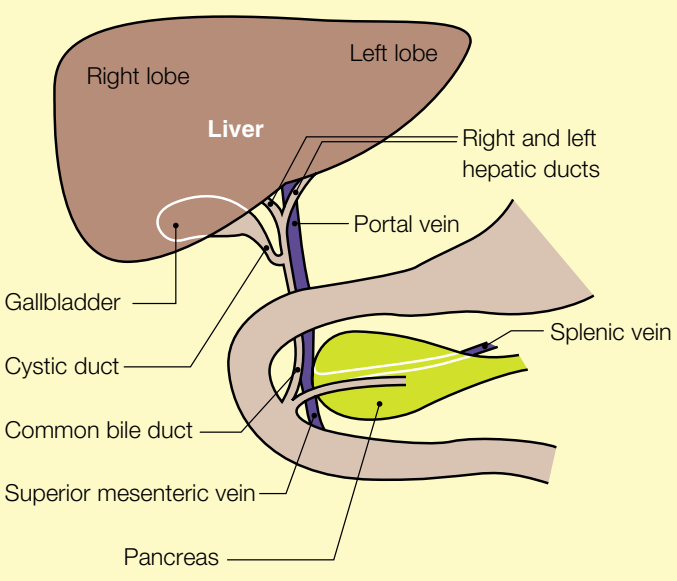
The liver is the largest organ in the body. It weighs 1–1.5 kg and lies in the right upper quadrant of the abdomen. It is wedge shaped, occupying almost the whole of the right hypochondrium and the greater part of the epigastrium and extends into the left hypochondrium. The liver is divided into a large right lobe and a much smaller left lobe (Figure 1). On its inferior surface is the porta hepatis, a deep fissure through which the portal vein, the hepatic artery and the hepatic plexus of nerves enter the liver and the right and left hepatic ducts and some lymph vessels emerge. The gallbladder lies on the inferior surface of the right lobe.

Relationships of liver, biliary and portal systems



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Blood supply
The main blood supply of the liver comes from the portal vein, which gives it a special place in the control of metabolism. The portal vein drains the spleen and the gastrointestinal tract, apart from the distal half of the colon. It thus receives, and processes to varying degrees, almost all the products of digestion and absorption. Total hepatic blood flow at rest is about 1500 ml/minute (i.e. 25–30% of cardiac output). Of this, 70% comes from the portal vein, the remainder from the hepatic artery.

The viscera and liver are supplied by the coeliac, superior mesenteric and inferior mesenteric arteries. The hepatic artery is a branch of the coeliac trunk. Blood flow to the stomach and small intestine (and thus to the liver) doubles after a meal and the increase lasts up to 3 hours. The whole system is capable of extensive autoregulation. Portal venous pressure is about 10 mm Hg and hepatic venous pressure 5 mm Hg. Hepatic arterial pressure is 90 mm Hg but the pressure within the venous sinusoids of the liver is lower than the portal pressure, therefore there is a large pressure drop in the hepatic arterioles. There is a reciprocal relationship between portal venous and hepatic arterial pressures so that when portal blood flow is reduced (e.g. between meals) the hepatic arterioles dilate and total blood flow is maintained. This is thought to be mediated by adenosine. However, portal blood flow is controlled by autoregulation and does not alter when arterial flow changes.

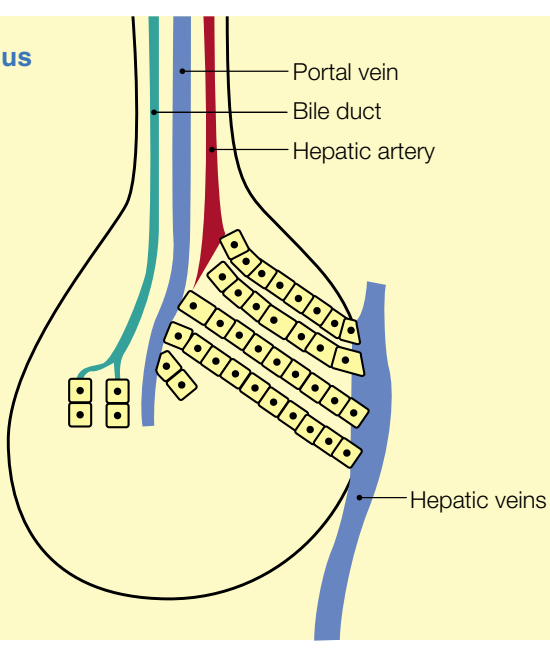
The portal vein is formed from the superior mesenteric and splenic veins in front of the inferior vena cava, behind the neck of the pancreas. It is about 7–8 cm long and enters the liver via the porta hepatis. It differs from other veins in that it has no valves and, in conditions such as cirrhosis, the flow can reverse. The intrahepatic portal vein radicles have smooth muscle in their walls and are innervated by noradrenergic sympathetic nerves, as is the hepatic artery, via the hepatic plexus. There are no vasodilator fibres. At rest, only a portion of the liver is perfused. With rises in venous pressure (e.g. congestive cardiac failure) the sinusoids distend. With diffuse noradrenergic discharge (e.g. hypovolaemic shock, the start of exercise) hepatic arterioles and portal venous radicles constrict and blood flow through the organ is brisk, bypassing most of it. Constriction of the mesenteric arterioles reduces portal inflow. In severe shock, patchy hepatic necrosis may occur. During exercise, constriction of the splanchnic bed, including the liver, effectively increases the circulating blood volume to the exercising muscles by up to 30%.

The pancreatic veins drain into the splenic vein, which joins the portal vein just before it enters the liver. These veins carry the pancreatic hormones, insulin and glucagon, from the endocrine part of the pancreas, therefore they exert their effects first on the liver. The concentrations of these hormones are much higher in the liver than in the systemic circulation, and so liver cells are exposed to higher concentrations than the other body tissues.

The liver is drained by the hepatic veins, which enter the infer-ior vena cava. These emerge from the posterior aspect of the liver and immediately join the inferior vena cava. They have no valves and are invested in fibrous tissue. On dissection they are held open, in contrast to the portal vein which tends to collapse.

Perhaps a more correct way of thinking about the anatomy of the liver is in terms of the acinus as the anatomical unit. There are about 100,000 acini, each composed of hepatocytes, endothelial cells and Küpffer cells arranged like grapes on a vascular stalk (Figure 2) containing terminal branches of portal veins via hepatic arteries and bile ducts. The 'central' vein of the lobule is on the periphery of the acinus.

Liver acinus



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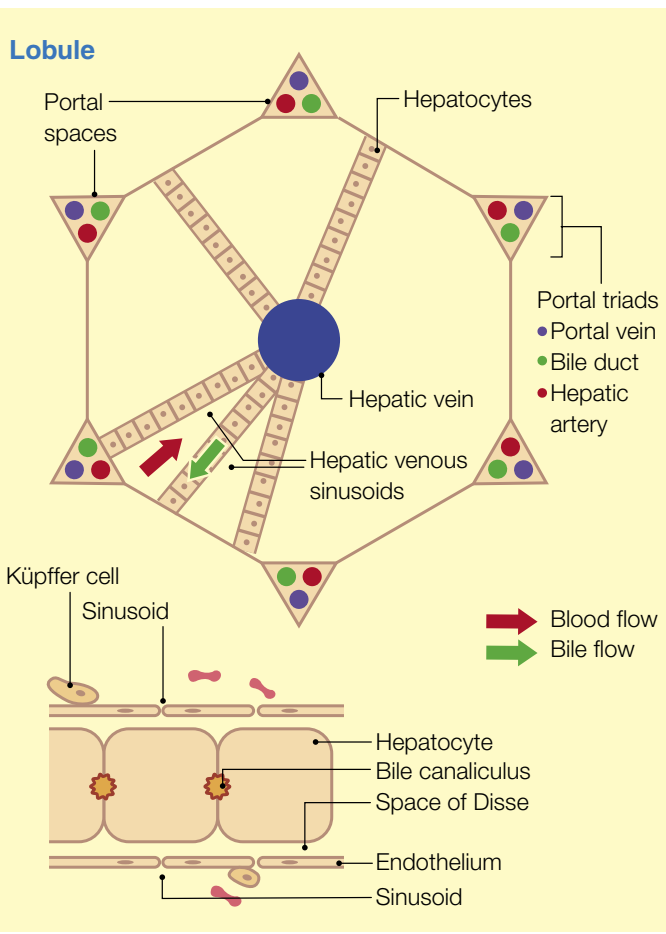
Biliary system
Hepatocytes excrete bile into canaliculi that coalesce to form the right and left bile ducts; one from each lobe. They join outside the liver to form the common hepatic duct. The cystic duct drains the gallbladder and unites with the common hepatic duct to form the common bile duct, which enters the duodenum at the duodenal papilla. Bile has several functions including involvement in fat absorption. When food enters the mouth, the sphincter around the duodenal papilla relaxes and when gastric contents enter the duodenum the hormone cholecystokinin, from the intestinal mucosa, causes the gallbladder to contract.

Functional anatomy
For an organ that has such an extensive range of functions, the liver is structurally remarkably homogeneous. 80% is made up of hepatocytes, which are metabolically extremely active. They contain extensive amounts of rough and smooth endoplasmic reticulum, which are involved in protein synthesis and drug metabolism, respectively. The other main cell types are the Küpffer and endothelial cells. The hepatocytes are organized into lobules 1 mm across (Figure 3).

Lobule



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Each lobule is hexagonal, with a portal space at each corner containing the portal triad, consisting of branches of the portal vein, the hepatic artery and a bile duct. Within the lobule, the hepatocytes are arranged radially in cords. The spaces between the cords constitute the sinusoids filled with blood, which drains from the portal vein and hepatic artery in the periphery of the lobule into the central vein, which drains ultimately into the hepatic veins and the vena cava. The transit time from the portal vein to the central vein is 8–9 seconds.

There is usually only one layer of hepatocytes between two sinusoids so the area of contact between the blood and the hepatocytes is huge. The sinusoid receives blood from both the portal vein and hepatic artery. The space between the endothelial cells and the hepatocytes (the space of Disse) contains the 'extracellular fluid' of the liver, some of which goes to form lymph. This drains via superficial vessels on the surface of the organ and converges on nodes at the porta hepatis or via deep vessels that accompany the hepatic veins.

The sinusoids are lined by endothelial cells that have large gaps between them, facilitating communication between the lumen of the sinusoid and the hepatocytes. Attached to the endothelial cells, also lining the sinusoids, are the Küpffer cells, which are macrophages. They form part of the endothelial system and are found mainly in the periportal region. They constitute 80% of all the resident macrophages in the body. They contain vacuoles and lysosomes and effectively sit astride the portal tract taking up bacteria, particulate matter and endotoxins that enter the portal blood from the gastrointestinal tract. In the fetus, hepatic Küpffer cells produce red cells and, with some diseases that destroy the bone marrow, some red cell production may occur in the liver.

The arrangement of vessels means there is an oxygen gradient within the lobule with cells on the periphery being better oxygenated than those around the central vein. This is reflected in the different metabolic processes that occur in the different areas of the lobule. The better oxygenated areas in the periphery are associated with protein metabolism and the poorer oxygenated areas in the centre with glycolysis and ketone body formation.

Bile secretion
Hepatocytes produce bile and the liver secretes about 500 ml/day, which circulates three times. Bile contains bile salts involved in fat absorption and bile pigments, the products of haemoglobin metabolism, all dissolved in an alkaline electrolyte solution. Cholesterol and alkaline phosphatase are excreted in the bile as are adrenocortical and other steroid hormones as well as a number of drugs. Many are subsequently reabsorbed (the enterohepatic circulation). Bile is excreted by the hepatocytes into bile canaliculi between the hepatocytes. These drain into intralobular bile ducts and coalesce to form the right and left hepatic ducts. While blood in the lobule passes centrally to the central vein, bile moves to the periphery to the bile ducts lying as part of the portal triad in the portal space. ◆

Liver: Metabolic Functions

Iain Campbell

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The liver plays a major role in the metabolic control of the body (Figure 1).

Bile formation
The liver produces about 500 ml/day of bile, which circulates three times. It is an alkaline electrolyte solution (97% water) containing bile salts and bile pigments. Bile salts are crucial to the digestion and absorption of lipids. Bile pigments are products of haemoglobin breakdown.

Bile salts are sodium and potassium salts of bile acids conjugated to glycine and taurine. The two primary acids are cholic and chenodeoxycholic acid. The two secondary ones (deoxycholic and lithocholic acid) are formed in the colon by bacterial action. The bile salts are amphipathic molecules, which means they have both hydrophilic (–OH, –COOH) and hydrophobic (steroid nucleus) groups. In conjunction with phospholipids (also amphipathic) they form micelles around lipid molecules and transport them to the brush border of the intestine where the lipids are absorbed. 90–95% of bile salts are actively absorbed from the terminal ileum. The absorbed salts return to the liver in the portal vein and are re-excreted in the bile (enterohepatic circulation). The bile salts that enter the colon are converted to salts of the secondary acids of which lithocholate is mainly excreted and deoxycholate is absorbed. The total bile salt pool is about 3.5 g of which 0.2–0.4 g are lost each day in the faeces; the pool recycles about twice per meal (i.e. about 6–8 times/day). Absence of bile is associated with fat malabsorption as is resection of the terminal ileum.

Functions of the liver

Formation and secretion of bile

Macronutrient metabolism
- Carbohydrate
- Fat
- Protein

Inactivation of:
- Drugs
- Toxins
- Steroids and hormones

Plasma protein synthesis
- Albumin
- Clotting factors
- Acute phase proteins
- Binding protein

Immunity
- Küpffer cells

Bile pigments: haemoglobin is broken down by macrophages in the tissues to biliverdin then to bilirubin. The globin part is degraded ultimately to amino acids and the iron complexes with transferrin. Bilirubin is transported, bound to albumin, to the liver where it is conjugated with glucuronic acid in the smooth endoplasmic reticulum to render it soluble. It is then secreted into the bile canaliculi. Some bilirubin glucuronide escapes into the general circulation where it is loosely bound to albumin. Some conjugated bilirubin in the intestine is reabsorbed (enterohepatic circulation) but most is converted by bacterial action in the intestine to urobilinogen, which is eliminated in the faeces as stercobilin, a brown pigment that colours stools. Some urobilinogen is also reabsorbed and excreted by the kidney which oxidizes it to urobilin – a pigment that gives urine its amber colour.

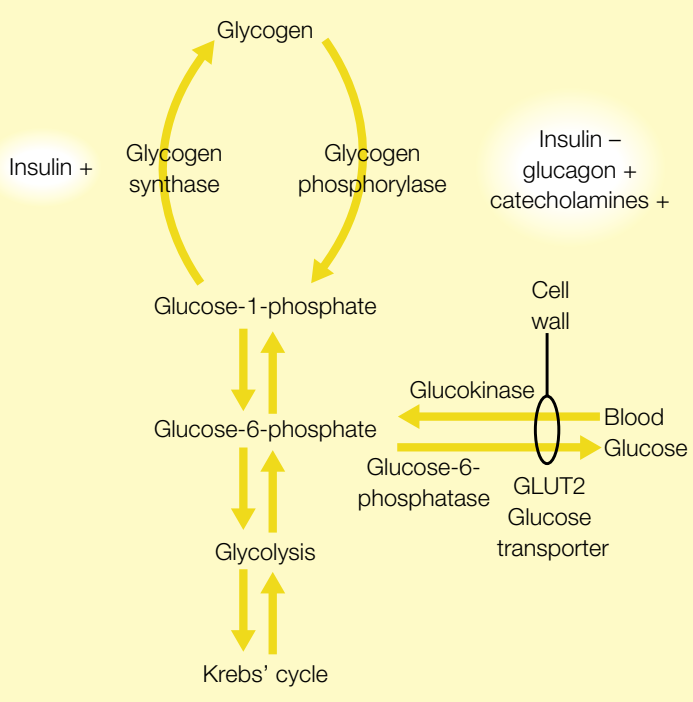
The gallbladder: bile is stored in the gallbladder where it is concentrated by the absorption of water, secondary to the active absorption of sodium. The average water content of gallbladder bile is 89%. Gall bladder contraction is stimulated by cholecystokinin produced by the duodenum in response to entry of fatty acids and amino acids from the stomach.

Glucose is stored in the body as glycogen in liver and muscle. The muscle stores are larger, but muscle lacks glucose-6-phosphatase so muscle glycogen is unable to contribute to blood glucose; only liver glycogen does this and, in the absence of a carbohydrate intake, glycogen stores are exhausted within 24–48 hours. The body normally obtains about 50% of its energy from glucose oxidation therefore in normal circumstances liver glycogen stores have to be replenished continuously.

Glucose is absorbed from the intestine into the portal vein where, after a meal, glucose concentrations can reach 10 mmol/litre. Glucose passes into liver cells via the GLUT2 glucose transporter molecule on the hepatocyte membrane. This transporter is not sensitive to insulin and the rate of entry into the hepatocyte is proportional to the extracellular glucose concentration; it is rapidly phosphorylated by gluco-(hexo-)kinase to glucose-6-phosphate (Figure 2). Glucokinase is increased by insulin. Glucose-6-phosphate may be metabolized to pyruvate via the glycolytic pathway or converted to, and stored as, glycogen. Most of the liver's energy requirements come from amino acid and fatty acid oxidation, therefore most of the glucose taken up by the liver is converted to glycogen.

The system has a high capacity and the liver acts as a glucose sink. Its uptake follows its concentration gradient and this is not insulin dependent. However, insulin is important in glycogen synthesis. Glucose-6-phosphate is converted to glucose-1-phosphate and glycogen is synthesized by the enzyme glycogen synthase, the activity of which is stimulated by insulin and glucose (Figure 2). Liver glycogen acts as a glucose buffer, storing glucose when blood concentrations are high and releasing it when glucose is required in other parts of the body. When blood glucose falls, glucose is released from glycogen through the action of the glycogen phosphorylase. Glucose-6-phosphatase is reformed and glucose released into the circulation via the action of glucose-6-phosphatase. Glycogen phosphorylase is stimulated by glucagon. The catecholamines, adrenaline and noradrenaline, also have a role in glycogenolysis but mostly in stressful situations (e.g. exercise, trauma, shock).

Carbohydrate metabolism



Glycogen is synthesized by glycogen synthase stimulated by insulin. Glycogen is broken down (glycogenolysis) by glycogen phosphorylase under the influence of glucagon, and during stress by catecholamines

Glucagon has a reciprocal relationship with insulin. When blood glucose decreases, insulin falls, glucagon rises and glyco-genolysis occurs. The proximity of the pancreas, with the pancreatic vein draining directly into the portal vein, means that the liver is rapidly exposed to high concentrations of these hormones in response to changes in blood glucose.

The liver is also the main site of gluconeogenesis (the synthesis of glucose from smaller molecules). The major gluconeogenic precursors are lactate, glycerol and the amino acids, principally alanine. The rate of gluconeogenesis is controlled by the rate of substrate supply and hormonal regulation. Release of gluconeogenic precursors from peripheral tissues occurs in situations such as starvation (amino acids from muscle) and severe exercise (lactate from muscle glycogen). The process is similar to glycolysis in reverse with differences in the enzymes involved at three points. The enzymes controlling gluconeogenesis are controlled by the hormones insulin and glucagon and, under stress (exercise, trauma or sepsis), cortisol and the catecholamines. Gluconeogenesis is stimulated by lack of insulin and high levels of glucagon. The relationship between glucagon and insulin is important in starvation, and in trauma and exercise the high cortisol and catecholamine levels provide additional stimuli.

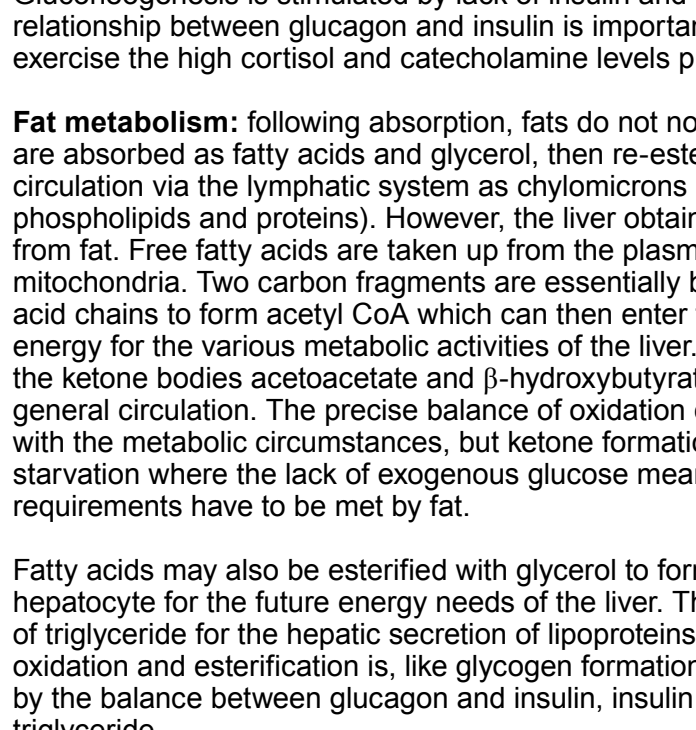
Fat metabolism: following absorption, fats do not normally enter the liver. They are absorbed as fatty acids and glycerol, then re-esterified and transported to the circulation via the lymphatic system as chylomicrons (packages of triglyceride, phospholipids and proteins). However, the liver obtains much of its energy needs from fat. Free fatty acids are taken up from the plasma and undergo β oxidation in the mitochondria. Two carbon fragments are essentially broken off the multicarbon fatty acid chains to form acetyl CoA which can then enter the citric acid cycle to provide energy for the various metabolic activities of the liver. Alternatively they may form the ketone bodies acetoacetate and β-hydroxybutyrate, which are released into the general circulation. The precise balance of oxidation or ketone body formation varies with the metabolic circumstances, but ketone formation is particularly important in starvation where the lack of exogenous glucose means virtually all the body's energy requirements have to be met by fat.

Fatty acids may also be esterified with glycerol to form tri-glyceride, stored in the hepatocyte for the future energy needs of the liver. These stores are also the source of triglyceride for the hepatic secretion of lipoproteins. The balance between fatty acid oxidation and esterification is, like glycogen formation and gluconeogenesis, controlled by the balance between glucagon and insulin, insulin stimulating the formation of triglyceride.

Protein metabolism: proteins are hydrolysed to amino acids and dipeptides for absorption. The intake of protein in a normal Western diet is 70–100 g/day but the body cannot store protein; protein accretion, in the form of muscle, occurs only in response to exercise or drugs such anabolic steroids and β-agonists. Total body protein is normally stable, but this is a dynamic stability with the processes of protein synthesis from, and protein breakdown to, amino acids and amino acid oxidation going on continuously. In this stable state, rates of amino acid oxidation to carbon dioxide, water and urea (also creatinine, ammonia and uric acid) approximate the rates of protein ingestion. The equilibrium is disturbed in starvation, when exogenous protein ceases to be available, and in trauma or sepsis when patterns of hepatic protein synthesis change dramatically (see later). When protein intake is in excess of requirements the excess is metabolized as described above and urea production rates are increased. The liver obtains about half its energy requirement from protein oxidation.

Amino acids are broken down in the liver in two stages (Figure 3). Deamination to the corresponding keto acids (e.g. pyruvate, α-ketoglutarate), which are oxidized, mostly in the citric acid cycle to carbon dioxide and water with the release of energy, occurs. The amine group is metabolized to urea via the urea cycle and the liver is the only site of urea production in the body. An exception is the branch chain amino acids, the metabolism of which occurs mainly in muscle.

Protein metabolism



Inactivation and excretion of toxins, drugs and cholesterol
The liver is a main site for the metabolism of toxic chemicals, many formerly of plant origin but now mostly pharmacological substances. Most drug metabolism occurs in the hepatic smooth endoplasmic reticulum. In general, metabolism involves in-activation of the substance and the creation of a more ionized molecule that allows excretion in the bile or urine. Filtration of a lipid-soluble substance by the kidney would be followed inevitably by reabsorption in the tubule. Making it more polar, stops the reabsorption. This occurs in two phases.

Phase I inactivates the molecule and involves oxidation, reduction or hydrolysis. It is carried out mainly by a nonspecific group of enzymes called the mixed function oxidase or P450 system. They are classified into families and subfamilies by the degree to which they share amino acid sequences. However, the system is not unique to the liver and these enzymes are also found in other tissues. Phase I processes are also carried out by other enzymes (e.g. dehydrogenases, glutathione-S-transferase).

Phase II reactions increase the water solubility of the substance by complexing or conjugating it with other substances such as glucuronide, sulphate, acetyl, methyl or glycine groups. Most reactions occur in the liver but not exclusively so. The smaller molecules are excreted in the urine, larger ones (including those with a steroid nucleus) in the bile.

Steroid hormones are also converted to less active substances in the liver, then conjugated to glucuronide or sulphate and excreted in the bile. Cholesterol is treated similarly and is also excreted in the bile.

Plasma protein synthesis
The plasma proteins consist of albumin, globulin and fibrinogen fractions. The globulin fraction is divided into α, β and γ globulins. Antibodies in the γ globulin fraction are manufactured in the plasma cells. The remainder are synthesized in the liver. Albumin is one of the smallest molecules (molecular weight 69,000). It exerts a plasma osmotic (oncotic) pressure and is important in the maintenance of fluid balance in peripheral tissues but it also binds a number of substances such as barbiturates, penicillin, bilirubin, urobilinogen, hormones (thyroxine) fatty acids and bile salts.

The normal plasma albumin level is 3.5–5 g/100 ml and the total exchangeable albumin pool 4–5 g/kg body weight. 40–45% of total albumin is intravascular and much of the rest is in the skin. 5–10% is degraded each day and hepatic synthesis is 200–400 mg/kg/day. Its production is closely regulated: synthesis is depressed in starvation and increased in the presence of abnormal albumin loss (e.g. in kidney disease). 40% of total plasma proteins are globulin (molecular weight 80,000–150,000). They form part of the lipoprotein complexes that transport lipid molecules and cholesterol between the liver and the tissues. They bind thyroxine, cortisol, vitamin B_{12}, copper and iron. Prothrombin, erythropoietin and angiotensinogen are all globulins.

Following trauma or sepsis, patterns of plasma protein synthesis change with plasma levels and the distribution of proteins between the intravascular and extravascular spaces in what has been termed the acute phase response. Circulating concentrations of albumin, transferrin and prealbumin diminish and fibrinogen (clotting factor), α_2-macroglobulin (protease inhibitor), ceruloplasmin (binds copper) and C-reactive protein (CRP denotes inflammation and tissue damage) all rise. CRP rises the most and is often used as an indicator of the severity of inflammation or tissue damage. Capillaries become ‘leaky’ and there is a redistribution of protein and fluid between the intra- and extravascular spaces.

Küpffer cells
Küpffer cells are tissue macrophages attached to the endothelium in the sinusoids. They are important because they come into contact with almost all the blood draining the gastrointestinal tract, which may contain endotoxins and bacteria. In response to an inflammatory stimulus they produce the cytokines, tumour necrosis factor, interleukin-1 and interleukin-6, which stimulate the liver to produce the acute phase proteins. Loss of integrity of the gastrointestinal tract (e.g. following major trauma or sepsis) may lead to endotoxins and bacteria entering the portal circulation, stimulating the Küpffer cells and causing a systemic inflammatory response. ◆

FURTHER READING

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Physiology: Nerves and CNS

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The Brain: Functional Divisions

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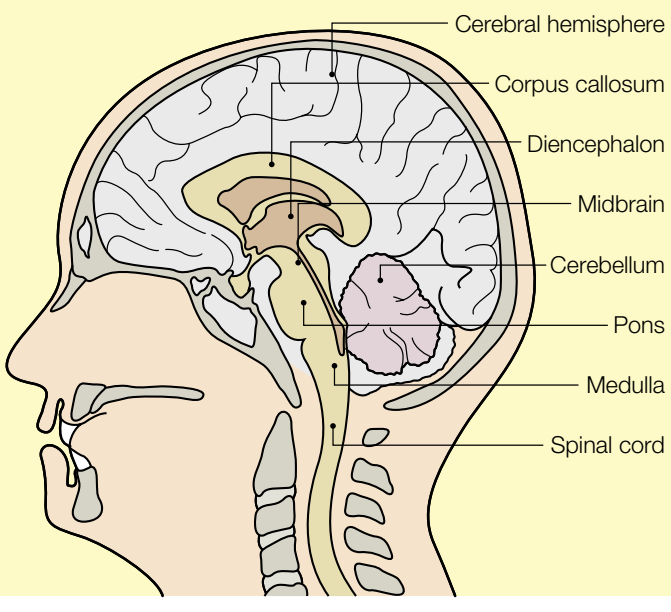
Anaesthesia is not the same as natural sleep. The basis of contemporary balanced anaesthesia is the use of the CNS as a target, specific regions of which yield a component of good anaesthesia. Hypnosis (elimination of consciousness) and amnesia are achieved by disrupting the normal function of the cerebral cortex and underlying brain structures. Progressively greater depths of anaesthesia cause progressive reduction in the global metabolic rate of the brain. The adult brain (Figure 1) weighs 1250–1450 g within a volume of 1400 ml. It comprises the:

- telencephalon (cerebral cortex, basal ganglia and olfactory bulbs)
- diencephalon (thalamus, hypothalamus and habenula)
- mesencephalon or midbrain (structures around the cerebral aqueduct, superior and inferior colliculi and the cerebral peduncles)
- metencephalon (pons and cerebellum)
- myelinocephalon (including the medulla oblongata).

The adult brain



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The most prevalent excitatory neurotransmitter in the brain is glutamate. γ-aminobutyric acid (GABA) receptors are the most important inhibitory receptors in the brain, apart from the brainstem, where glycine is also an important inhibitory neurotransmitter. There are many subtypes of receptor protein. This means that although a specific brain region may have a particular type of receptor, there is no guarantee that the receptor performs in the same manner as a slightly differently configured subtype of the same receptor in another region. For example, the potency of propofol and volatile anaesthesia at $GABA_A$ and glycine receptors is conferred by the protein receptor configuration directed by two amino acids; if those amino acids are substituted, the receptor is no longer sensitive to hypnotic anaesthetic agents

Cerebral cortex

The cerebral cortex comprises millions of neurons. One of the most common is the pyramidal cell. Axons from single pyramidal cells may terminate many centimetres from the cell body, against targets such as other pyramidal cells or, in the case of the corticospinal tract, even spinal interneurons linked to motor neurons.

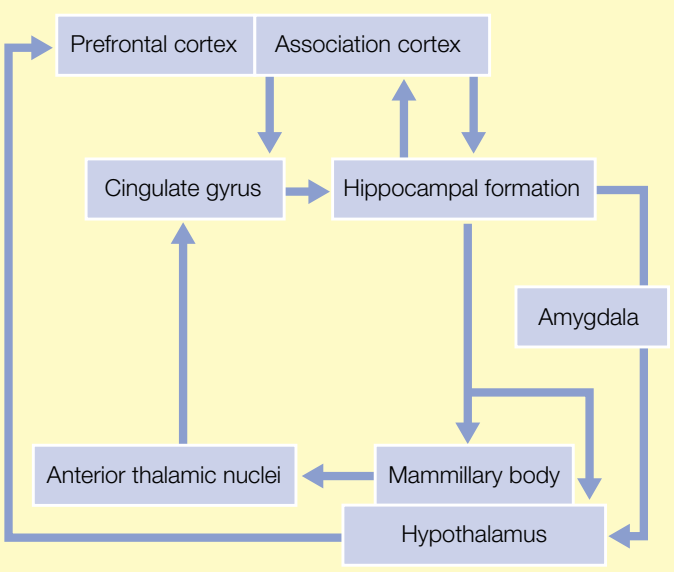
Graded potentials from thousands of pyramidal cells near recording electrodes are the basis for the electroencephalogram (EEG). Single neuron recordings from the sensory regions of the cerebral cortex, such as the primary visual cortex, have been performed since the 1960s and have revealed much about sensory processing. Histology of the cerebral cortex reveals six distinct layers. Layers I–IV receive input from other regions of the cerebral cortex and brain, mainly from the thalamus (layer IV). Layers V and VI house the cell bodies of cortical efferent interneurons. In the most heavily studied region, the primary visual cortex (V1 or Brodmann's area 17), much initial processing is performed by 'simple cells' (i.e. neurons sensitive to visual stimuli such as a line moving at a particular orientation of movement). 'Complex cells' receive input from simple cells along with parallel direct input from the lateral geniculate nucleus, and are selective to movement in a particular direction (not just orientation) and spatial frequency; they are actively inhibited by movement at other orientations. Complex cells are often 'end stopped' (hypercomplex) whereby only stimuli of a specific length, orientation and spatial frequency are encoded into action potentials. Subtle changes in action potential frequency, and hence the sensitivity of these neurons to different characteristics of visual stimuli, have been observed with increasing depths of volatile anaesthesia.

Visual neurons in the primary visual cortex are arranged in columns of similar orientation selectivity. These columns have been directly visualized by the use of voltage-sensitive dyes on the surface of the exposed cerebral cortex. Complex cells are also often sensitive to textured visual stimuli (e.g. wood grain pattern on a desk, or a 'hidden eye' visual illusion), to which simple cells are largely insensitive. Some have suggested that this is evidence for parallel processing of information in the primary visual cortex, rather than a strict hierarchy of function proposed by earlier researchers. It is likely that other sensory regions of the cerebral cortex have a similar organization, and most regions have been topographically mapped to the environmental spatial or frequency position of stimuli.

Limbic system

The limbic system (Figure 2) is responsible for the recall and expression of emotions such as fear, anger, pleasure and contentment. It is a prime target for anaesthesia, because elimination of emotion and the recall of unpleasant events is the basis of adequate hypnosis. Damage to different regions of the limbic system results in a characteristic loss of a component of emotion or memory.

Limbic system



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The limbic system is also a vital component of consciousness. Consciousness is not located in one particular region of the brain, though localized lesions in the solitary nucleus of the medulla oblongata (brainstem) or the anterior cingulate gyrus (a component of the limbic system) lead to coma. Consciousness appears to be the result of coordinated firing of large assemblages of neurons, whereas subconscious behaviour can be initiated and sustained by groups of relatively few neurons. Fast binding of relevant sensory inputs with large assemblage activity is probably required for the expression of consciousness and components of the limbic system are probably involved. Two types of consciousness (i.e. core consciousness, extended consciousness) have been suggested. Clinical sedation progressively abolishes extended consciousness, and general anaesthesia abolishes core consciousness.

Anterior cingulate gyrus

Ablation of the prefrontal cortex or cingulate gyrus eliminates concern over chronic pain, and pain no longer elicits powerful emotions. Functional imaging studies of the anterior cingulate gyrus have implicated it in the presence of conscious awareness during light sedation. Activity in the left anterior cingulate proportionally decreases with increasing depth of anaesthesia and appears to correlate with the level of hypnosis.

Hypothalamus and thalamus

The hypothalamus and thalamus form the diencephalon. The thalamus is the main relay for ascending information entering the cerebral cortex. The dorsomedial thalamus has to be active during light anaesthesia for explicit recall of events to occur; it is important for the formation of explicit memory and its subsequent retrieval. The dorsomedial thalamus is one example of the thalamic regions, each of which demonstrates varied functionality.

Unconscious regulation of autonomic function is integrated between the autonomic, somatic and endocrine systems by the hypothalamus, the main function of which is to keep internal conditions constant. The hypothalamus is responsible for homeostasis, especially by directing motivation (e.g. temperature, feeding, thirst). Control of core temperature is an important role performed by the hypothalamus, the posterior region of which compares information from relatively warmer neurons on the anterior hypothalamus with cold receptors in the skin. Internal heat is increased by raising the metabolic rate in combination with a decrease in peripheral blood flow in the skin. When core temperature rises, sweating is promoted and dilation of blood vessels in the skin promotes cooling. Anaesthesia disrupts homeostatic control originating from the hypothalamus, and this is a difference between natural sleep and anaesthesia. During natural sleep, the set point of temperature control falls, but it is still under active control by the hypothalamus. Natural sleep is regulated via the hypothalamus, partly by the release of endogenous sleep-promoting hormones.

Hippocampus

The hippocampus is involved in the acquisition of memory from experience, and is important for the recall of spatial position. Functional imaging has suggested that people with enhanced mapping skills have greater activity in the hippocampus. Lesions to specific regions of the hippocampus have resulted in subjects who are unable to recall any events that occurred after the lesion, even though memory of events up to the trauma is secure. Such subjects have proved that long-term memory is not necessary for consciousness, as long as subjects still have a functional working (real-time) memory they exhibit normal consciousness.

Amygdala

The amygdala comprises five nuclei in three groups: the central nucleus; the cortical and medial nuclei; the basal and lateral nuclei. There is extensive connectivity between the amygdala and the telencephalon, diencephalon, midbrain and brainstem (solitary nucleus). The amygdala integrates information from the senses and from within the body (visceral afferents) and associates it with the memory of past experience. Amygdala-driven aversion is particularly profound. Patients with amygdala lesions can see no wrong in people or places that have caused them particular emotional distress in the past. Paradoxically, such behaviour is considered to be mature by many cultures. Recent research suggests that memories mediated by the amygdala are disrupted profoundly during propofol anaesthesia.

Brainstem

The brainstem is the most densely packed region of the brain with vital function. It has little redundancy of function in the event of damage, which is likely, owing to the proximity of the aqueduct of Sylvius (cerebral aqueduct), which is susceptible to occlusion. The brainstem is not bilaterally paired in function, each side has a bias towards differing autonomic function. A specific example of this is the right vagus (X) nerve, which originates in the medulla oblongata and appears to direct chronotropic (beat to beat, as opposed to ionotropic or within beat) heart rate variability. Brainstem and cerebral laterality of autonomic function is a fascinating and clinically important topic that is surprisingly poorly reported in the literature.

Brainstem sensory nuclei are arranged in columns in a similar manner to sensory regions in the posterior horn of the spinal column. The tract of the solitary nucleus (nucleus tractus solitarius) is large and responsible for many crucial functions. The solitary nucleus lies within the visceral sensory column. The special sensory column and vestibular and auditory nuclei of the vestibulocochlear (VIII) nerve receive input from the vestibular organs and the cochlea. Auditory evoked potentials derived from these regions are largely resistant to the effects of hypnotic anaesthesia, their effects being more noted on the auditory cortex. The somatic sensory column receives input from the vagus (X), facial (VII), glossopharyngeal (IX), and trigeminal (V) nerves. The presence of noxious stimuli from the head, face and neck is transmitted through these nerves and via the trigeminal spinal nucleus, as is fine touch, which also uses the main sensory trigeminal nucleus. Vibration and position are encoded by the mesencephalic nucleus of the trigeminal nerve.

Midbrain: the midbrain primarily controls sensory and motor function, particularly the control of eye movement and the coordination of visual and auditory reflexes. The midbrain provides much of the processing necessary to maintain posture, walking, positioning and jumping behaviours. However, the midbrain does not initiate these behaviours. An animal with an intact brainstem, including the midbrain but no higher brain, exhibits righting reflexes (i.e. it can restore its normal posture from an unusual starting point) and normal muscle tone (though visual righting reflexes are eliminated in an animal with no higher brain). Without the midbrain, the righting reflexes disappear and the animal exhibits high muscle tonus (decerebrate rigidity) but can still remain upright because the inputs from labyrinth and neck proprioceptors are still intact.

Pons: the pons is the site of origin for the facial motor cranial nerves and their nuclei (e.g. trigeminal (V) nerve and its nucleus). The frontalis electromyogram (fEMG) has been studied extensively because it declines with increased anaesthetic depth, especially at relatively light levels of anaesthesia; the fEMG reflects activity in the pons. The pons falls within the territory of the medial branch of the basilar artery.

Medulla oblongata: the medulla is a region of the brainstem responsible for autonomic control and falls within the territory of the anterior spinal artery. Damage to the anterior medulla results in 'locked-in' syndrome in which a patient is unable to move or communicate but is otherwise conscious. Damage to the posterior medulla often results in profound coma. Less severe damage is apparent in conditions such as Wallenberg's syndrome, in which localized damage to the nucleus ambiguus causes disruption to motor fibres leading to the glossopharyngeal (IX), vagus (X) and accessory (XI) nerves, affecting muscles in the palate and the larynx, as well as fast control of heart rate.

The nucleus tractus solitarius is predominantly located in the medulla. It is a sensory nucleus, which receives input from many visceral receptors including stretch receptors in the lungs and the carotid sinus. The nucleus tractus solitarius is responsible for integrating the sensory information arriving for the baroreflex; the inferior nucleus tractus solitarius is responsible for encoding sensory information from the heart, lungs, blood vessels and gut. Vagally mediated spontaneous and evoked motor activity in the gut declines during anaesthesia, as does respiratory sinus arrhythmia. The superior nucleus tractus solitarius is also responsible for taste on the anterior 66% of the tongue from the glossopharyngeal (IX) nerve, and taste buds in the pharynx from the vagus (X) nerve. The nucleus tractus solitarius connects to the dorsal vagal motor nucleus and the nucleus ambiguus, both of which innervate the heart and modulate heart rate variability. The dorsal vagal motor nucleus also innervates secretory glands in the pharynx, lungs and gut, along with peripheral ganglia modulating smooth muscle tone in blood vessels, lung and gut.

Cerebellum: the cerebellum comprises 50% of the neurons in the brain, even though it occupies only 10% of the volume. The cerebellum adjusts the output of the major descending systems of the brain, acting as a comparator with information received from the spinal cord, vestibular apparatus and nuclei, medulla, pons, reticular formation and cerebral cortex. Cerebellar efferent pathways project to the brainstem and thalamus to modulate a variety of motor and other functions.

The cerebellum comprises three regions:

- vestibulocerebellum, receiving input from the semicircular canals and otolith organ and encoding the position and movement of the head
- spinocerebellum, regulating body and limb movement
- cerebrocerebellum, evaluating sensory information to evaluate the planning of movement.

The cerebellum is made up of three distinct layers: molecular layer, Purkinje cell layer and granular layer. Purkinje neurons in the cerebellum have large cell bodies and complex dendritic fields, and form many copies of the same basic neural circuit. The Purkinje cells are the only efferent axons leaving the cerebellum. Afferent climbing fibres pass through the granular layer and terminate at the granular layer at dendrites of the Purkinje cells, climbing through the dendritic tree. Afferent mossy fibres end in the granular layer at granule cells. Granule cells produce two collaterals (parallel fibres) in a T shape; collaterals viewed in cross-section explain the dot-like nature of the molecular layer. Climbing fibres synapse directly on the Purkinje neurons, whereas mossy fibres connect to the Purkinje cells via interneurons (granule and basket neurons).

Lesions in the cerebellum result in hypotonia, ataxia and action- or intention-tremor. Lesions in the vestibulocerebellum are characterized by impaired eye movement, difficulty in maintaining balance and irregular movement, which becomes normal when supine.

The spinocerebellum receives pathways from the spinal cord via precerebellar nuclei in the brainstem reticular formation. Different versions of the changing state of the subject and the environment are compared. ◆

Cerebral Blood Flow and Intracranial Pressure

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Bhaskar Saha

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The normal adult skull is a rigid bony structure of fixed volume, containing brain, cerebrospinal fluid (CSF) and blood. An understanding of the interaction between these components is essential for the anaesthetic management of patients with intracranial pathology.

Brain
The brain tissue is the largest component in the skull. It has a mass of about 1400 g and consists of supporting (glial) and neural elements, intracellular and extracellular water. The maintenance of an environment suitable for nerve cell function is achieved by the presence of the blood–brain barrier. This is formed by tight junctions (zona occludens) between the adjacent cerebral capillary endothelial cells, a lack of fenestrations and a region of astrocytes, closely applied to the endothelial cells. It is permeable to oxygen, carbon dioxide and water but not to low molecular weight ions including sodium, potassium and chloride, or plasma proteins. It acts as a semipermeable membrane and the administration of hypotonic solutions increases brain water. Other complex proteins also act to protect the brain against potentially harmful chemicals. The presence of the blood–brain barrier removes the need for lymphatic drainage of the brain. Pathological increases in brain tissue are the result of tumours, increased intracellular water (cytotoxic oedema) or extracellular water (vasogenic oedema).

CSF
There is about 150 ml of CSF in the craniospinal axis, of which about 75 ml is within the skull. It is produced constantly, at a rate of 0.3 ml/minute (500 ml/day), in a process of active secretion by Na^+/K^+-ATPase and carbonic anhydrase. The choroid plexus, situated within the lateral and fourth ventricles, produces about 70% of CSF and the remainder is produced by the non-choroidal surfaces of the ventricles. CSF is reabsorbed into the venous circulation via the arachnoid villi, a loose arrangement of arachnoid cells with large intercellular spaces, situated within the dural walls of the sagittal and sigmoid sinuses and in the dural sinusoids on the dorsal nerve roots. Most CSF (90%) is reabsorbed intracranially. Under normal circumstances, the pressure of CSF is 11 mm Hg and the pressure in the venous sinuses is 6 mm Hg, which results in a 5 mm Hg pressure gradient facilitating absorption across the villi. Increases in the CSF pressure (up to 22 mm Hg) result in an increased rate of reabsorption but do not alter the rate of production.

The CSF has a variety of functions. It helps to ensure a constant supply of glucose and maintains a chemically stable environment, necessary for neurotransmission. It also effectively reduces the mass of the brain to about 50 g, which reduces the inertia of the brain and allows rapid head movement without damage to the delicate neural structures.

Blood
The brain is supplied with blood via the internal carotid and vertebral arteries. Venous drainage is via the cerebral veins, sinuses and internal jugular veins. Under normal conditions (in the absence of any pathology or drugs) there is about 150 ml of blood in the skull, most of which (about 100 ml) is within the venous system. Although cerebral blood volume (CBV) is small, cerebral blood flow (CBF) is relatively high compared with other organs. Normal global CBF is about 50 ml/100 g/minute, grey matter receiving 80 ml/100 g/minute and white matter 20 ml/100 g/minute. This equates to 700 ml/minute or 15% of the cardiac output to an organ that is only 2% of body weight.

Control of CBF
The brain depends on oxidative phosphorylation of glucose to generate adenosine triphosphate (ATP) and as a result is intolerant of hypoxia. Several protective mechanisms control CBF. Blood flow to the neurons of the spinal cord is subject to similar control mechanisms.

Cerebral metabolism
CBF is closely linked to the metabolic activity of the brain to ensure adequate delivery of oxygen and substrates. This is often expressed as the cerebral metabolic rate for oxygen ($CMRO_2$), which under normal conditions is constant at 3.5 ml/100 g/minute. It accounts for 20% of the total body oxygen consumption. At any time, some regions may have relatively increased activity and blood flow, while other areas are less active. As a consequence, global oxygen demand and blood flow remain constant.

Any condition that reduces global metabolic activity will reduce $CMRO_2$ and CBF (e.g. hypothermia). At a brain temperature of 27°C, $CMRO_2$ and CBF are approximately halved. Below 20°C, CBF is approximately 10% of normal, virtually all of which is required to maintain cellular integrity because all neuronal electrical activity ceases at these low temperatures. It is the massive reduction in $CMRO_2$ at low temperatures that allows the brain to tolerate prolonged periods of ischaemia. Conversely, hyperthermia and seizures increase $CMRO_2$ and CBF. Other examples of a metabolically induced reduction in CBF include coma and anaesthesia.

Carbon dioxide and oxygen
The relationship between the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and CBF is almost linear. At a $PaCO_2$ of 10.6 kPa (80 mm Hg), CBF is approximately doubled. Beyond this, there is no further increase in flow, because the cerebral vessels are maximally vasodilated. Conversely, at a $PaCO_2$ of 2.7 kPa (20 mm Hg) flow is halved and plateaus as a result of maximum vasoconstriction. This is thought to be mediated (indirectly) by changes in the hydrogen ion concentration in the extracellular fluid surrounding the vascular smooth muscle.

The response of the cerebral vasculature to changes in $PaCO_2$ can be used therapeutically in patients with raised intracranial pressure. Hyperventilation causes vasoconstriction, a reduction in CBV and intracranial pressure. However, extreme hypocarbia ($PaCO_2$ < 4 kPa, 30 mm Hg) may be harmful, because the degree of vasoconstriction causes ischaemia.

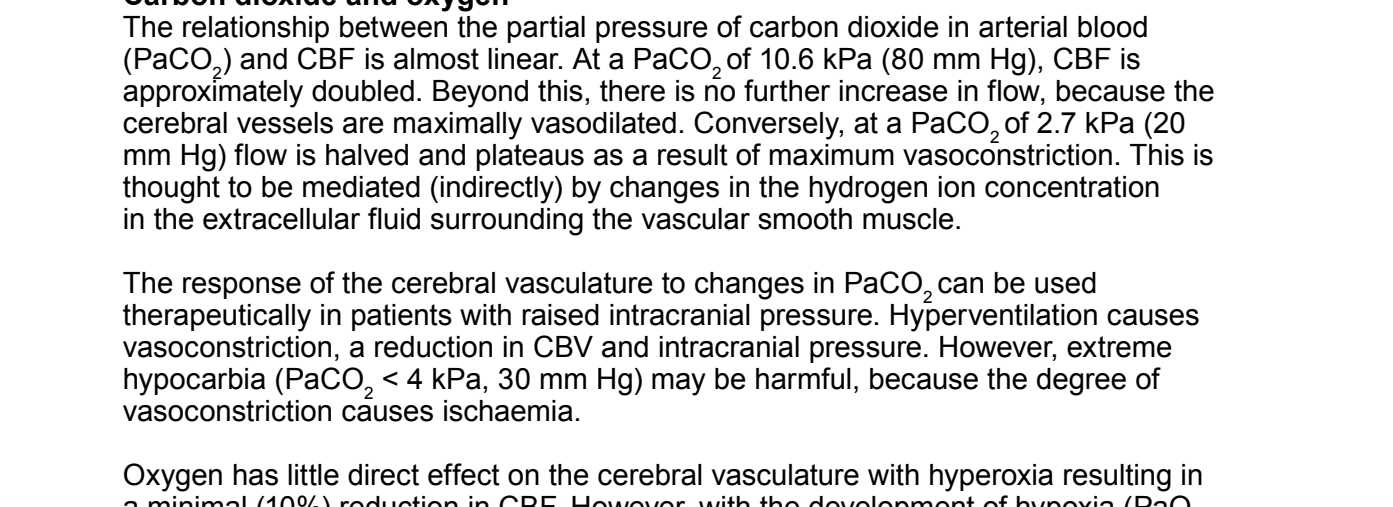
Oxygen has little direct effect on the cerebral vasculature with hyperoxia resulting in a minimal (10%) reduction in CBF. However, with the development of hypoxia (PaO_2 < 6.7 kPa, 50 mm Hg), there is a rapid, progressive increase in CBF secondary to the development of a metabolic acidosis as the total oxygen content of haemoglobin falls.

Autoregulation
Perfusion of the brain depends on the pressure gradient across the vasculature, termed the cerebral perfusion pressure (CPP). This is the difference between the mean arterial pressure (MAP) and venous pressure. However, the latter is difficult to measure and approximates to the more easily measured intracranial pressure (ICP), which is slightly less because the cerebral veins must maintain a higher pressure to remain patent.

$$CPP = MAP–ICP$$

The brain is intolerant of hypo- or hyperperfusion, and therefore requires a constant flow of blood over a range of pressures, this is achieved by autoregulation (Figure 1). This is thought to be a myogenic mechanism whereby pressure changes are sensed and induce either a reflex constriction (increased pressure) or relaxation (low pressure) of the vascular smooth muscle, predominantly in the arterioles. The stimulus to cerebral autoregulation is CPP not MAP. Under normal circumstances (ICP ≤ 10 mm Hg), the two are similar and CBF is held constant over the CPP range 50–150 mm Hg. In the presence of raised intracranial pressure, CPP must be calculated. The lower limit represents the point of maximal vasodilatation and below this flow is described as 'pressure-passive' and depends on the transmural pressure. At the upper limit, there is maximal vasoconstriction and further increases in CPP are accompanied by disruption of the blood–brain barrier, oedema formation and cerebral ischaemia (hypertensive encephalopathy). In patients with chronic untreated hypertension, the autoregulatory curve is shifted to the right to protect against the development of encephalopathy. Autoregulation is easily impaired by head injury, tumours and vasodilatory drugs (e.g. volatile anaesthetics).

Autoregulation



CPP, cerebral perfusion pressure; PaO_2, $PaCO_2$ partial pressure of oxygen/carbon dioxide in arterial blood.

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Autonomic nervous system
The cerebral vasculature is well innervated by the autonomic nervous system. The sympathetic supply to the extraparenchymal vessels arises from the cervical ganglia and the supply to the parenchymal microvasculature from the locus ceruleus. Their main action is vasoconstriction, which probably serves to protect the brain by shifting the autoregulatory curve to the right in hypertension. The parasympathetic nerves arise from the pterygopalatine and otic ganglia and contribute to cerebral vasodilatation. This is most apparent in conditions such as post-ischaemia reperfusion and hypotension. In addition to these effects it is now thought that initial changes in CBF to meet metabolic demands are initiated via neurogenic mechanisms and then sustained by local chemical factors.

Blood viscosity
Blood viscosity is directly related to the haematocrit. Although reductions in haematocrit improve flow, this will be offset by a reduction in the oxygen-carrying capacity of the blood. The optimum haematocrit at which there is a balance between flow and oxygen capacity is about 30%.

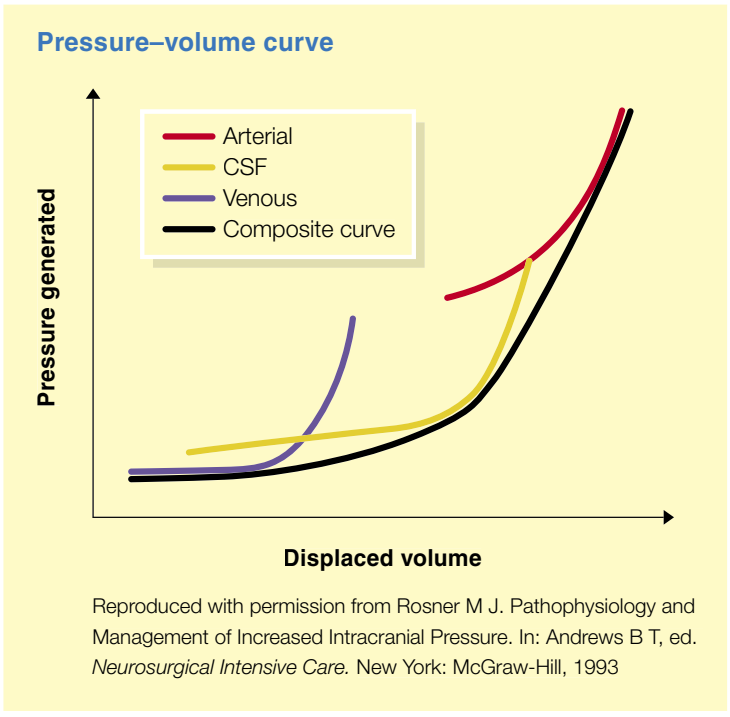
Critical CBF
In normotensive individuals, below the lower limit of autoregulation, CBF mirrors MAP and eventually a reduced flow will cause cerebral ischaemia. At a CPP of about 25 mm Hg, CBF is 20–25 ml/100 g/minute and this is accompanied by slowing of electrical activity on the electroencephalogram. When perfusion pressure reaches 15 mm Hg (CBF 15 ml/100 g/minute), electrical activity ceases and below 10 mm Hg, cellular integrity is lost with a massive efflux of potassium and eventually cell death.

Intracranial pressure
Brain tissue, CSF and blood are incompressible and contained within the skull, a rigid box of fixed volume. It is the relationship between the volumes of brain tissue, CSF and blood that gives rise to the intracranial pressure. In the normal adult, the ICP is 5–13 mm Hg (7–18 cm H_2O), with minor cyclical variations owing to the effects of the arterial pressure waveform and respiration. ICP also varies with posture, coughing, sneezing and straining.

Any increase in the volume of one of the three components within the skull must be compensated for by a decrease in the volume of one or more of the remaining components, otherwise the ICP will increase (this is often referred to as the Munro–Kellie doctrine). Brain tissue is not easily (or safely) displaced, therefore changes in venous blood or CSF volumes initially act as the major buffers against a rise in ICP.

The term compliance is often used to describe this relationship, however, compliance describes the relationship *dV/dP.* Within the skull it is the change in ICP for unit change in volume that is of interest or *dP/dV*, and the term elastance should be used. In the normal brain, with normal elastance, small changes in the volume of one of the contents (e.g. venous blood volume during coughing or straining) do not cause a sustained rise in ICP. However, once the compensation mechanisms have been exhausted or eliminated, for example by the presence of a haematoma or oedema, the ICP rises dramatically.

The traditional method of expressing this relationship has been the 'pressure–volume' curve, which suggests that pathological increases in ICP occur as a result of continuing increase in intracranial volume. However, if we accept that the volume of the skull is fixed, this is clearly inadequate. It is therefore more accurate to regard the relationship as the force required to displace volume from the cranium to accommodate the 'new' volume. As the force generated is difficult to measure it is the resultant pressure (ICP) that is normally measured (force = pressure x area). In fact, the resultant curve (Figure 2) is actually a composite of pressure versus displaced volume curves for venous blood, CSF and arterial blood, each of which is successively more difficult to displace.



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The relationship between CBF, CBV and ICP

CBV and CBF are independent of each other – a high CBV does not automatically imply a high CBF. Within the autoregulatory range, any increase in CPP induces a reflex vasoconstriction of the cerebral arterioles, reducing CBV. Conversely, any fall in CPP causes vasodilatation, increasing CBV. Any disturbance of ICP is short-lived because the volume of CSF changes in the opposite direction as a result of a change in the rate of absorption. If, however, the CPP falls below the point where no further vasodilatation is possible (i.e. the lower limit of autoregulation), the vascular diameter becomes dependent on the transluminal pressure, CBF follows the mean arterial blood pressure and as the latter falls, the vessels gradually collapse thereby reducing CBF and CBV.

This has important implications in the injured brain, when the autoregulation curve appears to be intact but ICP is increased (e.g. oedema, haematoma). If the CPP is allowed to fall, cerebral vasodilatation occurs increasing CBV and leading to a rise in ICP. This decreases CPP, leading to further vasodilatation, increased CBV and ICP. This process has been termed the ‘vasodilation cascade’. Conversely, if CPP is maintained or increased, it will result in vasoconstriction, reducing CBV and ICP. This increases CPP and induces further vasoconstriction, reducing CBV and ICP. This is termed the ‘vasoconstriction cascade’. For this reason, it is recommended that in the resuscitation phase of head injuries, MAP is maintained above 90 mm Hg or if ICP can be measured, CPP is maintained at 70 mm Hg at least. Paradoxically, if CPP is allowed to fall below the lower limit of autoregulation, passive collapse of the cerebral vessels will reduce CBV and ICP. However, this is achieved at the expense of CBF and oxygenation. ◆

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Nerve Cell Function and Synaptic Mechanisms

Chris J D Pomfrett

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There are three broad categories of neurons.

- Sensory receptors translate everything perceived from the external and internal environment into electrical potentials.
- Interneurons communicate between neurons, relaying all the functions of the CNS and processing the information; the human mind is a construct of interneuron activity.
- Motor neurons are the output from the CNS and the method by which we effect change on the environment.

Membrane physiology

All cell membranes, including those of neurons, are made up of an electrically insulating bilipid layer. The neuronal bilipid membrane has the electrical characteristics of a capacitor and can maintain an electrical potential difference across the membrane. The electrical excitability of a neuron is conferred by proteins spanning the membrane which allow the passage of ions. Each neuron has active and passive transport mechanisms to maintain a constant membrane potential across its cell membrane. Sodium and chloride ions are maintained in higher concentration outside the neuron, and potassium and inorganic anions are in higher concentration inside the neuron. The level of the membrane potential determines the excitability of the cell. More hyperpolarized membranes (–75 mV is more hyperpolarized than –50 mV) are less likely to reach the critical threshold necessary to initiate an action potential.

The equilibrium potential (Ex) of any ion is described by the Nernst equation. It is the electrical potential when there is no net flux of an ion across the cell membrane

$$Ex = \frac{RT}{ZF} \cdot \frac{\ln[X]o}{[X]i}$$

where R is the gas constant, T the temperature in degrees Kelvin, Z the valence of the ion, F the Faraday constant, and [X]o and [X]i are the concentrations of the ion outside and inside the neuron.

The equilibrium constant for potassium is typically –75 mV, that for sodium +55 mV and –60 mV for chloride. To maintain the resting potential, passive diffusion is vital to the neuron, but active transport occurs initially to set up the potential and to maintain the potential when the neuron is active. At rest, relatively few sodium channels are open, therefore the conductance to sodium is low. There are many resting potassium channels, and relatively large potassium conductance. The resting membrane potential produces a potassium efflux from the neuron equal to the sodium influx. There is an active Na^+/K^+ pump, consisting of a large membrane-spanning protein, which moves K^+ and Na^+ against their electrochemical gradients. One ATP molecule is used to transport three Na^+ ions out of the neuron and two K^+ ions into the neuron.

Ion channels in the cell membrane are proteins that form ion gates in the otherwise impermeable cell membrane. Voltage-gated channels are opened by changing the membrane potential and allowing specific passage of single types of ion. Voltage-gated channels are found in all electrically excitable regions of a neuron and can be blocked selectively (e.g. tetradotoxin blocks the sodium channel). Ligand-gated channels are found in chemical synapses and open when challenged with a specific neurotransmitter or an analogue (e.g. acetylcholine). The channel opening time can be increased or decreased by neuroactive agents, or the channels can be permanently forced open or shut by toxins.

Propagation of electrical signals

The two methods of propagating electrical signals within a neuron are graded potentials and action potentials. Most postsynaptic and receptor activity is in the form of graded potentials using Ca^{2+}, Na^+ and K^+ channel activity, which, in engineering terms, are analogue signals with information encoded in both the amplitude and decay (time course) of the signal. These potentials travel over a 'tree' of dendrites or fine neuronal processes that vary in anatomical complexity. Some of the most complex dendritic fields are located in the Purkinje cells of the cerebellum. A specialized region of the neuron, known as an integrating segment or axon hillock, adds the graded potentials in the neuron. This trigger zone is sensitive to small changes in membrane potential. If these summed potentials cross the membrane threshold of the integrating segment, an action potential is initiated. The action potential propagates along the axon of the neuron, which in certain interneurons (e.g. those of the corticospinal tract) may be over 1 m long.

Graded potentials

Graded potentials are the summed excitatory postsynaptic potentials (EPSP) and inhibitory postsynaptic potentials (IPSP) of a dendritic tree, which spread electrotonically along the neuron. Different regions of the neuron have different ion channels tailored to their function. The larger the diameter of the neuron, the further the electrotonic spread. For example, the largest diameter axons of the squid are 1 mm and conduct electrotonic potentials further than the dendrites of a mammalian neuron, which can be as small as 1 μm in diameter. This distance is known as the length constant, and typically ranges from 0.1 to 1.0 mm. This means that small graded potentials initiated from a single EPSP or IPSP play no role in the processing of a neuron if they do not summate with other graded potentials within the length constant of the dendrite. This mechanism allows the rejection of much electrical noise from the CNS.

Electrotonic spread of graded potential covers a relatively small area of a neuron, therefore the action potential is required to propagate neuronal conduction of information along a much greater distance than would otherwise be possible. The action potential is an 'all or nothing' (digital), frequency-modulated signal, with the amplitude being any level above a threshold and the information encoded purely in the frequency of successive action potentials. Such encoding is present in even the most primitive nervous systems.

Multiple synaptic connections allow complex and subtle convergence (where many neurons input on a single neuron) and divergence (when one neuron outputs to many neurons). For example, convergence allows a fully dark-adapted subject to perceive single photons of light; divergence allows one action potential in one axon to initiate the contraction of a large muscle.

Action potentials

Action potentials are initiated when summed graded potentials force the membrane potential of the neuron past a threshold of depolarization (e.g. from a resting potential of –75 mV to –50 mV). The time constant of a neuron defines how readily it will integrate successive graded potentials into the initiation of action potentials; a long time constant indicates a greater capability for temporal summation of individual graded potentials into a super-threshold potential. The depolarization opens sodium and sometimes calcium channels, which allow Na^+ (and Ca^{2+}) to flood into the neuron. As the neuron continues to depolarize (e.g. to +50 mV), potassium channels open, and K^+ floods out of the neuron. The sodium channels close, followed by the potassium channels, and the membrane returns to its resting potential. Using these voltage-gated and energy-independent mechanisms, the action potential propagates down the axon, away from the cell body towards terminal dendrites of the neuron. Artificial stimulation of the axon can elicit antidromic conduction of action potentials back up the neuron, towards the cell body. Such antidromic stimulation has been used to determine the presence of electrical synapses, which are bi-directional, as opposed to chemical synapses, which permit signal propagation in only one direction.

Action potentials are well suited to the transmission of fast, processed data over long distances. They are effectively digital, encoding information by frequency modulation. Phasic bursts of action potentials last a few seconds, rapidly decay in frequency and encode transient events. Tonic firing of axons appears as sustained activity lasting for many minutes. Phasotonic activity is seen as an initial burst of action potentials indicating that a change has occurred in the neural system, with a tonic sustained series of action potentials encoding that nothing has changed, but that the stimulus is still there. Adaptation is seen in neural systems as the prolonged stimulus results in increasingly fewer action potentials over time. The long process over which action potentials are transmitted in a neuron is called the axon. The larger the diameter of an axon, the faster its action potentials are propagated. The largest diameter axons are found in invertebrates such as squid and insects. These axons are generally involved in escape or flight reflexes that require fast transmission of action potentials to a large number of motor neurons in relatively simple neuronal networks. The large diameter of these invertebrate axons (greater than 10 μm), means that they are ideal for neurophysiological experimentation. Fine glass capillaries, drawn out to 1 μm tips, are pushed into the axon to measure intracellular potentials. Other advantages are that insect neurons function at room temperature and in the absence of anaesthesia (which must be used in all experiments on vertebrates and cephalopods). Evolution stopped with axon diameters of 1 mm, probably because of the need to produce small, flexible nerves comprising many axons. The classification of axons in terms of diameter, conduction velocity and function is given in Figure 1.

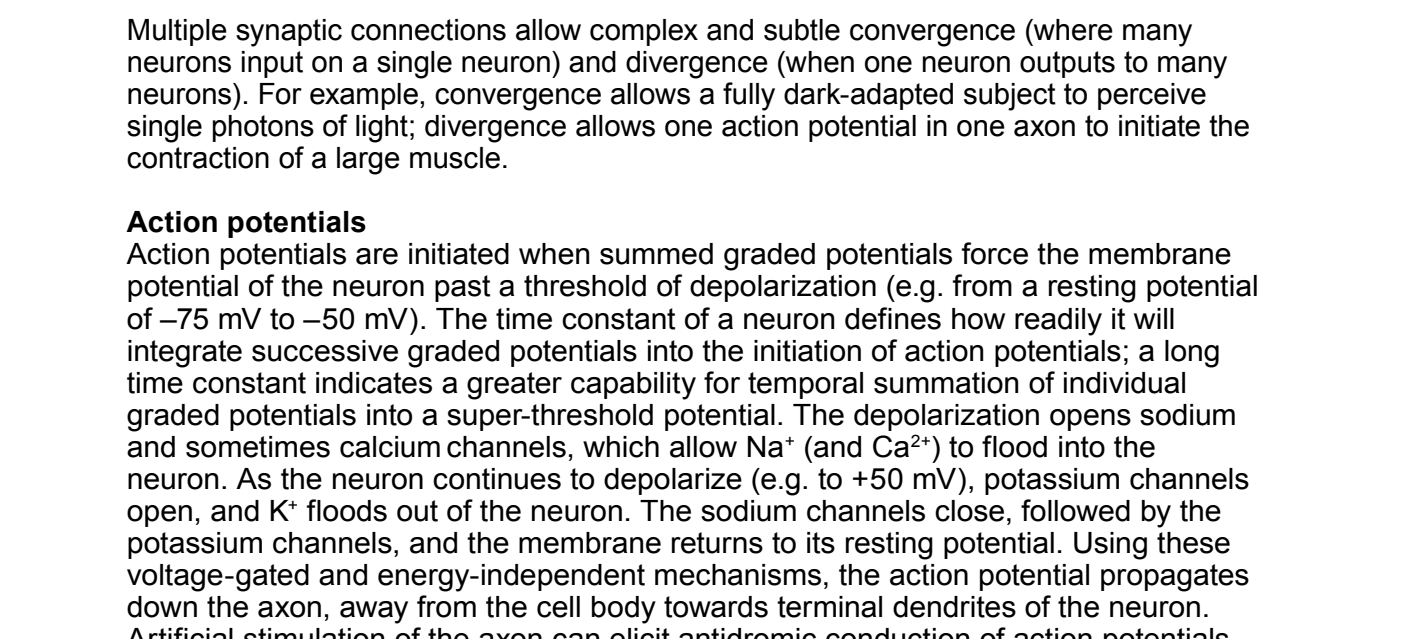
Nerve fibre types and characteristics

Fibre type	Typical function	Average fibre diameter (μm)	Velocity (m/s)
Erlanger/Gasser classification			
Aα	Primary muscle spindle afferents somatic motor	15	100
Aβ	Cutaneous touch and pressure afferents	8	50
Aγ	Motor to muscle spindles	5	20
Aδ	Cutaneous temperature and pressure	3	15
B	Sympathetic preganglionic	3	7
C	Unmyelinated cutaneous pain afferents	0.5	1
Lloyd/Hunt classification (afferent fibres only)			
I	Primary muscle spindle afferents	13	75
II	Cutaneous mechanoreceptors	9	55
III	Deep muscle pressure receptors	3	11
IV	Unmyelinated pain fibres	0.5	1

Conduction velocity

Many lower animal groups have loose myelin sheaths because of the need to insulate the axons electrically and provide a stable chemical environment for them. In more advanced nervous systems, myelin is tightly wrapped around certain axons as the result of Schwann cell development, which allows fast conduction velocities for action potentials with relatively narrow diameter axons. This is called saltatory conduction. Electrotonic potentials are propagated at nodes of Ranvier, which are unmyelinated regions with a high concentration of voltage-gated ionic channels. The internodes are myelinated, and therefore insulated, and promote the passage of electrotonic potentials between nodes (Figure 2). The velocity of action potential conduction falls at the nodes of Ranvier and rises at the internodes. Demyelinating disease makes gaps in the internodes that impair or block the propagation of action potentials. The effects of such demyelination are marked in sensory nerves with parallel pathways of information requiring fast transmission (e.g. the optic nerve).

Typical sensory to motor pathway



Unmyelinated axons have the slowest conduction velocities (e.g. nociceptor C fibres at 0.5 m/s). Intracerebral recordings from animal brains use extracellular electrodes adjacent to cell bodies because the diameter of the axons is so small, and the physical properties of a myelin sheath render intracellular axonal recordings difficult.

Synapses

Electrical synapses

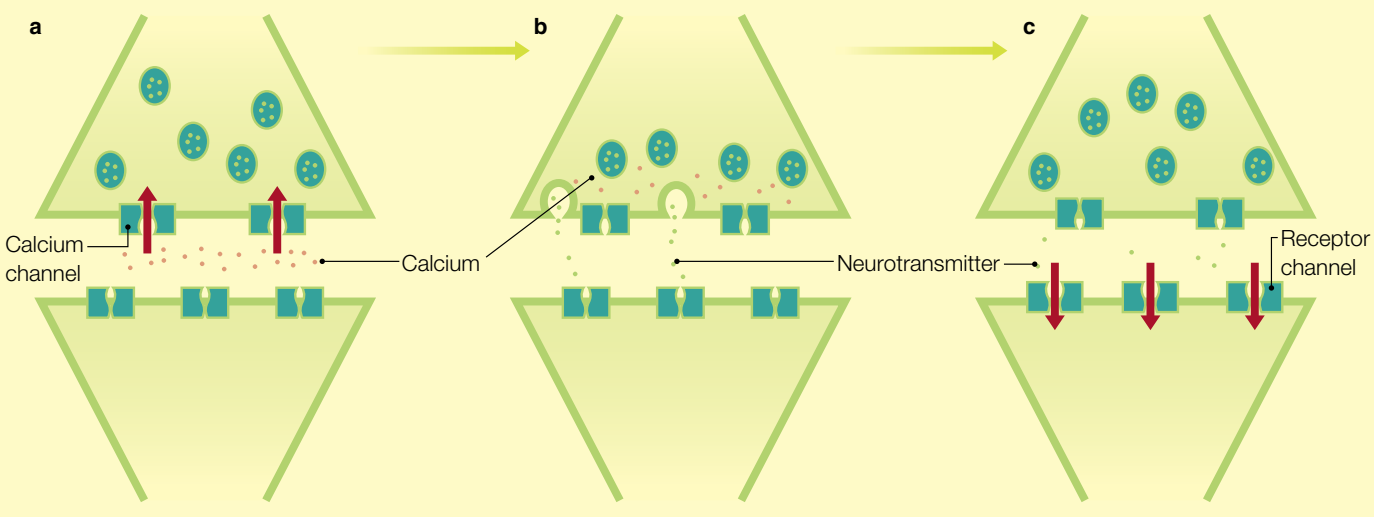
Electrical synapses form a close functionally equal electrical connection between some adjacent neurons, between neurons and glial cells, and between glia. Typically the gap between cell membranes is 2–4 nm. Graded and action potentials travel freely between cells with an electrical synapse, in either direction, and at high speed with no synaptic delay. Gap junctions made up of proteins (connexin) in both the presynaptic and postsynaptic membranes are characteristic of electrical synapses. The connexins can close the gap junctions in conditions of altered pH or high intracellular Ca^{2+} concentration. The flow of metabolites through gap junctions is affected in Charcot–Marie–Tooth disease, in which the connexin protein gene of Schwann cells is mutated, preventing the correct flow of metabolites between cells. The diameter of the junctional area ranges from 0.1 to 10 μm.

Chemical synapses

Protein and lipid synthesis for subsequent exocytosis occurs in endoplasmic reticulum. Proteins and lipids are transported to the Golgi complex and loaded into synaptic vesicles. All enzymes and neuroactive peptides have to be actively transported down the axon to the terminal dendrites. Neurotransmitters are loaded into synaptic vesicles by active transport, and are then physically relocated from a reserve pool to an active pool of vesicles ready for docking with the presynaptic membrane.

Chemical synapses (Figure 3) are excitatory or inhibitory, as defined by the receptor type in the postsynaptic membrane. Excitatory synapses produce EPSPs in the postsynaptic membrane, and inhibitory synapses produce IPSPs. Summed EPSPs cause depolarization of the postsynaptic membrane; IPSPs cause hyperpolarization. Synapses typically release one ‘classical’ neurotransmitter and several neuroactive peptides. Classical excitatory neurotransmitters in the CNS include acetylcholine and glutamate. Classical inhibitory neurotransmitters include acetylcholine, γ-amino butyric acid (GABA) and glycine. Contemporary theories point to the lengthening of opening time for inhibitory $GABA_A$ (higher brain; volatiles, ethanol, barbiturates) and glycine receptors (brainstem; volatiles, ethanol) in the presence of certain anaesthetics.

Typical chemical synapse



a Action potential reaches the presynaptic region, opening Ca^{2+} channels. **b** Ca^{2+} enters the presynaptic region and initiates vesicle fusion with the presynaptic membrane. **c** Neurotransmitters cross the synaptic cleft and initiate receptor channel opening in the postsynaptic membrane. This process takes time; each chemical synapse introduces latency, from 0.3 ms to several ms in a neural reflex

3

Chemical synapses are the principal targets for the action of neuroactive pharmacological agents. A chemical synapse permits the transmission of electrical potentials between neurons in one direction (from the presynaptic to the postsynaptic membrane). Chemical synapses have a synaptic cleft typically 10–40 nm across. Type I chemical synapses have a synaptic cleft of about 30 nm, a large junctional cross-sectional area of 1–2 μm diameter and appear asymmetrical. Type II chemical synapses have a synaptic cleft of about 20 nm, a smaller junctional area and appear symmetrical. Current flow does not cross this cleft. The graded electrical potential or action potential is transduced into a physical release of neurotransmitter(s) from vesicles, which fuse with the presynaptic membrane when calcium channels open on depolarization of the presynaptic region as a result of an incoming action potential. The enlarged presynaptic membrane eventually forms new vesicles by endocytosis, which are recycled by fusion with a specialized membrane compartment (endosome). Binding of the neurotransmitter with ligand- (as opposed to voltage-) gated ion channels then causes an EPSP or IPSP in the postsynaptic membrane. Typically, two molecules of transmitter are required to open an ion channel, so the thousands of transmitter molecules released by each synaptic vesicle can open thousands of postsynaptic receptors. For most agents, general anaesthesia works by potentiating IPSPs, for example inhibitory chloride channels are open for longer in the presence of anaesthetic agents. In contrast to these ionotropic, membrane-bound receptors, neurotransmitters such as noradrenaline (norepinephrine) and serotonin (5-HT) work by altering intracellular metabolism. They are metabotrophic receptors that initiate second messengers such as cAMP and diacylglycerol in the postsynaptic neuron. Iontotropic receptors produce fast synaptic actions lasting a few milliseconds, whereas metabotrophic receptors produce actions lasting for seconds or minutes.

The importance of synaptic protein receptors for the action of anaesthetic agents has been demonstrated by the enhanced action of certain isomers. Examples are the S(+) isomer of ketamine being two to four times more potent than R(–), and the S(+) isomer of isoflurane being 50% more potent than the R(–) isomer.

Acetylcholinesterase, in the synaptic cleft, is responsible for ‘mopping up’ excess neurotransmitter that has not been taken up through the presynaptic membrane by endocytosis. The resulting choline is taken up at axonal terminals by active transport and then used to synthesize acetylcholine with acetyl CoA produced from acetate, also from the synaptic cleft of neuromuscular junctions, or the citric acid cycle.

The location of a synapse on the postsynaptic neuron suggests its purpose. Most excitatory synapses are found on dendrites. Many inhibitory synapses terminate on cell bodies. ◆

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Neuromuscular Function and Transmission

Anthony C Wareham

Anthony C Wareham was Senior Lecturer in Physiological Sciences at the University of Manchester until taking early retirement in April 2001.

The initiation of contraction of skeletal muscle fibres requires the stimulus of an action potential from a motor neuron. One motor neuron connects to several muscle fibres to form a motor unit. A motor unit in a large limb muscle may contain 1000 fibres connected to one neuron. In contrast, the motor unit of an extraocular muscle may be composed of less than 10 muscle fibres. This correlates with the fineness of movement required from a muscle. The smallest movement possible is that produced by the simultaneous activation of all fibres in one motor unit.

The axon running to the motor unit is invisible to the naked eye. It may travel as far as 90 cm or more from the spinal cord to its muscle fibres. As it enters a muscle, the axon of the motor neuron divides into fine branches called telodendria, the endings of which each make close approximation with a specialized region of the sarcolemma of one muscle fibre. The specialized region is the motor end-plate, which covers an area of muscle surface of about 3000 μm^2.

The term neuromuscular junction (NMJ) refers to the axon terminal of the motor neuron plus the motor end-plate. In humans, after maturity, only one NMJ occurs per skeletal muscle fibre. During development, multiple NMJs are formed by several different axons on each muscle fibre but all except one are eliminated during maturation. The role of the NMJ is to ensure that a motor neuron action potential results in the generation of a muscle action potential on every fibre in the motor unit, and ultimately leads to contraction of the whole unit. Unlike CNS synapses, the NMJ does not modify signals but is a simple effector system carrying out the demands of the motor output. All of the physiology and pharmacology of the NMJ is directed towards achieving this aim. The role of the NMJ is so important that everything is done to excess, for example excess transmitter is released, there is an excess of postsynaptic receptors and the postsynaptic potential is several times greater than the minimum required to exceed the action potential threshold.

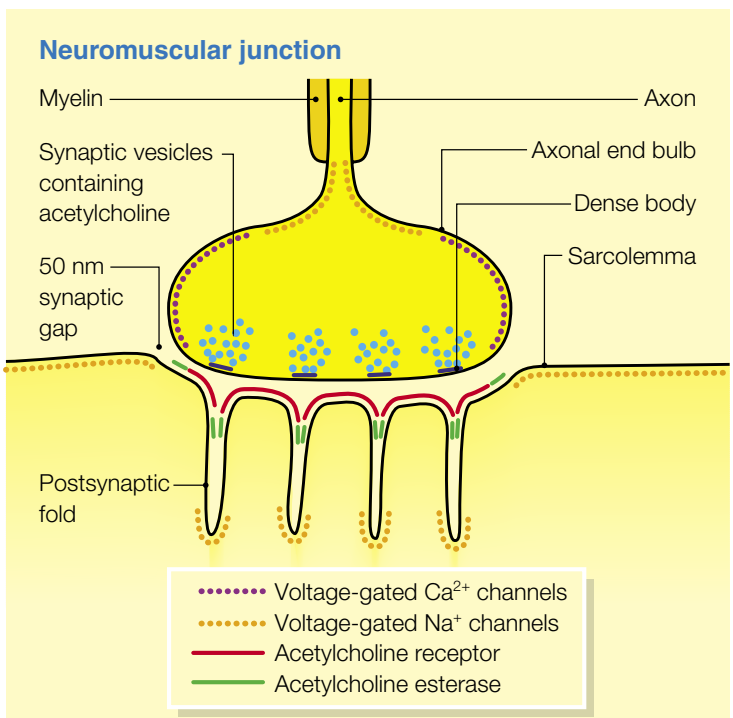
In order for the action potential in the motor axon to activate the muscle fibre by exciting the electrically excitable sarcolemma, several complex steps have to be completed. These include the release of the chemical transmitter acetylcholine (ACh) from the axon terminal by exocytosis, activation by transmitter of nicotinic ACh receptors at the end-plate, generation of an end-plate potential and finally the production of the sarcolemmal action potential. All of these events must be completed rapidly because some skeletal muscle fibres are able to respond to a frequency of motor neuron action potentials greater than 100 Hz for short periods. The process of chemical transmission at the NMJ induces a delay of about 0.5 ms between the time of arrival of an action potential presynaptically and the appearance of a muscle action potential.

Presynaptic transmitter release

The axon ending is typically enlarged and divided at the NMJ to form end bulbs arranged in the end-plate region like the fingers of a hand. The end bulbs contain ACh packaged into membrane vesicles (visible only under the electron microscope) at a high concentration of 5000–10,000 molecules per vesicle. Each end bulb contains thousands of these vesicles, a proportion of which have to release their contents synchronously to activate the end-plate region. This process, called excitation–secretion coupling, requires Ca^{2+}.

At rest, the free Ca^{2+} concentration in presynaptic endings is kept below 10^{-6} M by the low membrane permeability to Ca^{2+}, sequestration of Ca^{2+} by mitochondria and an active Na^+/Ca^{2+} exchange pump in the axolemma. Consequently, at rest, most ACh is kept sealed in the presynaptic vesicles. There is a low level of resting release, thought to represent the random collision of vesicles with the presynaptic membrane leading to exocytosis, manifested as very small postsynaptic depolarizations of about 0.5 mV, termed miniature end-plate potentials. Their function, if any, is unknown but at any one end-plate region they occur at intervals of 1/s or less. The arrival of an action potential at the presynaptic region opens voltage-gated Ca^{2+} channels, which occur at high density in this region of the axolemma. Although the absolute concentrations of Ca^{2+} on either side of the axolemma are low, there is a steep concentration gradient driving the diffusion of Ca^{2+} into the axon terminal because of the low intracellular concentration at rest. It is this subsequent influx of Ca^{2+}, increasing intracellular concentration above 10^{-6} M that is directly responsible for releasing vesicular ACh.

Vesicles are associated with specialized presynaptic areas called dense bodies, which occur opposite postsynaptic clefts and appear to be the sites of transmitter release (Figure 1). The vesicular membrane contains a variety of specialized proteins. One, synaptotagmin, has the ability to combine, in the presence of Ca^{2+}, with others including neurexin and SNAP-25 present in the axolemma of the terminal region. When they combine they form relatively large channels that effectively link the interior of the vesicle with the synaptic cleft between presynaptic and postsynaptic structures. The formation of numerous such channels permits the unloading, by simple diffusion, of ACh from the vesicle into the synaptic cleft. Within 1 ms the depolarizing phase of the presynaptic action potential is over, the Ca^{2+} channels close, Ca^{2+} influx ceases and the free intracellular Ca^{2+} concentration is rapidly returned to below 10^{-6} M. In the absence of Ca^{2+} the now empty vesicles are recycled by a mechanism which is not yet understood. The way in which the vesicles touch and bind to the presynaptic terminal under the influence of Ca^{2+} and are then released to be recycled has been called a 'kiss and run' mechanism. Every evoked response at the neuromuscular junction requires the synchronous release of acetylcholine (ACh) from up to 100 or more vesicles. The process of vesicle recycling and ACh production therefore has to be very active and efficient to keep up with high stimulation rates. In very active NMJs, released ACh feeds back to populations of ligand-gated ACh receptors on the axon terminals and acts via a second messenger system to increase transmitter production in the terminal.



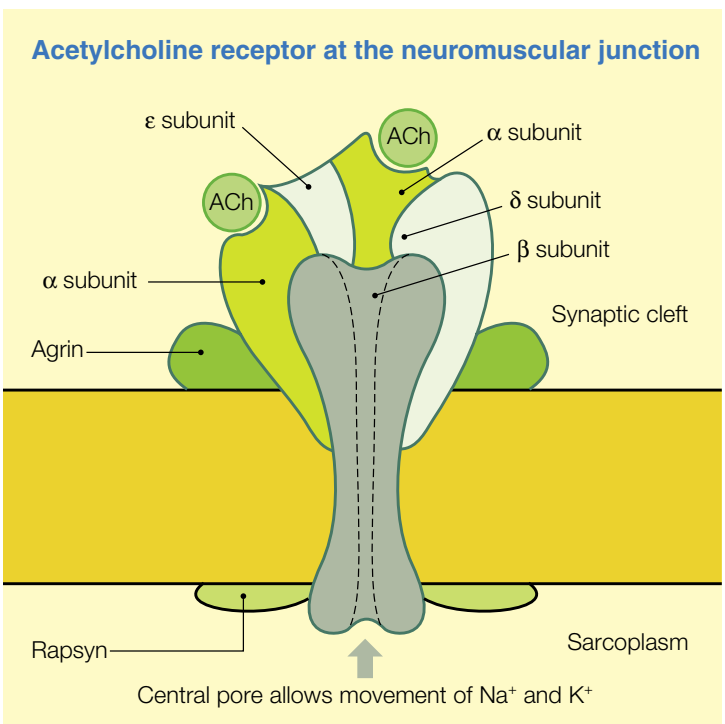
Presynaptic Ca^{2+} concentration is actively maintained below 10^{-6} M at rest. Activation of voltage-gated Ca^{2+} channels by an action potential invading the axonal end bulb increases Ca^{2+} concentration and initiates excitation–secretion coupling to release acetylcholine

1

Postsynaptic transmitter action

The postsynaptic region of the end-plate is separated from the axon by a 50 nm gap. Typically the end-plate region forms a series of folds that increase the contact area significantly (Figure 1). At a typical NMJ, the synaptic area is about 3000–6000 μm^2. This contrasts with about 1 μm^2 of contact at a CNS synapse where subsynaptic folding is absent and underlines the differences in their functions. While the postsynaptic response to most stimuli to a CNS synapse is small and could not reach threshold for an action potential in the absence of summation, the postsynaptic response at the NMJ is always large and is always suprathreshold for a muscle action potential.

The ACh released presynaptically diffuses rapidly across the synaptic cleft. At the crest of each subsynaptic fold there is a high density of nicotinic ACh receptors, which are held in place by two types of protein, agrin and rapsyn (Figure 2). At each NMJ there are about 3 x 10^7 ACh receptors, which equates to 10^4 ACh receptors per μm^2. Each ACh receptor is composed of five protein subunits, two of which, the α units, react with ACh. The ACh receptor at the NMJ, which is blocked by curare, is similar to the nicotinic ACh receptor that occurs widely in the nervous system except that one subunit, the γ unit, is replaced in the NMJ receptor by an ε subunit. The receptor present on fetal muscle fibres does not have this ε subunit, therefore it is considered to occur as part of the maturation process of muscle. The extrajunctional receptors that typically appear all over muscle fibres after denervation, leading to denervation hypersensitivity, do not have the ε subunit either.



When activated by two molecules of acetylcholine (ACh) the receptor acts as an ionopore to allow the passage of monovalent cations. The ε subunit is unique to the junctional receptor

2

The ACh receptor is also an ionopore and when the active sites of both units are each combined with a molecule of ACh the receptor changes its conformation to open a central pore through the receptor, which behaves as a non-specific cation channel (Figure 2). The receptor spans the postsynaptic membrane completely, which allows cations, mainly Na^+ and K^+, to move freely across the membrane. The net result is that the combined inward current flowing through all the activated ACh receptors at the end-plate results in depolarization of the postsynaptic membrane to about –10 mV. ACh is rapidly broken down by the enzyme acetylcholinesterase, located close to the ACh receptors at the crests of the subsynaptic folds (Figure 1). Therefore, the inward current is transient and is followed by repolarization of the end-plate region to the resting state. Unlike voltage-gated Na^+ channels, ACh receptors are not refractory and therefore there is no relative or absolute refractory period to the postsynaptic response. The transient depolarization and repolarization, termed the end-plate potential, is responsible for activating the sarcolemma to produce a muscle action potential.

Activation of the sarcolemma

The end-plate potential is a large depolarization of about 70–80 mV. However, it does not take the membrane potential above 0 mV (i.e. it does not overshoot zero potential as does the action potential). It is also slower than an action potential, lasting 10–15 ms, mainly owing to its slow repolarization. In the case of the end-plate potential, repolarization depends on the chemical breakdown of ACh by acetylcholinesterase to prevent further reactions with ACh receptors and to allow the channels to close. Thus, the properties of an end-plate potential differ in many respects from those of a normal action potential (Figure 3). Nevertheless, because the fast depolarizing phase of the end-plate potential is associated with a relatively intense current it is always strong enough to activate voltage-gated Na^+ channels on the sarcolemma. These Na^+ channels occur in high concentrations at the base of the subsynaptic folds and around the edges of the end-plate region (Figure 1). The end-plate potential activates Na^+ channels in the subsynaptic folds and the combination of the end-plate potential and the depolarization resulting from activated Na^+ subsynaptic channels, is sufficient to overcome the considerable membrane capacitance of the end-plate region and to excite the population of Na^+ channels outside the end plate. Once these Na^+ channels open, an all-or-none action potential is generated and a muscle action potential propagates in all directions from the end-plate across the sarcolemma. This action potential is responsible for activating muscle contraction via the process known as excitation– contraction coupling. ◆

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Comparison of the properties of an action potential and an end-plate potential

	Action potential	End-plate potential
Initiation	By depolarization	By acetylcholine
Rising phase	Selective increase in Na^+ permeability	Simultaneous increase in Na^+ and K^+ permeabilities
Falling phase	Selective increase in K^+ permeability	Passive decline in permeabilities due to acetylcholinesterase action
Potential change	Reverses polarity	Does not exceed –10 mV
Additional	Regenerative ascent followed by refractory period	No regenerative action and no refractory period
Pharmacology	Blocked by tetrodotoxin, not influenced by curare	Blocked by curare, not influenced by tetrodotoxin

Neural Reflexes

Chris J D Pomfrett

Chris J D Pomfrett is Lecturer in Neurophysiology Applied to Anaesthesia at the University of Manchester, UK. He qualified from Queen Mary College and The Medical College of St Bartholomew's Hospital, London. He has conducted research into cortical visual processing during anaesthesia and determining the depth of anaesthesia using measurements taken from the brainstem.

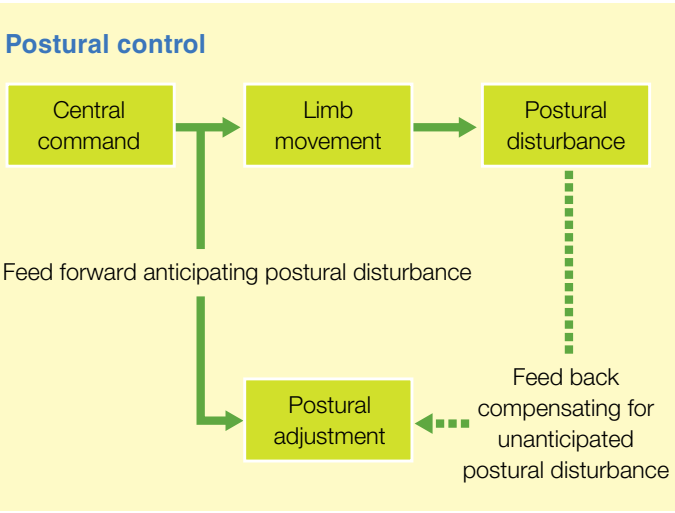
Anaesthesia and sedation are linked closely to neurophysiology. The components of balanced anaesthesia reversibly disrupt natural mechanisms in the CNS.

- Loss of consciousness (hypnosis) and amnesia during general anaesthesia are associated with reductions in the cerebral metabolic rate below thresholds. γ-aminobutyric acid (GABA), glutamate and glycine receptors are involved in the mechanisms of general anaesthesia, whereby anaesthetic agents either potentiate inhibition or antagonize excitation.
- Analgesia is most potently induced by the action of opioid agents on central endogenous opiate receptors.
- Local anaesthetics prevent the propagation of action potentials and disrupt nerve conduction.
- Neuromuscular transmission is disrupted during competitive neuromuscular blockade.

Posture

Posture is the orientation of any body segment relative to the gravitational vector (angular measurement from vertical). It is distinct from balance, which is the specific control of posture in order to prevent falling.

Humans are inherently unstable because they are bipedal and would fall over without an active control system. Control of posture is involuntary and automatic (Figure 1), and is disturbed by neurological deficits such as the reversible pharmacological effects of anaesthetics and ethanol, or the more permanent effects of degenerative disease. Much of this postural control, including righting reflexes, is controlled by the midbrain.



1

The three sensory systems that cooperate to maintain balance and posture are vision (information is almost instantaneous and permits route planning), proprioception (indicating joint and muscle state) and the vestibular system.

Monosynaptic spinal reflexes, particularly those involving proprioceptors, are an important component for the maintenance of posture. In the patellar tendon reflex (see later), afferent sensory input leads to efferent motor response without real-time control from the brain, though descending spinal pathways may modulate the sensitivity of the reflex loop. The afferent sensory fibres from muscle spindles are thick (10–20 μm in diameter) and myelinated, therefore action potential conduction velocities are fast, about 100 m/s. The total reflex time for the intact system is 25–30 ms; much faster than if the sensory and motor cortex of the brain were involved. Specific postural reflexes include:

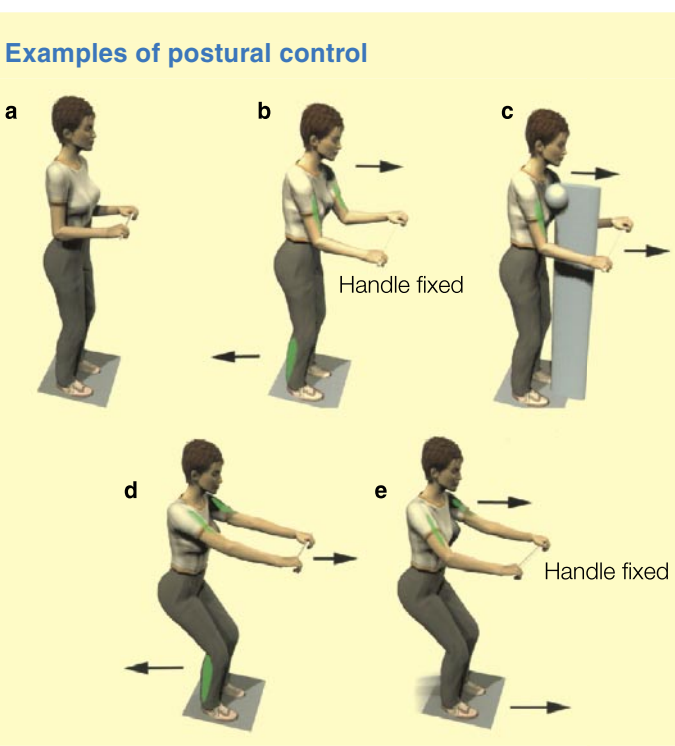
- vision (responsible for reflex and volitional gaze stabilization)
- vestibular-ocular reflex (compensates for head movements)
- cervico-ocular reflex (receptors in the neck take over if the vestibular system is compromised)
- optokinetic or optomotor reflex (detects retinal image slip and permits figure–ground discrimination of objects against a moving background).

Three main types of eye movement are related to the control of posture:

- saccadic movements direct a shift towards targets of interest
- smooth pursuit movements track moving targets
- vergence movements ensure binocular alignment on an object.

The control of posture falls into two broad categories (Figure 2).

- Anticipatory (feed forward). The CNS predicts disturbances and produces programmed responses in order to maintain stability.
- Compensatory (feed back). Movements are evoked by sensory events following loss of balance.



a Volunteer is standing quietly
b Volunteer pulls on a fixed handle. Posture is maintained by the gastrocnemius muscle contracting before the biceps pull the handle
c The handle is pulled while the volunteer's chest is supported. The biceps give a reflex contraction in response to the movement of the handle, but the gastrocnemius remains inactive
d The handle pulls the unsupported, unsuspecting volunteer. The biceps and gastrocnemius contract together to maintain balance
e The foot platform slides forward unexpectedly. The gastrocnemius does not activate, so the volunteer does not fall. The biceps contract, pulling the volunteer forward

(Adapted from GM Jones: In Kandel E R, Schwartz J H, Jessell T M, eds. *Principles of Neural Science*. London: Elsevier, 2000.)

2

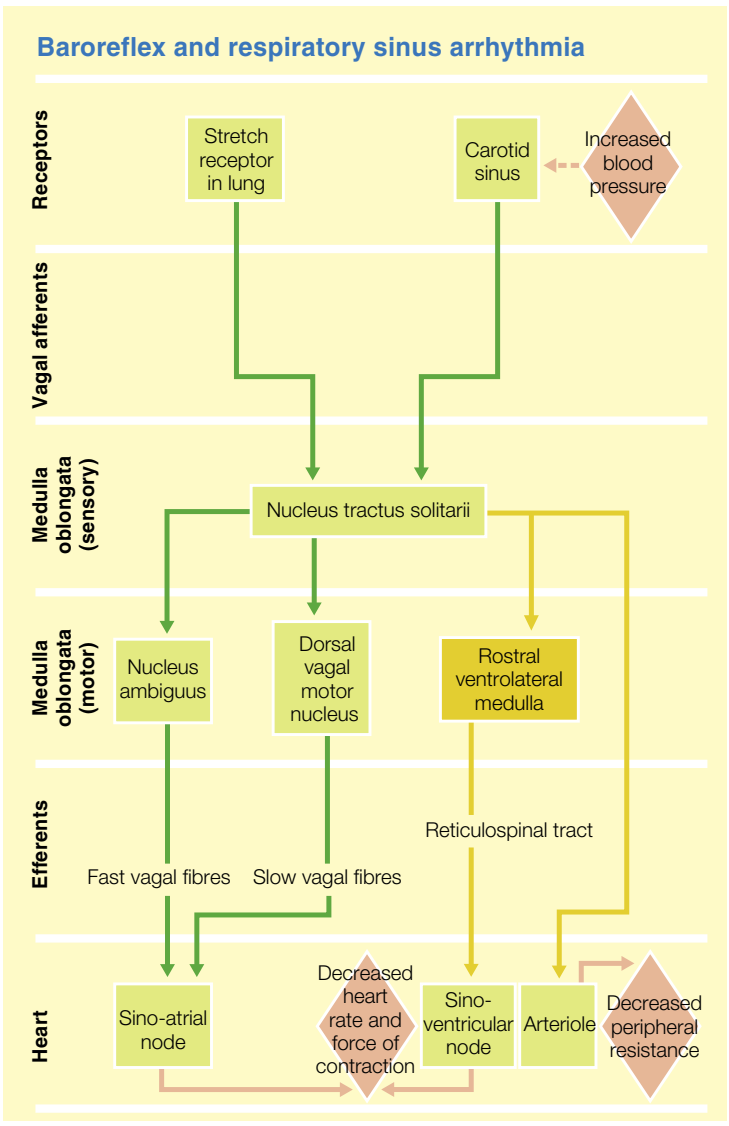
Autonomic nervous system

Sympathetic and parasympathetic systems work in balance to regulate breathing, circulation, body temperature, metabolism, secretion, digestion and the reproductive system involuntarily (Figure 3; see also *Anaesthesia and Intensive Care Medicine* **2:5:** 206). Much work has been done on the rat and care should be taken to ensure that the results are truly indicative of human physiology.

3

Cell bodies of preganglionic sympathetic neurons lie in the thoracic and upper lumbar spinal cord. Axons from these preganglionic neurons leave the spinal cord via the ventral roots and innervate the sympathetic ganglia arranged segmentally on either side of the spinal column. Although the cell bodies are situated in all segments of the spinal cord, anatomically the ganglia extend only as far as the first lumbar segment. Most preganglionic sympathetic axons are myelinated, and about 4 μm in diameter; they conduct action potentials at velocities lower than 20 m/s. The preganglionic fibres use acetylcholine as a neurotransmitter. Axons from the postganglionic neurons innervate effectors of the sympathetic system: the thoracic spinal fibres innervate the head, thorax, abdomen and upper extremities; lumbar spinal fibres innervate the pelvis and lower extremities. Postganglionic fibres may be long because the sympathetic ganglia are usually some distance from the effector target. Most postganglionic sympathetic fibres use noradrenaline as a neurotransmitter at the target. Specific effectors are cardiac muscle, smooth muscle and glands responsible for sweating (cholinergic not noradrenaline), lacrimation, salivation and digestion.

The vagus nerve (X) is an important autonomic sensory and parasympathetic effector pathway connecting the brainstem to visceral organs and the larynx. Therefore, stimulating input from visceral receptors can potentially bypass spinal or epidural blockade during surgery even after an epidural or spinal nerve block via transmission along the vagus nerve, though some visceral sensory fibres enter the spinal column at the dorsal roots. Such autonomic visceral sensory inputs include noxious stimuli, pH and electrolyte concentrations in blood and stomach, inflation of the lungs, intraluminal pressure in the arterial system, and distensions of the bladder, veins and intestine. The vagus nerve is a proven route for infection of the CNS by pseudorabies virus, and may be a route for neuroinvasion by transmissible spongiform encephalopathies (e.g. variant Creutzfeld–Jacob disease). Parasympathetic control of heart rate is via the vagus nerve, and is visible as both low and high frequency components (Figure 4). The low frequency control is most prominent in the baroreflex, driven by slow fibres originating in the dorsal vagal nucleus of the medulla. High frequency parasympathetic slowing of heart rate occurs breath by breath, and gives rise to respiratory sinus arrhythmia, the level of which falls with increasing depth of anaesthesia and is guided by fast fibres originating in the nucleus ambiguus of the medulla.



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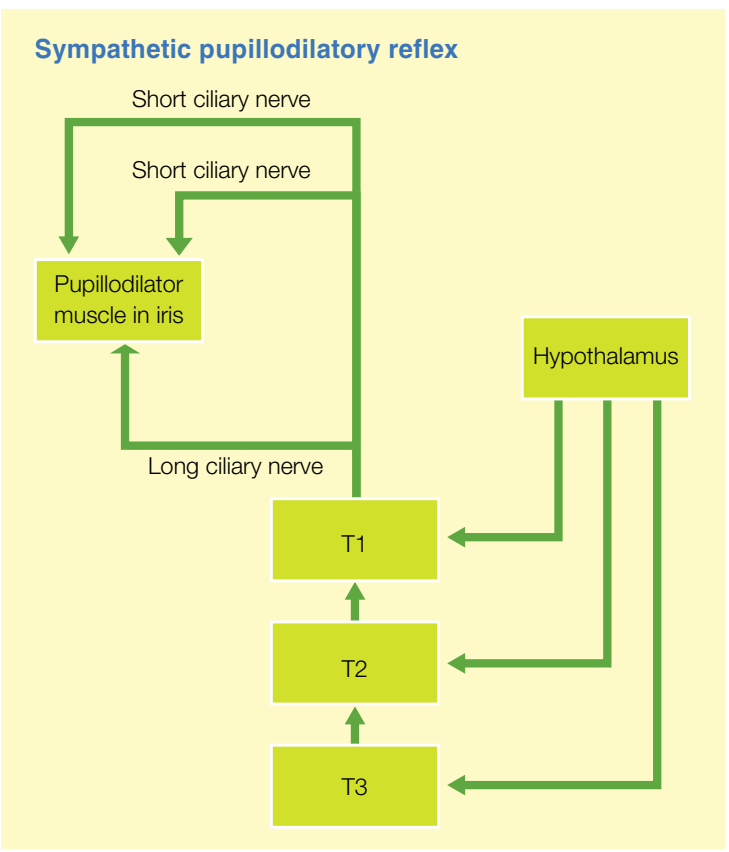
Neurological reflexes

Neurological reflexes are controlled by reflex arcs. They are complete neuronal networks originating at a sensory receptor, travelling through the CNS and ending at a peripheral effector. Reflex arcs are usually capable of functioning in isolation and exhibit standard responses to sensory stimuli. Descending influences from higher centres in the CNS can modulate the sensitivity of reflex arcs. The baroreflex is a typical reflex arc.

Reflex arcs are involved in controlling the pupillary light reflex, which depends on a balance between the sympathetic pupillodilator pathway and the parasympathetic pupillo-constrictor pathway (Figures 5 and 6).



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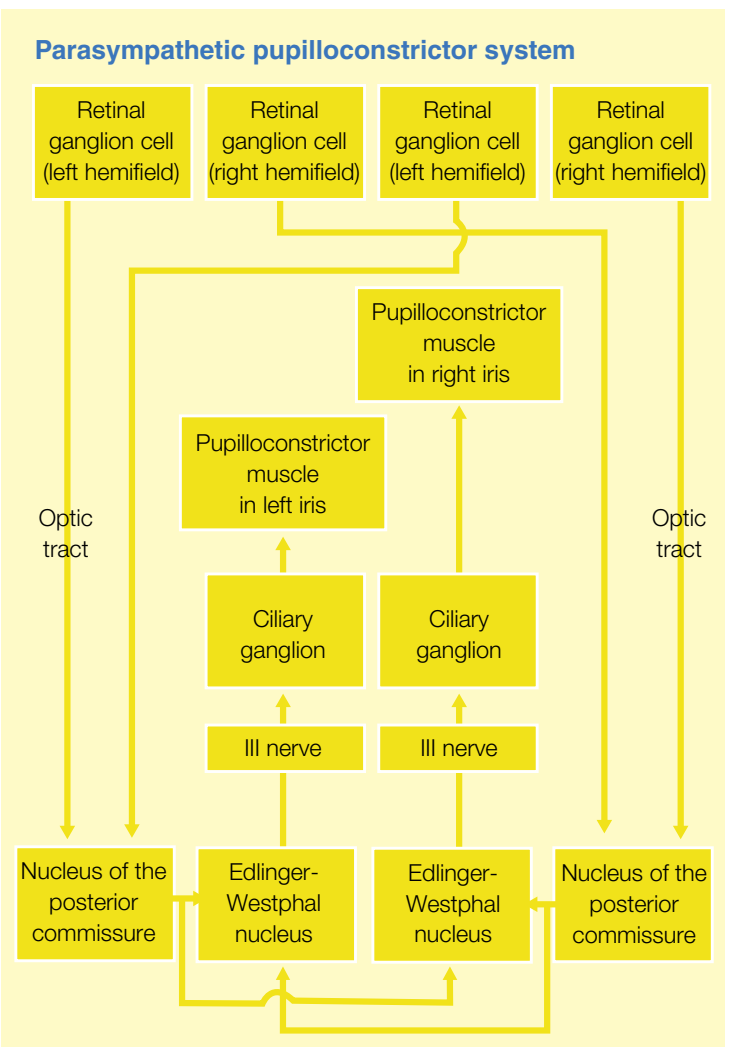

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Retinal ganglion neurons project to pretectal areas preserved for autonomic processing of retinal information via the optic nerve and optic chiasm. Pretectal neurons project to the accessory oculomotor nucleus. Axons from the accessory oculomotor nucleus innervate the optic ganglia via the brainstem and the oculomotor nerve (preganglionic parasympathetic nerve III). Motor neurons originating in the optic ganglia innervate the smooth muscle of the pupillary sphincter. Antagonism of parasympathetic pupilloconstriction with atropine leads to pupil dilation. Increasing concentrations of hypnotic anaesthetics inhibit the light reflex, as do opioids.

Brainstem death is tested by using the pupillary light reflex in conjunction with a number of other cephalic reflexes (i.e. corneal, oculoauditory, oculovestibular, oculocephalic, ciliospinal, snout, pharyngeal, cough and swallowing).

Monosynaptic stretch reflex

Voluntary muscles contain a number of specialized sensory receptors known as muscle spindles. The muscle spindle is an example of a stretch receptor. The frog has a single muscle spindle in each toe, making it a good experimental system because activity recorded in the sciatic nerve as a result of movement of one toe is from just one muscle spindle. In humans, the muscle spindle has intrafusil muscle fibres (15–30 μm in diameter, 4–7 mm long) that are anatomically parallel but separately innervated to the normal extrafusil fibres (50–100 μm in diameter, a few mm to tens of cm in length). Intrafusil muscle fibres are controlled by the gamma motor system, a completely separate neural system from the normal control of extrafusil fibres.

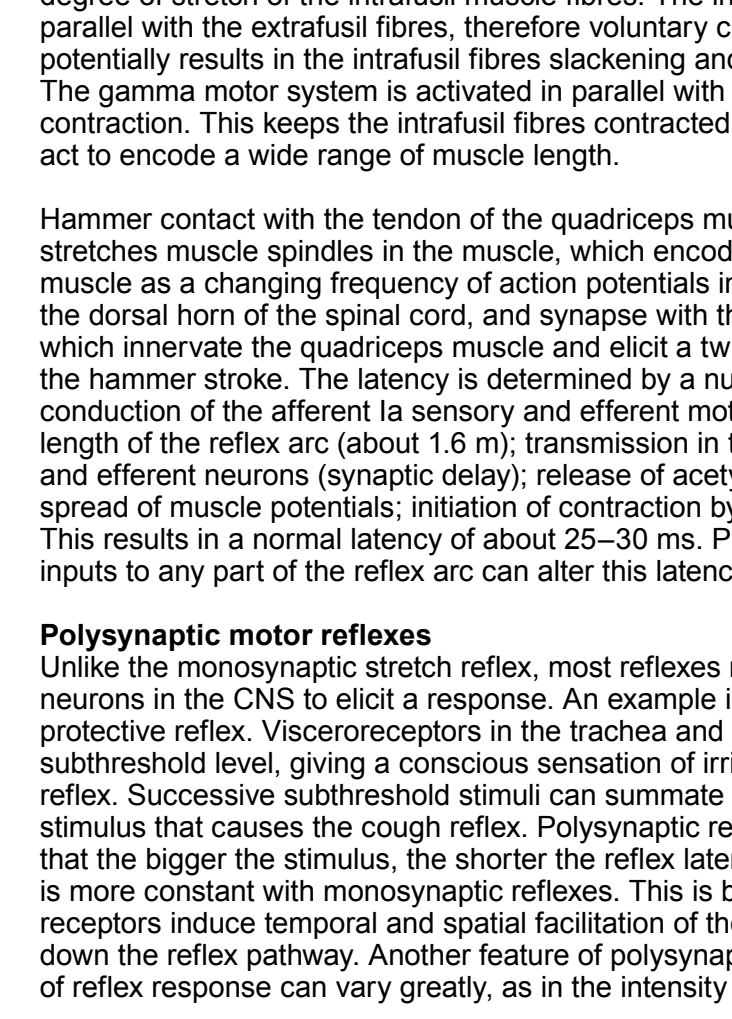
Sensory innervation of the muscle spindle comprises fast, group Ia myelinated afferent neurons wound round the intrafusil muscle fibres (annulospiral ending). The frequency of action potentials propagated in the afferent neurons is proportional to the degree of stretch of the intrafusil muscle fibres. The intrafusil fibres are anatomically in parallel with the extrafusil fibres, therefore voluntary contraction of the extrafusil fibres potentially results in the intrafusil fibres slackening and not communicating stretch. The gamma motor system is activated in parallel with normal, extrafusil muscle fibre contraction. This keeps the intrafusil fibres contracted, so that the muscle spindle can act to encode a wide range of muscle length.

Hammer contact with the tendon of the quadriceps muscle, below the patella, briefly stretches muscle spindles in the muscle, which encode the change in length of the muscle as a changing frequency of action potentials in Ia afferent nerves. These enter the dorsal horn of the spinal cord, and synapse with the cell bodies of motor neurons, which innervate the quadriceps muscle and elicit a twitch with a short latency after the hammer stroke. The latency is determined by a number of factors: the speed of conduction of the afferent Ia sensory and efferent motor fibres (about 100 m/s); the length of the reflex arc (about 1.6 m); transmission in the synapse between afferent and efferent neurons (synaptic delay); release of acetylcholine at the motor end plates; spread of muscle potentials; initiation of contraction by the muscle fibre action potential. This results in a normal latency of about 25–30 ms. Physiological damage or abnormal inputs to any part of the reflex arc can alter this latency or prevent the reflex.

Polysynaptic motor reflexes

Unlike the monosynaptic stretch reflex, most reflexes require the interaction of many neurons in the CNS to elicit a response. An example is the cough reflex, a typical protective reflex. Visceroreceptors in the trachea and bronchi can be stimulated to a subthreshold level, giving a conscious sensation of irritation that does not elicit the reflex. Successive subthreshold stimuli can summate to produce one suprathreshold stimulus that causes the cough reflex. Polysynaptic reflexes often exhibit the effect that the bigger the stimulus, the shorter the reflex latency, whereas the reflex latency is more constant with monosynaptic reflexes. This is because more intensely activated receptors induce temporal and spatial facilitation of their effects on interneurons further down the reflex pathway. Another feature of polysynaptic reflexes is that the magnitude of reflex response can vary greatly, as in the intensity of a cough.

A further example of a polysynaptic reflex is the withdrawal of a limb in response to a noxious stimulus (Figure 7). Flexor muscles ipsilateral to the noxious stimulus are stimulated as ipsilateral extensor muscles are relaxed. At the same time, local interneurons ensure that contralateral extensor muscles are stimulated and contralateral flexors are inhibited. The local interneurons are constantly under the influence of descending interneurons, which can influence the magnitude of this reflex depending on behavioural requirements.



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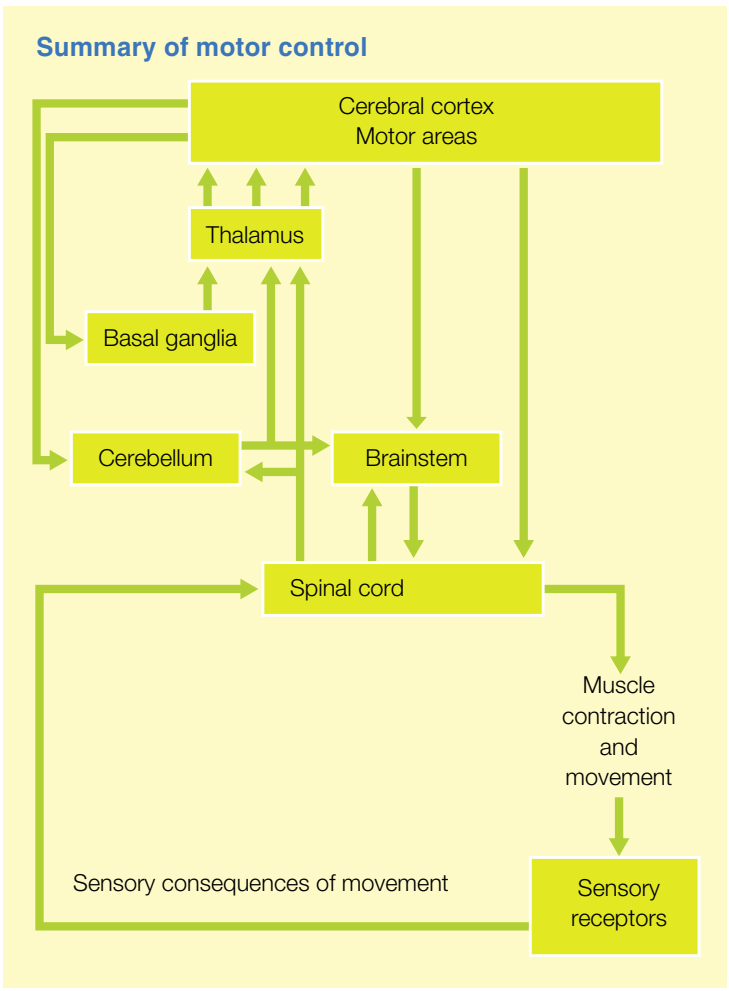
As the number of synapses increases, so does the number of potential sites of pharmacological action. Excessively high levels of hypnotic anaesthetic agents in animals increase the amount of simple peripheral motor activity, presumably because of a reduction in descending inhibition, which would otherwise damp these reflexes.

Polysynaptic reflexes also overlap in function. For example, motor neurons involved in the cough reflex may also receive input from interneurons responsible for the timing of normal respiration.

Motor function: spinal and peripheral

Motor function is based on a hierarchical structure (Figure 8). Simple, spinal, monosynaptic motor reflexes are the simplest motor pathways. All motor pathways end with a motor neuron, acting as an interface between the chemical electrical energy of the CNS and the mechanical action of the muscle.



8

Motor cortex and the corticospinal pathway

The motor cortex is topographically (somatotrophically) mapped to different motor structures. The precentral gyrus (primary motor cortex) is characteristically thick (3.5–4.5 mm) and comprises large pyramidal neurons (Betz cells) in layer V. The large pyramidal neurons, along with smaller pyramidal cells in layer III, comprise the corticospinal-tract neurons, with axons running through white matter, through the posterior limb of the internal capsule, and into the basis pontis of the basilar pons of the brainstem. The corticospinal tract descends into the medullary pyramids of the anterior brainstem, hence its alternative name of pyramidal tract. 70–90% of corticospinal axons cross over to the other side of the brainstem at the descussation of the pyramids. The axons of large pyramidal cells have the highest conduction velocities (60–90 m/s) of the corticospinal tract, and yet comprise only 3% (some 30,000 fibres) of all pyramidal cell axons. In the spinal cord, corticospinal neurons synapse on to motor neurons directly or segmental interneurons. Some corticospinal neurons in the adult are over 1 m long.

The corticospinal tract allows direct cortical control of fine movements in the face or distal extremities; these movements are fast and under the direct control of the higher brain. Examples of corticospinal tract control are buttoning a jacket or playing a trumpet. Interruption of the corticospinal tract results in symptoms predominantly on the side contralateral to the injury.

Basal ganglia

The basal ganglia comprise four large, subcortical nuclei participating in the control of movement: the striatum (comprising the caudate nucleus, the putamen and the ventral striatum); globus pallidus (or pallidum); the subthalamic nucleus; and the substantia nigra (comprising pars reticula and pars compacta). Large areas of the cerebral cortex, thalamus and brainstem innervate the striatum. The basal ganglia are responsible for the inhibition of unwanted motor programmes and the facilitation of desired movements. The basal ganglia are also responsible for the control of other functions in addition to voluntary movement, including cognition and oculomotor movement. Four segregated circuits connect the basal ganglia with the cerebral cortex and thalamus: skeletomotor circuit; oculomotor circuit; prefrontal circuit; and limbic circuit.

Lesions in the basal ganglia lead to Parkinson's disease, Huntington's disease, or hemiballismus. Parkinson's disease is a hypokinetic disorder characterized by impaired initiation of movement (akinesia), and reduced magnitude of voluntary movement (bradykinesia), accompanied by muscle rigidity and tremor. The region of damage is the dopaminergic tract connecting the substantia nigra to the striatum, and one treatment is the administration of L-dopa, the precursor of dopamine, which crosses the blood–brain barrier. Another treatment is surgical pallidotomy. Patients with Huntington's disease (a hereditary, hyperkinetic disease) exhibit adverse cognitive and emotional effects, as well as excessive motor activity, with involuntary movements (dyskinesias) and decreased muscle tone (hypotonia). The dyskinesias can be slow and writhing (athetosis), jerky random movements (chorea), violent large movements (ballism) or abnormal postures (dystonia). Damage in Huntington's disease is widespread in the brain, but appears earliest in the striatum and may be caused by excessive glutamate release. In hemiballismus, small strokes cause lesions in the subthalamic nucleus and the symptoms are violent movements of the contralateral limbs.

Rubrospinal and tectospinal pathways

The rubrospinal pathway originates in the midbrain, crosses over in the midbrain, descends in the dorsal labial column and terminates in the dorsal lobe grey matter of the spinal cord. It mediates voluntary control of movements, but excludes fine movement of the fingers, toes and mouth. The tectospinal pathway mediates head and body orientation in response to discrete visual, auditory and tactile stimuli, often originating from the same source. The reticulospinal pathways originate in the brainstem reticular formation and stabilize movement on uneven surfaces. ◆

Physiology of pregnancy

Anaesthesia
and intensive care medicine
on CD-ROM

Functions of the Placenta

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The placenta is an interface for the exchange of gases, nutrients and waste products and therefore has respiratory, nutritive and excretory functions. It is also a partial barrier to the transfer of drugs, bacteria and cells between mother and fetus. It is an important site of hormone production and, as an integral part of the fetomaternoplacental unit, has a profound influence on the endocrinology of pregnancy.

Placental blood flow
The fetal and maternal circulations interface in the placenta. The maternal circulation through the intervillous space of the placental bed is almost wholly pressure dependent, with little or no autoregulation. This is unusual because control of blood flow in the arterial tree of most organs depends on vasomotor activity in the arterioles. However, in the pregnant uterus the muscular walls of the spiral arterioles are destroyed by trophoblasts and become passive channels in the uterine circulation.

Blood flow to the uterus is difficult to quantify because the uterus is supplied by a number of arterial channels that anastomose with the ovarian and vaginal blood supplies. Blood flow to the uterus increases throughout pregnancy reaching about 500 ml/minute at term.

The fetal circulation through the placenta is altered by the resistance of the placenta. Usually there is forward flow in the umbilical artery throughout the cardiac cycle of the fetus. However, if placental resistance is increased, for example in pre-eclampsia, flow in the umbilical artery may be absent during diastole. Umbilical artery Doppler measurements are useful in monitoring high-risk pregnancies, because they reflect placental resistance.

Placental transfer
In a healthy human pregnancy the transfer of a substance from mother to fetus depends on:
- maternal uteroplacental blood flow
- fetal umbilical blood flow
- surface area (gross and functional)
- placental metabolism
- concentration in maternal circulation
- concentration in fetal circulation
- mechanism of transfer
- availability of carrier proteins and relative affinities (e.g. fetal haemoglobin).

The materials are transported across the placental membrane by simple diffusion, facilitated diffusion, active transport or pinocytosis. Transfer of a substance may be influenced by its molecular weight, ionization, lipid solubility and protein binding.

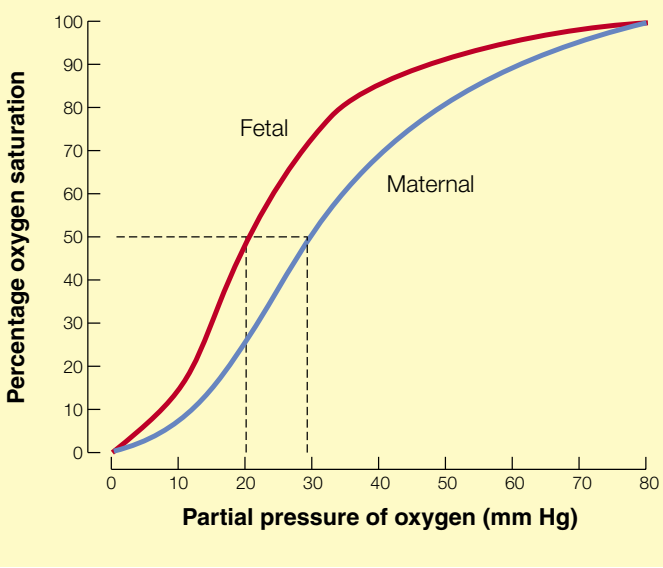
Gases
Respiratory gases cross the placenta by diffusion. The rate and quantity of gas transferred depends on the concentration of each on either side of the placenta, the dissociation curves in both maternal and fetal blood and the supply of blood to each side of the placenta.

Fetal haemoglobin has a greater affinity for oxygen than maternal haemoglobin. The fetal oxygen dissociation curve is shifted to the left of the maternal curve (Figure 1). The partial pressure of oxygen of fetal haemoglobin 50% saturated (P_{50}) is lower (20 mm Hg) than that of maternal haemoglobin (27 mm Hg). This is because the γ chains in fetal haemoglobin bind 2,3-diphosphoglycerate (2,3-DPG) less avidly than the β chains in adult haemoglobin. If the following equation is considered:

$$HbO_2 + 2,3\text{-DPG} = Hb\text{-}2,3\text{-DPG} + O_2$$

it can be seen that in maternal blood, where 2,3-DPG binds to haemoglobin, the equation is tipped to the right and oxygen is liberated. However, in fetal blood where the binding of 2,3-DPG is less, the equation is tipped to the left, and more oxygen is bound to the fetal haemoglobin.

Oxygen–haemoglobin dissociation curves for fetal and maternal haemoglobin



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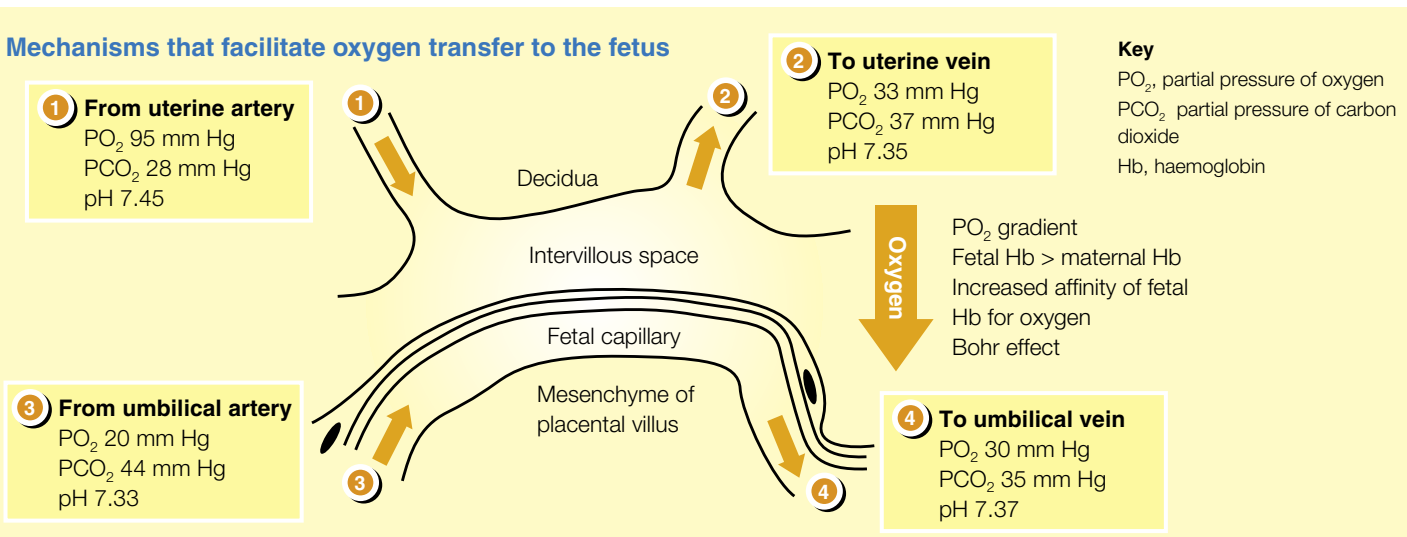
The increased haemoglobin concentration (17 g/dl) in the term fetus compared with the maternal haemoglobin concentration also favours oxygen transfer to the fetus. Therefore, at term, the amount of oxygen carried per ml of fetal blood is greater than that of maternal blood.

The decrease in oxygen affinity of haemoglobin when the pH of blood falls is called the Bohr effect. As fetal blood passes through the placenta, carbon dioxide is excreted into the maternal circulation. Consequently, maternal blood becomes more acidic and the oxygen affinity of the maternal haemoglobin decreases. Fetal blood becomes less acidic as it passes through the placenta and its oxygen affinity increases. There is therefore a double Bohr effect in the placenta. Figure 2 shows mechanisms, that facilitate oxygen transfer to the fetus.

Mechanisms that facilitate oxygen transfer to the fetus



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Carbon dioxide is very soluble and once in the blood soon passes into the red cells. There, about 30% combines with haemo-globin, about 10% is in physical solution, and 60% combines with water to make H_2CO_3 which ionizes almost immediately. The H^+ is buffered by fetal haemoglobin so there is only a slight drop in pH and the fetus is able to carry more carbon dioxide. The HCO_3^- passes out of the red cell. Because of the high haemoglobin content of fetal blood, there are smaller pH changes for any given increase in the partial pressure of carbon dioxide.

Deoxygenated haemoglobin binds more H^+ than oxygenated haemoglobin and forms carbamino compounds more readily, therefore venous blood can carry more carbon dioxide than arterial – the Haldane effect. At the placental surface, maternal blood releases oxygen and so its deoxygenated haemoglobin is free to bind to H^+ and carbon dioxide. At the same time in fetal blood, oxygen binds to the fetal haemoglobin molecule and carbon dioxide is released, facilitating the excretion of carbon dioxide into the maternal circulation. This is a double Haldane effect and occurs in the placenta only because of the relative positions of the fetal and maternal oxygen dissociation curves.

Fetal haemoglobin is a major buffer and in acidosis the oxygen dissociation curve shifts to the right so that for any given partial pressure of oxygen the oxygen saturation falls. This releases oxygen for use in the tissues and makes more fetal deoxyhaemoglobin available for buffering (deoxygenated haemoglobin is a better buffer than oxygenated haemoglobin).

Excretion
Excretion of carbon dioxide is discussed above. Urea and uric acid pass through the placental membrane by simple diffusion and bilirubin is cleared quickly.

Nutrients
Glucose passes through the placenta at a faster rate than might be expected on the basis of simple diffusion alone because there is a carrier system (intramembrane protein carrier molecules) that selectively binds glucose molecules. This facilitated diffusion mechanism can be saturated, but only with extreme hyper-glycaemia. Placental glucose carriers are insulin independent.

Amino acids cross the placenta against a concentration gradient – the concentrations in fetal blood are higher than in maternal blood. An energy-dependent, active-transport mechanism is employed. Transfer of amino acids is limited by the capacity of the placental membrane proteins to transfer amino acids, rather than by placental blood supply. Alcohol and nicotine inhibit placental amino acid transfer.

Essential fatty acids – linoleic and linolenic acids cannot be synthesized by the fetus and must be obtained transplacentally. Lipid transport across the placenta is less in humans than in some other mammals and appears to be non-selective.

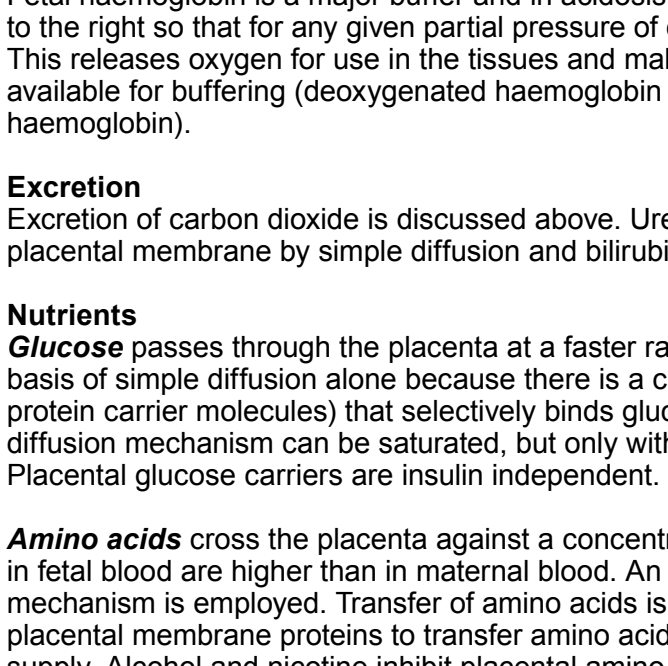
Calcium is transferred across the placenta by active transport against a concentration gradient.

Maternal antibodies such as immunoglobulin G are transferred across the placenta to the fetus by pinocytosis. Immuno-globulins are mainly protective and confer passive immunity to the immunologically immature fetus. However, in some situations transplacental transfer of maternal immunoglobulin can cause problems, for example in haemolytic disease of the newborn.

Drugs
Many drugs cross the placenta; some are beneficial to the fetus (e.g. prophylactic corticosteroids) but others may be teratogenic. A comprehensive review of pharmacokinetics in pregnancy is beyond the scope of this article; those drugs most relevant to the obstetric anaesthetist are discussed.

Anaesthetic agents: non-ionized lipophilic molecules cross the placenta more readily than ionized molecules. The structures of some of these drugs are illustrated in Figure 3.

Structure of some anaesthetic drugs



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Inhalational anaesthetic agents cross the placenta rapidly even with relatively short induction to delivery times. Nitrous oxide concentrations may reach 80% of that in the mother within 3 minutes and may cause diffusion hypoxia during prolonged delivery.

Induction agents cross the placenta rapidly. Some studies suggest that thiopental (thiopentone) crosses more freely than propofol. Etomidate crosses the placenta less easily because of its lower lipophilicity.

Muscle relaxants are quaternary ammonium salts (fully ionized) and do not cross the placenta readily. Maternal doses of suxamethonium greater than 300 mg are required before the drug can be detected in umbilical venous blood. Fetal neuromuscular blockade can occur if the mother is given repeated high doses of drug or if the fetus has pseudocholinesterase deficiency.

Anticholinergic agents – atropine crosses the placenta easily. Glycopyrrolate does not because of its highly polar structure.

Anticholinesterase agents – neostigmine and edrophonium are quaternary ammonium compounds that are ionized at physiological pH, therefore they do not readily cross the placenta.

Vasopressor agents are often used in regional obstetric anaesthesia. Ephedrine crosses the placenta easily but does not reduce uterine blood flow to a significant degree, unlike metaraminol.

Opioids – morphine crosses the placenta rapidly (fetomaternal ratio 0.92). Fentanyl, and its analogues, cross the placenta less readily because protein binding to albumin is high and this offsets the high lipophilicity.

Corticosteroids may be indicated for the treatment of maternal medical conditions during pregnancy. There are concerns that if large quantities of corticosteroid cross the placenta, fetal adrenal suppression could occur. In practice this does not happen with corticosteroids such as prednisolone because placental 11β dehydrogenase deactivates prednisolone. Under other circumstances it is important that glucocorticoids cross the placenta, for example to promote fetal lung maturity. The maternal:fetal concentrations of predisolone are 10:1 and those of betamethasone are 3:1; therefore betamethasone or dexamethasone should be used.

Anticoagulants: warfarin readily crosses the placenta. If the mother uses warfarin in the first trimester, warfarin embryopathy occurs in 15–25% of fetuses. The risk is reduced if warfarin is discontinued prior to 7 weeks' gestation. Heparin does not cross the placenta and its shorter half-life makes it a more suitable anticoagulant in pregnancy. Self-administered low molecular weight heparin is increasingly being used throughout pregnancy if anticoagulation is required.

Non-steroidal anti-inflammatory drugs may be used in pregnancy for their tocolytic effect. They cross the placenta and reduce fetal renal perfusion, resulting in reduction in liquor volume. There are isolated reports associating their use with premature closure of ductus arteriosus after 32 weeks' gestation.

Captopril is associated with fetal nephrotoxicity and fetal anuria. Its use is contraindicated in pregnancy, particularly in the second and third trimesters.

Anti-epileptics: 33% of infants born to mothers taking phenytoin have minor anomalies and 10% have major anomalies such as cleft lip and palate, hypertelorism, a broad nasal bridge, hypoplasia of distal phalanges and nails, growth deficiency and mental deficiency. Carbamazepine was thought to be relatively safe, but there is an increasing realization that it can be associated with similar abnormalities to phenytoin. Sodium valproate has been associated with a specific valproate syndrome and with an increased risk of neural tube defects (1–2%). Prophylactic folic acid, 5 mg/day, is recommended throughout pregnancy.

Hormone production

Maintenance of pregnancy

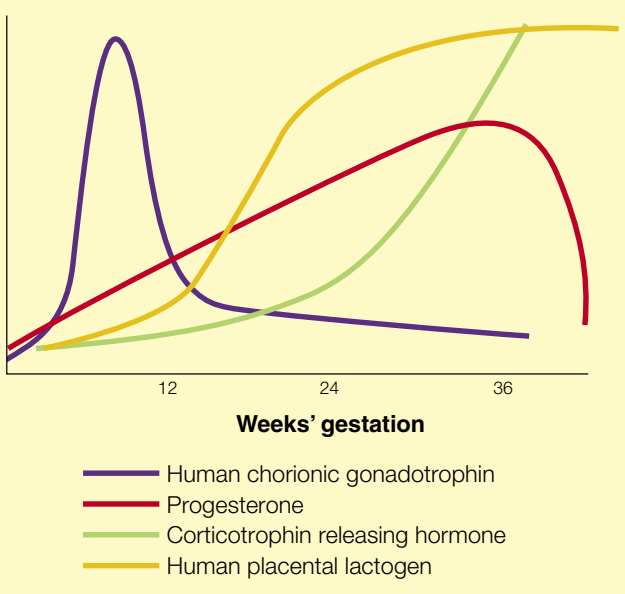
Following ovulation, a progesterone-producing corpus luteum is formed in the ovary. If fertilization does not occur the corpus luteum degenerates, levels of progesterone fall and menstruation occurs. If the egg is fertilized and implantation occurs the syncytiotrophoblast produces human chorionic gonadotrophin (hCG). This enters the maternal blood and maintains the activity of the progesterone-producing corpus luteum in the ovary during the first 7 weeks of pregnancy.

Detection of the β subunit of hCG in maternal urine forms the basis for pregnancy tests. Enough hCG is produced by the syncytiotrophoblast at the end of the second week following fertilization to give a positive pregnancy test. hCG and β-hCG levels peak at 9–11 weeks' gestation.

The placenta also produces oestrogen and progesterone from maternal and fetal precursors. By the sixth week of pregnancy these hormones are being produced in sufficient amounts in the placenta for the corpus luteum to become redundant. hCG secretion declines after 11 weeks' gestation but oestrogen and progesterone secretion increase until parturition.

Progesterone is produced by the placenta at all stages of gestation. Progesterone depends on the presence of oestrogen to exert its biological effects. It maintains uterine quiescence, is thermogenic and increases the respiratory minute volume, thereby reducing the partial pressure of carbon dioxide in the alveoli and the blood. Figure 4 shows how the secretion of placental hormones changes with gestation.

Patterns of change in placental hormones with gestation



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The maternofetoplacental unit

Some of the progesterone synthesized in the placenta enters the fetal circulation and provides the substrate for the formation of cortisol and corticosterone in the fetal adrenal glands. Pregnenolone, also synthesized in the placenta, is the substrate for formation of dehydroepiandrosterone (DHEA) in the fetal adrenal, and this is subsequently converted to 16-hydroxy-dehydroepiandrosterone in the fetal liver, and then to androstenedione and oestrogens in the placenta. The principal oestrogen formed is oestriol, which enters the maternal blood and is excreted in maternal urine. Maternal urinary oestriol therefore reflects the activity of fetus and placenta, and gave rise to the concept of the maternofetoplacental unit. Previously, maternal urinary oestriols were used as a measure of placental function. However, they have been shown to be of poor predictive value in assessing fetal well-being.

Human placental lactogen (hPL) is a protein hormone, secreted exclusively by the villus trophoblast. It has growth hormone-like effects in both the mother and the fetus. Circulating hPL levels are detected in maternal plasma by about 6 weeks' gestation. It acts as an antagonist to insulin by enhancing insulin resistance in the mother and increasing lipolysis and proteolysis, with the net effect of promoting the transfer of glucose and amino acids to the fetus. Levels of hPL increase linearly throughout gestation to peak at the 30th week. It disappears rapidly after delivery of the placenta.

Onset of parturition

The mechanism that initiates the onset of labour remains obscure. One of the many theories is that placental corticotrophin releasing hormone (CRH) may play an important role in the timing of its onset. CRH is synthesized in the syncytiotrophoblast and secreted into the maternal circulation. It rises steadily to 35 weeks and then increases markedly to term (Figure 4). CRH activity in both maternal and fetal circulations is modulated by CRH binding protein. This is synthesized in the liver, placenta and brain and its circulating levels are in excess of those of CRH, such that most of the circulating CRH is bound. However, towards term when the levels of CRH are rising those of the binding protein are declining, resulting in increasing free levels of circulating CRH. CRH enhances the release of placental adrenocorticotrophin (ACTH) and increases the production of prostaglandins by the trophoblast and fetal membranes. The prostaglandins further increase CRH production, resulting in a feed forward loop and a further increase in prostaglandin release. Once labour begins, it appears to be a self-perpetuating process involving many factors, including prostaglandins and oxytocin.

Endocrinology of pregnancy

Carbohydrate metabolism and diabetes

Insulin resistance develops in pregnancy, though the aetiology remains uncertain. The effect is likely to be mediated by the increased production of one or more of the hormones associated with pregnancy, possibly hPL or free cortisol. Women with pancreatic β cell insufficiency before pregnancy are unable to increase their insulin secretion adequately and tend to be hyperglycaemic in pregnancy.

The plasma glucose concentration of the fetus closely follows that of the mother. Insulin appears in the fetal circulation from 10 weeks' gestation. Insulin does not cross the placenta, therefore it has been postulated that in pregnancies complicated by diabetes, fetal hyperglycaemia resulting from maternal hyperglycaemia stimulates fetal pancreatic β cell hypertrophy, resulting in release of insulin. Fetal hyperinsulinaemia then leads to macrosomia and the subsequent complications of a traumatic delivery, neonatal hypoglycaemia, increased erythropoiesis and reduced surfactant production.

Conversely, in non-diabetic women with growth-restricted fetuses the fetus may have fewer pancreatic β cells. In later life these adults may have increased insulin resistance.

If a woman with diabetes needs treatment with prophylactic corticosteroids to enhance fetal lung maturity, insulin requirement may increase. It may also increase in labour. Insulin requirements reduce rapidly in the post-natal period. If an insulin infusion is used it needs to be reduced or stopped immediately after delivery, otherwise hypoglycaemia might result.

Thyroid

In pregnancy, the increased maternal glomerular filtration rate causes an increased loss of iodine in the urine, a reduction in serum iodide and increased size and vascularity of the thyroid gland. hCG produced in the first trimester has thyroid-stimulating properties. Total triiodothyronine (T3) and thyroxine (T4) are increased. Oestrogens also increase thyroid-binding globulin levels. Therefore free T3 and T4 are usually unchanged. In view of the alteration in thyroid-binding globulin it is important to measure TSH and free T3 or free T4 levels, when assessing thyroid function in pregnancy. Very little maternal TSH, T3 or T4 crosses the placenta. However, iodine is actively transferred by the placenta and fetal thyroid function begins at 10 weeks' gestation. ◆

FURTHER READING

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Uterine Physiology

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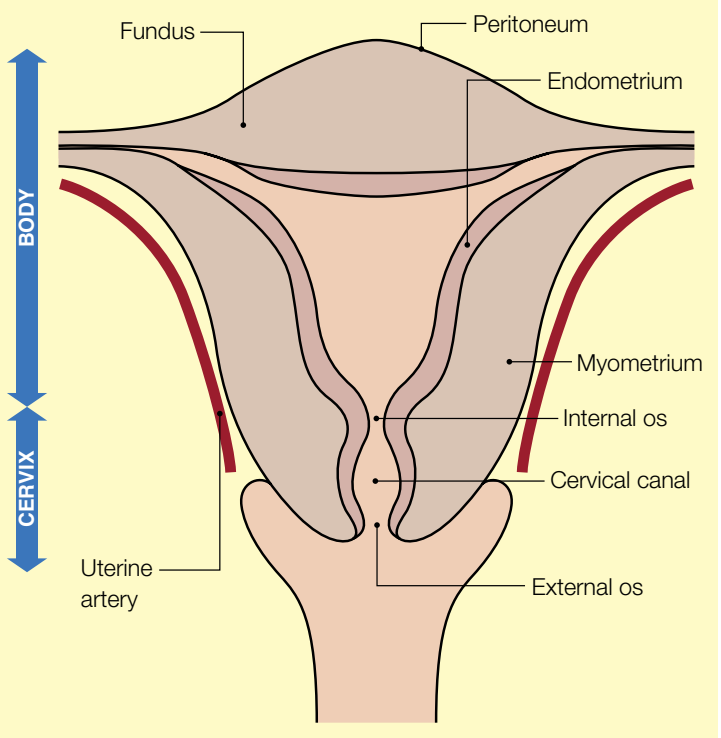
The role of the uterus is to nurture the fetus until parturition. Functionally it consists of a lower cervix (which acts at different times as a passageway, a barrier and a reservoir) and an upper body in which the fetus develops.

Anatomy

The superior part of the uterus is called the fundus; on either side of this the uterus communicates with the Fallopian tubes at the cornua (Figure 1). It is connected to and supported at its lower end by a number of ligaments connected to the bladder, the rectum and the walls of the pelvis. Some of these are peritoneal folds, others consist of unstriped muscle and fibrous tissue. The two broad ligaments pass from the margins of the uterus to the lateral wall of the pelvis. In 80% of women the uterus tilts up towards the abdominal wall, in 20% it is retroverted, tilting back into the pelvis.

The uterus has three layers (serosa, myometrium and endometrium). The serosa is formed by peritoneum. The muscular coat or myometrium is the middle layer and is composed of smooth muscle with areolar tissue, blood and lymph vessels and nerves. It is arranged in three distinct layers and the muscle fibres hypertrophy in pregnancy. The muscle of the uterus is not an anatomical syncytium like the heart, but in late pregnancy it forms a functional syncytium by the electrical coupling of the branching bundles of cells at gap junctions which greatly increase in number towards term. The formation of gap junctions is stimulated by the rise in the oestrogen/progesterone ratio (see later). The cervix is a more collagenous structure with a muscle content of only 10–15%. This gives it the capacity to undergo profound tissue remodelling during pregnancy and labour and to return to its former state after parturition. The endometrium or inner layer of the uterus is lined by columnar epithelium. It contains many tube-like glands that open into the uterine cavity and secrete mucus.

Anatomy of the uterus



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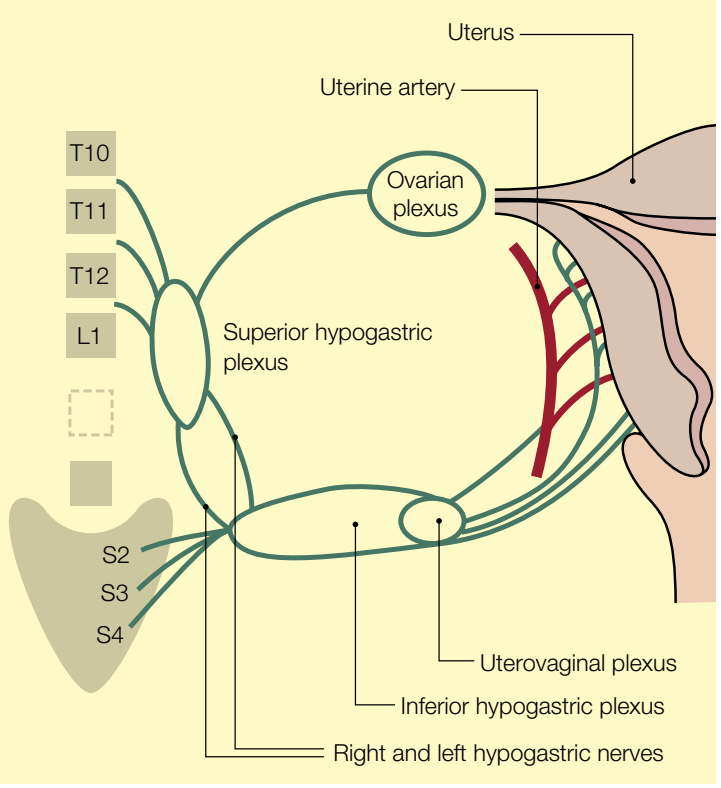
The uterus is supplied by the uterine branch of the internal iliac artery; it anastomoses with the ovarian artery (a branch of the aorta) and inferiorly with vessels of the upper vagina. The arteries supplying the uterus are remarkable for their tortuous course within the substance of the organ. The lymphatic drainage from the body of the uterus goes to the pelvic nodes, but lymph from the upper part drains to the para-aortic nodes. Occasionally, infection or malignancy may spread to the inguinal nodes.

Nerve supply

The nerve supply to the uterus is via autonomic pathways (Figure 2): the body is supplied predominantly by sympathetic fibres from T10–L1, the cervix by parasympathetic pathways from the sacral outflow S2–4. The sympathetic nerves pass via the superior hypogastric plexus; this is formed from the union of branches from the aortic plexus and the third and fourth splanchnic nerves and lies in front of the abdominal aorta. It gives off branches to the ovarian plexus, then divides below into the right and left hypogastric nerves. These lie in the extraperitoneal connective tissue before passing into the pelvis where they are joined by parasympathetic fibres from the pelvic splanchnic nerves and a few fibres from the sacral sympathetic ganglia to form the inferior hypogastric plexus which lies on the front of the sacrum. Branches from this plexus are distributed to the pelvic viscera either directly or accompanying the branches of the internal iliac artery.

Nerve supply to the uterus



2

The uterine nerves come from the inferior hypogastric plexus, predominantly from the part that lies in the base of the broad ligament of the uterus and is known as the uterovaginal plexus. They pass directly to the uterus and upwards with the uterine artery in the broad ligament. They communicate with branches of the tubal nerve and nerves of the ovarian plexus. Branches of the uterine nerves ramify in the myometrium and endometrium, most of them accompanying blood vessels. Some nerves from the uterovaginal plexus pass to the uterine cervix. The ovarian plexus is formed from branches of the renal and aortic plexuses. It accompanies the ovarian artery and is distributed to the ovary and Fallopian tube.

Motor function: while sympathetic activation normally produces uterine contraction and vasoconstriction, and parasympathetic activity produces uterine inhibition and vasodilatation, these actions, particularly in pregnancy and parturition, are complicated by the hormonal control of uterine function (see later).

Sensory function: pain fibres from the body of the uterus pass centrally to T10–L1 in the sympathetic nerves via the superior hypogastric plexus and the lumbar splanchnic nerves. Afferent pain fibres from the cervix pass via the parasympathetic nerves S2–4.

Physiology

Myometrial contractility

Growth and activity of the uterus is largely under hormonal control. In broad terms, oestrogen stimulates myometrial activity, the muscle becomes more active and excitable and action potentials in the individual fibres more frequent. An 'oestrogen primed' uterus is also more sensitive to oxytocin. Progesterone on the other hand depresses the excitability of the uterine musculature, decreasing spontaneous electrical activity and sensitivity to oxytocin. During the normal menstrual cycle, circulating oestrogens are at their highest immediately before ovulation, increasing the motility of the uterine tubes and thus potentially aiding conception. Progesterone is secreted by the ovary in the second half of the menstrual cycle and, by depressing uterine activity, potentially aids implantation. Uterine contractions during menstruation are stimulated by prostaglandin.

In pregnancy, the uterus increases from 30–60 g to 750–1000 g owing to hyperplasia and hypertrophy of the myometrium, largely under the influence of oestrogens. Muscle cell size increases from 50 to 500 μm, glycogen is laid down and there is an increase in ATP. Muscle contraction is induced by intracellular liberation of calcium from intracellular stores and from extracellular fluid. Spontaneous depolarizing pacemakers occur and if these exceed a critical threshold a sharp increase in intracellular calcium is seen and a contraction follows. Contractility can therefore be modulated by changing pacemaker potentials and the threshold for contraction. Prostaglandins enhance the liberation of intracellular calcium and oxytocin lowers the excitation threshold for contraction.

Cervical 'ripening'

In order for the fetus to be expelled the collagenous nature of the cervix changes or 'ripens.' There is a reduction in collagen and an increase in glycosaminoglycans (mucopolysaccharides). These are complex carbohydrates with a high amino sugar content. They have a high water content and occupy space, cushioning and lubricating. There is an influx of inflammatory cells and proinflammatory cytokines rise, the inducible form of nitric oxide synthase (iNOS) rises as does nitric oxide output. The pharmacological inhibition of iNOS prevents ripening. Prostaglandins also affect cervical ripening; both PGE_2 and $PGF_{2\alpha}$ increase the compliance of the cervix when given intravaginally or intracervically.

Parturition

During pregnancy, prostaglandin synthesis is inhibited, but at parturition this inhibition is lifted and prostglandins are synthesized and released, principally by the endometrium, but also by the myometrium, cervix, placenta and fetal membranes. This occurs because of alterations in the stability of membranes binding phospholipase A2 and the consequent production of arachidonic acid. Oestrogens promote phospholipase A2 production and progesterone inhibits it. Thus a rise in the oestrogen:progesterone ratio results in an increase in prostaglandin synthesis and release. Oestrogen also increases the number of myometrial oxytocin receptors and oxytocin stimulates the release of prostaglandin directly. A rising oestrogen:progesterone ratio is also responsible for induction of iNOS activity. Release of oxytocin from the posterior pituitary is produced by tactile stimuli from the reproductive tract. In addition to myometrial contraction it contributes to cervical softening in interactions with oestrogen/progesterone, prostaglandins and possibly nitric oxide. This is known as the Ferguson reflex and is facilitated by a high oestrogen:progesterone ratio.

In animals, the pattern of change and the role of these various 'hormones' are well described. A decrease in progesterone is brought about by regression of the corpus luteum, which produces progesterone. Luteal regression is induced by $PGF_{2\alpha}$ produced by the placenta, which in turn is dependent on an increased output of glucocorticoids produced by the fetal adrenal cortex. Fetal corticosteroids also induce oestrogen release by the fetal adrenal cortex and these enhance the placental production of $PGF_{2\alpha}$. Thus the oestrogen:progesterone ratio is increased, the 'block' on the myometrium is removed and the myometrial contractions commence, reinforced by oxytocin release induced by the Ferguson reflex. In some animals the main site of progesterone production is the placenta.

The precise mechanisms surrounding the induction of parturition in the human are less certain. Maternal progesterone does not generally fall at parturition but the fetal adrenal gland stimulates placental oestrogen synthesis via secretion of androgen precursors from a specialized zone of the fetal adrenal cortex, which regresses soon after birth. They form the major substrates for oestrogen synthesis by the placenta. In humans the onset of labour does not appear to be critically dependent on any consistent alterations in oestrogen synthesis, though this does not rule out the possibility of alterations in binding or local tissue concentrations. Likewise elevations in circulating $PGF_{2\alpha}$ concentrations have not been consistently described in humans in advance of labour though they do rise in amniotic fluid and increase as labour progresses. Myometrial oxytocin receptors increase, even in the absence of changes in the oestrogen: progesterone ratio.

Pharmacology

A number of drugs affect uterine function, directly and indirectly. Some are used in the management of labour (sympathomimetics, prostaglandins), others have effects that are usually regarded as undesirable (inhalational anaesthetic agents). Prostaglandins are used to induce abortion and are administered intravaginally. α-sympathomimetics (e.g. ergotamine, ergometrine) produce smooth muscle contraction. They cause the uterus to contract and are used in the control of uterine bleeding, both post-partum and following incomplete abortions. Syntocinon is a synthetic oxytocin. On the other hand, the β_2-sympthomimetics (terbutaline, salbutamol) produce smooth muscle relaxation and are used to delay the onset of labour. Inhalational anaesthetic agents depress smooth muscle contraction and given at concentrations in excess of 1 MAC can result in uterine haemorrhage. At less than 0.5 MAC they probably have little effect. The use of spinal-epidural local anaesthetics and/or opiates, or opiates administered systemically can affect the progress of labour, but have no direct effect on the uterine musculature. ◆

FURTHER READING

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Physiology: Respiratory

Anaesthesia
and intensive care medicine
on CD-ROM

Applied Respiratory Physiology

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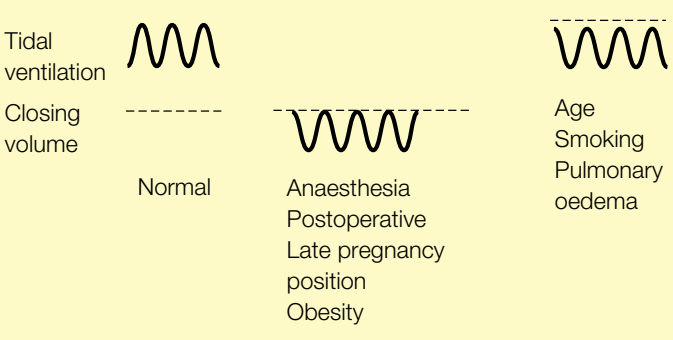
The respiratory system adapts in response to a number of physiological stimuli. This article briefly describes the effects of ageing, obesity, exercise, pregnancy, smoking, general anaesthesia and surgery on respiratory function. Adaptation to the chronic hypoxia of high altitude and to increased pressures (diving) are described elsewhere.

Functional residual capacity and closing capacity

Functional residual capacity (FRC) is the volume of air in the lungs at the end of a quiet tidal ventilation. It is the reservoir from which oxygen is replenished and via which carbon dioxide is eliminated and is one of the main influences on oxygenation. At rest, tidal volume is about 0.5 litre and FRC is 3 litres, therefore with each breath about 15% of the FRC is exchanged with the atmosphere. A decrease in FRC means a decrease in alveolar volumes, a decrease in ventilation–perfusion (V_A:Q) ratio and a worsening of the partial pressure of oxygen in the alveoli at the lung bases where the alveoli are the smallest and in arterial blood (PaO_2). The situation is made worse by small airway closure.

Small airways in the fit young healthy individual in the upright position normally start to close at 10% of vital capacity (i.e. above residual volume, but significantly below FRC). In these circumstances, small airway closure is not usually a factor in oxygenation. Airway closure affects oxygenation when closing capacity exceeds FRC; small airways start to close during normal tidal ventilation and gas becomes trapped distal to the collapsed airway. This is seen either when FRC is reduced or closing capacity elevated (Figure 1).

Functional residual capacity (FRC) and closing volume



Relative positions of closing volume and normal tidal ventilation (FRC) and their alteration under a variety of circumstances

1

Position: FRC is reduced in the supine position when the abdominal contents tend to push the diaphragm into the chest. The same occurs to a lesser extent when sitting.

Obesity is effectively a restrictive pulmonary defect and FRC is reduced. There is an inverse relationship between body size and PaO_2. In more severe cases (e.g. obesity with hypoventilation syndrome) severe hypoxaemia may develop accompanied by raised pulmonary artery pressures, oedema, congestive cardiac failure and carbon dioxide retention, but the more usual blood gas changes associated with obesity are mild hypoxaemia with a normal or slightly reduced partial pressure of carbon dioxide ($PaCO_2$).

Abdominal surgery: after open upper abdominal surgery the FRC decreases by 30% because of pain and spasm of the abdominal muscles and diaphragmatic splinting, and PaO_2 is reduced by about 20 mm Hg on the day after the operation. FRC is also reduced after lower abdominal surgery and the reduction in PaO_2 is about 10 mm Hg. A decrease in FRC and PaO_2 is also seen following laparoscopic surgery but to a lesser degree. PaO_2 returns towards normal values over the ensuing month as FRC recovers. $PaCO_2$ does not normally change unless opiate administration has produced hypoventilation.

Ageing: closing capacity increases as the lung ages and small airways narrow with the loss of supporting elastic tissue. Forced expiratory volume in 1 second (FEV_1) declines steadily from the age of about 30 years. With the decrease in FRC on lying down, closing volume impinges on normal tidal ventilation in the mid-forties and when sitting in the early sixties. The rise in closing volume results in a steady decline in PaO_2 of about 0.5 mm Hg/year. PaO_2 in the twenties is typically about 95 mm Hg and in the sixties about 80 mm Hg but with a wide spread of individual values. Most studies indicate that FRC does not change with age.

Chest disease: small airways close with the decrease in lung volume seen in restrictive chest disease (e.g. chronic bronchitis) and hypoxaemia can be severe. Small airways narrow with obstructive chest disease but FRC tends to increase and severe hypoxaemia is not often a major problem. Improvement in PaO_2 with small airway closure can sometimes be obtained with continuous positive airways pressure or positive end-expiratory pressure. With acute respiratory disease this may work best when applied before the alveoli distal to the closed airway have collapsed. Breathless patients can often be seen breathing out against pursed lips, thus applying their own positive pressure to expiration.

Smoking

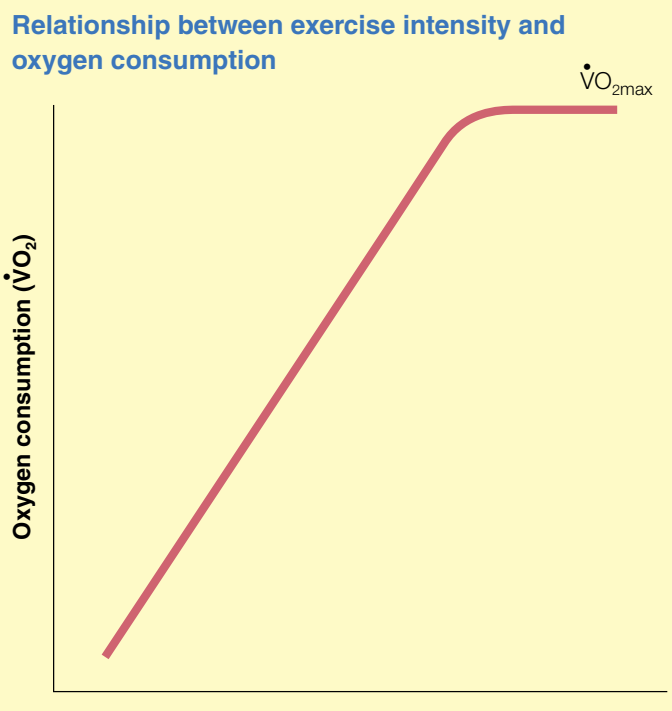
Smoking affects many aspects of respiratory function. Airway reflexes are more sensitive in smokers and inhaled histamine has an enhanced effect in producing more airway narrowing than it does in non-smokers. Smokers are also more sensitive to the irritant effects of inhalational anaesthetic agents. Mucus production is increased and the ciliary activity of the bronchial mucosa is impaired. Airway diameter is narrower due to bronchoconstriction and increased mucus production. This results in airway closure and disturbed ventilation–perfusion relationships. Airway narrowing is also reflected in a decrease in FEV_1. Dead space as a percentage of tidal volume (V_D/V_T) is increased and there is evidence of damage to the barrier function of the alveolar capillary membrane.

Exercise

Oxygen consumption

Oxygen consumption increases with exercise in proportion to its intensity. The respiratory and cardiovascular systems respond to meet the demand. As the intensity of exercise increases, oxygen consumption (VO_2) rises to a maximum; further increases in running speed, or power output on a cycle ergometer do not produce any further increase in VO_2 (Figure 2). This maximum VO_2 (VO_{2max}) is a measure of cardiorespiratory or aerobic fitness and is normally limited by cardiovascular function, specifically the maximum heart rate that an individual can achieve. Maximum heart rate normally declines with age, as does $VO_{2\,max}$.

Relationship between exercise intensity and oxygen consumption



Exercise intensity increases with for example speed of running or power output on a cycle ergometer. At $\dot{V}O_{2max}$ oxygen consumption does not rise with increasing exercise intensity

2

Resting VO_2 is about 250 ml/minute. VO_2 walking briskly is about 1 litre/minute and running at 12 km/hour about 3 litres/minute. VO_{2max} of a fit healthy 70 kg adult is about 3 litres/minute (42 ml/kg), of an athlete about 5 litres (70 ml/kg) and in elite athletes figures of 6 litres (85 ml/kg) have been recorded. VO_{2max} declines to about 2 litres at 70 years and may be reduced by inactivity by 50% of that expected. It can be increased by regular exercise, but most of the adaptations are cardiovascular, such as increased myocardial size and stroke volume and capillary proliferation in peripheral tissues. An improvement in cardiorespiratory fitness means that any task of a given exercise intensity takes place at a lower percentage of VO_{2max}. This puts less strain on the oxygen delivery systems (respiratory, cardiovascular and metabolic).

Respiratory reserves are larger than cardiovascular reserves. With exercise, oxygen extraction from the alveoli increases slightly and there is a decrease in mixed expired oxygen concentrations, but there is a much more marked extraction of oxygen from blood, and mixed venous PO_2 declines markedly. At rest, mixed venous blood is 70% saturated, but with severe exercise this may drop to 20%. This occurs over the steep part of the haemoglobin–oxygen dissociation curve so a large volume of oxygen is given up for a relatively small decrease in PO_2. Temperature is elevated and pH decreased so the dissociation curve moves to the right which assists unloading of oxygen in the periphery (*Anaesthesia and Intensive Care Medicine* **3:9:** 342).

Ventilation

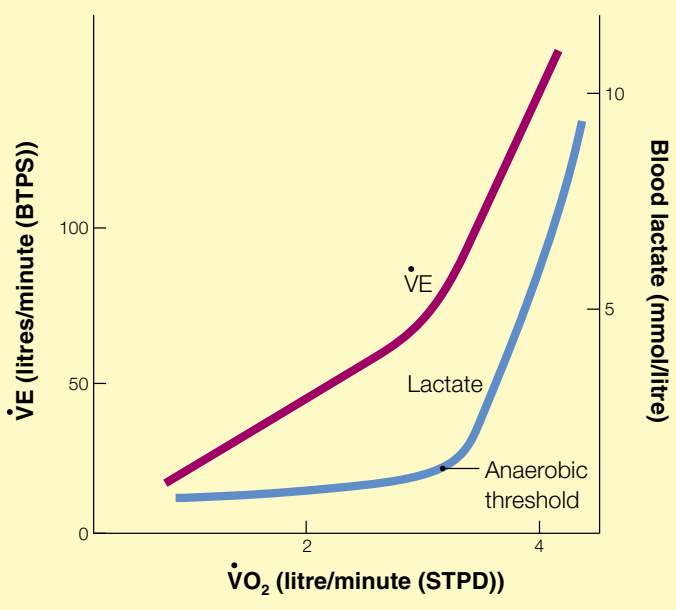
Maximum breathing capacity is about 200 litres/minute and cardiac output in severe exercise about 25 litres/minute. At VO_{2max} individuals are usually breathing at about 60% of their maximum breathing capacity (120 litres/minute), thus ventilation rises about 15-fold compared with a fivefold increase in cardiac output. Oxygen delivery mechanisms are able to keep pace with oxygen demand up to about 60% of VO_{2max}. At higher intensities, energy requirements are increasingly met by anaerobic mechanisms. Rates of muscle glycogenolysis and glycolysis exceed the rate at which pyruvate can enter the citric acid cycle and lactic acid accumulates at a rate proportional to the severity of the exercise. It diffuses from muscle into the general circulation and affects both the metabolic and respiratory responses. The exercise intensity (expressed as a percentage of VO_{2max}, the relative intensity) at which lactate accumulation starts is known as the anaerobic threshold.

Lactic acid is stronger than carbonic acid and therefore lactate accumulation due to anaerobic metabolism is associated with an increased loss of carbon dioxide, relative to oxygen consumption, in the expired air. Therefore the respiratory exchange ratio (R) rises (Figure 3). In severe exercise, lactate concentrations rise progressively; levels of 11–12 mmol/litre are seen and in elite athletes lactate may be as high as 20 mmol/litre. The R value may rise to 1.1 or 1.2. Lactate accumulation is one of the factors that limit sustained heavy exercise. Fit individuals produce less lactate than unfit ones but can also tolerate higher lactate concentrations.

Minute volume is normally well matched to exercise intensity and oxygen consumption. The oxygen equivalent of ventilation is the amount of ventilation per unit of oxygen consumed and is in the range 20–30 litres ventilation/litre of oxygen. It is remarkably constant up to the anaerobic threshold, but above that ventilation rises disproportionately because of the excess carbon dioxide production. At VO_{2max} about 80% of the oxygen consumed is used by exercising muscles. The percentage of VO_2 used by the respiratory muscles at rest is about 1–2%. This rises to 5% with moderate exercise and to 10% with severe exercise.

Ventilation rises immediately with the onset of exercise and like cardiac output may even occur before the exercise starts. The control of ventilation during exercise is not entirely understood, but it seems to be remarkably efficient. Chemoreceptors become more sensitive to hypoxia, possibly through local stagnant hypoxia mediated via the sympathetic nerves to the chemoreceptors. Blood gases do not normally change much from the resting state. Chemoreceptor activity does not account for much of the increase in ventilation. Large disturbances in blood gases occur on the venous side but no chemoreceptors have been found in the venous side of the vasculature and it is thought that afferents arising from the exercising muscles and joints may play a major role in stimulating ventilation as well as CNS activation due to stress or excitement.

Relationship between oxygen consumption ($\dot{V}O_2$) and pulmonary ventilation ($\dot{V}E$) at increasing intensities of exercise



$\dot{V}E$ starts to increase at the anaerobic threshold where significant amounts of lactate start to accumulate. Carbon dioxide production increases to compensate for lactic acidosis and this results in increased $\dot{V}E$

BTPS, body temperature, ambient pressure and saturated with water vapour; STPD, standard temperature and pressure dry

3

With severe sustained exercise the oxygen consumption may continue to rise despite the intensity of the exercise, such as speed of running or power output on a cycle ergometer, remaining the same. This is known as the 'slow component' of oxygen consumption. Why it occurs is unknown. Oxygen consumption declines when exercise ceases, but it does so gradually as the oxygen debt is paid off (i.e. accumulated lactate is oxidized and other energy stores such as high energy phosphates are replenished). As lactate is removed, carbonic acid levels are replenished and the respiratory exchange ratio may fall to as low as 0.5.

Diffusion

The diffusing capacity of the lung is well able to cope with exercise. The pulmonary capillaries expand (distension) and unperfused capillaries open up (recruitment) particularly in the underperfused upper part of the lung and the volume of blood in the pulmonary capillaries increases. Pulmonary arterial and venous pressures rise and the amount of V_A/Q mismatch diminishes because of the more uniform blood distribution. Diffusing capacity as a consequence increases about fivefold. Blood gases are thus normally unaffected by exercise; PaO_2 is usually normal and $PaCO_2$ may be reduced slightly by hyperventilation. There are problems with oxygenation during exercise at altitude, when the driving pressure of oxygen across the alveolar capillary membrane is diminished, and oxygen in the alveoli may not have equilibrated by the time the blood leaves the capillary.

Anaesthesia (Figure 4)

Respiratory control: inhalational anaesthetic agents affect responsiveness to both carbon dioxide and to hypoxia. The effect on carbon dioxide responsiveness is predictable, with a dose-dependent depression of the ventilation response curve. Inhalational anaesthetic agents also depress the hypoxic ventilatory response in doses as low as 0.1 minimum alveolar concentration, but the response is more variable than the response to carbon dioxide. Much of the variation can be ascribed to methodological differences in the studies reported, dependent on whether $PaCO_2$ was maintained constant or had been allowed to change. Hyperventilation induced by hypoxia results in hypocarbia and this can depress the response to the hypoxia. Attenuation of the hypoxic ventilatory response is important in individuals dependent on their hypoxic drive, such as those in chronic respiratory failure or at altitude or, potentially, in the early postoperative period.

Changes in respiratory function associated with general anaesthesia

- Depression of hypoxic and hypercarbic responses and hypoventilation
- Upper airway obstruction
- Decrease in functional residual capacity
- Atelectasis
- Impairment of gas exchange
  - Increased dead space
  - Increased venous admixture

4

Respiratory muscles: anaesthetic agents relax the muscles of the pharynx and depress the muscles of ventilation. In the supine position, the soft palate falls back and occludes the nasopharynx; the tongue tends to do the same but does not occlude the pharynx completely. Activity of the intercostal muscles is depressed leading to decreased thoracic excursions, but phasic activity of the diaphragm is maintained. This can result in paradoxical ventilation with diaphragmatic contraction causing expansion of the abdomen and lower ribcage, while the upper ribcage is drawn in owing to the decreased intrapleural pressure and the lack of support from the ribcage respiratory muscles. General anaesthesia can cause phasic activity of the abdominal muscles in expiration, not normally seen in the conscious individual. The reason is unknown and it does not appear to have any useful function.

FRC falls during anaesthesia by about 15–20% with or without muscle relaxants. It occurs within a few minutes of induction but does not fall beyond that and recovers within hours of the end of anaesthesia. The cause is uncertain but it has been suggested that the diaphragm, particularly the dependent posterior part moves cephalad and decreases lung volume. Blood shifts into the pulmonary circulation from the periphery and this may decrease thoracic lung volume.

Atelectasis: alveoli tend to collapse under anaesthesia, most commonly in the dependent lung regions (i.e. posteriorly and close to the diaphragm). The fall in FRC decreases alveolar volume and may cause airway trapping, reducing V_A/Q ratios and rendering alveoli liable to collapse. This is worse if the patient breathes highly soluble gases such as nitrous oxide or 100% oxygen. Even a few minutes breathing pure oxygen predisposes to the condition; the alveoli fill with oxygen but mixed venous PO_2 alters relatively little because of the nature of the haemoglobin-dissociation curve. There is thus a huge gradient between alveolus and blood, and absorption takes place rapidly. A 'skeleton' of relatively insoluble nitrogen delays the process.

Gas exchange is impaired. Alveolar dead space increases and there are increases in shunt and in V_A/Q mismatch. The reason for the increase in alveolar dead space is unknown. Venous admixture in the healthy individual normally amounts to about 1–2% of cardiac output. Under general anaesthesia this increases to 10%. About half of this is due to atelectasis, the remainder to a deterioration in ventilation–perfusion relationships with the increase in alveolar dead space already referred to and the redistribution of perfusion to areas of poor ventilation. This deterioration in venous admixture with general anaesthesia appears to worsen with age. Inhalational anaesthetics inhibit hypoxic pulmonary vasoconstriction and this also contributes to the deterioration in gas exchange.

Preoxygenation

Preoperative oxygenation is performed routinely if the patient is to be paralysed and difficulties are anticipated in securing the airway, or in the presence of a full stomach. Inhaling 100% oxygen washes nitrogen out of the lungs. Classically, the time to complete denitrogenation is 7 minutes, but this is an exponential function and is about 80% complete after only 1 minute. The store of oxygen in the functional residual capacity increases over this period from about 0.5 litres to about 2 litres. A similar increase in stores of oxygen in the FRC can be produced by two or three vital capacity breaths. This degree of preoxygenation supports about 3 minutes of apnoea time before arterial saturation drops to 90%. 3 minutes' preoxygenation significantly increases the oxygen stores in other body tissues, and apnoea times in excess of 5 minutes are observed before saturation drops to 90%.

Pregnancy and the fetus

Pregnancy

Fluid balance changes in pregnancy, with fluid retention caused by oestrogen and an increase in cardiac output. Oxygen consumption rises in proportion to the increase in body weight. Minute volume rises by 40% owing to an increase in tidal volume; $PaCO_2$ drops to 30 mm Hg and PaO_2 rises by 5–10 mm Hg. This is attributed to an increase in progesterone levels which rise sixfold during pregnancy and is associated with an increased sensitivity of the central chemoreceptors to carbon dioxide and an increase in steepness of the ventilation/$PaCO_2$ curve (*Anaesthesia and Intensive Care Medicine* **3:9:** 345). Sensitivity to hypoxia is also increased. These changes facilitate gas exchange for the fetus. The increase in ventilation is seen at the start of the second trimester.

In the third trimester the enlarging uterus interferes with the mechanics of ventilation. The diaphragm is pushed cephalad and FRC is reduced by about 25–30%. This effectively reduces the largest store of oxygen in the body and renders the pregnant woman susceptible to hypoxia. Despite this, arterial oxygen saturation is normal; the potential problems arise perioperatively during intubation.

Fetal respiration

The lungs are present in the fetus in a functional state from about 24–26 weeks of pregnancy. At birth only about 15% of the alveoli are present and development continues up to about 2 years. Fetal lung contains liquid secreted by alveolar cells maintained at a positive pressure relative to the amniotic fluid. This maintains the lungs in a partially expanded state. Breathing movements are present from the second trimester.

Fetal circulation

The fetal circulation is different from that of the adult. Blood enters the inferior vena cava from the umbilical vein via the sinus venosus in the liver where it is joined by the portal vein. Umbilical vein blood has a partial pressure of oxygen (PO_2) of 30 mm Hg and is depressed to about 25 mm Hg by blood from the portal vein, but fetal haemoglobin has a dissociation curve to the left of adult haemoglobin and therefore for a given PO_2 is better saturated (80% in the umbilical vein). Only about 10–15% of the blood entering the right side of the heart goes to the lungs. The rest passes to the left side of the heart via the foramen ovale or traverses the right side of the heart to the pulmonary artery and enters the aorta, via the ductus arteriosus, beyond the origin of the carotid arteries. Inferior vena caval blood is the best oxygenated (about 67%) and passes predominantly via the foramen ovale to the brain. Blood returning to the right atrium from the brain goes via the pulmonary artery and the ductus arteriosus to the aorta to supply the lower part of the body. The PO_2 of blood in the aorta is about 20–25 mm Hg (about 60% saturated) and the PCO_2 about 40–45 mm Hg. Blood returns to the placenta via two umbilical arteries that arise from the iliac vessels.

Neonatal respiration

Normal infants take their first breath within 20 seconds of birth and regular breathing is established within 90 seconds. Chest compression during delivery followed by recoil of the ribcage contribute to drawing air into the lungs but major stimuli are probably the cooling of the skin and the nonspecific mechanical stimulation of being born. As air enters the lungs, large surface tension forces have to be overcome and with the first breath intrapleural pressures fall to atmospheric (A) – 40 cm H_2O. FRC is achieved in a few moments but it may be several days before the whole lung is ventilated evenly.

There are massive changes in pressure in the two circulations. Pulmonary circulatory pressure falls partly as a result of chest expansion and partly because of changes in blood gases, possibly mediated by nitric oxide. There is an increase in resistance of the systemic circulation; left atrial pressure rises as a result of which the foramen ovale closes. The ductus arteriosus closes within a few minutes of birth in response to the increased PO_2; prostaglandins are also involved. ◆

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Barometric Pressure: Extremes and Challenges

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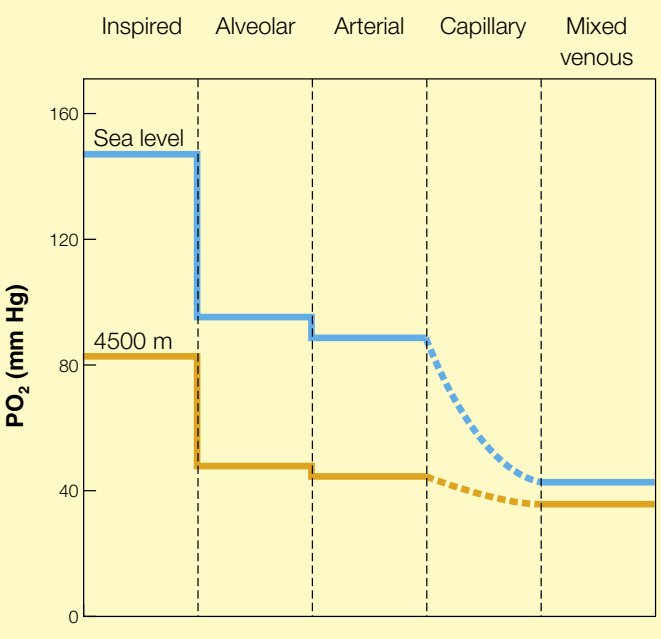
Oxygen sustains life in physiologically controlled amounts, yet is fatal in excess. Exposure to high altitude and ocean depths provide extremes of barometric pressure and oxygen availability.

Low pressures – high altitude

The decrease in barometric pressure with altitude means that there is less atmosphere pressing down on us. The concentration of oxygen in atmospheric air at 20.9% is independent of altitude, so the inspired pressure (P_IO_2) is a function of barometric pressure only and is given by the equation: $P_IO_2 = 0.209$ (barometric pressure – saturated water vapour pressure at body temperature (47 mm Hg)).

The decrease in P_IO_2 produces a decrease in the flux of O_2 to the tissues (Figure 1), due to a lowered partial pressure of O_2 in alveolar gas (P_AO_2). The movement of gases relies on a concentration gradient from high to low pressure. The partial pressures of O_2 and CO_2 determine the driving force of the gas. At altitude, this flux is diminished because of the decreased number of molecules per unit volume. The opposite is true when breathing compressed air under water.

Oxygen cascade at sea level and at 4500 m



Note reductions in the inspired alveolar gradient due to hyperventilation, alveolar–arterial PO_2 difference due to improved gas transfer and arterial–venous PO_2 difference due to increased capillary density in peripheral tissue

1

Hypoxia – the symptoms vary depending on altitude. Impairment in night vision occurs at about 1500 m; tingling in the mouth and fingers at 4000–5000 m. On acute exposure to a barometric pressure equivalent to the height of Mount Everest, consciousness is lost after 2 minutes. Exposure to the barometric pressure on the summit of Mount Everest is not fatal to the successful climber because he acclimatizes over the gradual ascent. Maximal oxygen consumption (VO_{2max}) is diminished at altitude. Deterioration occurs at about 1500 m, reducing by 5% for each increase of 500 m above sea level; this rate becomes more profound at higher altitudes. A healthy climber on the summit of Mount Everest has a VO_{2max} as low as 15 ml/kg/minute, similar to that of a congestive heart failure patient at sea level.

Respiratory system

Oxygen uptake within the pulmonary capillary – in the healthy lung, the first limitation at altitude is the reduced diffusive (partial) pressure of O_2. At sea level, at rest, and with moderate exercise, oxygenation in the pulmonary capillary occurs rapidly. It takes place in two stages: diffusion through the blood–gas barrier (capillary membrane, plasma and intracellular); and reaction with haemoglobin (Hb). At sea level, blood arrives in the lung with a PO_2 of 40 mm Hg, this rises rapidly to equilibrate with P_AO_2 when it has traversed only one-third of the capillary. There is a negligible PO_2 difference between alveolar gas and end-capillary blood. This indicates no diffusion limitation. On the summit of Mount Everest, where P_AO_2 is 35 mm Hg, blood enters the lung with a PO_2 of 21 mm Hg. The PO_2 rises slowly along the pulmonary capillary, reaching a value of 28 mm Hg. There is thus a large PO_2 difference (7 mm Hg) between alveolar gas and end-capillary blood, which increases with exercise.

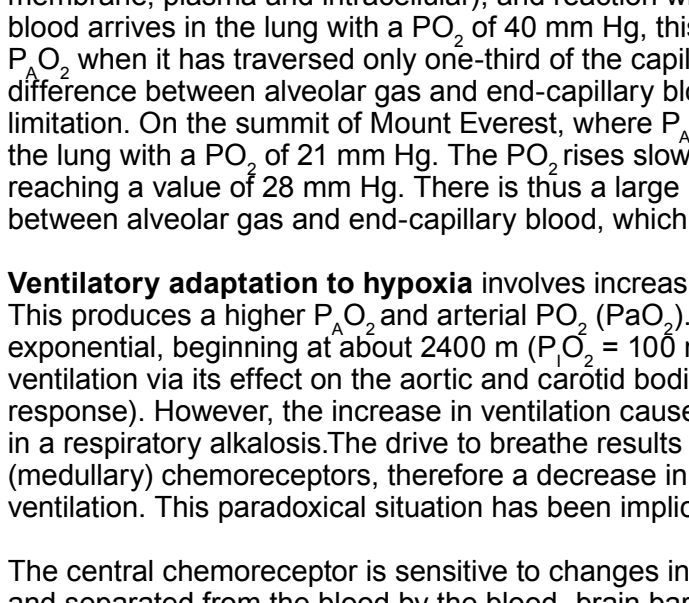
Ventilatory adaptation to hypoxia involves increasing the minute ventilation. This produces a higher P_AO_2 and arterial PO_2 (PaO_2). The increase in ventilation is exponential, beginning at about 2400 m (P_IO_2 = 100 mm Hg). Hypoxia stimulates ventilation via its effect on the aortic and carotid bodies (the hypoxic ventilatory response). However, the increase in ventilation causes $PaCO_2$ to decrease, resulting in a respiratory alkalosis.The drive to breathe results from PCO_2 acting on the central (medullary) chemoreceptors, therefore a decrease in PCO_2 leads to a reduction in ventilation. This paradoxical situation has been implicated in acute mountain sickness.

The central chemoreceptor is sensitive to changes in PCO_2 and pH. It is bathed in CSF and separated from the blood by the blood–brain barrier, which is impermeable to H^+. The H^+ concentration is determined from the buffering of CO_2, which passes freely into the CSF, by bicarbonate. This relationship is defined by the Henderson–Hasselbalch equation.

During the first days at altitude, blood and CSF bicarbonate decrease through increased excretion of bicarbonate by the kidney, or active transport of bicarbonate from the CSF. The decrease gradually restores pH towards normal, resulting in ventilation steadily increasing over the first few days at altitude. The second form of respiratory acclimatization is an increase in the sensitivity of the respiratory centre to PCO_2. Higher ventilation is thus achievable in the face of lower PCO_2 values.

Hb oxygen affinity*:* in the range of PO_2 normally encountered, the binding and unloading of oxygen to Hb usually occurs over relatively flat portions of the oxyhaemoglobin dissociation curve (Figure 2). Thus, at a PO_2 of 50 mm Hg (at about 4300 m) Hb maintains a saturation of about 85%. However, O_2 delivery and gas exchange over the steep part of the curve predispose to diffusion limitation. Also, the polycythaemia of high altitude increases blood oxygen concentration per unit change in PO_2. Increasing Hb affinity for oxygen by moving the curve to the left increases the loading of O_2 in the pulmonary capillary under conditions of diffusion limitation at high altitude, but decreases unloading of O_2 in the systemic capillaries to the working tissues. At altitude, the low $PaCO_2$ moves the curve to the left. An increase in 2,3-diphosphoglycerate, a by-product of the glycolytic pathway under hypoxic conditions, tends to move it back to the right, but the effect of the respiratory alkalosis predominates.

Relative positions of the haemoglobin and myoglobin dissociation curves



2

Cardiovascular response

Heart rate – acute exposure to altitude causes an increase in resting and sub-maximal heart rate. Acclimatization to high altitude generally leads to a return in resting heart rate to sea-level values but maximal heart rate is reduced. Theories include an adaptation that spares myocardial workload under hypoxaemic conditions and a relationship between circulating catecholamines and down-regulation of myocardial β-adrenergic receptors.

Stroke volume is reduced after a few weeks' acclimatization at altitude and for a given pulmonary filling pressure oxygen breathing does not rectify the decrement.

Cardiac output during acute hypoxia is increased at rest and during sub-maximal exercise compared with normoxia. In well-acclimatized lowlanders, cardiac output returns to its sea level–work intensity relationship. Increasing cardiac output at high altitude has no effect on VO_{2max} perhaps because of diffusion limitation in the lung and systemic tissues. The return of cardiac output to near sea-level values may be attributed to the polycythaemia associated with altitude acclimatization as the increase in the oxygen-carrying capacity of the blood may be adequate to sustain cellular O_2 needs.

Systemic and pulmonary arterial blood pressure do not change up to altitudes of 4600 m. However, acute hypoxia results in pulmonary hypertension due to an increase in pulmonary vascular resistance. Pulmonary hypertension persists and is also present in high-altitude natives. O_2 breathing relieves the pulmonary hypertension caused by acute exposure but does not alter the pulmonary hypertension found in acclimatized subjects or highlanders. The resting pulmonary artery pressures increase considerably during exercise at altitude. Pulmonary vasoconstriction directs blood away from hypoxic regions of the lung and improves ventilation–perfusion inequalities. Pulmonary hypertension results in right ventricular hypertrophy in acclimatized lowlanders and high-altitude natives.

Haematology – red cell mass increases with altitude, maintaining O_2 content at sea-level values (20 ml of O_2/100 ml of blood) up to about 5300 m. This increased carrying capacity acts as a countermeasure to the decreased SaO_2. The initial increase in packed cell volume and Hb is due to a reduction in plasma volume not an increase in the number of circulating red cells. Hypoxia causes the release of erythropoietin from the kidneys and liver, which stimulates the bone marrow and increases the red cell mass over days to weeks. After several weeks, plasma volume increases but remains slightly below that at sea level. Blood volume increases.

Passage of oxygen into the cell – oxygen diffuses from the Hb molecule to the capillary wall. Diffusion distances in tissues are typically higher than at the blood–gas membrane in pulmonary capillaries. During exercise, when an increased flux of oxygen is required, additional capillaries open, reducing the diffusion distance and increasing the surface area of the capillaries. Once in the cell, oxygen transport is aided by facilitated diffusion via myoglobin. Myoglobin has similar properties to Hb, though it has a hyperbolic curve (Figure 2) with a very low P_{50} of about 5 mm Hg compared with 27 mm Hg for Hb. This assists in the release of oxygen at the low partial pressures found in the cells. The PO_2 around the mitochondria is very low.

Skeletal muscle

Capillary–fibre interface – capillary density in the tissues increases with exposure to high altitude but whether this is a true increase or a relative decrease in fibre size is uncertain.

Myoglobin concentration and mitochondria – hypoxia increases myoglobin concentration. Adaptation to moderate altitude (4500 m) increases mitochondrial number but over 6000 m, mitochondria decrease.

Biochemical pathways – at the mitochondria, oxygen is used to generate adenosine triphosphate by the electron transport chain on the inner mitochondrial membrane and the Krebs' cycle in the cytosol of the mitochondria. Anaerobic glycolysis provides a valuable source of energy in anoxic conditions. Exercise training and exposure to moderate altitude (4500 m) increase key enzymes in the two aerobic pathways whereas exposure to higher altitudes causes a decrease.

Other adaptations
The authors' laboratory has investigated further adaptations at high altitude. A mass action effect has been explained for the exercise-induced oxidative stress, whereby an increase in flux of O_2 through the mitochondria produces the superoxide radical. Paradoxically, when exposed to intermittent hypoxia, free-radical generation increases independently of the exercise undertaken. During a prolonged stay at high altitude, these radicals may contribute to the pathogenesis of high-altitude illness. The prophylactic benefits of antioxidant supplement-ation against acute mountain sickness add further support to these findings.

Acute mountain sickness (AMS): benign symptoms, including frontal headaches, lassitude, insomnia, emesis, fatigue, irritability, occasional photophobia and peripheral oedema, normally subside within 4–5 days but may develop into the life-threatening malignant forms of high-altitude pul-monary (o)edema (HAPE) and high-altitude cerebral (o)edema (HACE). The mechanisms of AMS are unknown. It is a self-limiting condition seen after rapid ascent to altitude. Once the symptoms have subsided they do not recur at that altitude. Its pathogenesis is complex, the prominent aspects are the rate of ascent and the elevation reached, but with wide individual variations.

The hypoxic ventilatory response has been implicated in AMS. Increased vascular permeability may precipitate subclinical pulmonary oedema, which exacerbates arterial hypoxaemia. Fluid balance and water retention are also critical. Individuals prone to AMS usually respond to altitude exposure with an antidiuresis, which would expand plasma and extracellular volume. The symptoms are thought to be the result of cerebral oedema and raised intracranial pressure. Damage to muscle membranes associated with free radicals is also implicated.

A controlled slow rate of ascent to high altitude reduces AMS. Above 3000 m, each night should not be spent higher than 300 m above the last with a rest day every 2–3 days. Acetazolamide, which functions as a respiratory stimulant by inhibiting carbonic anhydrase, and effectively producing a metabolic acidosis, or offsets the respiratory alkalosis, is effective. Increased ventilation improves arterial hypoxaemia. Nutritional supplementation with antioxidants may also be useful.

HAPE is a potentially lethal form of AMS. It presents at a wide range of altitudes from 2000 to 7000 m. The patient shows signs of AMS that develop into tachycardia, tachypnoea, crackles at the lung bases and a dry cough that becomes productive. A more pronounced pulmonary pressor response is a constitutional risk factor and susceptibility has a genetic basis in the variation of the angiotensin-converting enzyme gene. Patients with HAPE have a high pulmonary artery pressure (about 100 mm Hg) and normal wedge pressures. Other factors proposed include uneven pulmonary vasoconstriction and perfusion, stress failure of pulmonary capillaries, venular constriction, arterial leakage, multiple pulmonary emboli, increased vascular permeability and inflammation.

HACE is a severe malignant form of AMS which progresses to ataxia, hallucinations, coma and eventually death. Blood counts and biochemistry are usually normal. The relative proportions of the brain to the cranial cavity may be critical in the disease process as is the vascular integrity of the blood–brain barrier.

High pressures

While nobody lives permanently under water, SCUBA (self- contained underwater breathing apparatus) diving is a popular activity and professional divers may live under high environmental pressures for several weeks. Civil engineers building tunnels may also work in pressurized chambers. The two basic physiological problems are the effect of pressure and its effect on gas solubilities.

Pressure
Under water, pressure increases by 1 atmosphere for every 10 m of depth (at a depth of 30 m a diver is exposed to 4 atmospheres). The body is composed largely of incompressible solids and water. However, gas is present in the lungs, the gastrointestinal tract, the sinuses and inner ear. Gases follow Boyle's law: at constant temperature, volume (V) is proportional to 1/pressure (P) or PV is a constant, so for an increase in pressure of 1 atmosphere (10 m depth) the volume of a fixed mass of gas halves. For an individual to breathe under water, gases have to be supplied at the ambient pressure at depth. In an individual breathing via a snorkel, the work of breathing is increased because the water pressure compresses the chest. To expand the lungs against this restriction the work of the respiratory (inspiratory) muscles has to increase. The greatest pressure the respiratory muscles can generate is about 90 cm H_2O. When water pressure exceeds this (at a depth of 1.2 m) inspiration from the surface is impossible. In practice, divers breath from a pressurized source, either compressed air from cylinders carried on their back, via a demand valve, or air is supplied via hoses from the surface at a pressure equal to that at which the diver is working. In these circumstances, transthoracic pressure (i.e. the difference between intra-alveolar and water pressure at depth) is normal. In a breath-holding dive from the surface, the lung volumes are compressed with the increasing pressure, then re-expand to their original volume on ascent. If the diver goes so deep that the water pressure exceeds the intrathoracic pressure the lungs are damaged, developing congestion, oedema and haemorrhage.

It is important when breathing under pressure that the diver breathes normally on ascent (i.e. he continues to exhale). Gas expands and if exhalation does not occur (i.e. he holds his breath) alveoli rupture with the development of a pneumothorax, mediastinal and tissue emphysema (barotrauma). Provided the mass of gas in the gastrointestinal tract remains constant the volume shrinks on descent and re-expands to its former volume on ascent. There are some relatively inaccessible gas spaces in the inner ear and the sinuses. These have to equilibrate with the increased pressure on descent via the Eustachian tube. If these structures cannot equilibrate (e.g. due to mucosal swelling), capillaries may rupture or the tympanic membrane may burst. With increasing pressure, gas density rises and the work of breathing goes up. Airflow may become turbulent and the work of breathing increases further. The increased density also slows intra-alveolar diffusion, and gas exchange is impaired. Maximum ventilatory volume and VO_{2max} diminish, the latter due to respiratory causes.

Cardiovascular responses – normally there is a hydrostatic pressure gradient in the upright individual with fluid pooling in the lower half of the body. However, when submerged, the surrounding pressure forces about 500 ml of blood centrally, raising right atrial pressure and cardiac output. There is an improvement in ventilation–perfusion relationships and the pressure receptors in the cardiovascular system detect the increased volume. This promotes a diuresis mediated via a decrease in antidiuretic hormone and increased atrial natriuretic peptide. Immersion in cold water, specifically exposure of the face to cold water, also induces the 'diving reflex'. The heart rate falls and peripheral vasoconstriction occurs.

High pressures and gas solubility
Although the tissues are compressible compared with gas volumes, lipids are more compressible than water, and this disturbs membrane function. The result is the high-pressure neurological syndrome. Symptoms include tremor, decreased manual dexterity, loss of attention and nausea. It is seen at depths over 200 m and is worse when the rate of descent is rapid. The symptoms may be lessened by adding nitrogen to the helium/oxygen mixtures normally breathed at these depths.

Nitrogen narcosis occurs when breathing compressed air at depths over 30 m. The symptoms resemble alcohol intoxication and include euphoria, irrational behaviour, reduced manual dexterity and mental function. They are marked at depths below 50 m. Below 90 m, the diver approaches unconsciousness. The cause is thought to be an effect on cell membranes producing narcosis, similar to that seen with anaesthetic gases.

Oxygen toxicity – oxygen is toxic under pressure. 100% oxygen at atmospheric pressure is toxic when breathed for over 9–10 hours. It affects the CNS and lungs. Neurons become hyperexcitable causing convulsions, vertigo, paraesthesia, twitching and nausea. In the lungs, pulmonary oedema and intra-alveolar haemorrhages occur due to disruption of endothelial and epithelial cells. The onset is hastened by increasing depth and is due to the high PO_2 itself, so occurs with compressed air. At a P_IO_2 of 1500 mm Hg, symptoms occur after 5 hours. Below 50 m divers usually breathe a mixture of helium and oxygen. Helium is less soluble than nitrogen so problems of nitrogen narcosis are avoided, but because of oxygen toxicity, the percentage of oxygen in the mixture is decreased the deeper the diver goes, in order to keep the P_IO_2 below 300 mm Hg. At 300 m the oxygen content of the mixture is 1.26%. Helium is less dense that nitrogen and the work of breathing is decreased.

Decompression – when gases are breathed under pressure they dissolve in body fluids. Breathing air at sea level, the body contains about 1 litre of nitrogen. When breathing compressed air, this increases by a further 1 litre for every 10 m increase in depth. Equilibration takes 6–8 hours and depends on the depth, and thus the amount of nitrogen dissolved, and on the vascularity of the tissues supplied. When ascent is too rapid, bubbles of dissolved gas appear in the tissues and circulation. The problem lies with the inert gases nitrogen and helium; helium has 40% of the solubility of nitrogen. Oxygen is used by the tissues and CO_2 is not a problem because there is none in the inspired air. Signs and symptoms may appear up to 48 hours after the dive. They include joint pains due to bubbles in the relatively poorly perfused joint and bone tissues, dyspnoea and cough due to bubbles trapped in the lungs and a combination of motor and sensory deficits due to bubbles in vessels supplying the spinal cord. Avascular bone necrosis may be a long-term problem.

Decompression sickness is avoided by slow ascent, the precise rate depending on the depth and duration of the dive, and controlled in accordance with published tables. This may be done in a pressurized chamber and if the individual is at depth for a prolonged period 'saturation' techniques may be used where he lives under pressure for several weeks. 'Saturation' means the gases dissolved in the body equilibrate fully with those of the environment. He then requires several days to de-compress. The likelihood of decompression sickness is less when breathing helium. It is increased if the diver immediately exposes himself to hypobaric pressures (i.e. goes to altitude or flies).

Other problems
Under water, the diver is effectively weightless so greater effort is required to perform manual tasks (and VO_{2max} is reduced). Cold may be a physiological stress because the thermal conductivity of water is greater than air. Helium is a better conductor than nitrogen. Deep-sea divers usually need heating in their diving suits. ◆

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Fluid Balance and Non-respiratory Functions of the Lung

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Fluid balance

The factors affecting fluid balance in the lung are similar to those governing fluid balance in peripheral tissues. There is a balance between the oncotic (colloid osmotic) pressures and the hydrostatic pressures in the capillaries and in the interstitial tissues. Forces pushing fluid out of the pulmonary capillaries are the hydrostatic pressure in the capillary minus the hydrostatic pressure in the interstitium. The pressures pulling fluid into the pulmonary capillary are the oncotic pressure of the blood minus the oncotic pressure of the interstitium.

The oncotic pressure in the blood is 28 mm Hg; the oncotic pressure of the interstitial fluid in the lung is unknown, but the oncotic pressure of lung lymph is 20 mm Hg. Particular features of the pulmonary circulation are that the hydrostatic pressure at the base of the lung is higher than at the apex. Although the hydrostatic pressure of the interstitium is uncertain, some measurements have shown it to be below atmospheric.

The net pressure is thought to be outwards and normally there is a net lung lymph flow of about 20 ml/minute. Lymphatics flow in the perivascular and peribronchial tissues. In the early stages of pulmonary oedema, as a result of fluid overload, left ventricular failure or increased permeability of the pulmonary capillary membrane, these peribronchial and perivascular tissues become engorged (interstitial oedema). When the drainage capacity of the interstitium is exceeded, fluid passes into the alveoli. If an alveolus floods completely, oxygenation ceases.

Non-respiratory lung functions

The lung functions primarily as an organ of gas exchange. It is the sole recipient of the output of the right ventricle and has a huge area of delicate epithelium and pulmonary endothelium potentially exposed to the atmosphere. Endothelium, including pulmonary endothelium, is extremely active metabolically. In addition to its primary function the pulmonary circulation acts as a reservoir, a filter and a site of metabolism for endogenous and exogenous substances.

Reservoir

The pulmonary circulation is able to act as a reservoir because of its distensibility. It can accommodate the large shifts in blood volume that occur during the day, for example the increase in venous return when an individual lies down or undertakes dynamic exercise. One of the main factors governing cardiac output is venous return and ventricular filling pressures; the ability of the pulmonary circulation to accommodate varying volumes of blood means it can act as a reservoir and allows fine adjustment of left ventricular filling.

Filter

The pulmonary circulation receives the entire blood volume on average once a minute and is therefore well placed to act as a filter for particulate matter in the systemic venous return. Without this filter the systemic circulation would be at risk of embolization, particularly the cerebral and coronary circulations.

Pulmonary capillaries are about 7 μm in diameter, though particles much larger than this (e.g. air and fat emboli) have been known to gain access to the systemic circulation via the pulmonary vessels. 25% of the population have a patent foramen ovale which is normally kept closed by the higher pressures on the left side of the heart. Circumstances that raise right-sided pressures (e.g. a Valsalva manoeuvre) can open it. There may also be arteriovenous shunts in the lung.

Because of its huge area, the pulmonary circulation is well adapted to coping with microemboli, but a large venous embolus that blocks a significant proportion of the circulation has an adverse effect on ventilation–perfusion relationships. Microemboli, blocking significant numbers of pulmonary capillaries, may also cause neutrophil activation with increases in endothelial permeability and alveolar oedema. The lung has proteolytic, fibrinolytic and anti-coagulant systems (e.g. plasmin activator, thromboplastin, heparin) to clear its vessels of thromboemboli, and it may also have a role in overall blood coagulability.

Inhaled substances: the alveolar capillary membrane is thin and leaves the lung open to a number of airborne hazards such as inhaled irritants, chemicals and infective agents. Particles of 5 μm and above impact on the mucous membrane of the airways, in the nose and large airways, but particles of 1 μm and below can penetrate to the alveoli. Particles impacting on the bronchial mucosa are swept into the pharynx by the flow of mucus. Neutrophils and macrophages deal with infecting organisms in the bronchial tree and these cells can also move to the pulmonary capillaries. Activation of neutrophils involves release of proteases, particularly elastase and trypsin, which may cause lung damage. Proteases are normally conjugated by α_1-antitrypsin in plasma, but those in whom α_1-antitrypsin is deficient are vulnerable to lung damage and the development of emphysema.

Metabolic functions

Two important substances synthesized in lung and bronchial tissue are phospholipids, which form components of surfactant and are secreted by type II alveolar epithelial cells, and the mucopolysaccharides of bronchial mucus.

Metabolism of toxic substances follows a two-stage pattern similar to that seen in the liver. Oxidation, mostly by P450 mono-oxygenase and to a lesser extent by a flavin-based mono-oxygenase, is followed by conjugation to glucuronide or glutathione. The lung is one of the main extrahepatic sites of cytochrome P450 oxidation.

Despite an apparent paucity of organelles, the cells of the pulmonary endothelium are active. A number of substances are removed or inactivated during passage through the lungs. 30% of noradrenaline (but not adrenaline) is removed by pulmonary endothelium. Catecholamines in all tissues are metabolized by monoamine oxidase and catecholamine-O-methyl-transferase, but in the pulmonary vasculature it appears to be the uptake site for noradrenaline that makes it different from adrenaline. Dopamine is not metabolized. About 98% of 5-hydroxy-tryptamine (5-HT) is removed by the pulmonary circulation as is acetylcholine, though its half-life in the circulation is about 2 seconds. Histamine is not affected. Angiotensin I is the major peptide hormone affected by passage through the lungs where it is converted to angiotensin II by angiotensin-converting enzyme (ACE) bound to the surface of the endothelium. Other substances removed by the lung are bradykinin (also by ACE) and atrial natriuretic peptide.

Various arachidonic acid metabolites are synthesized and released by lung tissue. Some ($PG_{E2\alpha}$, $PG_{F2\alpha}$) are metabolized in the lung whereas others (PG_{A2}, PG_{I2}) pass unchanged. Some drugs (particularly basic and lipophilic ones) are taken up by the pulmonary circulation where they may act as a reservoir to be released later. Acid drugs bind to plasma proteins. Some chemicals (e.g. paraquat, nitrofurantoin, bleomycin, amiodarone) accumulate in the lung and are toxic.

The lung releases a variety of inflammatory mediators on exposure to inhaled allergens, notably histamine, endothelin and arachidonic acid derivatives that have undesirable effects on the rest of the body (e.g. hypotension, rashes). It also produces nitric oxide, but this is probably important only in the local control of blood flow and the regulation of perfusion in relation to ventilation. ◆

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Measurement of Respiratory Function
Part 1: Ventilation

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The mechanics of getting oxygen into the bloodstream and removing carbon dioxide from it is brought about by a combination of the movement of air in and out of the lung (ventilation) and the ability to transfer oxygen and carbon dioxide in and out of the bloodstream via the alveoli (perfusion). A typical value for alveolar ventilation with the individual at rest is about 4–5 litres/minute and pulmonary blood flow (cardiac output) is about 5 litres/minute, thus the ratio of ventilation ($\dot{V}$) to perfusion ($\dot{Q}$) is about 0.8: 1. Minute ventilation, calculated from tidal volume (500 ml) and respiratory frequency (15 breaths/minute) is about 7.5 litres, anatomical dead space is 150 ml and alveolar gas volume (functional residual capacity: FRC) is 3 litres. The volume of blood in the pulmonary capillaries is only about 70 ml.

Gas transfer may be limited by the time the blood spends in the capillary. When blood is diverted from other parts of the lung (e.g. following a large pulmonary embolus) the time taken for the blood to traverse the capillaries that are still open is reduced and gas transfer may be incomplete. With exercise at altitude, the lower atmospheric partial pressure of oxygen results in a decrease in the driving pressure of oxygen across the capillary membrane, and equilibration may be incomplete, worsening the hypoxaemia.

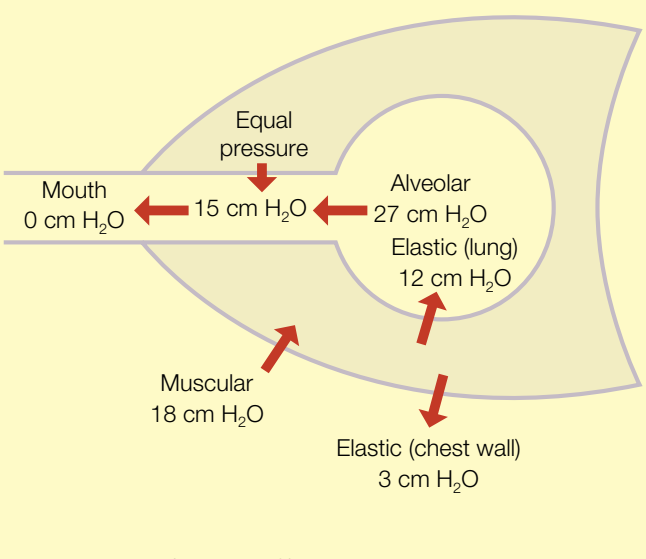
Equilibration between the alveolus and the blood is normally limited by perfusion. However, it may be limited if the resistance to gas transfer is increased by diffusion, for example in chronic chest diseases with thickening of the alveolar capillary membrane or if fluid is present. In health, diffusion reserves are huge and, with a normal alveolar-capillary membrane, disturbances in gas transfer are mainly caused by alterations in the matching of perfusion to ventilation.

Lung volumes

Airflow in and out of the lung is dependent on the generation of pressure differences between the alveoli and the atmosphere. Air flow is a mixture of laminar and turbulent flow, the latter occurring particularly at airway junctions. At high rates of flow, the amount of turbulence increases and resistance rises disproportionately.

Quiet expiration to FRC is a passive process driven by elastic forces in the lung, while the inspiratory muscles gradually relax. At FRC, intrapleural pressures are negative, but in the upright individual there is a difference between the top (atmospheric pressure (A) – 8 cm H_2O) and the base (A – 2 cm H_2O) of the lung, as a result of which, alveoli at the base of the lung (in the upright position) are relatively compressed and smaller (less full with gases) than those at the top. During expiration to residual volume the intrapleural (intrathoracic) pressure becomes positive and compresses alveoli and airways. Alveolar pressure is thus made up of the intrapleural (intrathoracic) pressure plus the elastic recoil pressure of the lung (Figure 1). Pressure at the mouth is atmospheric, therefore there is a point along the airway from alveoli to the mouth where the intraluminal pressure equals the surrounding intrathoracic pressure – the so-called 'equal pressure point'.

Respiratory pressures during a forced expiration



Muscular effort (18 cm H_2O) produces a positive intrathoracic (intrapleural) pressure equal to the effort (18 cm H_2O) minus the elastic recoil of the chest wall (3 cm H_2O) of 15 cm H_2O. The pressure gradient down the airway ranges from the intra-alveolar pressure (27 cm H_2O) to zero at the mouth. Intra-alveolar pressure (27 cm H_2O) is made up of the elastic recoil of the lung (12 cm H_2O) plus the positive intrathoracic pressure (15 cm H_2O) therefore a point must exist along the airway where airway equals intrathoracic pressure. Any further increase in pressure compresses the airways at and below the equal pressure point and does not increase the rate of airflow which is thus determined only by the elastic recoil of the lung (12 cm H_2O) and so is independent of muscular effort

1

Towards the mouth from this equal pressure point mainly comprises the large, relatively rigid, airways and towards the alveoli, the smaller airways, which are less well supported and less rigid. Any increase in muscular effort tends to compress these small airways at or on the alveolar side of the equal pressure point. The alveolar pressure is thus a combination of elastic recoil of the lung plus the raised intrathoracic pressure, but this raised intrathoracic pressure is also compressing the airways at the equal pressure point, therefore the expiratory flow rate is determined by the elastic recoil of the lung only and is independent of muscular effort (Figure 1). When the rise in intrathoracic pressure completely blocks off the airways, the alveoli cease to empty and gas trapping occurs. In a healthy young adult, breathing quietly down to residual volume in the upright position, this is seen at about 10% of vital capacity.

Other factors that predispose to premature small airway closure and air trapping are those that cause a reduction in calibre of the smaller airways (e.g. smooth muscle contraction, mucosal swelling, secretions), a loss of supporting tissues and elasticity (emphysema, age), increased intrathoracic pressure (obesity), or decreased elastic recoil of the lung. This occurs first at the lung bases because of the higher intrapleural (intrathoracic) pressure. With a forced expiratory manoeuvre and high intrathoracic pressure, airway closure occurs at a higher lung volume.

Tests of ventilation

Ventilation is normally assessed from measurement of static lung volumes and various indices of expiration, namely forced expiratory volume (FEV), forced expiratory volume in 1 second (FEV_1), peak expiratory flow rate (PEFR) and flow–volume curves.

Static lung volumes

Static lung volumes are traditionally measured using a conventional bell-type spirometer or a dry rolling seal-type spirometer, which is essentially a piston in a cylinder with a pliant seal between the two which is free to move as the piston moves in and out. The volumes obtained are compared with published tables of normal values for age, height, weight and gender. All measurements can be read directly from the spirometer trace except for FRC (and residual volume) which is measured with helium dilution, or using a whole body plethysmograph or calculated from nitrogen washout.

FRC is the oxygen reservoir from which gas exchange takes place and which is replenished by tidal ventilation. It is affected by a number of conditions (e.g. obesity, pregnancy, abdominal surgery) and such changes affect oxygenation mechanisms, particularly via the relationship between FRC and small airway closure. FRC cannot be read off the spirometer trace and is most commonly measured using helium dilution because helium is easily analysed and virtually insoluble in the tissues.

The spirometer is filled with a mixture of a known concentration of helium (C_1) and oxygen-enriched air. The volume (V_1) of the spirometer is known. The individual, wearing a nose clip, breathes into the spirometer via a mouthpiece. The mouthpiece is initially open to room air. At the end of a normal quiet expiration (i.e. at FRC:V_2) the individual is switched into the spirometer circuit and continues to breath quietly via the circuit. Carbon dioxide is absorbed and oxygen added as necessary to maintain the end-tidal position. The helium equilibrates between the spirometer and the lung and its concentration in the circuitry is observed to fall to a final concentration C_2. Thus:

$$C_1 V_1 = C_2(V_1 + V_2)$$

$$\text{from which } V_2(\text{FRC}) = V_1 \times \frac{C_1 - C_2}{C_2}$$

The individual normally takes a couple of quiet vital capacity breaths to facilitate mixing. The whole process takes 5–10 minutes depending on the type and degree of lung pathology (poorly ventilated alveoli take longer to equilibrate).

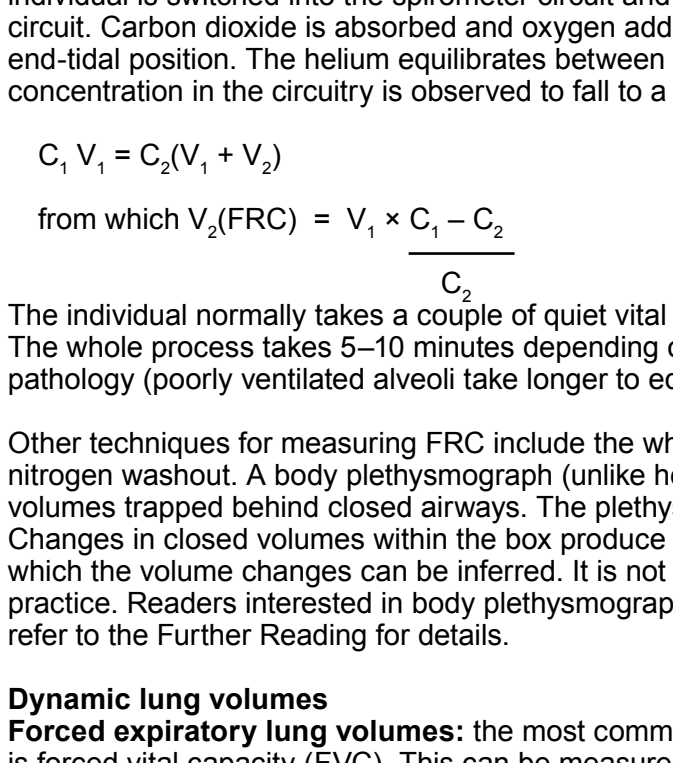
Other techniques for measuring FRC include the whole body plethysmograph and nitrogen washout. A body plethysmograph (unlike helium dilution) measures gas volumes trapped behind closed airways. The plethysmograph is a closed airtight box. Changes in closed volumes within the box produce changes in box pressures from which the volume changes can be inferred. It is not in common use in anaesthetic practice. Readers interested in body plethysmography and nitrogen washout should refer to the Further Reading for details.

Dynamic lung volumes

Forced expiratory lung volumes: the most common measurement of ventilation is forced vital capacity (FVC). This can be measured using a wedge spirometer (or Vitalograph) which is easily transported to the bedside. A typical FVC trace is shown in Figure 2. The individual takes a maximal inspiration then breathes out as far and as forcibly as possible. FVC and FEV_1 are derived from the tracing. The ratio FEV_1: FVC (x 100) gives a measure of airways obstruction; its normal value is 75–80%. FVC is slightly less than VC (measured with a slow quiet expiration) because of airway trapping. It is affected by diseases of the thoracic cage (e.g. kyphosis, acute injury), of the respiratory muscles (e.g. poliomyelitis), of the pleural cavity (e.g. pneumothorax) or by decreased compliance (e.g. chronic bronchitis, fibrosis, obesity). It is also affected by obstructive conditions (e.g. asthma). The ratio FEV_1:FVC gives more information about obstruction than either of the two measurements alone.

The point of greatest resistance in the normal respiratory tract is in the medium-size bronchi, about the fourth or fifth generation, just beyond the origin of the bronchopulmonary segments. With a forced expiratory manoeuvre, the intrathoracic pressure rises and compresses the alveoli, causing the small airways to be compressed as well. In the latter part of such a manoeuvre, the point of greatest resistance is the small airways. Other measurements of flow that can be derived from the FVC curve are PEFR (by taking a tangent to the steepest part, normally the start of the curve) and mid-expiratory flow rate ($FEV_{25–75}$: by measuring the slope of a line drawn between the two points on the curve at 25% and 75% of FVC).

Forced expiratory lung volume measured by wedge spirometry



The graph shows the derivation of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1) and the line from which peak expiratory flow rate (PEFR) can be determined

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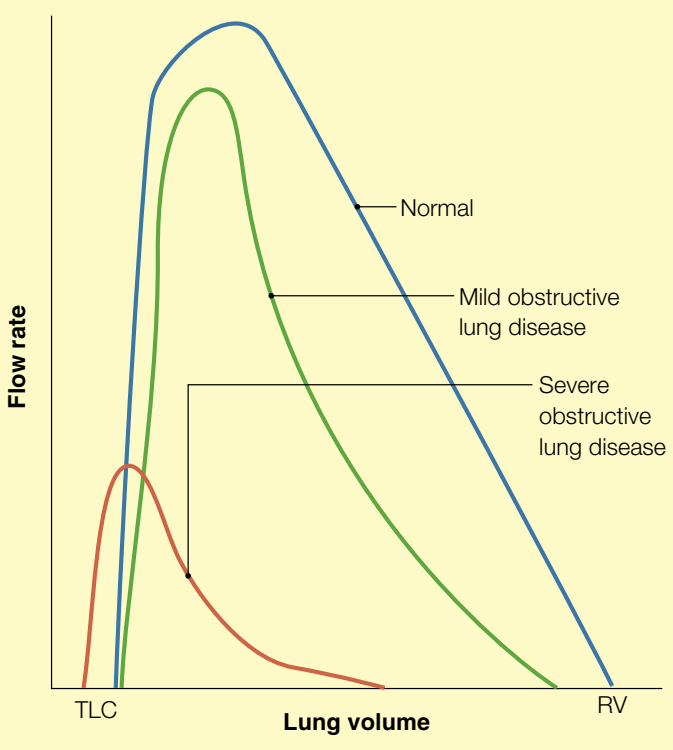
Flow volume loops: the above measurements are more an index of large or medium airway function. Small airways are studied specifically using the flow volume loop, an example of which is shown in Figure 3. The individual carries out an FVC manoeuvre; flow rate is measured and plotted against lung volume. The peak of the curve denotes peak flow; beyond that point, airway compression occurs and increased muscular effort does not increase the expiratory flow rate. With worsening disease of the small airways the flow rate declines earlier in expiration to give a typical scooped out appearance (Figure 3). With obstructive disease, vital capacity may be decreased and residual volume increased (i.e. the patient breathes at a higher lung volume because of the obstruction to expiration).

Flow volume loops



Note the scooped out appearance of the obstructive curves and the limitation of peak flow with severe obstructive lung disease
RV, residual volume; TLC, total lung capacity

3

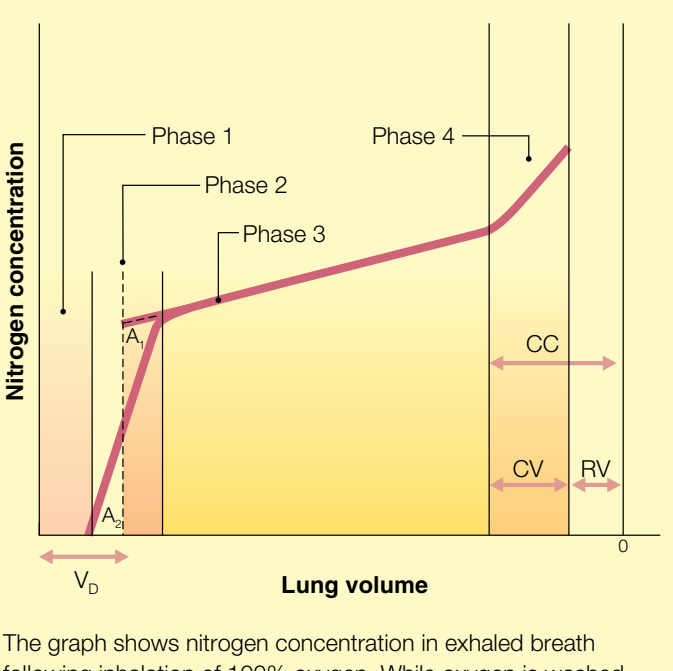
Modern spirometers are often electronic, integrating flow signals from various types of flowmeter to derive volumes such as FVC, FEV_1, $FEV_{25–75}$. All of the parameters discussed above can be derived electronically from a single forced expiration. Lightweight portable instruments are available, but have to be calibrated and, though more convenient than the traditional ones, are not as robust nor as accurate.

It is conventional to present respiratory volumes at body temperature and pressure saturated (BTPS). All of the measurements are made under ambient conditions, therefore volumes are corrected for temperature, including the difference in saturated vapour pressures at ambient and body temperatures.

Assessment of uneven ventilation
Two tests give a ready assessment of uneven ventilation. The single breath nitrogen test is a research tool, but is much loved by examiners and has other applications in terms of measuring the volume at which small airways start to close. The single breath carbon dioxide washout curve is used in everyday anaesthetic practice.

The single breath nitrogen test: the individual takes in a single vital capacity inspiration of pure oxygen then exhales to residual volume and the concentration of nitrogen at the mouth is monitored. A typical tracing is shown in Figure 4. Four phases are recognized.
- Phase 1: pure oxygen is exhaled from the upper airways and the nitrogen concentration is zero.
- Phase 2: there is a rapid rise in nitrogen concentration as the anatomical dead space is washed out with alveolar gas.
- Phase 3 is known as the alveolar plateau. With uneven ventilation the nitrogen concentration rises steadily. The slope is a measure of the unevenness of ventilation.
- Phase 4: towards the end of phase 3 there is a sharp rise in nitrogen concentration. This signals the onset of small airway closure at the base of the lung.

Single breath nitrogen test



The graph shows nitrogen concentration in exhaled breath following inhalation of 100% oxygen. While oxygen is washed out of the upper airway (phase 1) nitrogen concentration rises (phase 2) to alveolar plateau (phase 3). Closing volume (CV) is the transition from phase 3 to phase 4. Steepness of phase 3 denotes unevenness of ventilation. RV, residual volume; CC, closing capacity; V_D anatomical dead space

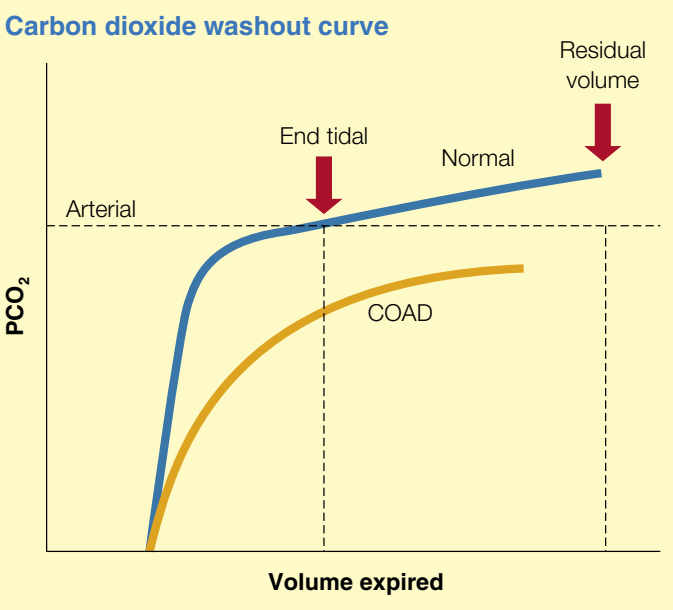
4

Alveoli fill and empty at different rates. When the individual breathes in 100% oxygen the nitrogen present in the airways essentially acts as a tracer. During inspiration, the alveoli at the base of the lung open last and expand the most. During expiration, the 'fast' or better-ventilated alveoli empty first; they contain more oxygen with lower nitrogen concentrations than the 'slower' ones, resulting in an increase in nitrogen concentration during expiration. The steeper the slope the more uneven the ventilation.

The inflection from phase 3 to phase 4 occurs because at residual volume, alveoli at the base of the lung are smaller and expand more than those at the top. Towards residual volume, the (small) airways to some of them are closed, because the intrathoracic (pleural) pressure exceeds the airway pressure. With a vital capacity inspiration the alveoli at the base of the lung, which are closed at residual volume, expand far more than those at the top, so when breathing in 100% oxygen, the nitrogen in the alveoli at the base is more diluted by oxygen than in those at the apex. During expiration, upper and lower zones tend to empty together, producing the alveolar plateau, but as soon as the airways at the base start to close, the higher nitrogen concentrations in alveoli in the upper zones, which are still emptying, produce the abrupt rise in nitrogen concentration.

Carbon dioxide washout curve: expired carbon dioxide concentrations are monitored routinely during anaesthesia. Figure 5 shows a typical carbon dioxide concentration curve during a slow quiet expiration to residual volume in a normal individual and in a patient with airway obstruction and uneven ventilation. Also indicated are the normal end-tidal points, the expired partial pressure of carbon dioxide (PCO_2) at residual volume and the partial pressure of carbon dioxide in arterial blood ($PaCO_2$). The slope of the curve is analogous to the slope of the nitrogen washout curve following a vital capacity inspiration of 100% oxygen. End-tidal PCO_2 at the end of a normal quiet tidal expiration approximates closely to $PaCO_2$ and in clinical practice can be used as an indicator of $PaCO_2$. If the individual breathes slowly and steadily to residual volume, $PaCO_2$ rises further and tends to venous PCO_2. The slope of the tracing is an indication of abnormalities in ventilation (and perfusion), the steeper the slope the more uneven the ventilation in relation to alveolar perfusion. The lower curve in Figure 5 shows the type of curve seen in individuals with obstructive airways disease. It is also similar to that seen during a forced expir-atory manoeuvre; airway trapping occurs at relatively high lung volumes, the alveolar slope is steeper and there is a significant difference between end-tidal (end expiratory) PCO_2 and $PaCO_2$. ◆

Carbon dioxide washout curve



Expired partial pressure of carbon dioxide (PCO_2) breathing quietly from normal inspiration to residual volume. End-tidal PCO_2 approximates to the partial pressure of carbon dioxide in arterial blood ($PaCO_2$). The steepness of the alveolar plateau gives an index of unevenness of ventilation. PCO_2 at residual volume is higher than $PaCO_2$. The lower trace shows that in chronic obstructive airways disease (COAD) end-tidal PCO_2 does not approximate to $PaCO_2$

5

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Measurement of Respiratory Function
Part 2: Gas Exchange

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Blood normally spends about 0.75 seconds in the alveolar capillary. Equilibration of carbon dioxide occurs in about 0.25 seconds and of oxygen in about 0.4 seconds. Therefore, equilibrium occurs rapidly and is normally complete when the blood has traversed only about half the capillary. Within the pulmonary capillary there is thus a large reserve for gas transfer. Although pulmonary blood flow may rise fivefold with exercise, gas transfer (at sea level) is still normally complete. The pulmonary circulation has a large reserve. With increases in cardiac output, pulmonary capillaries have the capacity to expand (distension) and capillaries that are closed at rest or have no blood in them, open up (recruitment).

The carbon monoxide transfer test is used in chest medicine as a noninvasive method of quantifying gas transfer. Carbon monoxide is more soluble in blood than carbon dioxide or oxygen. When it is present in inspired air, equilibrium is not reached by the time the blood has perfused the alveoli. No appreciable loss of diffusion gradient develops in the alveolus and the gas continues to move rapidly into the bloodstream, therefore its uptake is normally independent of blood flow, and thus limited by diffusion. Its rapid uptake from the alveolus makes it a sensitive test of gas transfer. It is considered principally as an index of diffusion, but probably is also affected by ventilation–perfusion abnormalities. The carbon monoxide transfer test is not widely used in anaesthetic practice.

Measurement of ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}$) involves the inhalation or injection of radioactive isotopes, respectively. These methods are in common use in chest medicine to assess localized abnormalities. Multiple gas elimination is a research technique that allows ventilation–perfusion abnormalities to be quantified precisely. It involves injection of tracer gases of varying solubilities and allows distribution curves to be plotted for pulmonary blood flow and ventilation in relation to $\dot{V}_A$:$\dot{Q}$ ratios. Such techniques are not in routine use in anaesthetic practice and are beyond the scope of this article, which focuses on the common clinical techniques used to measure ventilation and gas exchange, and the derivation of parameters that can be calculated from them.

Blood gases

The ultimate test of how well ventilation is matched to perfusion is the measurement of blood gases. Inadequate ventilation (hypoventilation) is always accompanied by a raised partial pressure of carbon dioxide in arterial blood ($PaCO_2$). Mismatch of ventilation to perfusion results in hypoxaemia. $PaCO_2$ does not rise with ventilation–perfusion abnormalities unless ventilation is inadequate, because of depression of the respiratory centre (e.g. opiates) or pathology of the ventilatory apparatus (e.g. muscle paralysis, crush injury of the chest).

$PaCO_2$ is a function of CO_2 production ($\dot{V}CO_2$) and alveolar ventilation ($\dot{V}_A$) and is given by the relationship:

$$PaCO_2 = \dot{V}CO_2/\dot{V}_A \times K$$

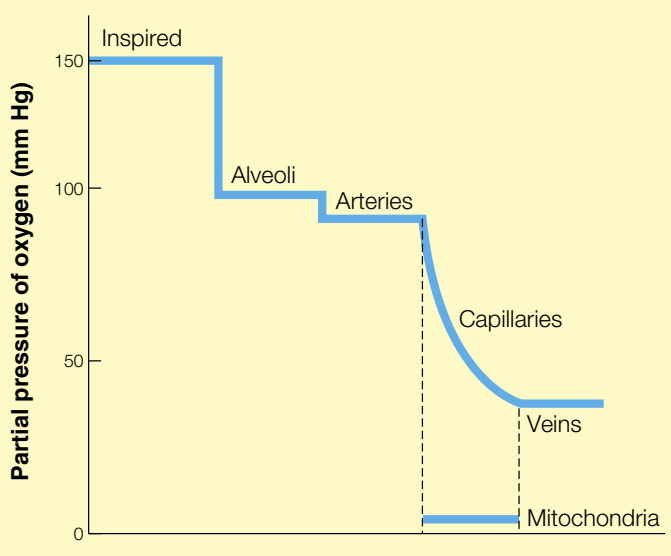
where K is a constant.

Thus, halving $\dot{V}_A$ results in doubling $PaCO_2$.

The oxygen cascade

Figure 1 illustrates how the partial pressure of oxygen (PO_2) falls as gas is moved from the inspired air to the tissues. Inspired air is humidified in the upper airways and gas exchange with the alveoli is a function of ventilation. From the alveoli, oxygen moves into the arteries. The difference between PO_2 in the alveoli (P_AO_2) and in the arteries (PaO_2) is a function of ventilation–perfusion relationships and, in some chest diseases, diffusion across the alveolar capillary membrane. From the arteries, gas exchange with the peripheral tissues occurs in the capillaries. O_2 and CO_2 diffuse through the tissues. Most oxygen is used, and most CO_2 produced, in the mitochondria where PO_2 is very low (1–4 mm Hg).

Oxygen cascade



1

Inspired PO_2 (P_IO_2) is calculated from barometric ressure (760 mm Hg at sea level) and the proportion of O_2 in inspired air (F_IO_2 – for atmospheric air 20.9%) allowing for humidification of the inspired air; the saturated vapour pressure of water at 37°C is 47 mm Hg. Thus:

$$P_I O_2 = (760 - 47) \times 20.9/100 = 149 \text{ mm Hg}$$

The decrease in PO_2 from the inspired air to the alveolar air is due to dilution by the CO_2 in the alveoli, but the body produces less CO_2 than it uses O_2. The ratio of CO_2 produced to O_2 consumed is given by the respiratory quotient or respiratory exchange ratio (R). This is normally 0.7–1. It is seldom measured and a value of 0.8 is normally assumed. Based on this, P_AO_2 can be calculated from the simplified form of the alveolar air equation:

$$P_AO_2 = P_IO_2 - P_ACO_2/R$$

P_ACO_2 can be taken as end-tidal CO_2, though it is more usual to use $PaCO_2$. In terms of the figures quoted above:

$$P_AO_2 = 149 - 40/0.8 = 99 \text{ mm Hg}$$

P_AO_2 can be influenced by raising or lowering the F_IO_2 or by changing ventilation, which changes $PaCO_2$ and thus alters the P_AO_2 in line with the alveolar air equation. O_2 uptake from the alveoli may also have an effect, particularly in patients with respiratory impairment and a raised oxygen consumption caused by shivering, pain, anxiety or fever.

The difference between P_AO_2 and PaO_2 (the alveolar–arterial oxygen difference or gradient) is due mainly to ventilation–perfusion mismatch, specifically alveoli overperfused relative to their ventilation (i.e. $\dot{V}_A$:$\dot{Q}$ < 0.8) ranging from alveoli with a $\dot{V}_A$:$\dot{Q}$ ratio only slightly less than 0.8 to alveoli that are perfused and not ventilated at all (i.e. $\dot{V}_A$:$\dot{Q}$ = 0; atelectasis, lobar collapse, pneumonia). In health (in the upright position), the alveoli with $\dot{V}_A$:$\dot{Q}$ ratios less than 0.8 occur in the lower part of the lung. There is a gradation of $\dot{V}_A$:$\dot{Q}$ ratios from about 3.3 at the top (overventilated and underperfused) to 0.63 at the base (underventilated and overperfused). This distribution of $\dot{V}_A$:$\dot{Q}$ ratios leads to a spread of P_AO_2 values, with those at the top of the lung being high (about 130 mm Hg) and those at the base being low (about 80 mm Hg). With such a spread of P_AO_2 values how can one justify using a single figure? The figure given by the alveolar air equation is conventionally taken to be an average value for P_AO_2 over the whole lung. However, the figure is heavily weighted by basal alveoli which is where most of the ventilation (and perfusion) takes place. It is also known as the ideal P_AO_2.

The principal factor affecting ventilation and perfusion in the lung is gravity in relation to the weight of the lung and the low pressures in the pulmonary circulation. All of the above arguments about the distribution of ventilation and perfusion have applied to the conscious individual in the upright position. When the individual lies down gravity still applies, so the areas of high $\dot{V}_A$:$\dot{Q}$ ratios move to the anterior aspect of the chest and of low $\dot{V}_A$:$\dot{Q}$ to the posterior. Airway closure then takes place posteriorly rather than at the base.

Measurement of gas exchange

The causes of hypoxaemia are broadly classified as impairment of diffusion (abnormalities of the pulmonary capillary membrane, pulmonary embolus, exercise at altitude), ventilation–perfusion abnormalities (specifically overperfusion of underventilated alveoli) and 'shunt', the most extreme form of ventilation–perfusion mismatch ($\dot{V}_A$:$\dot{Q}$ = 0). In normal circumstances, most arterial hypoxaemia is due to ventilation–perfusion mismatch.

Alveolar–arterial difference

The difference between P_AO_2 and PaO_2 can be used as an indicator of ventilation–perfusion mismatch. In the young healthy individual, the alveolar–arterial difference is less than 10 mm Hg, but it increases with age and with any condition that impairs gas exchange. It exists because of the shape of the haemoglobin dissociation curve. Consider three alveoli of equal size and equal perfusion in the upper, mid and lower zones with PO_2 of 120, 80 and 40 mm Hg (i.e. in an individual with some ventilation–perfusion mismatch; Figure 2). The average P_AO_2 is 80 mm Hg. The blood leaving these three alveoli has partial pressures corresponding to the P_AO_2, but there is little difference in the oxygen content between the 120 and 80 mm Hg alveoli because they both lie on the flat part of the oxygen–haemoglobin dissociation curve and the blood from them will be 98% and 95% saturated, respectively. However, the blood leaving the 40 mm Hg alveolus lies on the steeper part of the dissociation curve and its saturation is only 75%. Assuming equal blood flow through each of the three alveoli gives an overall arterial saturation of 89%, corresponding to a PaO_2 of 57 mm Hg and an alveolar–arterial difference of 23 mm Hg. In other words, the relative overventilation of the 80 and 120 mm Hg alveoli has little effect on arterial saturation and does not compensate for the underventilation of the 40 mm Hg alveolus which, because of its position on the curve, has a very marked effect. This is even greater in practice because blood flow through the base of the lung is normally much greater than through the apex.

Shunt

True shunt refers to blood that enters the arterial system without passing through ventilated lung such as occurs with pneumonia, (consolidation) or pulmonary collapse. There is a small amount of shunt in the normal lung; blood supplying the bronchi (bronchial arteries) drains into the pulmonary veins and a small amount of coronary venous blood drains directly into the cavity of the left ventricle through the Thebesian veins. The addition of this desaturated blood depresses PaO_2. The same occurs in individuals with a defect between the right and left sides of the heart. In clinical practice, true shunt is mainly seen in pneumonia with inflammatory consolidation of the alveoli or with the alveolar flooding of pulmonary oedema.

If all hypoxaemia were caused by true shunt it would be possible to quantify the shunt from measurements and calculation of the oxygen content of arterial and mixed venous blood and a knowledge of P_AO_2. Figure 3 shows a shunt with a proportion of the cardiac output ($\dot{Q}t$) passing through ventilated lung ($\dot{Q}c$) and a proportion through the shunt ($\dot{Q}s$):

$$\dot{Q}t = \dot{Q}c + \dot{Q}s$$

Oxygen content (C) for each component can be calculated from the haemoglobin concentration and the PO_2 of each component, such as mixed venous blood (CvO_2), arterial blood (CaO_2) and end pulmonary capillary blood ($Cc'O_2$) the pressure of which is assumed to equal P_AO_2.

Thus:

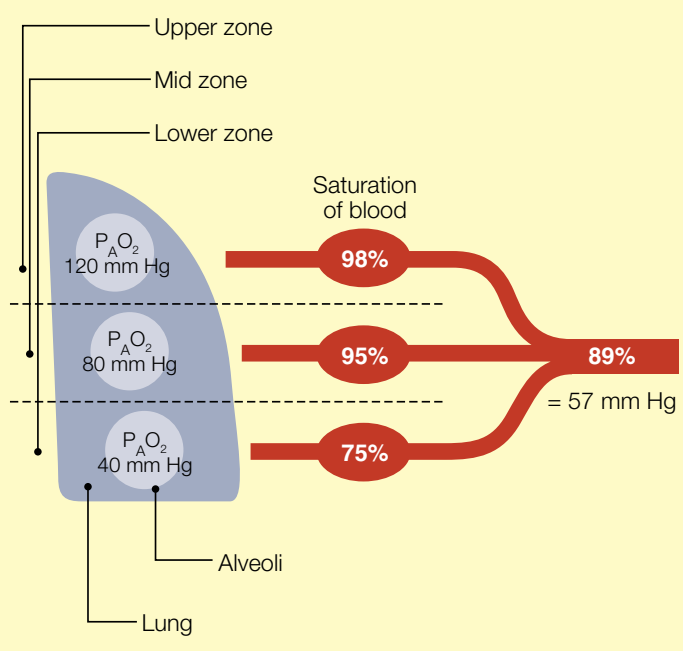
$$\dot{Q}t \times CaO_2 = \dot{Q}c \times Cc'O_2 + \dot{Q}s \times CvO_2$$

Rearranging

$$\frac{\dot{Q}s}{\dot{Q}t} = \frac{Cc'O_2 - CaO_2}{Cc'O_2 - CvO_2}$$

gives shunt as a percentage of cardiac output. Calculation of CvO_2 necessitates the measurement of mixed venous oxygen pressure using a pulmonary artery catheter. This also allows the measurement of cardiac output and a figure for shunt could be obtained in terms of volume/minute.

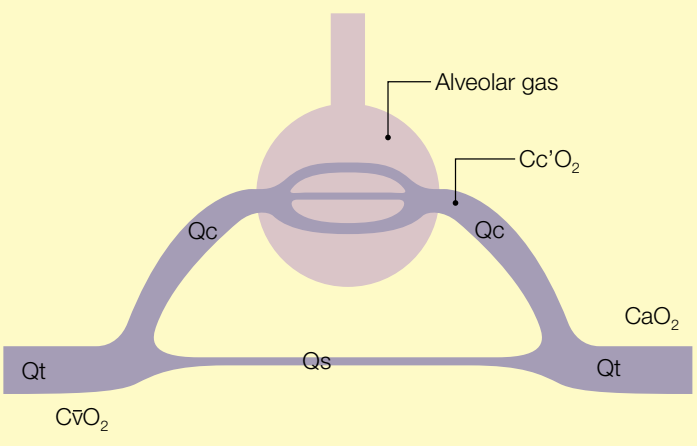
Origin of the alveolar–arterial gradient



Mean partial pressure of oxygen in alveoli (P_AO_2) is 80 mm Hg
Alveolar–arterial gradient = 80 – 57 = 23 mm Hg

2

Shunt



Degree of venous admixture can be quantified by assuming that it is all due to true shunt and calculating the amount of shunt that would be required to produce that degree of hypoxaemia. End pulmonary capillary oxygen content ($Cc'O_2$) is calculated assuming $Cc'PO_2$ to be the same as partial pressure of oxygen in alveoli (P_AO_2)
Qt, cardiac output; Qc, blood flow through ventilated lung; Qs, shunt.
Partial pressure of oxygen in arterial blood (CaO_2) and mixed venous blood $C\bar{v}O_2$

3

Ventilation–perfusion mismatch

Hypoxaemia is seldom caused by true shunt; much of it arises from ventilation–perfusion mismatch. To measure this requires the sophisticated laboratory-based techniques referred to earlier, which are not readily available. A method of quantifying impairment of oxygenation in clinical practice is to assume that all the hypoxaemia, including ventilation–perfusion mismatch is caused by true shunt and to calculate the amount of shunt that would be required to produce that degree of hypoxaemia. The lung is considered to consist of:

- alveoli that are ventilated but not perfused (dead space)
- alveoli that are perfused but not ventilated (shunt)
- alveoli that are perfused and ideally ventilated (i.e. blood leaving these alveoli (end pulmonary capillary blood) has the same PO_2 as ideal alveolar air).

In terms of ventilation–perfusion mismatch, the overperfused underventilated alveoli at the base of the lung contribute to ‘shunt’ and hypoxaemia. This is often referred to as venous admixture. Similarly the overventilated underperfused alveoli at the top of the lung contribute to ‘dead space’.

A feature of hypoxaemia caused by true shunt is that increasing the F_IO_2 makes little difference to the severity of the hypoxaemia whereas hypoxaemia caused by ventilation–perfusion mismatch can be abolished by increasing the inspired concentration of oxygen.

Dead space is gas that takes part in ventilation but not in gas exchange. It is made up of anatomical dead space and alveolar dead space; both of which constitute physiological dead space. Physiological and anatomical dead space can both be measured and alveolar dead space can therefore be calculated.

Anatomical dead space is measured using Fowler’s technique. This is a research tool not commonly used in clinical practice. The method is based on the nitrogen washout curve. Following a single inspiration of 100% O_2 expired N_2 is monitored at the mouth as described previously but is plotted against expired volume. In phase 2 of the curve a vertical line is dropped such that area A_1 is equal to area A_2. The anatomical dead space is the volume expired up to the vertical line.

Physiological dead space can be measured in clinical practice and is calculated from the Bohr equation:

$$\frac{V_D}{V_T} = \frac{PaCO_2 - P_ECO_2}{PaCO_2}$$

Where V_D is physiological dead space, V_T is tidal volume, and P_ECO_2, the partial pressure of mixed expired CO_2, is calculated from barometric pressure and the fractional concentration of CO_2 in the mixed expired air.

Mixed expired air is a mixture of all the air breathed out over a period and includes both the anatomical dead space and the alveolar gas. It is collected either into a spirometer or reservoir (Douglas) bag for analysis or passed through a mixing box and sampled. The important feature is that it includes all the dead space air and all the air that has taken part in gas exchange. Mixed expired CO_2 concentration is usually about 2–4% CO_2 depending on the amount of dead space. It must be distinguished from end-tidal CO_2 which normally reflects $PaCO_2$ and is about 5–5.5% CO_2. Rearranging the Bohr equation:

$$V_D = V_T \frac{PaCO_2 - P_ECO_2}{PaCO_2}$$

The calculation of V_D thus entails measuring V_T, $PaCO_2$ and P_ECO_2 all at the same time. This can be done by collecting expired air over a timed period and measuring its volume, its CO_2 content and $PaCO_2$ during the period of collection. V_T can be calculated from the timed expired volume and the respiratory rate. It is important to maintain a steady state throughout; in a conscious individual this can be difficult when a mouthpiece and the sampling of arterial blood both tend to induce hyperventilation. With an intubated unconscious patient undergoing mechanical ventilation it is relatively easy and some ventilators calculate physiological dead space automatically using end-tidal CO_2 as an approximation of $PaCO_2$. As discussed earlier, in the diseased lung this can cause problems because the assumption that end-tidal CO_2 approximates arterial CO_2 may not be valid.

Alveolar–arterial gradients and mixed expired PCO_2: in practice, shunt can be measured only with a pulmonary artery line in place, but the alveolar–arterial PO_2 difference in breathing air is a reasonable reflection of the extent of ventilation–perfusion mismatch. At a high F_IO_2 the relationship is more complex. From the Bohr equation it is self-evident that the mixed expired CO_2 concentration has an inverse relationship with the size of the dead space. ◆

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Respiration: Control of Ventilation

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The control of ventilation involves control of:
- the rhythmical process of inspiration and expiration
- the overall rate of ventilation and gaseous exchange with the environment.

Animal experiments show that the respiratory centres are in the pons and medulla, and the vagi are also involved. Figure 1 shows the breathing patterns after sectioning the brainstem at different levels, with the vagi remaining intact or sectioned.
- The basic inspiratory–expiratory cycle originates from the medulla, but it is irregular in tidal volume and frequency.
- A 'smoothing' of the respiratory cycle takes place in the pons. If the medulla and pons are intact, then respiration is normal, though voluntary influences, needed for speech and singing, are impossible.
- Making a section above (rostral to) the medulla but below (caudal to) the nuclei parabrachialis (the pneumotaxic centre), causes inspiration to be prolonged; if the vagi are also sectioned, then apneusis develops – expiratory gasps for air from a position of exaggerated inspiration. Inspiration is normally inhibited by the pneumotaxic centre and the vagi.

Inspiratory–expiratory cycle
Neurons in the medulla and pons discharge mainly during the inspiratory or expiratory phase of the respiratory cycle; they are often referred to as 'inspiratory' or 'expiratory' neurons, respectively. There are also neurons that fire during the inspiration–expiration and expiration–inspiration transitions known as 'switching' neurons. The inspiratory neurons are most common in the dorsal medulla, the expiratory neurons in the ventral medulla, and the 'switching' neurons in the pons, but there is overlap between the sites.

The inspiratory and expiratory neurons send efferent impulses to the intercostal muscles and diaphragm, and the inspiratory neurons in particular receive inputs from the vagi and chemoreceptor areas (see below).

The origin of the respiratory rhythm is not known in detail, but the following account covers the main principles. The respiratory cycle consists of coordinated phases of inspiration and expiration, and smooth transitions between the two.

Inspiration causes the inspiratory cells to fire in unison, and the expiratory cells to be quiescent. This is achieved by the inspiratory cells exciting their inspiratory agonists and inhibiting their expiratory antagonists. Lung volume increases.

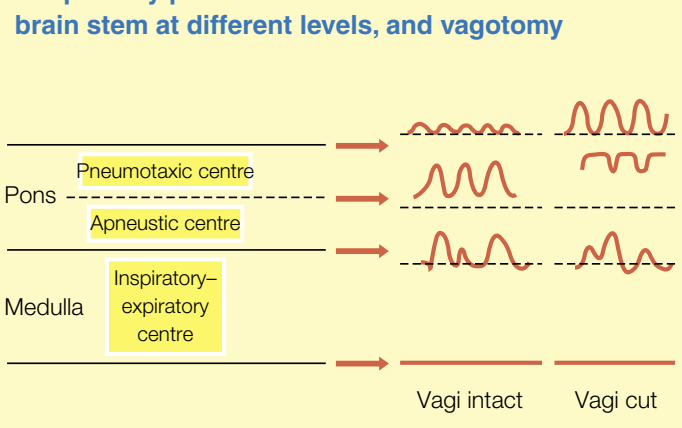
Inspiration is terminated by several simultaneous influences. First, the excitability of the inspiratory cells falls (fatigue); second, the excitability of the quiescent expiratory cells rises; third, inhibitory inputs from stretch receptors in the bronchial tree of the expanding lungs (the Hering–Breuer reflex) travel to the inspiratory neurons via the vagi; fourth, inhibitory inputs reach the inspiratory cells from the pneumotaxic centre. This combination reaches a point when activity of the inspiratory neurons begins to decline. At this point, the expiratory neurons are released from their inhibition, and the system switches to the expiratory mode.

Expiration takes place, often passively (see above), using the force of lung recoil. However, this does not negate the need for expiratory neurons. They are required firstly for rapid or deep expirations when expiratory muscle effort is necessary and secondly to reset the gamma-loops of the muscle spindle-extrafusal fibre system of the respiratory muscles, so that they do not oppose being stretched during expiration. Like inspiratory neurons, expiratory neurons also show self-re-excitation of their agonist neurons and inhibition of antagonistic neurons. The lungs decrease in volume.

Expiration is terminated when the declining excitability of the expiratory neurons, the increasing excitability of the quiescent inspiratory neurons, and the falls of inhibitory impulses to the inspiratory neurons from the vagi and the pneumotaxic centre, all combine to switch the system back to the inspiratory mode. The cycle then starts again.

The vagi and the control of respiratory work
The vagi play an important role in terminating inspiration and thus in determining the tidal volume (Figure 1). The system is set so that the combination of frequency and depth of breathing at rest minimizes the work to be performed.

Respiratory patterns associated with sections of the brain stem at different levels, and vagotomy



The horizontal dashed lines indicate normal functional residual capacity.

1

Achieving total alveolar ventilation of 4 litres/minute (required at rest) can be by an infinite combination of frequencies and depths of breaths. A low frequency of ventilation, such as 4/minute, requires 1000 ml of air to be taken into the alveoli with each breath. Since about 150 ml of each breath is dead space, the tidal volume required is 1150 ml, about 13% of which is wasted. The rate of air flow required (1150 ml in 7.5 s of inspiration) is about 150 ml/s. The main problem is the large amount of work required to be done against recoil forces.

Decreasing the size of each breath and increasing the frequency of ventilation requires less work to be performed against recoil forces. However, this change increases the effect of resistance. A high frequency of ventilation such as 25/minute, requires 160 ml of air to be taken into the alveoli with each breath. For a tidal volume of 310 ml, about 48% would be wasted. The rate of airflow required (310 ml in 1.2 s of inspiration) is 258 ml/s. This more rapid airflow requires an increase in the work done against pulmonary resistance forces. The problem is exacerbated because there are more breaths per minute and an increased risk of turbulence in the airways. When air flow becomes turbulent rather than laminar, the pressure gradient required to move the air is increased.

The total work done per minute equals the sum of work done against compliance and resistance forces. As the above analysis indicates, breaths that are too large or too rapid increase the respiratory effort required and the amount of work wasted. There is an intermediate frequency and depth of ventilation that requires a minimum of effort, and the natural frequency and depth – determined in part by the Hering–Breuer reflex acting via the vagi – are close to this.

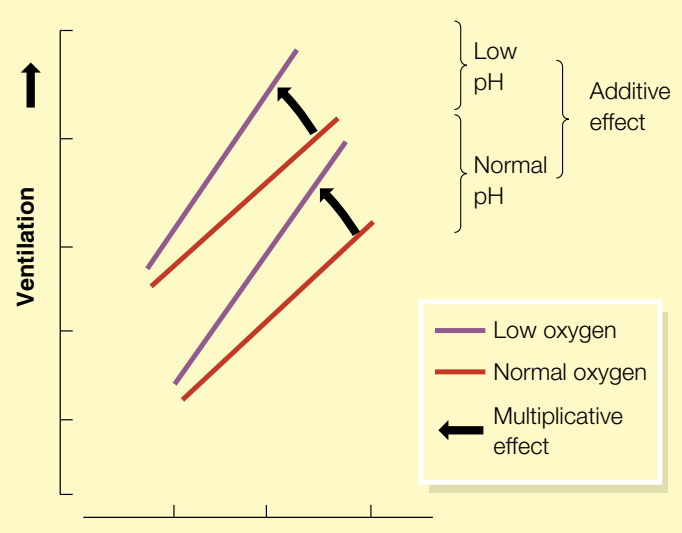
Whole body chemoreceptor reflexes

The basic respiratory cycle must be able to change in depth and frequency in order to keep oxygen and carbon dioxide levels normal, and to be able to deal with changes in metabolic demand (exercise), the partial pressure of ambient oxygen (altitude), and acid–base balance. Marked deviations from normal values lead to a deterioration in the body's performance and even to death. Under normal circumstances (breathing atmospheric air at sea level), increasing the respiratory minute volume replenishes the alveolar air with atmospheric air that is higher in oxygen (about 150 mm Hg) and lower in carbon dioxide (< 1 mm Hg). Since the blood is in equilibrium with the alveolar air, this raises the partial pressure of oxygen in the blood and lowers that of carbon dioxide. This does not significantly affect the amount of oxygen carried in the blood because the haemoglobin is already saturated, but it increases the amount of carbon dioxide blown off and decreases the amount of carbon dioxide carried in the blood. Moreover, since carbon dioxde is in equilibrium with carbonic acid, the pH of the blood rises.

Control of the respiratory gases in the blood is achieved by chemoreceptor reflexes. Considering the responses of the whole body, the most powerful stimulus to ventilation is asphyxia – the simultaneous presence of high carbon dioxide (and low pH) and low oxygen. This is the natural consequence of the respiration falling below that required to maintain normal values of the gases in blood.

The effects of changing only one or two of the variables have been investigated experimentally (Figure 2). A rise of carbon dioxide in the body (hypercapnia), oxygen and pH being unchanged, is also a strong stimulus to ventilation, but not as strong as asphyxia. If the pH is lowered at the same time as carbon dioxide is raised, it exerts an independent (additive) effect. By contrast, if oxygen is lowered (hypoxia) in the presence of hypercapnia, then there is an interaction between the two stimuli (multiplicative effect), the hypoxia sensitizing the body to the hypercapnia.

Relationship between ventilation and partial pressure of carbon dioxide



Effects due to simultaneous changes in oxygen (multiplicative) and pH (additive) are also shown.

2

The body's response to hypoxia is weak until it approaches dangerous levels (about 40 mm Hg). This appears to be partly because any increase in ventilation that hypoxia might produce also reduces respiratory drive by lowering carbon dioxide levels and raising the pH. If the levels of carbon dioxide and acid are kept at normal values during hypoxia, then the hypoxic response is greater, but is still comparatively weak until oxygen tensions have fallen below about 50 mm Hg.

Chemoreceptors
The sensory limb of the chemoreflexes are the peripheral and central chemoreceptors. The peripheral chemoreceptors (aortic and carotid bodies) are wholly responsible for the reflex responses to hypoxia, but are also sensitive to hypercapnia and to lowered pH. The central chemoreceptors (found on the floor of the fourth ventricle) are not sensitive to hypoxia, but are sensitive to the pH of the CSF.

Carotid bodies
Of the peripheral chemoreceptors, the carotid bodies have been studied more than the aortic bodies. The carotid bodies consist of round glomus cells surrounded by flattened sustentacular cells, and the sensory nerves abut the glomus cells. Hypoxia causes the nerves to increase their rate of firing, the release of dopamine probably being involved, but the link between hypoxia and transmitter release is not understood. What is known is that anaemic hypoxia (due to a decreased amount of haemoglobin in the erythrocytes) is not a stimulus – the glomus cells monitor the blood plasma rather than the erythrocytes. The fact that the glomus cells are influenced by the oxygen supplied by the blood plasma rather than the oxygenated haemoglobin is less surprising when it is appreciated that, relative to its size, the carotid body receives the greatest blood flow of any organ in the body.

The carotid body receives a sympathetic innervation. It is believed that, at the onset of exercise, an increase in sympathetic outflow constricts the blood vessels and this reduces the blood flow through the carotid body. This constriction produces a local stagnant hypoxia, and this contributes to the immediate increase in ventilation.

How the carotid bodies respond to hypercapnia and increased acidity is unknown, though individual glomus cells appear to respond to all three stimuli. This gave rise in the 1930s to the unitary hypothesis, by which all stimuli acted by a common pathway, intracellular acidity. (For hypoxia, this is postulated to be *via* glycolysis and the production of lactic acid.) This hypothesis cannot be tested until simultaneous recordings have been made of intracellular acidity, oxygen and carbon dioxide from the same glomus cell and activity in the nerve arising from it.

Central chemoreceptors
The central chemoreceptors comprise large neurons in the medulla, and are distinct from the respiratory centres described above. They monitor the CSF, particularly its pH. Owing to the blood–brain barrier, hydrogen ions from the blood cannot pass freely into the CSF, but changes in the partial pressure of carbon dioxide in the blood are reflected rapidly because there is no blood–brain barrier to this gas (nor to oxygen). The buffering capacity of the CSF is low; it contains no proteins. Accordingly, small changes in the partial pressure of carbon dioxide produce large changes in pH, and it is these changes that stimulate the chemoreceptors.

Integrating the receptor responses and the whole-body chemoreflexes
How the responses of the chemoreceptor areas are integrated into the whole-body responses is unknown. It appears that the central chemoreceptors guard the CSF against changes in pH, and this protection extends to brain tissue, which is in equilibrium with the CSF. This stability of the brain tissue pH is vital if changes in excitability of the neurons (influenced by the level of free calcium which is, in turn, controlled by pH) are to be avoided.

Oxygen levels are unimportant until they deviate markedly from normal. This is because there is a plateau at the top of the oxygen dissociation curve and small falls in the partial pressure of oxygen at the lungs are without effect; blood leaving the lung continues to be saturated. It is only when the blood leaving the lung is no longer fully saturated with oxygen that its role as a transporter of this gas becomes compromised. This loss of saturation is not marked until the partial pressure of oxygen in blood has fallen below about
50 mm Hg, and this is the point at which the hypoxic drive begins to increase markedly. Considered in this way, the lack of sensitivity of the body to hypoxia is apparent rather than real, and this aspect of the chemoreceptor reflexes is suited to the needs of the body. ◆

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Respiration: Gas Transfer

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Diffusion of gases across the alveoli
In the pulmonary circulation, gases move down the concentration gradient between the alveoli and the blood by diffusion. The rate of diffusion of a gas (D) between sites 1 and 2, is given by Fick's law of diffusion, which states that:

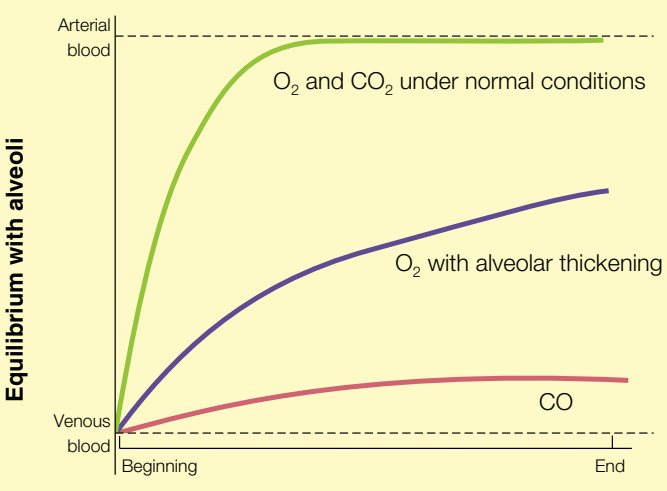
$$D = K \times (PP_1 - PP_2) \times \text{Area/Path length}$$

where: PP_1 is the partial pressure of the gas at site 1; PP_2 is the partial pressure of the gas at site 2; Area is the surface area across which diffusion can take place; Path length is the distance between sites 1 and 2; and K is a constant (the diffusion coefficient). K is directly proportional to the solubility of the gas, and inversely proportional to the square root of its molecular weight.

The thin alveolar walls and dense pulmonary capillary network ensure that the path length and area are conducive to diffusion. The continual replenishment of the air in the alveoli maintains the gradients of partial pressure of oxygen (down into the blood) and carbon dioxide (down out of the blood). In health, the processes of diffusion in the lung are so effective that equilibrium for oxygen has been achieved well within the time (less than 1 s) that the blood is in the pulmonary capillaries. This also applies to carbon dioxide, even though the partial pressure gradient (about 8 mm Hg) is small and it is a larger molecule, because it is very soluble.

The rates at which oxygen is removed from the alveoli, and carbon dioxide is delivered to them, are limited by pulmonary blood flow (Figure 1). For this reason, the excretion of carbon dioxide or the uptake of oxygen can be used to measure the cardiac output (or, more pedantically, the pulmonary blood flow). For the same reason, pulmonary diffusion capacity (a measure of the maximum rate at which a gas can diffuse across the lungs between the alveoli and the blood) cannot be measured using these gases.

Rates at which gases in the pulmonary blood equilibrate with alveolar air during passage through the capillaries



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By contrast, when carbon monoxide is breathed into the alveoli, the capacity of the blood for this gas is so great that the blood and alveoli have not equilibrated by the time the blood leaves the pulmonary capillaries (Figure 1). The uptake of this gas is not flow-limited, but diffusion-limited; its rate of uptake therefore can be used to assess pulmonary diffusion capacity, but not cardiac output.

A perfusion gradient down the lungs
Just as there is a gradient of ventilation from the apical to the basal alveoli, there is also a gradient of their perfusion by pulmonary blood. This gradient is in the same direction as that of ventilation (more perfusion at the base than the apex), and it arises because of the effects of gravity on the pulmonary circuit.

The peak pressure of the pulmonary circuit is about 25 cm H_2O during systole. Low capillary pressures reduce the loss of fluids into the surrounding tissue and alveoli, which is beneficial, because fluid accumulation would decrease diffusion by increasing the path length. The low pressures in the pulmonary circuit are achieved despite having to carry the whole of the cardiac output. This requires the resistance of the circuit to be low, which means that, compared with the systemic circuit, there is far less smooth muscle in the pulmonary arterioles. Because of this, the pulmonary arterioles do not damp the cardiac pulse and the vasculature is much more affected by transmural pressure changes caused by gravity and posture.

Any point, x, in a column of fluid has a pressure, P_x, that differs from the pressure, P_f, at some fixed point, f, by an amount given by the equation:

$$P_x = P_f \pm h.\rho.g$$

where: h is the vertical distance between the two points (it is + $h.\rho.g$ if x is below f, and – $h.\rho.g$ if x is above f); ρ is the density of the fluid; g is the acceleration due to gravity.

This can be used to calculate the extra changes in blood pressure in blood vessels that arise because the site under consideration is above or below the heart. If the pressure is measured in cm H_2O, then, since the density of blood is about that of water, the pressure changes can be calculated simply. For example, when an individual is standing up, the blood pressure in the retinal artery is about 25 cm H_2O lower than when lying down. This is because the eyes are about 25 cm above the heart when standing, but about level with the heart when lying down. Similarly, the pressure inside the arterioles and veins in the feet when standing is raised by about 100 cm H_2O, because these vessels are 100 cm below the heart. Note that all vessels in a circulation are affected equally, so the force driving blood through the capillaries is not changed. However, whereas the raised pressure in the veins of the feet causes them to become distended, and causes the opening of more blood vessels (recruitment), this does not occur with the arterioles. This is because the veins contain little smooth muscle, and so cannot resist the distending force, whereas the arterioles contain much smooth muscle, which contracts automatically when distended by the increased pressure inside the vessel.

The pulmonary circuit behaves more like systemic veins because it contains less smooth muscle. The distension caused reduces the resistance to blood flow provided by the arterioles. Thus, even though the arteriovenous pressure difference is unchanged, the resistance of the system is decreased. As a result, the pulmonary blood flow increases from the apical to the basal alveoli in an upright individual. Recruitment of blood vessels adds to this effect.

In practice, the position is more complicated for two reasons. The first concerns the pressures in the surrounding tissues (including the alveoli). The lungs in an upright individual can be divided into three zones, each covering about one-third of the lung. In the basal zone, both arterial and venous blood pressures are greater than those in the surrounding tissue throughout the respiratory cycle, and so the above description (of the effects of hydrostatic forces on the amount of distension of the arterioles) applies directly. Blood flows are highest in this zone of the lung. In the middle zone, even though the arterial pressure is always greater than the pressure in the surrounding tissues, the venous pressures are lower. In these circumstances, blood flow is determined by vessel resistance and the difference between arterial and tissue pressure. Blood flows here are lower than in the basal zone. In the apical zone, there is no blood flow during diastole, the fall in pressure due to the height of the apex of the lung being greater than the blood pressure at this time. During systole, however, the blood pressure is raised sufficiently for the system to act like the middle zone. Blood flows are lowest in this zone. Nevertheless, in spite of these differences between the three zones, the pressure relationships change in such a way that there is also, within each of them, an increase in blood flow from the top to the bottom of the zone.

The second complication arises because as the lungs are expanded, so too are all the blood vessels and bronchioles. This reduces the resistance of both sets of vessels, but it is most evident at the base of the lung, owing to the proximity of the diaphragm and its role in promoting inspiration.

In summary, in the upright individual there is a gradient of blood flow past the alveoli from the apex (where it is lowest) to the base of the lung (where it is highest).

Ventilation–perfusion balance
Blood flow past the alveoli (perfusion) and airflow into them (ventilation) increase from the apex to the base of the lungs, and both are caused in part by gravity. (For this reason, the gradients are in the reverse direction if the subject is inverted, and disappear in a zero-gravity environment.) However, the causes of these two gradients are not identical, and their sizes are unequal. The gradient of perfusion is greater than that of ventilation. Accordingly, there is a gradient in the ventilation–perfusion ratio, which decreases from the apex to the base of the lung. The alveoli at the apex are over-ventilated for the (very small) amount of perfusion that they receive, while those at the base of the lung are under-ventilated, the larger amount of ventilation being less than the much increased perfusion.

Such ventilation–perfusion imbalances threaten to decrease the efficiency with which gas exchange takes place in the lung. Further, there is wasted work because the respiratory muscles over-ventilate the apical alveoli, and the heart over-perfuses the basal alveoli. In practice, these inefficiencies are minimized by local reflexes that act to balance perfusion and ventilation.

At the lung apex, the over-ventilation results in a fall of carbon dioxide levels in the bronchiolar tree. This causes broncho-constriction, tending to direct airflow away from the over-ventilated/under-perfused regions at the lung apex. At the base of the lung, the excessive perfusion results in an increased uptake of oxygen from the alveoli and a tendency for hypoxaemia (a low tension of oxygen in the blood) to develop. However, the pulmonary arterioles show a remarkable property that is the opposite of that shown by systemic arterioles. In systemic arterioles, hypoxaemia leads to vasodilatation, therefore an exercising tissue gets more blood, and a balance exists between the metabolic need and local perfusion of the tissue. In pulmonary arterioles, hypoxaemia has the opposite effect, causing vasoconstriction. This property, though not fully understood, is vital when the relationship between alveolar ventilation and perfusion is considered, because it means that blood tends to be directed away from the over-perfused/under-ventilated regions at the base of the lung. The stimulus to hypoxic vasoconstriction comes mainly from the low partial pressure of oxygen in the alveolus and also in the mixed venous blood (pulmonary artery). In the presence of chronic hypoxia (high altitude and some forms of lung disease) pulmonary artery pressure rises due to pulmonary vasoconstriction.

Transport of gases by the blood

Oxygen
Oxygen is carried in the erythrocytes, bound reversibly to haemoglobin. Haemoglobin is a complex molecule consisting of four subunits, each containing a molecule of ferrous iron, a tetrapyrrole ring and a protein chain. The reaction involves four molecules of oxygen and one of haemoglobin; it is one of oxygenation, reduced haemoglobin being converted to oxy-haemoglobin.

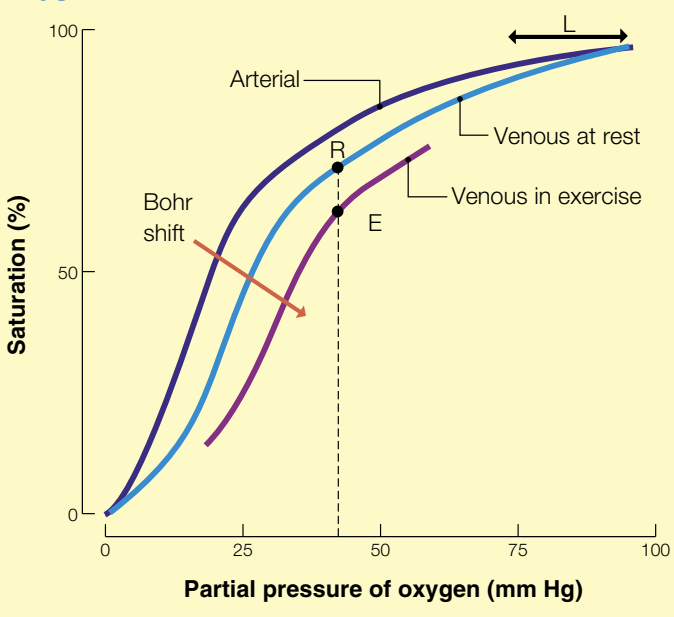
At the lungs, where the partial pressure of oxygen is high, the reaction can be represented as:

$$Hb_4 + 4O_2 \text{ Æ } Hb_4O_8 + \text{heat} + H^+$$

At the tissues, where the partial pressure of oxygen is low, the opposite reaction takes place. In health, the haemoglobin is saturated during its passage through the lungs, and the amount of oxygen carried is about 200 ml/litre of blood.

The relationship between the partial pressure of oxygen (expressed as mm Hg partial pressure of oxygen) and the amount of oxygen bound to haemoglobin is complex because the binding properties of haemoglobin depend on several factors including pH, the amount of carbon dioxide, temperature, and the amount of 2,3-diphosphoglyceric acid (2,3-DPG). In practice, therefore, it is conventional to describe the relationship under two conditions, those found in arterial and venous blood. Also, as is shown in Figure 2, it is often the case that the ordinate is percentage saturation of haemoglobin rather than amount of oxygen carried. Several aspects of the oxygen dissociation curves are important physiologically.

Oxygen dissociation curve



L, line representing the situation in the lungs; R, the situation in the tissues at rest. See text for explanation.

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The curves show a plateau region – the molecule is almost saturated with oxygen at partial pressures as low as 75 mm Hg. This is important because oxygen is being lost from the alveoli (and the partial pressure of oxygen in them is falling) all the time between the end of one inspiration and the beginning of the next (about 2–3 s). The plateau means that blood leaving the lungs (a point somewhere on the line L in Figure 2) continues in health to be saturated with oxygen during the time when alveolar oxygen is not being replenished. It also means that whereas breathing 100% oxygen leads to huge increases in the partial pressure of oxygen in arterial blood (> 600 mm Hg) the rise in oxygen content is small, and the rise in PVO_2 produced by breathing 100% oxygen is also small.

The curves show a steep portion – this arises because the affinities for oxygen of the subunits of reduced haemoglobin increase as oxygen binds to the other subunits. (The affinity of haemoglobin is determined by the partial pressure of oxygen which produces 50% saturation of the molecule. The lower this value, the greater the affinity.) The steepness begins when the percentage saturation of haemoglobin falls below about 70%. Since this value is that found in venous blood in subjects at rest (point R, Figure 2), it means that the steep part of the curve is not used at rest but acts as a reserve for use during exercise. The steepness means that further unloading of oxygen can take place with only a small further change in the partial pressure of oxygen.

Bohr shift – the curve can be shifted towards the right by several circumstances. This is illustrated by a comparison of the arterial and venous curves. It can be predicted from the equation above and an application of Le Chetalier's principle. The oxygenation of haemoglobin releases heat and hydrogen ions, therefore increased acidity (carbonic acid and 2,3-DPG) and temperature promote unloading of oxygen from oxyhaemoglobin. This is particularly the case with exercising tissues, when the curve is shifted even further to the right by the rises in lactate and temperature. The curve is also shifted to the right by increases in the amount of carbon dioxide carried by the blood (the Haldane effect). This is partly because the carbon dioxide is carried as carbonic acid in the blood, partly because some of the carbon dioxide is carried attached to the protein chains as carbamino compounds (a process that promotes the release of further hydrogen ions from the globin molecules), and possibly also because of the steric effects of carbon dioxide molecules on the oxygen-carrying power of the haemoglobin molecule. Whatever their causes, these shifts mean that extra oxygen can be unloaded with no further fall in the partial pressure of oxygen (compare points R and E in Figure 2).

Partial pressure of oxygen – the properties of the haemoglobin molecule ensure that the fall in this pressure is minimal. This is important because the oxygen is being carried in the blood and it is required in the tissues. Oxygen passes to the tissues by diffusion, and this requires a concentration gradient (see Fick's law of diffusion, above). Keeping the partial pressure of oxygen as high as possible ensures that the gradient is maintained. The factors that aid this phenomenon (raised acid, temperature and carbon dioxide) are produced by exercising tissues, and they also promote vasodilatation of the arterioles of the systemic circulation. The effect of this is to increase blood flow (and oxygen delivery to the tissues) and to cause the opening of capillaries by recruitment. This aids diffusion by increasing the area over which it can take place and by decreasing the path length.

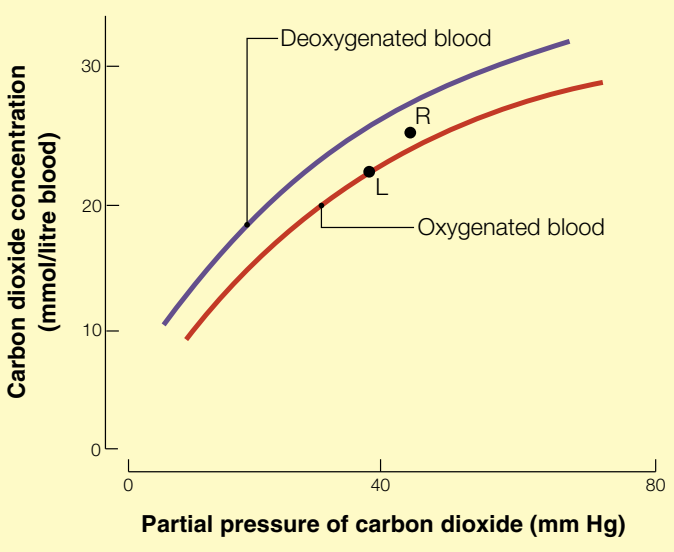
Anaemia – in a patient suffering from anaemia there is no change in the oxygen dissociation curve shown in Figure 2, because anaemia (by itself) does not affect the interaction between oxygen and the reduced amount of haemoglobin. However, if the ordinate were the amount of oxygen carried, then the plateau value would fall below the normal value of 200 ml/litre of blood by an amount that indicated the severity of the anaemia.

Carbon dioxide

About 10% of the carbon dioxide that is picked up from the tissues is dissolved in the plasma (carbon dioxide is 20 times more soluble in plasma than is oxygen). The rest is carried, directly, or indirectly, by haemoglobin. About 10% of the carbon dioxide is carried as carbamino-haemoglobin. In this reaction, the carbon dioxide molecule combines with an amino ($-NH_2$) residue from the globin molecule, a $NH.COO^-$ (carbamino) residue being formed and a hydrogen ion released. Most carbon dioxide is carried in the plasma as bicarbonate. This is achieved by the combination of carbon dioxide with water, a process catalysed by the enzyme carbonic anhydrase found in the cell membranes of erythrocytes. The carbonic acid splits up spontaneously into hydrogen and bicarbonate ions, the bicarbonate ions passing out of the erythrocyte into the plasma in exchange for chloride ions (the Hamburger shift). A further role of haemoglobin is to buffer the hydrogen ions, produced from the formation of carbonic acid or carbamino-haemoglobin.

The carbon dioxide dissociation curve (Figure 3) shows the relationship between the partial pressure of carbon dioxide and the amount that is carried in the blood (about 50 ml/100 ml of blood). It is almost linear, therefore reducing the partial pressure of carbon dioxide in the alveoli by 10% (by hyperventilation) reduces the amount of carbon dioxide carried in the blood by the same amount, the carbon dioxide being expired into the atmosphere. Figure 3 also shows that reduced (deoxygenated) haemoglobin can carry more carbon dioxide than the oxygenated form (the Haldane effect). This means that the entry of carbon dioxide into the blood from the tissues aids the unloading of oxygen. The reverse situation holds at the lungs.

Carbon dioxide dissociation curve



L, point representing the situation in the lungs
R, the situation in the tissues at rest.

3

Given the concentrations of bicarbonate ions and carbonic acid in the blood, the pH of the blood can be deduced from the Henderson–Hasselbalch equation:

$$pH = 6.1 + \log_{10}\{[HCO_3^-]/[H_2CO_3]\}$$

Normally, the concentrations of bicarbonate ions and carbonic acid are 24 and 1.2 mmol/litre, respectively. This gives a normal pH of 7.4. Since the carbonic acid is in equilibrium with carbon dioxide, it can be seen that ventilation and the pH balance of the body are interrelated. In metabolic acidosis, when there is an increase in the amount of acid in the body at the expense of the concentrations of the buffer reserve, bicarbonate levels fall and carbonic acid levels rise. Increased ventilation can remove the excess carbonic acid by driving off carbon dioxide. Also, hyperventilation raises the pH of the blood by lowering the levels of carbon dioxide and carbonic acid, and this influences the chemoreceptor reflexes. ◆

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Respiration: Ventilation

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SI units are not routinely used in respiratory physiology and we have chosen to follow convention in these articles. For comparison 1 atmosphere = 100 kPa = 760 mm Hg = 1000 cm H_2O

The primary function of the lungs is to deliver oxygen to the blood and to remove carbon dioxide from it. This exchange of gases takes place across an intricately folded respiratory exchange surface, consisting of the alveoli surrounded by capillaries from the pulmonary circuit. Gaseous exchange is passive, by diffusion, and the process continues only so long as the partial pressure of oxygen in the alveoli is greater than that in blood, and the partial pressure of carbon dioxide in the alveoli is lower than that in blood. Therefore, the air in the alveoli must be continually replenished by atmospheric air that is high in oxygen (about 20 kPa) and low in carbon dioxide (< 0.1 kPa). This is achieved by alternate inspiratory and expiratory movements of the lungs.

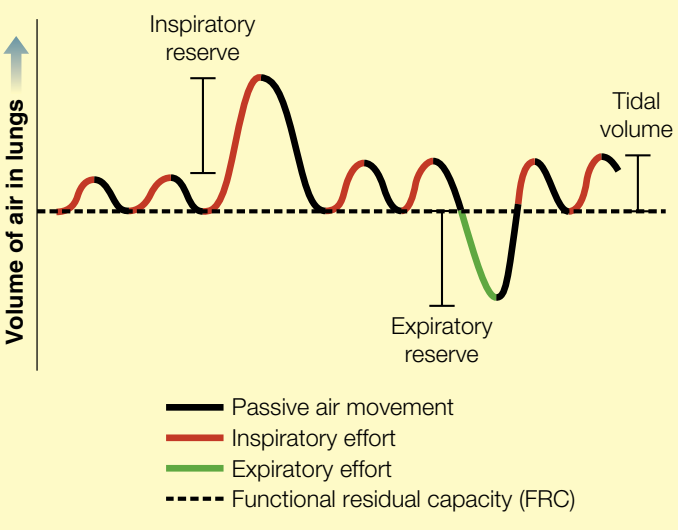
Respiratory movements

Inspiration is caused by sucking air into the alveoli. During inspiration, the alveolar pressure is made subatmospheric, so air flows into the alveoli down a pressure gradient. This decrease in alveolar pressure is caused by an increase in lung volume brought about by two factors. The first is a contraction of the external intercostal muscles, as a result of which the ribs are moved upwards and outwards, thus increasing the cross-sectional area of the chest. The second is activity in the phrenic nerve which results in contraction of the diaphragm which moves downwards. The lungs follow this increase in volume of the thoracic cavity because they are attached to the inner surface of the chest wall and the upper surface of the diaphragm by the two pleural membranes. These membranes slide over one another, allowing the lungs to unfold and to expand. They also provide protection for the delicate respiratory exchange surface.

Lung volumes

Figure 1 shows a spirometer trace from a healthy seated individual breathing at first normally (the tidal volume) and then producing a maximal voluntary inspiration and, after a few more normal breaths, a maximal voluntary expiration. At all times, the airway was open. The trace shows when inspiratory or expiratory muscle effort is required, and when the volume of air in the lungs changes passively without muscle effort. It shows that muscle effort is required to change the volume of air in the lungs away from functional residual capacity (FRC). Conversely, if the volume of air in the lungs differs from FRC then relaxation of the muscles causes air flow, so that FRC is approached. At FRC, there is no air flow even though the airways are open; that is, alveolar pressure is atmospheric.

Relationship between volume of air in the lungs and whether air movement is passive or requires muscle effort

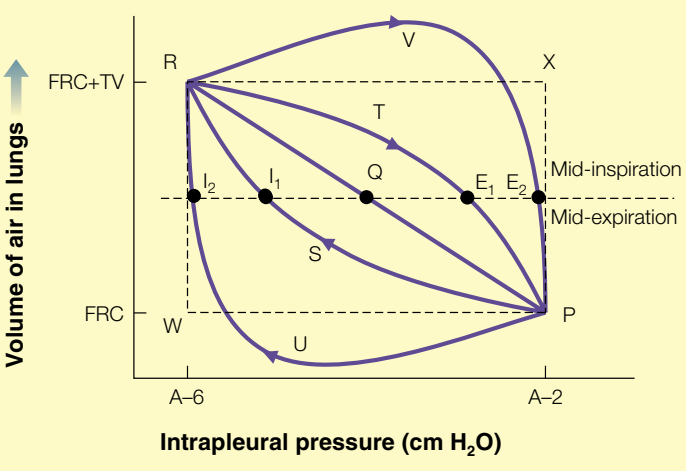


FRC is an equilibrium position for the recoil forces in the chest wall. If the pleural membranes were to be separated, the lungs would recoil inwards and tend to collapse, and the chest wall would recoil outwards. When the pleural membranes join these two structures together, the two recoil forces oppose one another; at FRC, they are equal in size. To change the volume of air in the lungs away from this equilibrium position requires muscle effort. After inspiration, the expanded lungs recoil inwards with a greater force and the chest wall recoils outwards with a lesser one, therefore the system is no longer in equilibrium. The moment that muscle effort ceases, this disequilibrium causes air to leave the lungs, forced out because the recoil of the lungs inwards is greater than the recoil of the chest wall outwards. This expulsion of air ends when FRC has been attained again.

Intra-pleural pressure

From the above, it can be understood that the two pleural membranes are being pulled in opposite directions by the recoil forces, and this suggests that the intrapleural pressure is low. Intrapleural pressure can be measured using an intra-oesophageal balloon, provided the individual is not swallowing and the oesophagus is passive and not showing any muscular activity. Figure 2 shows the intrapulmonary pressures during a normal inspiration (PQR), with the individual starting at P (FRC) and ending the inspiration at R (FRC + tidal volume, TV). To produce this trace, the airway would have to be open, with the breath being held at the end of the inspiration by muscular effort. Intrapleural pressure starts at A – 2 cm H_2O; where A is atmospheric pressure, and falls to A – 6 cm H_2O.

Relationship between intrapleural pressure and volume of air in the lungs during a single breath



A, atmospheric pressure; FRC, functional residual capacity; TV, tidal volume. For explanation see text.

At FRC, the pressure difference across the lungs – with the pressure in the intrapleural space lower – causes an outward force on the lungs that balances their inward recoil. This gradient is 2 cm H_2O; since the intra-alveolar pressure is A, the intrapleural pressure is A – 2 cm H_2O. At FRC, the pressure difference across the chest wall – with the pressure immediately inside it in the intrapleural space lower – is also 2 cm H_2O, since the pressure outside the chest wall is A. This causes an inwards force that balances the outward recoil of the chest wall.

At point R, the expanded lungs recoil inwards with a greater force. To prevent their movement (the breath is being held), a greater pressure difference across them is required, with the intrapleural pressure lower than alveolar pressure. This gradient is 6 cm H_2O and, since alveolar pressure is A (the airway is open and there is no air flow), the intrapleural pressure becomes A – 6 cm H_2O. This means that, at point R, the pressure drop across the chest wall is also 6 cm H_2O (the pressure outside the chest wall remaining atmospheric). However, the chest wall is nearer to its equilibrium position and therefore a pressure drop of 1 cm H_2O (pressure inside the chest wall in the intrapleural space being lower) would balance its recoil force outwards. That is, the chest wall is not in equilibrium. This is exactly why inspiratory muscle effort is required to maintain this position at the end of inspiration – it imposes a force that balances this disequilibrium.

There are two other ways in which the volume of air in the lungs could be held at FRC + tidal volume. First, the mouth could be closed and then no muscle effort would be required. In this circumstance, the inward recoil of the lungs would be greater than the outward recoil of the chest wall, and this would cause the alveolar and mouth pressures to rise to A + 5 cm H_2O; it would also decrease venous return slightly (a very mild Valsalva manoeuvre). Second, if the airway were open to the atmosphere and the pressure outside the chest wall were decreased to A – 5 cm H_2O, inspiration would occur without the need for muscle effort. This is how inspiration is achieved during negative pressure artificial ventilation.

Origin of the recoil forces

The recoil of the chest wall is due to the elastic properties of the muscles, tendons and joints. The recoil of the lungs is more complex. In part, it is due to the presence of elastic fibres in the lungs, but it is also due to surface tension forces.

Surface tension forces arise at an air–water interface (the alveoli are lined with fluid), because the attraction between molecules of water is stronger than that between air and water molecules. The effect of this is for the air–water interface to become as small as possible. (It is for this reason that bubbles are spherical, because a sphere has the smallest surface area for a given volume.) The tendency for surface tension to decrease the area of an air–water interface results in the alveolus becoming smaller, and this contributes to the recoil force of the lungs. This is a function of the surface tension of the liquid lining the alveoli. The relationship between pressure in a bubble (P) or alveolus, and the size of the bubble (radius r) is given by the law of Laplace: $P = 2T/r$ where T is the surface tension of the liquid. It follows from this, that if the lung is filled with saline rather than air, its volume can be increased more easily, because the recoil force is due only to the elastic fibres, there being no air–water interface.

Pulmonary surfactant

Surface tension forces can be decreased by substances called surfactants (washing-up liquid is a common example). Type II pneumocytes produce a pulmonary surfactant. These cells are not thin like the type I alveolar cells, but more spherical in shape, and have lamellate inclusions that are the source of the surfactant. They continuously secrete the surfactant onto the alveolar surface.

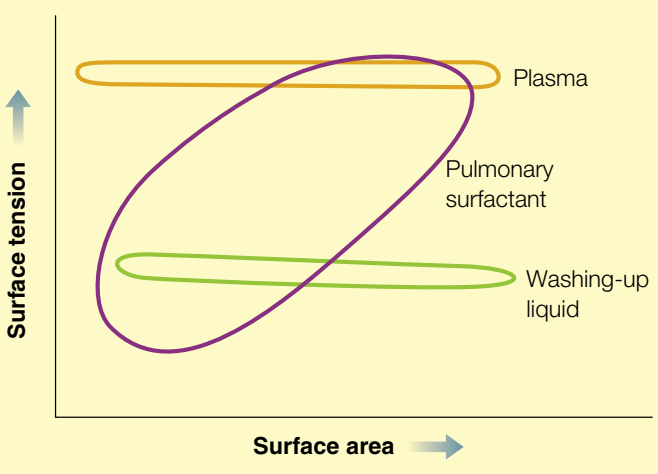
Chemically, pulmonary surfactant is complex, but one of its constituents is dipalmitoyl choline. Like other surfactants, it is an amphipathic molecule, one end being charged and hydrophilic, and the other lipophilic, consisting of a long chain of hydrocarbon residues. The hydrophilic parts of the molecules insert themselves into the surface of the water layer and form a boundary layer. The lipophilic parts interact with each other, as a result of which the cause of the surface tension – the increased attraction of molecules in the aqueous phase – is reduced.

Pulmonary surfactant is produced under the influence of cortisol, and its production starts in the fetus towards the end of a normal pregnancy. For premature babies, therefore, production might be low, which gives rise to difficulty in breathing (due to the extra forces required to overcome the surface tension forces) leading to 'respiratory distress of the newborn'.

Pulmonary surfactant also stabilizes the alveoli of the lungs. The millions of alveoli in the lung tend to be similar in size, but those at the apex of the lung in an upright individual are larger than those towards the base (see below).

In terms of Laplace's law the intra-alveolar pressure in the smaller alveoli (r is less) tends to be greater than that in the larger ones. This implies that the system is unstable; with the smaller alveoli tending to collapse at the expense of the larger ones. Such damage to the lungs does not occur because of the second property of pulmonary surfactant (Figure 3). Unlike washing-up liquid, in which the surface tension-reducing effect is independent of the area of the air–water interface, the surface tension-reducing effect of pulmonary surfactant increases as the surface area of the interface decreases. (This is possibly because the amount of interaction between the molecules increases as the molecules are squeezed together.) Whatever the reason, as r decreases, so does the value of 2T; that is, the pressure excesses inside the alveoli (2T/r) become independent of alveolar size.

Relationship between surface area and surface tension



3

Air flow and pulmonary resistance

In Figure 2 the line PR joins the two points during a single inspiration when there is no movement of air or the lungs and chest wall system – the beginning and end of the inspiration. It is called the compliance line, and is a measure of the distensibility of the lungs. Since the normal tidal volume is about 400 ml, and the pressure change required to produce it is about 4 cm H_2O, the compliance of the lung at these volumes (also known as 'static' compliance) is about 100 ml/cm H_2O.

It would be expected that, during inspiration, the intrapleural pressure would move along the line PQR, and that it would follow the line RQP during expiration. In practice, this would be the case only if inspiration and expiration were extremely slow; during a normal inspiration, the trace follows one curve (PSR), and, during expiration, another (RTP). The pressure changes follow a loop which illustrates hysteresis. The width of the hysteresis loop is determined by the speed of air movement and by the degree of constriction of the airways. Thus, both when the breath is of a normal size, but inspiration and expiration are both quicker, and when the breath is of a normal size and speed, but the airways are constricted, the loop is wider (PUR during inspiration, and RVP during expiration).

Considering the moment when the breath is midway between its start and end (the horizontal line) and air flow is taking place, it can be seen that the intrapleural pressure is more negative during inspiration and less negative during expiration. Moreover, the deviations of the observed trace from point Q on the compliance line are greater if the breath is being taken faster or the airways are constricted. This is illustrated by comparing points Q, I_1 and I_2 for changes during inspiration, and Q, E_1 and E_2 for changes during expiration.

These deviations from the compliance line represent the extra pressure gradient across the lung (extra force) involved in changing the volume of the lung and moving air through the airways. They reflect the resistance of the system, also known as 'dynamic' compliance. By analogy with an ohmic resistor, the resistance, R, can be defined as R = pressure gradient/flow. This can be re-arranged to give pressure gradient = resistance x flow. This equation explains why the loop widens if the breath is taken more quickly (flow is higher) or the airways are constricted (resistance is greater).

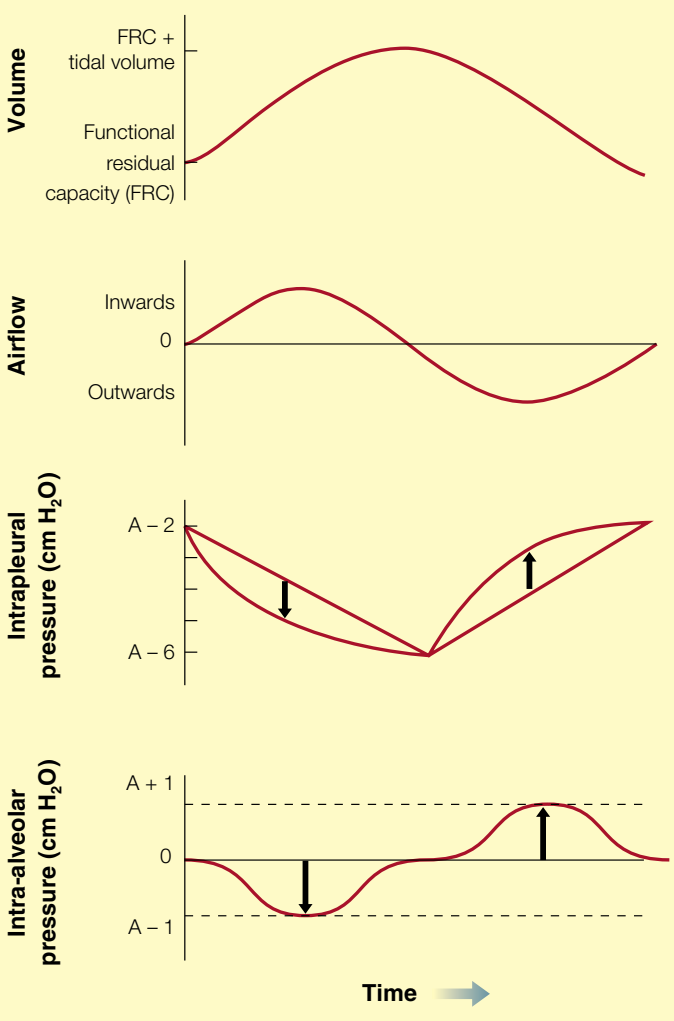
Figure 2 indicates that the extra pressure required during the normal breath at the mid-point of a normal inspiration, point I_1, was 1.0 cm H_2O. (The compliance line predicted an intra-pleural pressure of A – 4 cm H_2O, but the observed value was A – 5 cm H_2O.) Given that the air flow at this moment was 0.5 litre/s, then the total pulmonary resistance was 2 cm H_2O/litre/s.

Total pulmonary resistance can be divided into airway resistance (the resistance of the airways to the flow of air through them) and lung tissue resistance (the resistance of the lung tissue elements to being distorted). Normally, airway resistance accounts for 80% of total pulmonary resistance. This means that the pressure gradient required to suck air into the alveoli from the mouth – to overcome airway resistance – is about 0.8 cm H_2O (80% of the difference between points Q and I_1 in Figure 2). Since the mouth is at atmospheric pressure, intra-alveolar pressure becomes subatmospheric by 0.8 cm H_2O at this moment. It becomes supra-atmospheric by this amount during the mid-point of a normal expiration (80% of the difference between points Q and E_1).

At point I_1, when the intrapleural pressure is A – 5 cm H_2O and the intra-alveolar pressure is A – 0.8 cm H_2O, the pressure gradient across the lungs is 4.2 cm H_2O. Since the pressure gradient required to overcome the compliance of the lungs (given by point Q on the compliance line) is 4 cm H_2O, this leaves 0.2 cm H_2O as the pressure required to overcome lung tissue resistance.

The time courses of the volume, flow and pressure changes in the alveoli and the intrapleural space during the course of a normal breath are summarized in Figure 4.

Volume and pressure changes during a normal breath



Note that at mid-inspiration (downward arrows), intrapleural pressure is 1 cm H_2O below the compliance line, and intra-alveolar pressure is 80% of this. The opposite holds during expiration (upward arrows).

A, atmospheric pressure

4

Work done in breathing

As indicated in Figure 1, when muscle effort is required during breathing, work is being done. The amount of work entailed is calculated as follows:

Work done = Force x Distance
Work done = Force/Area x (Distance x Area)
Work done = Pressure x Volume

This last equation means that the areas contained by different components of the pressure–volume curves in Figure 2 can be used to calculate the amount of work done. (Area within a curve equals length x breadth; if the axes are pressure and volume, then, from the above equation, this becomes work done.)

- The work done against elastic recoil during inspiration is the area of the triangle PWR.
- The work done against total pulmonary resistance during a normal inspiration is the area of the secant PSRQP.
- The total work done during a single inspiration is the sum of these two areas.

During expiration, the work done against total pulmonary resistance is the area RTPQR, but the area of the triangle RXP is the amount of work released by the recoil of the lungs. Since the triangle is larger in area than the secant, expiration is passive. This difference between the two areas, the work released during an expiration, can be used for talking or singing, for example.

In the case of a more rapid breath, or one against a higher airway resistance (with the same compliance line, PR, but a wider loop, PURVP), the calculation is performed in the same way. It shows that the work done against total pulmonary resistance during inspiration is greater than before, though the work done against elastic recoil is unchanged. Note, however, that the work that has to be performed to overcome total pulmonary resistance during expiration is now greater than the work released by lung recoil (the area RVPQR is greater than the area RXP). This means that expiration is also an active process.

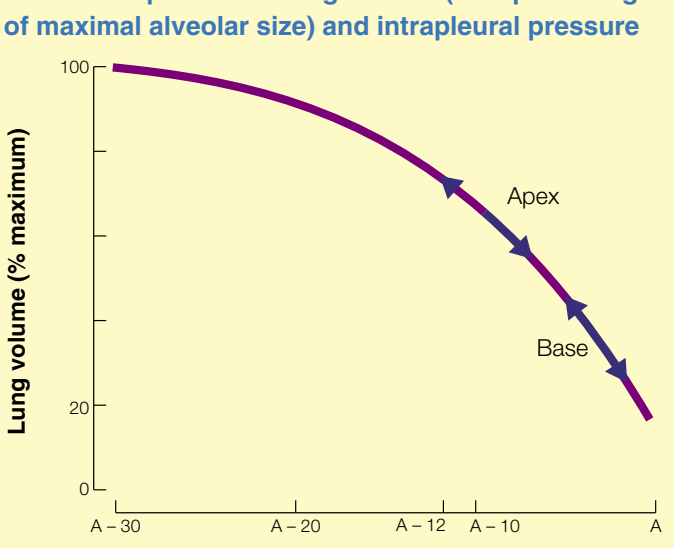
Ventilation gradient down the lungs

The apical alveoli are more distended than those at the base of an upright individual.

Figure 2 indicates that the intrapleural pressure is A – 2 cm H_2O at FRC. In fact, this is correct only towards the base of the lung. Nearer the apex, the pressure is more negative. The system acts as though the lung were a fluid with a density 0.2 times that of water. Therefore, at the lung apex, about 30 cm above the lung base in an upright individual, the intrapleural pressure is 6 cm H_2O less than at the base (A – 8 rather than A – 2 cm H_2O). This explains why the apical alveoli are more distended than those at the base of the lung.

Figure 2 also indicates that the relationship between lung volume and pressure gradient across the lungs, the compliance, is linear (the line PR). This is essentially true for breaths of a normal size, but, if volume changes from maximal voluntary inspiration to maximal voluntary expiration are considered, then compliance is found to be less with larger lung volumes (Figure 5).

Relationship between lung volume (as a percentage of maximal alveolar size) and intrapleural pressure



A, atmospheric pressure

5

Putting these two facts together, it can be seen that, during an inspiration of normal size starting at FRC, whereas the intra-pleural pressure falls by 4 cm H_2O (see Figure 2) at all levels of the lung, the different levels of the lung are described by different parts of the compliance curve. Therefore (see Figure 5), the fall in intrapleural pressure of 4 cm H_2O associated with the inspiration causes the alveoli at the lung apex (A – 8 to A – 12 cm H_2O) to expand less than those at its base (A – 2 to A – 6 cm H_2O; Figure 5). That is, the alveoli at the apex are more distended at FRC than are those at the base of the lung, but they inflate less for any given fall in intrapleural pressure. ◆

FURTHER READING

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Regional anaesthesia

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Regional Anaesthesia: Choice of Agents, Additives, Systemic Effects and Toxicity

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Local anaesthetics reversibly block nerve impulses and are the mainstays of regional anaesthesia. Local anaesthetics can be divided into two main groups, esters (e.g. cocaine, procaine, chloroprocaine, tetracaine (amethocaine)) and the more commonly used amides (e.g. lidocaine (lignocaine), prilocaine, bupivacaine) and the new drugs, ropivacaine and L-bupivacaine, which are single enantiomers.

The onset, potency and duration of action of each agent are determined by the physical properties of the drug, in particular its pK_a, lipid solubility, protein binding and its intrinsic vasodilator activity (Figure 1).

pK_a – the pK_a of a chemical compound represents the pH at which its ionized form and non-ionized forms are in equilibrium. The pK_a of a local anaesthetic determines its speed of onset of action because only the uncharged form is lipid soluble and is able to diffuse quickly across the myelin layers of nerve fibres. Local anaesthetics are weak bases but are injected in acidic solutions as hydrochloric salts. The tertiary amine (hydrophobic or water insoluble) becomes quaternary and is thus soluble in water and suitable for injection. At physiological pH, the proportion of the drug that dissociates into a free base (which is lipid soluble) is determined by its pK_a. This un-ionized portion passes through the lipid cell membrane to the inner axon where re-ionization takes place. It is the re-ionized portion of the local anaesthetic that blocks sodium channels. The closer the pK_a of the drug is to physiological pH (7.4) the greater the amount of free base or un-ionized drug that will be present and the faster the onset of block. The higher the pK_a, less un-ionized drug is available and the slower the onset of block. For example, at pH 7.4, lidocaine (lignocaine) (pK_a 7.7) is 35% un-ionized and bupivacaine (pK_a 8.4) is 12–13% un-ionized, therefore lidocaine (lignocaine) has a faster onset of action than bupivacaine in equipotent doses.

Lipid solubility determines a local anaesthetic's potency. Potency is defined as the minimum amount of a drug required to produce a given effect. In simple terms, a local anaesthetic that is more lipid soluble will have more of its molecules penetrate the nerves; therefore less drug is required to give the same blockade.

Protein binding – the duration of action of each local anaesthetic depends on its degree of protein binding. The sites of action for local anaesthetics are sodium channels, which are protein molecules, therefore highly bound drugs have a long duration of action. However, the intrinsic vascular effects of the drug may also influence its duration of action as well as the total dose given.

Local vascular effects – all local anaesthetics are vasodilators, except for cocaine, ropivacaine and L-bupivacaine, which are vasoconstrictors. The degree of vasodilatation influences the toxicity and potency of local anaesthetics because a higher degree of vasodilatation causes more systemic absorption of the drug, particularly in vascular sites and thus less drug is available for neural blockade.

Differential block – ropivacaine is said to produce more selective blockade for sensory fibres when used in lower concentrations than bupivacaine. It has lower lipid solubility and a similar high pK_a and this reduces its affinity and penetration of the myelin sheath. Therefore, blockade of C fibres is greater than that of larger myelinated A fibres.

Physical properties of local anaesthetics

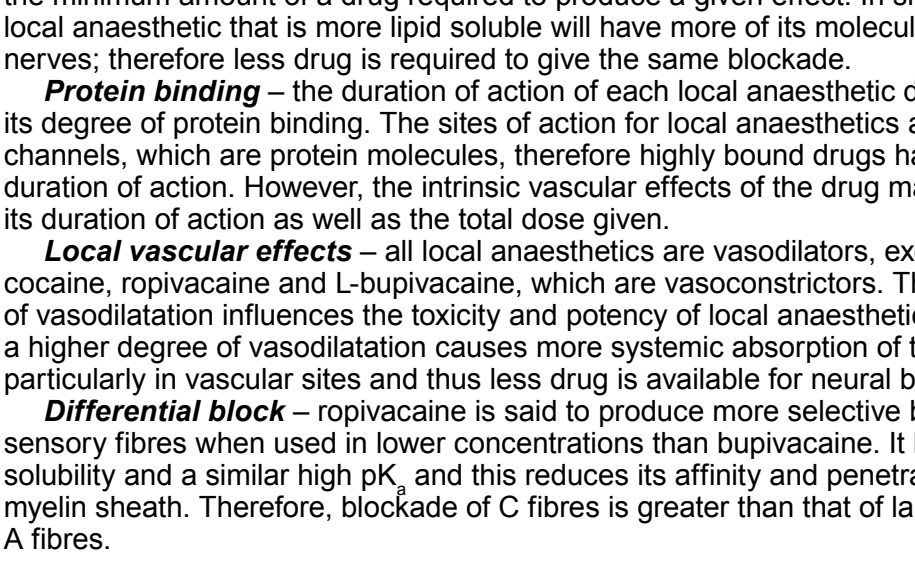
Drug	pK_a	Relative lipid solubility	Plasma protein bound (%)	Onset of action	Duration of action
Procaine	8.9	1	6	Slow	Short
Lidocaine (lignocaine)	7.7	200	65	Fast	Moderate
Prilocaine	7.8	50	55	Fast	Moderate
Bupivacaine	8.1	1000	95	Moderate	Long
Ropivacaine	8.1	400	94	Moderate	Long
L-bupivacaine	8.1	1000	95	Moderate	Long

Systemic effects and toxicity

The two potentially lethal complications of local anaesthetic systemic toxicity are CNS and cardiovascular system collapse, which are nearly always the result of rapidly rising plasma drug concentration caused by inadvertent intravascular injection. Other forms of local anaesthetic toxicity include neural toxicity, methaemoglobinaemias and allergic reactions.

Early signs of systemic effects should be sought. Mild symptoms, such as numbness of the tongue or light-headedness should alert the anaesthetist to more ominous problems (Figure 2).

Development of toxic effects with rising plasma concentrations of lidocaine (lignocaine)



Adapted from: Cousins M J, Bridenbaugh P O. *Neural Blockade in Clinical Anesthesia and Management of Pain.* 3rd ed. Philadelphia: Lippincott-Raven. 1998. With permission from the publisher

CNS toxicity: local anaesthetic toxicity causes CNS excitation before coma because of selective neural blockade. Inhibitory pathways in the cerebral cortex are inhibited first by local anaesthetics, allowing the excitatory pathways to become unchecked. Increased cortical activity may result in convulsions.

Cardiovascular system: initially there is increased blood pressure and tachycardia from CNS excitation. This is followed by:

- decreased cardiac output (negative inotropy)
- vasodilatation and profound hypotension
- prolonged QRS and PR intervals therefore arrhythmias
- ventricular arrhythmias with bupivacaine
- cardiac arrest.

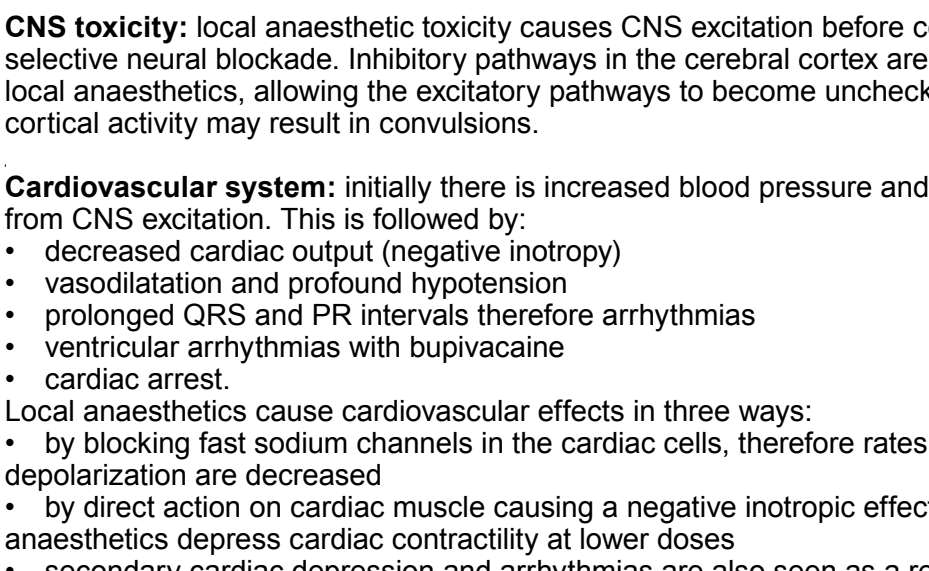
Local anaesthetics cause cardiovascular effects in three ways:

- by blocking fast sodium channels in the cardiac cells, therefore rates of depolarization are decreased
- by direct action on cardiac muscle causing a negative inotropic effect: potent local anaesthetics depress cardiac contractility at lower doses
- secondary cardiac depression and arrhythmias are also seen as a result of direct effects on brainstem cardiovascular centres.

Cardiovascular collapse to CNS ratio (CC/CNS) is the ratio of the dose of drug that will cause cardiovascular collapse and CNS toxicity. The ratio for lidocaine (lignocaine) is much higher (7.1) than that for bupivacaine (3.7), which means a proportionately much higher dose of lidocaine (lignocaine) is needed to cause cardiovascular toxicity than to produce symptoms of CNS toxicity. It is desirable to have a high ratio so that the anaesthetist is alerted by CNS symptoms before cardiovascular collapse occurs. With bupivacaine, cardiovascular collapse has been reported without previous signs of CNS toxicity.

Bupivacaine induces arrhythmias that are refractory to treatment because its inhibition of sodium channels is prolonged. Bupivacaine dissociates from myocardial sodium channels slowly, particularly at physiological heart rates and therefore tends to accumulate. Lidocaine (lignocaine) disassociates in one diastole time and tends not to accumulate (Figure 3). Diastole time is the period of myocardial relaxation and is dependent on heart rate. The time constant for dissociation of lidocaine from the cardiac sodium channel is much briefer than the R:R interval enabling drug dissociation from the channel during diastole. Bupivacaine also blocks slow calcium channels and potassium channels. It is 16 times more likely than lidocaine (lignocaine) to induce ventricular arrhythmias. Bupivacaine is a racemic mixture with the R isomer being more toxic; hence L-bupivacaine and S-ropivacaine are marketed as safer options. There are reports suggesting that resuscitation from cardiac arrhythmias induced by L-bupivacaine and S-ropivacaine is less prolonged and more successful than those induced by racemic bupivacaine.

Time constants for dissociation of local anaesthetics



Adapted from: Arlock P. Actions of Three Local Anaesthetics: Lidocaine, Bupivacaine and Ropivacaine on Guinea Pig Papillary Muscle Sodium Channels. *Pharmacol Toxicol* 1988; **63(2):** 96–104. With permission from the publisher.

Neural toxicity: local anaesthetics at clinically used concentrations are unlikely to cause direct neural toxicity. There has been some concern with spinal lidocaine (lignocaine) following reports of cauda equina syndrome with intrathecal microcatheters (32 G) and 5% lidocaine (lignocaine) with dextrose. These fine-bore catheters allow extremely slow injections to be made, preventing the drug from mixing and being diluted by CSF, allowing it to pool undiluted around the nerves of the cauda equina and exposing them to high concentrations of lidocaine (lignocaine). This is not to be confused with the controversial transient radicular irritation syndrome in which patients complain of transient buttock pain, which responds to simple analgesics.

Methaemoglobinaemia most commonly follows prilocaine exposure but has also been reported with lidocaine (lignocaine), tetracaine (amethocaine) and benzocaine. Prilocaine is converted by hepatocytes to O-toluidine, which oxidizes haemoglobin to methaemoglobin. Pulse oximetry may be helpful in detecting this by showing a saturation of about 85%. Methaemoglobinaemia is treated with intravenous methylene blue, 1 mg/kg.

Allergic reactions to the more commonly used amide local anaesthetics are uncommon. There have been reports of anaphylaxis to the para-amino-benzoic acid (PABA) moiety ester local anaesthetics.

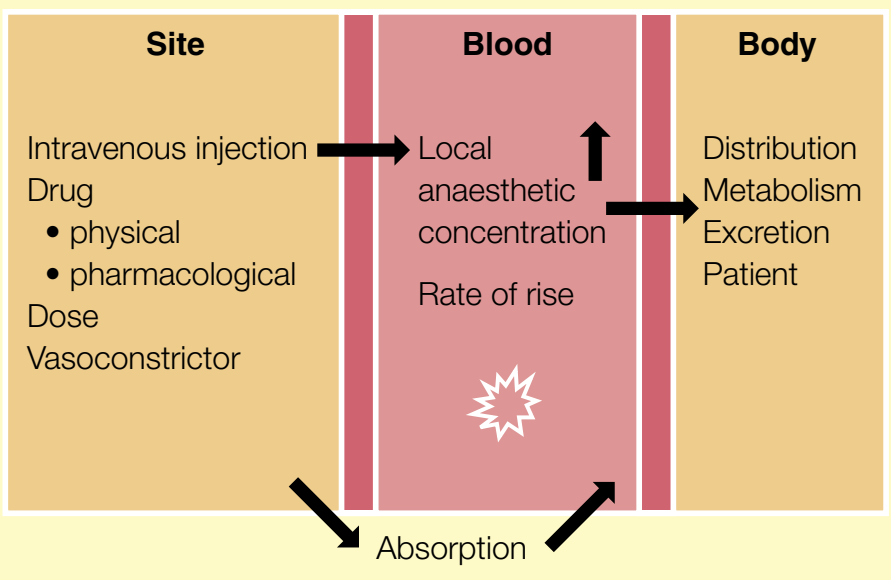
Management

Prevention of local anaesthetic toxicity involves the avoidance of intravascular injection. This is done by careful needle placement, aspirating before injecting and not giving the whole dose at once, but in several smaller doses as separate injections. Close verbal contact should be maintained with the patient so that any symptoms may alert the anaesthetist to problems. If symptoms of toxicity occur, injection should be stopped immediately.

Safe doses of local anaesthetic, as recommended in the British National Formulary are useful as a guide, but consideration should be given to the site of injection, additives, drug, patient, absorption and metabolism (Figure 4). Factors that affect the systemic absorption of a local anaesthetic include:

- dose injected into tissues
- blood supply to site of injection
- use of vasoconstrictors (e.g. adrenaline (epinephrine) 1:200,000 decreases absorption by one-third), but only local anaesthetics with intrinsic vasodilatory properties have systemic uptake decreased by addition of vasoconstrictors; the uptake of ropivacaine is not influenced by vasoconstrictors because ropivacaine itself has vasoconstricting properties
- characteristics of the local anaesthetic. Different systemic absorption of local anaesthetics also occurs at different sites. The descending order of uptake is intercostal, caudal, epidural, brachial plexus, sciatic, femoral (Figure 5).

Toxicity of local anaesthetics



Adapted from: Denny N M. *Local Anaesthesia Course.* Cambridge: Anglia Society of Regional Anaesthesia. 1999.

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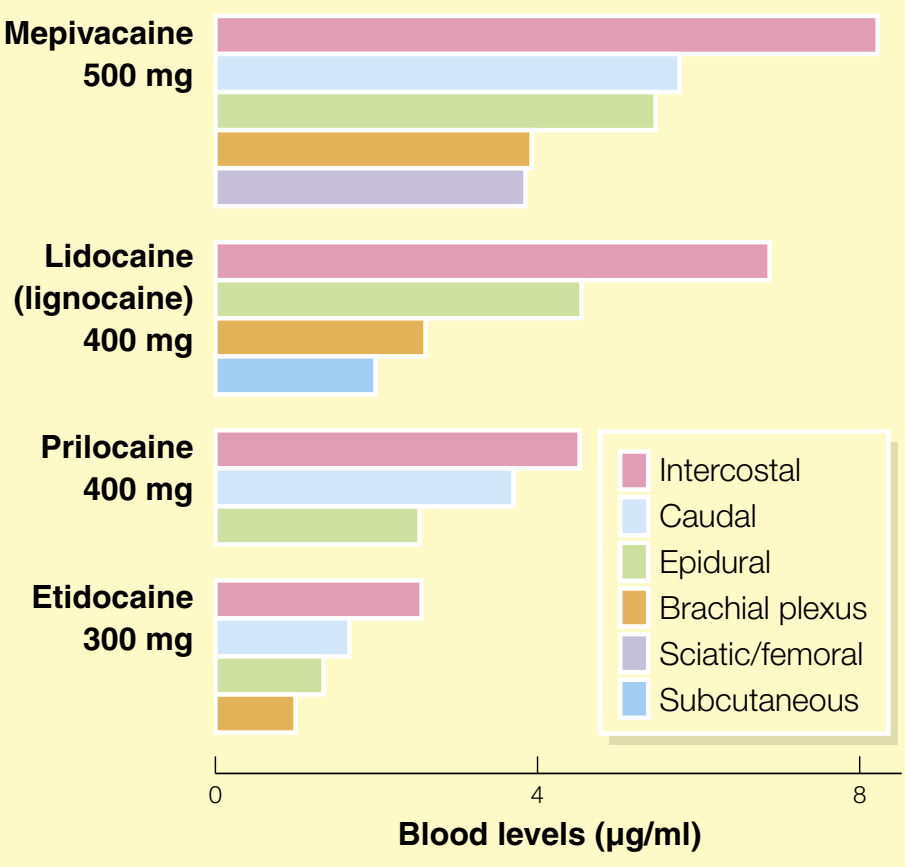
Comparative peak blood levels of local anaesthetic drugs following injection at differing sites



Adapted from: Covino B G, Vassallo H G. In: *Local Anesthetics: Mechanisms of Action and Clinical Use.* Orlando: Grune & Stratton, 1976. With permission from the publisher

5

Treatment involves management of the airway, breathing and circulation. Seizures should be controlled with benzodiazepines or sodium thiopentone. Early management of the airway, venti-lation and control of seizures reduces mortality (Figure 6).

Treatment of systemic toxicity

• Airway	Secure if necessary, give oxygen
• Breathing	Ventilation, get patient to take deep breaths, provide oxygenation
• Circulation	Inotropic support, cardiopulmonary resuscitation if necessary, bretylium for arrhythmias
• Seizures	Treat with diazepam, thiopental (thiopentone)
• Correct	Acidosis, electrolyte imbalances

6

Choice of agents and additives

Neuroaxial blockade

The most commonly used local anaesthetics for neuroaxial blockade are bupivacaine and lidocaine (lignocaine). More recently, levobupivacaine and ropivacaine have also been used. The factors that affect the duration and spread of intrathecal blockade are the type and total dose of local anaesthetic, its specific gravity relative to CSF and the additives used (Figure 7).

Studies evaluating the use of ropivacaine for intrathecal use have found it to be half as potent as bupivacaine, but it does not have a product licence. Many substances have been used intrathecally or epidurally as additives or sole agents; the most popular remain opioids and vasoconstrictors. Many of these additives have also been used in the management of chronic pain conditions. Some substances that have been used by the neuroaxial route are:

- bicarbonate
- clonidine
- cholinergic drugs (e.g. neostigmine)
- N-methyl-D-aspartate (NMDA) antagonists (e.g. ketamine)
- other pharmacological agents (e.g. somatostatin, calcitonin, adenosine, baclofen).

Duration of local anaesthetic solutions in spinal anaesthesia

Agent	Concentration (%)	Volume (ml)	Baricity	Total dose (mg)	Duration (minutes)	Duration with adrenaline (epinephrine) 0.2 mg
Bupivacaine	0.5	2–4	Isobaric	10–20	140–200	90–240
	0.5		2–4	Hyperbaric	10–20	120–180 90–180
	0.25		2–5	Isobaric	5–12.5	120–180 90–240
2% Lidocaine	2.0		2–4	Isobaric	40–80	100–140 90–180
(lignocaine)	5.0		1–2	Hyperbaric	50–100	30–60 30–60

7

Vasoconstrictors: adrenaline (epinephrine) is the most common vasoconstrictor added to local anaesthetic solutions for intrathecal anaesthesia. Adrenaline (epinephrine), 5 µg/ml, is used for epidurals and is said to have no β-mimetic side-effects. Phenylephrine has also been used. Vasoconstrictors are thought to increase the intensity and duration of the block by two mechanisms. Firstly, vasoconstriction of epidural vessels has been shown to reduce systemic uptake and more of the drug becomes available to the nerves. Secondly, vasoconstrictors may exert a direct antinociceptive effect by acting on α_1- and α_2-receptors, thus modulating dorsal horn action. This has been shown to have a dose-dependent analgesic effect. However, vasoconstrictors do not prolong spinal anaesthesia to the same degree with all local anaesthetic agents. Lidocaine (lignocaine) and prilocaine benefit the most because they have intrinsic vasodilatory properties.

Bicarbonate: alkalinization of local anaesthetic solutions (which are weak bases in an acidic solution), increase the un-ionized component, allowing faster penetration of nerves and therefore theoretically a quicker onset of block after epidural administration. The literature is controversial, with some studies unable to demonstrate a difference when bicarbonate is added to 0.5% bupivacaine or 2% lidocaine (lignocaine) for epidurals; however, other studies have demonstrated this technique to be effective. There is a risk of precipitation with bicarbonate and solutions with concentrations ranging from 1 to 8.4% have been used.

Clonidine has been shown to prolong neuroaxial blockade and extends the duration of postoperative analgesia beyond the period of anaesthesia. Clonidine has two mechanisms of action. It is an agonist at the α_2-receptors by activating a negative-feedback mechanism; it decreases the release of catecholamines thus modulating nociceptive input at the dorsal horn. It also has cholinergic effects by increasing the amount of acetylcholine available centrally. Oral premedication with clonidine also prolongs intrathecal anaesthesia. However, administration of clonidine via the neuroaxial route produces better analgesia than systemic administration and at lower doses. Clonidine, 150 µg, is commonly used for epidural administration; problems include hypotension, bradycardia and sedation.

Opioids: opioid receptors are found in the dorsal horn as well as in the brainstem. Binding of opioid receptors causes the nerve membranes to become hyperpolarized, decreasing nerve transmission. Substance P and glutamate release are also inhibited. Many different types of opioids have been used in neuroaxial blockade. Their onset and duration of action depends on their physicochemical properties. For example, morphine, which has relatively low lipid solubility, has a delayed onset but prolonged duration of action of up to 24 hours. Fentanyl is more lipid soluble than morphine and therefore produces quicker onset of analgesia, but has a shorter duration of action. The properties of diamorphine lie in between. Only 4% of epidural-administered morphine reaches the CSF. Most of the morphine is taken up by the epidural fat where it is absorbed rapidly by the vertebral venous plexus.

Animal experiments suggest that opioids and local anaesthetic may have a synergistic effect. The addition of opioids allows more dilute solutions of local anaesthetic to be used for both epidural and intrathecal blockade.

Respiratory depression seen with neuroaxial opioids occurs because of rostral spread of the opioids to the brainstem. This is more likely with the less lipid-soluble agents. The common side-effects of opioids such as pruritus, urinary retention and vomiting are also associated with its rostral migration to the brainstem. Opioids and α_2-adrenergic agonists have an additive effect when administered by the neuroaxial route.

Cholinergic drugs: the cholinergic nerves play a role in central pain mechanisms. Drugs that increase the amount of acetylcholine available centrally (e.g. clonidine, neostigmine) have been shown to produce analgesia. However, intrathecal neostigmine, 25–100 µg, is associated with a high incidence of nausea and vomiting and should not be used intrathecally. Neostigmine should not be administered epidurally because rapid systemic uptake occurs.

NMDA antagonists: the NMDA receptor is activated by glutamate, an excitatory neurotransmitter that plays a key role in central transmission of pain signals. Ketamine blocks the open calcium channel on the NMDA receptor complex. Ketamine, 0.7 mg/kg, has been used intrathecally but is often associated with a high incidence (up to 30%) of psychomimetic effects. This dose produces inadequate analgesia (though sufficient motor blockade) and therefore should not be used as the sole anaesthetic agent. There have been some concerns about the neurotoxicity of intrathecal ketamine but this could be due to the preservatives in commercial preparations. There have been reports of ketamine, 1 mg/kg, being used caudally as a sole analgesic, producing surgical and postoperative analgesia equivalent to that of bupivacaine.

Peripheral nerve blockade

The choice of agent for peripheral nerve blockade depends on the site, the nature of the operation and whether the purpose of the block is primarily for anaesthesia or postoperative analgesia or both.

Generally, agents such as lidocaine (lignocaine) and prilocaine, with a faster onset time, are best used in anaesthetic blocks for short operations in which prolonged postoperative analgesia is not required. Long-acting local anaesthetics, such as bupivacaine, L-bupivacaine and ropivacaine are best suited for painful procedures requiring prolonged analgesia. In the arm, bupivacaine and ropivacaine have a duration of action of about 12 hours. In the leg, bupivacaine acts for 24 hours and ropivacaine lasts for about 15 hours.

In the arm, where neither bupivacaine nor ropivacaine last for more than 12–14 hours, catheter techniques have been used to provide a longer period of analgesia. Ropivacaine has been shown to have quicker onset and better quality anaesthesia when used for axillary blocks compared with bupivacaine.

Various agents have been used to enhance peripheral nerve blockade:

- vasoconstrictors (e.g. adrenaline (epinephrine), felypressin)
- pH modifers (e.g. bicarbonate)
- opioids (e.g. tramadol, fentanyl)
- enzymes (e.g. hyaluronic acid)
- others (e.g. neostigmine, clonidine, ketamine).

Adrenaline (epinephrine) and felypressin: owing to the intrinsic vasodilator properties of local anaesthetics (with the exception of ropivacaine and L-bupivacaine, which are vasoconstrictors in low concentration), vasoconstrictors decrease vascular uptake and thus allow more anaesthetic molecules to reach the nerve membrane in vascular sites. They improve the depth and duration of anaesthesia in the order lidocaine (lignocaine), prilocaine, bupivacaine, L-bupivacaine and ropivacaine.

Adrenaline (epinephrine), 5 μg/ml, is commonly used. Lidocaine (lignocaine), and prilocaine have been shown to benefit greatly from addition of adrenaline (epinephrine) for peripheral nerve blocks. However, prilocaine and bupivacaine are not markedly enhanced for epidural blockade when vasoconstrictors are added.

Felypressin, 0.03 IU/ml, is added to prilocaine for eye blocks. It is a synthetic octapeptide that is chemically related to vasopressin.

Bicarbonate: the onset and duration of peripheral nerve blocks may be improved by the addition of sodium bicarbonate. Sodium bicarbonate increases the pH of the local anaesthetic solution and thus more un-ionized drug is available for diffusion into the nerve sheath. This technique is useful in brachial plexus blockade. 1 ml of 1% sodium bicarbonate for each 20 ml of local anaesthetic solution has been shown to alkalinize a range of local anaesthetics without risk of precipitation. However, ropivacaine precipitates at a pH of 6.0 and is unsuitable for alkalinization.

Clonidine: in a recent review of adjuncts to local anaesthesia in brachial plexus blockade, clonidine, up to 150 μg, was shown to enhance the duration and quality of the block. However, trials using a control group of patients receiving clonidine systemically are yet to be done. Clonidine may enhance analgesia via a direct effect on nociceptor α_2-receptors. Alternatively, it may reduce vascular uptake of local anaesthetic via effects on vascular adrenergic receptors.

Neostigmine: studies using neostigmine, up to 500 μg, as an adjunct to peripheral nerve blockade have not been convincing. This acetylcholinesterase inhibitor potentiates endogenous acetylcholine. Activation of acetylcholine receptors is thought to contribute to an endogenous form of analgesia and the administration of systemic neostigmine has been shown to display a dose-dependent analgesic effect. Muscarinic receptors have also been found on peripheral nerves.

Opioids: opioid receptors have been found on peripheral nerves and it seems logical to add opioids to local anaesthetic solutions for peripheral nerve blockade. However, there is insufficient evidence to recommend the use of opioid analgesia in peripheral nerve blockade. Studies involving the addition of fentanyl, tramadol, morphine and alfentanil have been performed but results are unconvincing. Adverse effects of opioid administration are not avoided by using them in peripheral nerve blockade.

Hyaluronidase: this enzyme is used in combination with local anaesthetics for eye blocks. It is said to increase the speed of onset and quality of block by enhancing penetration through fascial planes. It is manufactured as a powder for reconstitution and the dose for ophthalmology is 15 IU/ml.

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Regional Anaesthesia: Physiology and Pharmacology

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The role of the nociceptive sensory system is to alert the individual to potential or actual tissue damage arising from internal pathology or external injury. Although pain may have evolved to serve a protective function, it is clear that pain and associated physiological consequences create significant morbidity and even mortality following trauma or surgery. Regional anaesthesia aims to alleviate or prevent this morbidity and to minimize mortality by selective blockade of afferent sensory input from the periphery to the CNS.

The practice of regional anaesthesia necessitates a sound grasp of three-dimensional anatomy in order that the practitioner may safely place a needle and appropriately access central or peripheral nervous system targets. Once a route of administration of drug towards neural tissue is established it is paramount that an appropriate agent, in an appropriate dose, is administered and that the consequences of such administration are understood. A precise knowledge of the applied physiology and pharmacology of neurotransmission is therefore required to determine the appropriate choice of anaesthetic or analgesic drug. The consequences of the interruption or modulation of both afferent and efferent transmission must clearly be appreciated.

Nociception and pain perception

The nociceptive system requires a means of transducing physical, thermal or chemical stimuli into neurally encoded information that may be relayed via nociceptive pathways to appropriate integrative higher centres. It is at such spinal and higher centres that nociceptive sensory information activates autonomic and endocrine-mediated stress responses and ultimately achieves conscious perception as 'pain'. It is essential to appreciate that the nervous system is not a hard-wired 'Cartesian' network of neurons, rather it functions with a dynamic balance between excitatory and inhibitory inputs; each synapse having the potential to exhibit plasticity over a variety of time scales.

Ion channels, neurotransmitters, receptors and second messenger systems of the neurons comprising pain transduction and perception represent potential targets for the manipulation of nociceptive information and the production of analgesia. Where molecular mechanisms are specific to nociceptive transmission the potential exists for selective analgesia with a minimum of side-effects. As yet, there are relatively few molecular targets that have absolute localization to the nociceptive system. Of those targets with apparent nociceptive specificity few have clinically available drugs to target them.

Regional anaesthetic techniques enable physical and anatomical localization of nociceptive pathways such that systemic side-effects can be minimized while analgesia is optimized. Most regional anaesthetic techniques involve the reversible blockade of axonal conduction by 'classical' local anaesthetic drugs. Central nerve blocks, and to a lesser degree plexus and peripheral nerve blocks, may also be supplemented by a range of analgesic and adjunctive agents.

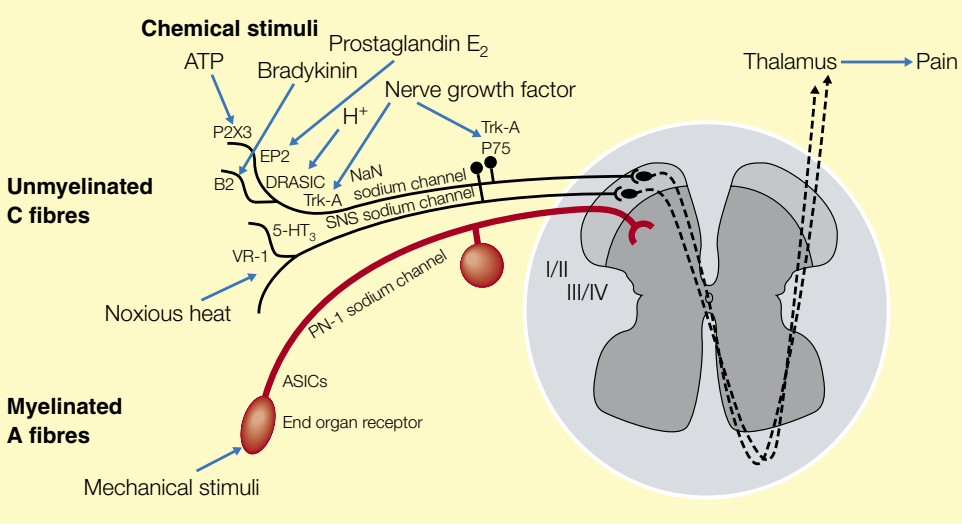
Neurophysiology

The diffusely ramifying unmyelinated terminals of Aδ and C fibres provide the initial transduction mechanism for mechanical, thermal and chemical noxious insult. The resultant action potentials evoked in unmyelinated C fibres and myelinated Aδ fibres propagate to the dorsal horn of the spinal cord where they synapse with both spinal interneurons and projection neurons (Figure 1): however, it must also be appreciated that retrograde action potential transmission may evoke local 'axon reflex' mediated peripheral release of neuropeptides contributing to inflammation and peripheral sensitization following injury. C fibres synapse primarily in the ipsilateral lamina II of the spinal cord dorsal horn, whereas Aδ fibres synapse in both laminae I and V. Projection neurons form the spinothalamic, spinoreticular and other ascending tracts that relay nociceptive information via thalamic nuclei to cortical centres of pain representation. Sensory discriminative components are relayed primarily via the lateral thalamic nuclei to somatosensory cortical areas SI and SII, while medial thalamic nuclei projecting to the anterior cingulate and prefrontal cortex mediate the affective-motivational components.

Sensory neuron-specific receptors and ion channels

Key:
ASICs, acid-sensing ion channels; B2, bradykinin receptor; DRASIC, dorsal root acid-sensing ion channel; EP2, prostaglandin E_2 receptor; P2X3, purinergil receptor; VR-1, vanniloid receptor; P75 and Trk-A, nerve growth factor receptors; I/II, III/IV, Rexed's laminae.

Source: Wood JN *et al.* In: *Proceedings of the 9th World Congress on Pain.* Seattle: IASP Press, 2000: 47–62. Reproduced with kind permission of the publishers.



1

$$E_m = \pm 61 \log \frac{C_{Na^+_i} P_{Na^+} + C_{K^+_i} P_{K^+} + C_{Cl^-_o} P_{Cl^-}}{C_{Na^+_o} P_{Na^+} + C_{K^+_o} P_{K^+} + C_{Cl^-_i} P_{Cl^-}}$$

where: C = concentration, P = permeability, o = extracellular concentration of ions, i = intracellular concentration of ions.

However, K^+ is the major contributor to the resting E_m which is more simply approximated by the Nernst equation:

$$E_m = \pm 61 \log \frac{[K^+]_i}{[K^+]_o}$$

Neural conduction

Aδ and C fibres at rest have a transmembrane potential of about –70 mV with the intracellular aspect of the phospholipid neuronal plasma membrane negative with respect to the extracellular membrane. The neuronal plasma membrane, selectively permeable to K^+ permits their outward diffusion from an internal concentration of about 140 mmol/litre toward the extracellular fluid (about 4 mmol/litre) with a relative loss of intracellular cations and the development of negative intracellular potential. A corresponding tendency for extra-cellular Na^+ (about 140 mmol/litre) to diffuse inwards towards the intracellular fluid (12–15 mmol/litre) is prevented by selective impermeability of the neuronal membrane. Differential permeability of the membrane and ATP-dependent Na^+/K^+ pumps maintains the distribution of ions across the neuronal plasma membrane. The resultant resting membrane potential (E_m) represents the equilibrium state between the concentration and electrochemical gradients of cations and ions across the membrane (Gibbs–Donnan equilibrium). It is formally described by the Goldmann equation in which sodium, potassium and chloride are the major contributory ions:

However, K^+ is the major contributor to the resting E_m which is more simply approximated by the Nernst equation:

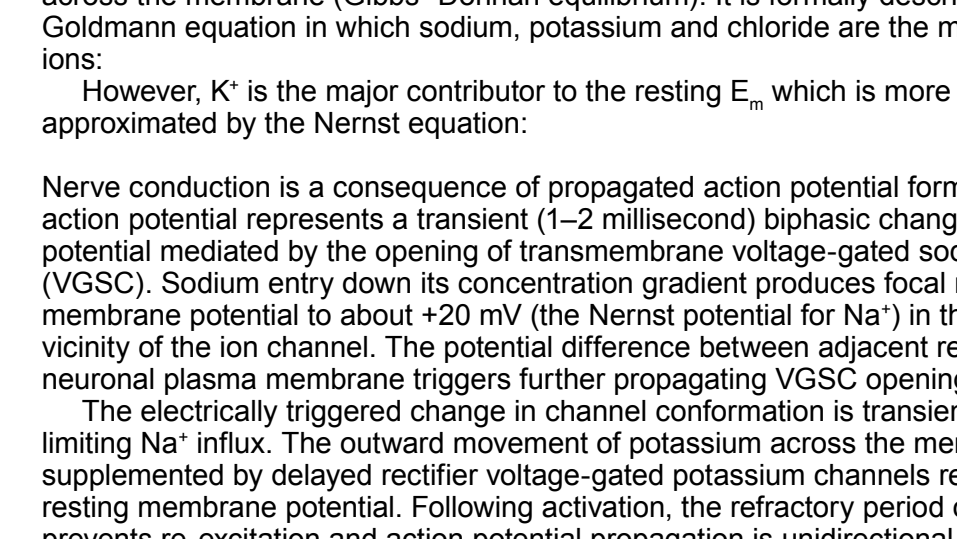
Nerve conduction is a consequence of propagated action potential formation. The action potential represents a transient (1–2 millisecond) biphasic change in membrane potential mediated by the opening of transmembrane voltage-gated sodium channels (VGSC). Sodium entry down its concentration gradient produces focal reversal of the membrane potential to about +20 mV (the Nernst potential for Na^+) in the immediate vicinity of the ion channel. The potential difference between adjacent regions of neuronal plasma membrane triggers further propagating VGSC opening.

The electrically triggered change in channel conformation is transient, thereby limiting Na^+ influx. The outward movement of potassium across the membrane supplemented by delayed rectifier voltage-gated potassium channels restores the resting membrane potential. Following activation, the refractory period of the VGSC prevents re-excitation and action potential propagation is unidirectional under normal circumstances.

Sodium channels: the neuronal VGSC is not a single entity but encompasses a large multigene family. All VGSC comprise a large membrane spanning a polypeptide β-subunit of 260 kDa with smaller regulatory β_1 and β_2 subunits. Most VGSC have a low threshold for activation (about –55 mV), rapid inactivation kinetics and nanomolar sensitivity for tetrodotoxin. There is now clear evidence for populations of novel tetrodotoxin-resistant sodium channels that are selectively expressed in small diameter nociceptive neurons (e.g. SNS/PN3 channel)

Sodium channel blockade – classical local anaesthetics are aromatic amino-esters (procaine) or amino-amides (lidocaine (lignocaine), bupivacaine) that bind selectively to the gating mechanisms of VGSC located at the intracellular region of the transmembrane channel. The drugs are weak bases existing in equilibrium between charged (membrane-impermeant) and uncharged (membrane-permeable) moieties dependent on tissue pH and drug pK_a (the pH at which the ionized and non-ionized forms of a chemical compound are in equilibrium). VGSC blockade occurs in a use-dependent manner (i.e. local anaesthetics block the channel preferentially in its 'open state') once they have accessed the neuronal intracellular compartment (Figure 2).

Local anaesthetic equilibrium and binding to sodium channel



2

Currently available local anaesthetic drugs appear to block all VGSC subtypes. The relative selectivity of bupivacaine and ropivacaine for nociceptive transmission reflects primarily pharmacokinetic aspects of penetration of myelinated and unmyelinated fibres in mixed nerves. Subtype selective sodium-channel blockers aimed at selectively targeting the SNS/PN3 channel are under development and may provide the potential for pharmacodynamically specific blockade of nociceptive transmission without motor or proprioceptive dysfunction.

With peripheral nerve and plexus techniques, blockade of axonal VGSC is unequivocally the mechanism of action of local anaesthetics. Likewise, epidural local anaesthesia initially represents segmental blockade of VGSC in nerve roots within the dural sleeve. Epidurally administered local anaesthetic diffuses through arachnoid villi with resultant high CSF concentrations of drug. Therefore, both epidural and, more significantly, subarachnoid local anaesthesia has a direct effect on the outer regions of the spinal cord where although VGSC effects predominate, anaesthesia will also encompass more subtle effects on synaptic mechanisms, which may involve potassium channel and calcium channel modulation.

Peripheral nociceptor

Transduction of injurious mechanical, thermal and chemical stimuli into Aδ and C fibre action potentials occurs at the peripheral axon terminal of the primary afferent nociceptor, the cell body of which resides in the dorsal root ganglion. Peripheral nociceptor transduction represents the selective activation of thermal, chemical or mechanically gated ion channels and is amplified following injury by the release of chemical mediators of inflammation. These include ATP, bradykinin, prostanoids, histamine, 5-HT, adenosine, catecholamines, potassium and hydrogen ions with the development of peripheral sensitization. Furthermore, inflammation results in increased local levels of nerve growth factor (NGF) and resultant unmasking of 'silent nociceptors', thereby enhancing the number of functional nociceptors and amplifying pain transduction.

The molecular structure and activation of mechanoreceptors are poorly understood; however, the recently cloned VR-1 vanniloid receptor is a thermally activated non-selective cation channel for thermal nociception. The VR-1 receptor selectively binds and is ultimately inactivated by capsaicin (hence chilli peppers produce the sensation of heat). Similarly the dorsal root acid-sensing ion channel may mediate hydrogen ion associated nociception. These receptors provide theoretical targets of analgesic action such as the delayed inactivation of VR-1 expressing C fibres by topical capsaicin in osteoarthritic and neuropathic pain. However, it is the modulation of nociceptor VGSC activation and attenuation of action potential generation that forms the basis of current regional anaesthetic action.

Peripheral opioid actions

In situ hybridization and immunohistochemical studies of opioid binding demonstrate the synthesis and expression of OP1 (δ), OP2 (κ) and OP3 (μ) receptors (see below) in the dorsal root ganglion; these receptors are transported peripherally via axonal transport and a similar population of receptors exist on terminals of Aδ and C nociceptive fibres. In common with spinal and supra-spinal opioid receptors, the binding of opioid agonists results in potassium-channel mediated neuronal hyperpolarization, attenuation of Ca^{2+} entry through voltage-gated calcium channels and reduced cAMP availability with resultant reduction in nociceptor activity.

Experimental peripheral opioid-mediated antinociception is enhanced under conditions of inflammation where the axonal transport of opioid receptors from the dorsal root ganglion and peripheral expression of opioid receptors is increased. Clinical studies have demonstrated significant peripheral opioid analgesia after intra-articular administration. However, a systematic review of data from opioid supplementation of local anaesthetic brachial plexus blocks suggests lack of efficacy.

The α_2-agonist clonidine has been demonstrated to potentiate local anaesthetic brachial plexus block. However, clonidine alone fails to produce analgesia at this site, suggesting that potentiation of analgesia may reflect altered vascular reuptake of local anaesthetic as much as a direct peripheral α_2-receptor-mediated analgesia within major nerve plexuses.

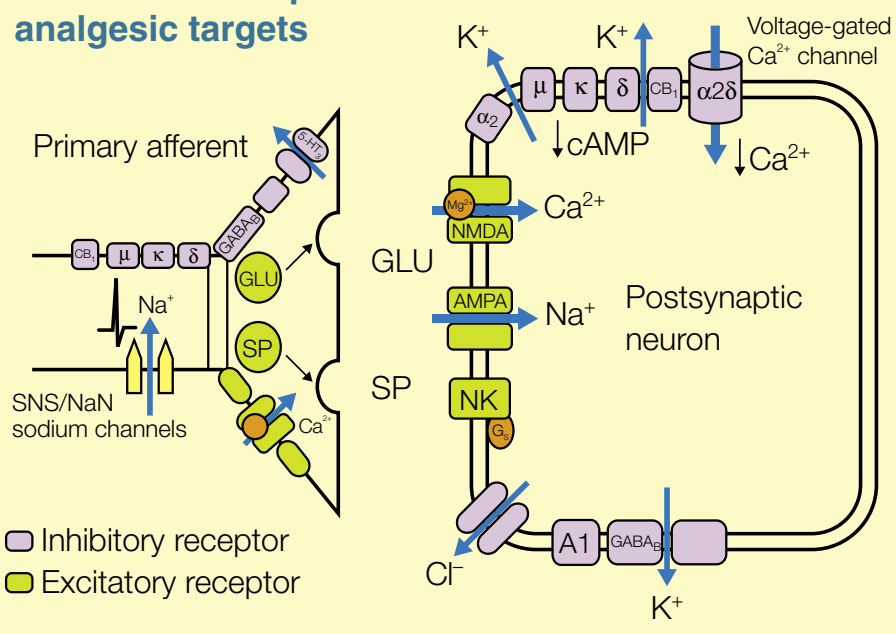
Dorsal horn

Epidural and intrathecal administration of opioids and other adjunctive drugs has a clear pharmacodynamic effect within the dorsal horn of the spinal cord. Aδ and C fibre nociceptors project to the superficial and deeper laminae of the dorsal horn where they synapse with both interneurons and projection neurons. Nociceptive afferent fibres co-release the excitatory amino-acid transmitter glutamate with neurokinins (predominantly substance P), calcitonin gene-related peptide (CGRP) and other peptide transmitters. At this locus, initial excitatory transmission is initiated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor activation, sodium ion entry and fast depolarization of postsynaptic neurons supplemented by potassium channel inactivation through neurokinin NK1 receptor activation. Depolarization of sufficient duration and magnitude to remove magnesium ion block of the N-methyl-D-aspartate (NMDA) receptor channel results in the entry of calcium ions, amplification of nociceptive transmission and initiation of central sensitization at both presynaptic and postsynaptic sites, which may be further supplemented by metabotropic glutamate receptor activation.

Excitatory transmission within the dorsal horn is under complex inhibitory tone mediated in part by γ-aminobutyric acid (GABA), glycine, catecholaminergic and opioid systems. Critically, dorsal horn mechanisms of neural transmission exhibit remarkable plasticity as illustrated in Figure 3.

The dorsal horn therefore provides a multiplicity of potential analgesic targets: only a few of which are exploited by analgesics in clinical use. Receptor classification and localization within the dorsal horn has recently been reviewed, and it is appropriate to consider briefly the role of certain of these as analgesic targets within the spinal cord dorsal horn.

Potential nociceptor afferent and dorsal horn analgesic targets



Key: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate; CB_1, CB_1 cannabinoid receptor; GABA, γ-aminobutyric acid; GLU, glutamate; NMDA, N-methyl-D-aspartate; NK, neurokinin; SP substance P

Inhibitory targets

Opioid receptors: within the spinal cord, OP3 (μ), OP2 (κ) and OP1 (δ) opioid receptors are localized primarily within laminae I–II (and possibly deeper laminae) of the dorsal horn. Dorsal rhizotomy results in a variable loss (40–70%) of receptor expression within the superficial dorsal horn indicating a predominant localization on presynaptic terminals of primary afferent nociceptors. In consequence, pain following de-afferentation (neuropathic pain such as phantom limb or brachial plexus avulsion) may be opioid resistant.

Opioid receptors mediate spinal analgesia by presynaptic inhibition of nociceptive transmitter release from Aδ and C fibres together with attenuation of postsynaptic depolarization via inhibition of voltage-gated calcium channels, activation of potassium channels and a reduction of cAMP. Neuraxial administration of opioids alone provides significant analgesia from a spinal site of action. However, mechanically triggered incident pain is often poorly controlled without co-administration of local anaesthetic. There is clear evidence of synergy between neuraxially administered local anaesthetic and opioid which is likely to reflect both nerve root attenuation of afferent action potential transmission to the dorsal horn and opioid inhibition of Aδ and C fibre transmitter release within the dorsal horn. This synergy provides the basis of most postoperative epidural analgesic regimens in which the co-administration of opioid and local anaesthetic enables high-quality analgesia with minimal motor deficit, minimal sedation and low risk of respiratory depression from supraspinal opioid receptor activation.

α_2 receptors: spinally administered α_2-agonists attenuate nociceptive transmission within the dorsal horn and produce analgesia. Binding sites for α_2-ligands are concentrated in laminae I–II of the dorsal horn, though there is dispute as to their relative presynaptic and postsynaptic distribution. Activation of α_2-receptors triggers an inwardly rectifying potassium conductance thereby hyperpolarizing both dorsal horn neurons and dorsal horn nociceptive neurons. α_2-mediated inhibition of N-type calcium channels has been shown to reduce dorsal horn glutamate and substance P (SP) release.

Alone, clonidine (and the more selective α_2-ligand dexemedetomidine) produce spinally mediated analgesia, though efficacy is limited by hypotension and supraspinally mediated sedation. While multiple α_2-receptor subtypes exist, and most data suggest that analgesia is mediated by spinal α_{2A}-receptors, the same subtype appears to subserve locus coeruleus-mediated sedation and spinal/medullary mediated hypotension. Co-administration of α_2-agonist with local anaesthetic and opioid provides the basis for synergistic analgesia.

Recent data indicate that (at least in neuropathic pain) α_2-mediated analgesia involves spinal muscarinic and cholinergic receptor activation with nitric oxide, suggesting that α_2-receptors may be primarily located on spinal cholinergic interneurons.

Cholinergic mechanisms: spinal cholinergic mechanisms may play a key integrative role in both spinally mediated α_2-adrenergic and supraspinal opioid analgesia. Spinal administration of cholinergic agonists or potentiation of endogenous acetylcholine release within the dorsal horn of the spinal cord by cholinesterase inhibition produces both experimental antinociception and clinical analgesia. Cholinergic spinal analgesia involves primarily muscarinic (and to a lesser extent nicotinic) receptors mediating antinociception via nitric oxide synthesis and release. Studies of pre-clinical or clinical use of intrathecal neostigmine have demonstrated effective analgesia at the expense of severe nausea.

Excitatory targets

NMDA receptors: the established role of the NMDA receptor in the initiation of central sensitization together with their anatomical localization to presynaptic and postsynaptic nociceptor synapses within the dorsal horn presents an attractive target and has generated a vast literature in multiple models of inflammatory and neuropathic pain. Many clinical studies have demonstrated analgesia after epidural administration of ketamine and much of this effect may be presumed to be a consequence of NMDA channel blockade. However, in a number of these studies, dose requirements were similar to those producing analgesia by the intravenous route, suggesting that supraspinal effects may be important. Recent clinical studies have demonstrated benefit in combining ketamine with local anaesthetic/opioid epidural infusion. Caudal epidural administration of ketamine in neonatal and paediatric surgery provides effective analgesia and potentiates local anaesthetic analgesia.

Systemic considerations of regional anaesthesia

Local anaesthetic drugs are non-selective blockers of VGSC. Consequently, inadvertent intravascular administration or excessive absorption of local anaesthetics results in direct toxic effects on myocardial (cardiotoxicity) and CNS neuronal (CNS toxicity) sodium channels. The mechanisms and management of these reactions are described on page 89.

While it is possible to achieve relative selectivity of sensory and motor blockade with low concentrations of bupivacaine and ropivacaine which reflects relative sparing of sodium channel blockade of Aα fibres (see page 88) it is clear that the small myelinated B fibres of preganglionic sympathetic efferents (hence white rami communicantes) and unmyelinated post-ganglionic sympathetic efferents (grey rami communicantes) are exquisitely sensitive to local anaesthetic blockade. Consequently, epidural or spinal local anaesthesia affecting the T1–L2 segments results in inevitable sympathetic blockade, manifest as vasodilatation and loss of reflex tachycardia if the cardiac fibres exiting at T4 are blocked. The risk of hypotension must be appreciated and its management is discussed on page 87. The sympathetic chains may also be selectively blocked in the cervical (stellate ganglion block), thoracic or lumbar paravertebral regions, and it must also be appreciated that brachial plexus or lumbar plexus anaesthesia will also produce sympathetic blockade; single limb sympatholysis is seldom associated with significant cardiovascular compromise.

Regional Anaesthesia: Recognition and Management of Adverse Effects

Jonathan Francis

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The reversible inhibition of nerve conduction has long been of interest to physicians as a means of providing analgesia and anaesthesia. Mechanical methods (cold and pressure) were superseded when cocaine, the first local anaesthetic, was identified. Safer amide local anaesthetics and improved equipment technology have increased the use of spinal, epidural (neuroaxial) and regional anaesthesia. Neuroaxial and regional techniques permit optimal peroperative analgesia and improve postoperative recovery (Figure 1).

Benefits of spinal, epidural and regional anaesthesia

Cardiovascular
- Inhibits neuroendocrine response
- Reduces plasma catecholamines
- Reduces cardiovascular stress
- Improves organ perfusion
- Reduces intraoperative blood loss
- Reduces postoperative thromboembolic complications

Respiratory
- Maintains functional residual capacity
- Maintains peak expiratory flow rate
- Maintains ability to cough
- Reduces tendency to basal airway collapse

Gastrointestinal
- Maintains splanchnic perfusion
- Enhances gastrointestinal motility

Sympathetic inhibition
- Improves blood flow locally to potentially ischaemic areas (e.g. peripheral vascular disease and free flap surgery)

1

Management of neuroaxial and regional anaesthesia

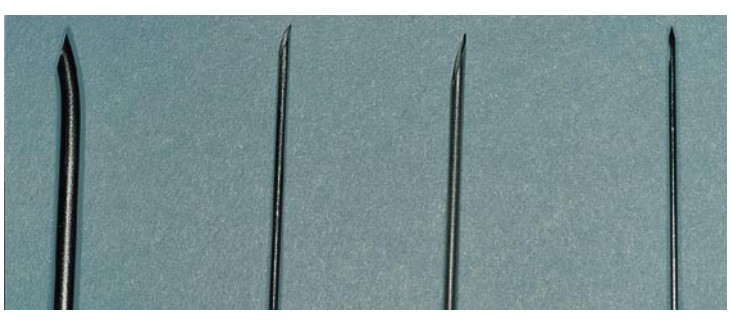
Preoperative preparation
Patients having neuroaxial and regional anaesthesia should be prepared as for a general anaesthetic. Physiological disturbances should be investigated and treated. Pre-existing neurological deficits and haemostatic disturbances should be identified. When obtaining informed consent from the patient, the procedure and any common or potentially serious risks should be explained.

Patient refusal is an absolute contraindication to neuroaxial and regional techniques. Psychiatric or psychological disturbance, haemostatic disturbances and local sepsis are often considered contraindications and the benefits and risks have to be determined for the individual. Similarly, pre-existing neurological deficit, low cardiac output states, previous spinal surgery or serious spinal pathology and systemic sepsis necessitate careful consideration before undertaking regional anaesthesia. For procedures in which loss of consciousness is a potential complication, the patient should observe the same fasting rules that would apply to general anaesthesia.

Perioperative management
Neuroaxial and regional procedures should be carried out in an environment staffed and equipped to deal with common and serious adverse effects. Intravenous access and basic monitoring should be observed, and full resuscitation facilities should be available immediately.

Procedures carried out after the induction of anaesthesia may enable greater patient acceptability, but this introduces a potentially greater risk of nerve or spinal cord injury, particularly when considering the use of thoracic epidural analgesia in abdominal surgery. It may be safer to carry out procedures before the induction of anaesthesia in a cooperative and informed patient.

Needle type: a variety of needles has been designed to allow the safe and accurate placement of drugs around neural structures (Figure 2). In general, the smallest needle possible should be used to carry out a procedure. The insertion of catheters through needles requires larger gauge needles (e.g. 16 G Touhy epidural needle). Long-bevel needles (a bevel cut at 12° ± 2°) tend to cut tissues and carry an increased risk of traumatizing nerves. Short-bevel needles (cut between 18° and 45°) part tissues and reduce the likelihood of nerve injury. They also allow greater operator feel and are more commonly used in regional anaesthetic techniques. Pencil-point needles with a side hole to prevent intraneural injection have been developed for intrathecal anaesthesia. Such needles are said to part the dural fibres and are less likely to cause post-dural puncture headache (PDPH).



2 Needles commonly used in neuroaxial and regional anaesthesia.
Left to right: 16 G Touhy needle, 22 G short-bevel regional block needle, 21 G long-bevel hypodermic needle, 25 G pencil-point spinal needle.

Needle position: the following techniques allow the operator to assess whether the needle is in the correct position.
- A potential space may be identified by a ‘loss of resistance' using saline or air. Saline is gaining popularity because it is sterile and has a more distinct loss of resistance end-point.
- The feeling of a ‘click’ or ‘pop’ can be used to identify correct needle placement. When appropriate, this end-point is more easily felt with a short-bevel needle.
- The presence of paraesthesia in the distribution of the target nerve is indicative of close proximity between needle and nerve. There is no clinical evidence to suggest that this is associated with nerve injury, though it remains a possibility.
- Nerve stimulators use low-power electrical stimulation at a frequency of 1–2 Hz to electrolocate peripheral nerves with a motor component. The observed motor twitch is related to current strength. A motor twitch at 0.5 mA is consistent with needle placement within 2 mm of the nerve. The use of sheathed (insulated) needles allows the needle tip to be the sole current source and improves the accuracy of needle placement.

Drugs: local anaesthetic drugs form the mainstay of neuroaxial and regional anaesthesia. Other drugs (e.g. opioids) have been shown to act centrally and peripherally and can be used to complement local anaesthetics. Ester agents (cocaine, procaine, tetracaine (amethocaine)) have been superseded by the amides (lidocaine (lignocaine), prilocaine, bupivacaine, ropivacaine) because they do not hydrolyse readily, penetrate tissues more easily and are less likely to produce allergic-type reactions.

Local anaesthetics exist in isomeric forms and toxic effects may be isomer specific. Ropivacaine and levobupivacaine are isomerically selective and may be less toxic. Vasopressors (e.g. adrenaline (epinephrine)) can be added to local anaesthetics to prolong their action and reduce systemic absorption and subsequent toxicity, allowing the administration of larger doses. Vasopressors are contraindicated around end arteries.

Administration – the injection of drugs should be smooth, painless and easy; a painful and difficult injection suggests intraneural injection. Regular aspiration protects against inadvertent intravascular injection. A test dose can help to identify incorrect needle or catheter placement, particularly in the epidural space. Controversy surrounds the ideal test dose, but 2 ml of 2% lidocaine (lignocaine) with 1:200,000 adrenaline (epinephrine) allows detection of intrathecal or intravascular placement.

The volume of injectate varies according to the anatomical site and the desired effect. Brachial plexus blocks require a large volume (0.5 ml/kg) to occupy the fascial sheath. Epidural drug volume depends on the desired dermatomal block and the level of catheter placement. When drugs are injected into the intrathecal space, small volumes of drugs circulate within the CSF and can produce profound and widespread anaesthesia. The height of the block depends on the drug dose, the posture of the patient, the spinal level of injection and the relative baricity of the drug compared with CSF.

Post-procedure care
The operating theatre is a hostile and intimidating place for the patient, every step of the procedure should therefore be explained to make them feel confident and comfortable. The developing block should be assessed by dermatomal distribution using pinprick or cold sensitivity. Anaesthesia of deep structures is also required but is more difficult to assess. Demonstration of the sensory block can be used to reassure patients. They should be informed that not all sensation will be lost and some feeling should be expected. If significant motor weakness occurs, care should be taken of the affected limb and patients should be encouraged to mobilize only when significant motor function has returned.

During the recovery period, the likelihood of adverse events should always be borne in mind and any suspicious symptoms or signs should be investigated (e.g. shortness of breath following a supraclavicular brachial plexus block may indicate pneumothorax).

Recognition and management of adverse effects

Complications can be minimized by careful patient assessment, planning and induction of the block and by monitoring the patient during and after the procedure.

Adverse effects of neuroaxial and regional anaesthesia (Figure 3)
Allergic reactions to local anaesthetics are usually the result of vasopressors or preservatives. Although uncommon, anaphylactic and anaphylactoid drug reactions can be severe. They present with skin reactions (skin wheals, flares, rashes), breathing difficulties (wheeze, breathlessness, bronchospasm) and cardiovascular collapse (hypotension, tachycardia, arrhythmias, cardiac arrest). Early clinical recognition allows treatment with basic life support, oxygen administration and the intravenous administration of adrenaline (epinephrine), bolus of 50–100 µg, fluid, 20 ml/kg, hydrocortisone, 100–300 mg, and chlorphenamine (chlorpheniramine), 10–20 mg.

Adverse effects of neuroaxial and regional aesthesia

Systemic adverse effects
- Adverse drug reaction (e.g. allergic hypersensitivity)
- Local anaesthetic toxicity (e.g. drug overdose, intravenous injection)
- Vasovagal faint

Local adverse effects
- Neurological injury (e.g. direct trauma, ischaemia, abscess, drug toxicity)
- Block failure
- Damage to surrounding structures (e.g. pneumothorax)
- Sepsis
- Haematoma formation

3

Local anaesthetic toxicity is determined by the rate of plasma concentration rise, peak plasma level and individual drug characteristics. The rise in plasma concentration depends on the rate of injection and regional blood flow. Peripheral subcutaneous tissue has a poor blood supply and drug absorption is slow. The epidural space, paravertebral space and oropharynx have a generous blood flow and rapid absorption is more likely to produce dangerously high plasma drug levels. Intravenous injection leads to a rapid rise in plasma concentration. Intra-arterial injection, particularly into the cerebral vessels, leads to a high intracerebral drug concentration and CNS toxicity.

Signs and symptoms of local anaesthetic toxicity range from light-headedness, periorbital paraesthesia and slurred speech, to tinnitus and muscle twitching. At higher plasma concentrations, loss of consciousness and coma occur before the development of myocardial depression, cardiac arrhythmias and ventricular arrest. Bupivacaine can cause malignant ventricular arrhythmias without warning. Intravenous bretylium, 5 mg/kg, is the anti-arrhythmic of choice.

Maintaining verbal contact with the patient allows early detection of toxic symptoms. In the event of local anaesthetic toxicity, the injection should be stopped. Hypoxia and acidosis exacerbate local anaesthetic toxicity and should be prevented. Basic life support and oxygen administration are essential. Convulsions should be treated with intravenous benzodiazepines.

Vasovagal faint is a common complication of regional anaesthesia. The profound vagal response is usually self-limiting and venous return should be enhanced by a supine posture. Anticholinergic drugs such as atropine, 1 mg, are effective.

Adverse effects of spinal and epidural anaesthesia (Figure 4)
Post-dural puncture headache: needle puncture of the dura mater (either deliberate, as in the case of spinal anaesthesia, or accidental, as a complication of epidural anaesthesia) can produce a prolonged headache. Headaches are more common in the young and when the dura is punctured by large-bore cutting needles (e.g. Touhy needle). The conservative treatment of PDPH includes bed rest, hydration and simple analgesics. Intravenous caffeine, 300–500 mg, epidural saline infusions, sumatriptan and adrenocorticotrophic hormone have all been tried with varying degrees of success. An epidural blood patch relieves PDPH in 85–90% of patients within 24 hours.

Adverse effects of spinal and epidural anaesthesia

- General adverse effects
- Post-dural puncture headache
- Nausea and vomiting
- High block/ total spinal
- Hypotension
- Pruritus
- Inadequate block/ block failure
- Prolonged block
- Backache
- Neuronal injury

Hypotension: local anaesthetic drugs administered by the intrathecal and epidural routes rapidly penetrate small-diameter, unmyelinated sympathetic fibres, producing a sympathetic block. The resulting peripheral vasodilatation and loss of reflex tachycardia with blocks extending above T4 produce hypotension. Hypotension is more profound and of quicker onset following spinal anaesthesia, and is proportional to the height of the block. Hypovolaemia and low cardiac output states (aortic stenosis and left ventricular failure) can produce catastrophic hypotension and circulatory collapse. Correction to normovolaemia, vigilant assessment of block progression and liberal use of vasopressors (ephedrine or methoxamine) limits troublesome hypotension. The practice of fluid pre-loading patients is controversial; colloid solutions seem to be more effective than crystalloid solutions in reducing hypotension.

Total spinal: inadvertent intrathecal injection of a large dose of local anaesthetic results in rapid ascension of motor and sensory blockade. Phrenic nerve (C3–5) involvement produces apnoea, and intracranial spread results in loss of consciousness, fixed dilated pupils and profound hypotension. This is usually the result of intrathecal administration of an epidural dose, therefore careful assessment of epidural catheter position by aspiration guards against it. Excessive drug delivery can occur in short, elderly or pregnant patients. Regular assessment of block progression allows early identification. Basic airway maintenance should be followed by tracheal intubation and lung ventilation. Cardiovascular support with intravenous fluids and vasopressors are needed until the block regresses.

Backache: the chance of prolonged backache following neuroaxial anaesthesia is a common concern of patients. Epidural analgesia during labour can be associated with backache for up to 6 months. Backache is also common during normal pregnancy and labour. Complicated or prolonged labour is more likely to require epidural anaesthesia, and this may be a confounding factor. Epidural analgesia may mask an uncomfortable patient position and result in ‘acute back strain’. A careful technique, posture awareness and avoidance of dense motor blockade should reduce the chance of backache, but patients should be warned of the possibility.

Haematoma formation following peripheral nerve blockade is usually of little consequence, but in the spinal canal it can be disastrous. Spontaneous epidural haematoma formation is associated with haemostatic disturbances, anticoagulant and antiplatelet therapy. Haemostatic abnormalities are a relative contraindication to neuroaxial and regional procedures, including the removal of an epidural catheter.

Warfarin should be stopped several days before any procedure. Heparin allows short-term control if anticoagulation is essential (e.g. prosthetic heart valve). International normalized ratio and activated partial thromboplastin time ratio should be less than 1.5 at the time of surgery. Procedures should be delayed for 2 hours following the administration of subcutaneous heparin, and for 12 hours following low molecular weight heparins. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit platelet function, and prolong bleeding time for up to 10 days. There are few reports of haematoma formation following NSAID use, but care should be exercised when other coagulation abnormalities exist. Antithrombotic agents (e.g. streptokinase) actively lyse clot and prevent clot formation, and are an absolute contraindication to neuroaxial and regional anaesthesia.

An unexplained increase in spinal pain or prolonged neurological block is suspicious and should be investigated rapidly. Epidural haematomas should be surgically evacuated at the earliest opportunity if neurological function is to be preserved.

Renal

Anaesthesia
and intensive care medicine
on CD-ROM

Clinical Assessment of Renal Problems

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Renal impairment, whether acute or chronic, affects many organs, and presents a challenge for the anaesthetist.

Renal impairment reduces the body's ability to autoregulate fluid status, electrolytes and pH. For example, a patient with renal failure is less able to tolerate the potassium release that follows succinylcholine administration.

Many drugs (e.g. opiates, muscle relaxants) or their metabolites, are renally excreted, and therefore their pharmacokinetics are modified in renal failure.

It is also important to identify patients with renal dysfunction before surgery so that their postoperative management can be planned effectively. Such patients are more likely to require a period on an intensive care or high-dependency unit postoperatively.

Questions to be addressed

The anaesthetist assessing a patient preoperatively should address the following questions.

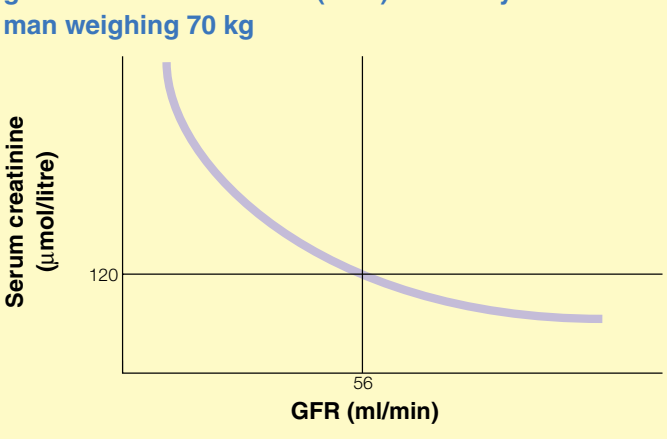
Is the renal function normal?

A normal serum creatinine level is commonly assumed to represent normal renal function. However, the serum creatinine concentration depends not only on creatinine clearance by the kidneys, but also on muscle mass, and to a lesser extent on dietary meat intake. Therefore, patients with low muscle bulk may have a misleadingly normal serum creatinine despite significantly impaired renal function. This is most commonly seen in the elderly, the malnourished and in women. As Figure 1 shows, the relationship between serum creatinine and glomerular filtration rate (GFR) is far from linear, and a rise in creatinine outside the normal range indicates significant loss of glomerular filtration. If time allows, a paired assay of serum and a 24-hour urine collection permits a calculation of creatinine clearance, which is a useful guide to GFR. Alternatively, if the patient's weight is known, the Cockcroft–Gault equation can be applied to the serum creatinine to estimate GFR:

$$\text{GFR (ml/min)} = \frac{1.2 \times [140 - \text{Age (years)}] \times \text{Weight (kg)} \times 0.85 \text{ (if female)}}{\text{Plasma creatinine } (\mu\text{mol/litre})}$$

Therefore, a 60-year-old man weighing 70 kg with a serum creatinine at the upper end of normal (120 μmol/litre) has an estimated GFR of 56 ml/min. This formula applies only in a steady state and not when the serum creatinine is rapidly changing due to acute renal failure.

Relationship between serum creatinine and the glomerular filtration rate (GFR) for a 60-year-old man weighing 70 kg



1

Is renal impairment acute or chronic?

Chronic renal failure is often associated with co-morbidity such as hypertension, left ventricular hypertrophy or ischaemic heart disease.

Patients with acute renal failure are generally less stable in terms of electrolyte and fluid control. They are likely to have co-morbidity in association with the aetiology of their renal dysfunction, particularly if they have sepsis or trauma.

It is important to assess the chronicity of renal impairment. This may be determined reliably only if old notes or test results are available, for example from the general practitioner. However, a careful history and examination may provide clues, as may some basic investigations.

Are there issues requiring urgent treatment?

It is vital that the life-threatening complications of renal dysfunction are detected early, so that appropriate treatment can be provided. The most common are hyperkalaemia, fluid overload resulting in respiratory embarrassment, and uraemic pericarditis. It is also imperative that easily reversible causes of acute renal failure (e.g. hypovolaemia, renal outflow obstruction, sepsis) are diagnosed and treated.

Is renal replacement necessary?

In a patient with severe renal impairment, anaesthesia and surgery often precipitate the need for renal replacement. It is therefore important to decide whether dialysis should be instigated before surgery, or planned for afterwards. This may require discussion with the local renal team.

Haemodialysis patients should be dialysed less than 24 hours before surgery. If they are acutely ill and likely to be catabolic, more recent haemodialysis may be required.

What is the underlying diagnosis?

The underlying diagnosis is valuable because it helps to anticipate problems associated with co-morbidity. For example, a 40-year-old man with end-stage renal failure due to diabetes mellitus is at considerably greater operative risk than an equivalent patient whose renal failure is due to polycystic kidney disease. An accurate diagnosis is also important because acute renal failure is reversible in some circumstances.

History

Clinical assessment should begin with the history.

Does the patient have pre-existing renal disease? Many renal patients are well informed about their condition, to the extent that they can cite their latest biochemical and haematological results. Is the patient undergoing any renal replacement therapy such as haemodialysis (and, in the acute setting, haemofiltration, and haemodiafiltration), peritoneal dialysis or renal transplantation? In the case of renal transplantation, it is important to determine which immunosuppressive treatment the patient is taking, and to consider drug interactions in the subsequent management.

The family history can provide useful clues about aetiology, and sometimes about chronicity. The most common familial causes of renal impairment in adults are autosomal dominant polycystic disease, and reflux nephropathy, which has the same pattern of inheritance.

It is important to enquire about a previous diagnosis of hypertension, which often arises with renal disease, and previous vascular events or symptoms such as claudication.

Though common in men, nocturia may indicate obstructive uropathy or loss of urinary concentrating ability due to chronic renal failure. Oliguria may be part of the stress response of normal kidneys and non-oliguric acute renal failure is well recognized. Nevertheless, oliguria makes fluid management more difficult and may give important diagnostic clues (Figure 2).

Case history

Mrs X, a 67-year-old woman saw her general practitioner 10 days ago with gout, for which she was prescribed indomethacin. 5 days later, she suffered an acute myocardial infarction, with a 36-hour period of hypotension. She now has acute renal failure. She is able to provide a clear history that her oliguria began before her cardiac event. This makes a diagnosis of drug-related interstitial nephritis likely with the possibility of superimposed acute tubular necrosis

2

A detailed, accurate drug history is imperative for diagnostic and management considerations (Figure 3). It must include the use of over-the-counter drugs, particularly self-medication with analgesic agents. Use of herbal preparations may also be relevant (e.g. St John's wort reduces plasma theophylline levels). Acute renal failure in hospitals is often associated with the combined use of diuretics, angiotensin-converting enzyme inhibitors or non-steroidal anti-inflammatory drugs, including topical preparations. An accurate drug history reduces the risk of causing dangerous drug interactions, such as the potentiation of ciclosporin by diltiazem.

Drugs commonly implicated in acute renal failure

Functional reduction in glomerular filtration
- Angiotensin-converting enzyme inhibitors
- Angiotensin II blockers
- Non-steroidal anti-inflammatory drugs (NSAIDs)

Glomerulopathy
- Gold salts
- D-penicillamine
- NSAIDs
- Mesalazine

Acute tubular necrosis
- Aminoglycosides
- Sulphonamides
- Aciclovir
- Foscarnet
- NSAIDs
- Cisplatin

Interstitial nephritis
- β-lactam antibiotics
- NSAIDs

3

Special situations should be considered when taking the history of a patient with acute renal failure, because of the profound metabolic disturbances that may ensue. These patients are likely to require early, aggressive dialysis.
- Care should be taken to elicit any risk factors for rhabdomyolysis. Trauma should be evident, but status epilepticus, prolonged stasis (as in the case of an elderly patient who has fallen at home and sustained a hip fracture), and even vigorous exercise in a patient with a metabolic myopathy, may not be apparent unless the appropriate questions are asked.
- Tumour lysis syndrome, in which administration of chemotherapeutic drugs causes massive cell lysis, may result in rapidly fatal hyperkalaemia, hyperphosphataemia and hyperuricaemia.
- In certain poisoning situations, early dialysis is useful in reducing the toxin levels. In particular, a history of lithium, aspirin or ethylene glycol poisoning should be sought.

Examination

The aim of examination is to determine the presence of complications of renal impairment, to elicit any aetiological clues and to assess the patient's co-morbidity.

Urgent assessment of the patient's airway, oxygenation and circulation takes priority over history taking. Subsequently, signs that might indicate an urgent need for renal replacement must be sought. These include encephalopathy (confusion, metabolic flap), pulmonary oedema and pericardial rub. Remember it takes time to organize dialysis, especially if transfer of the patient to another unit or hospital may be involved.

A careful assessment of fluid status is mandatory. Signs of volume depletion are a low jugular venous pressure, hypotension (a postural drop is a sensitive marker of early hypovolaemia), tachycardia and peripheral shutdown. Occasionally it may be useful to give a therapeutic trial of fluid. The aim is to increase the intravascular volume, by giving a relatively small volume (usually 250 ml) of intravenous fluid rapidly, before inter-compartmental equilibration can occur. If there is no clinical deterioration after 5 minutes, the trial may be repeated. Fluid overload may manifest in a raised jugular venous pressure, hypertension, peripheral and pulmonary oedema, and a gallop rhythm.

A careful examination of the cardiovascular system should include assessment of all the pulses. Vascular disease is a common cause of chronic and acute renal impairment in at-risk patients, and is important for prognosis. Complications of long-standing hypertension (chronic hypertensive retinopathy, left ventricular hypertrophy) may be evident.

It is easy to miss a palpably distended bladder unless it is sought.

Signs of chronicity may be found, but are often absent. Leuconychia or brown nail arcs may suggest chronic disease. Uraemic pigmentation is often seen in patients who have reached end-stage renal failure without previous medical attention.

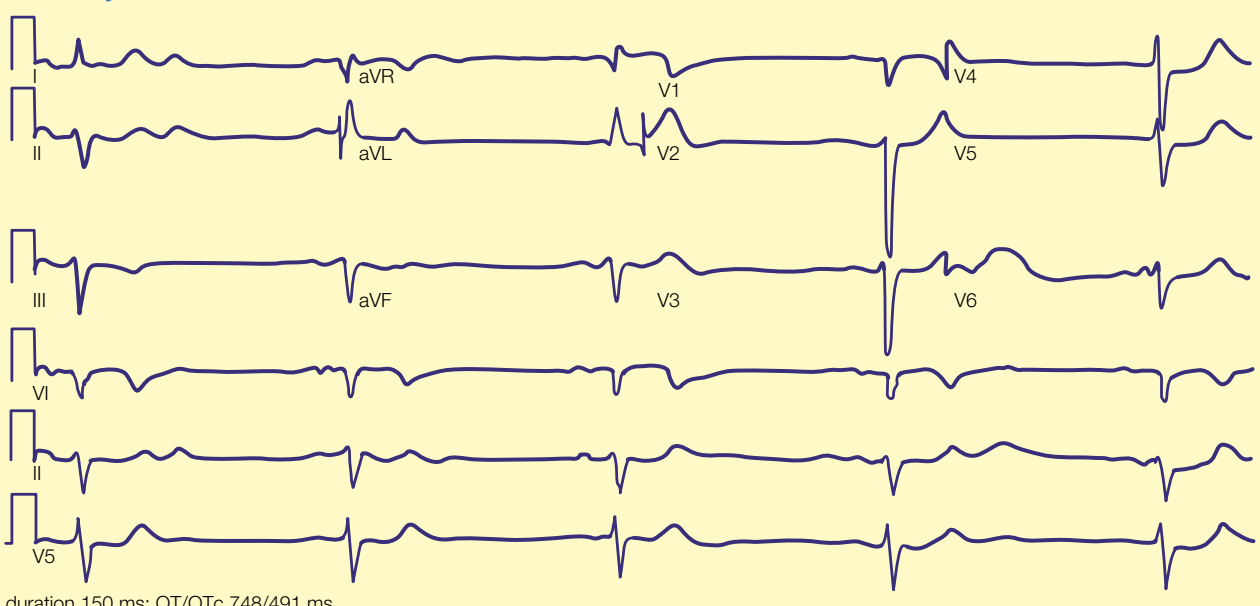
Investigations

One of the most useful, and under-rated, investigations in renal practice, is dipstick urinalysis. This should be performed on a urethral rather that a catheter specimen of urine, to make interpretation of haematuria more reliable. Heavy proteinuria makes glomerular disease more likely than prerenal or obstructive failure. Urine that is strongly positive for blood, but contains no red cells on microscopy, may indicate myoglobinuria or haemoglobinuria seen in rhabdomyolysis or haemolysis, respectively. Red cell casts on microscopy indicate glomerular disease.

A full blood count and clotting profile are important to assess the degree of anaemia, and to diagnose disseminated intravascular coagulation or microangiopathy. It is important not to overlook disturbances of calcium and phosphate metabolism often associated with acute or chronic renal failure.

An electrocardiogram is mandatory. It allows assessment of left ventricular wall thickness, and permits diagnosis of life-threatening hyperkalaemia (Figure 4).

ECG of a patient with a serum potassium of 7.8, showing bradycardia and broadened QRS complexes, peaked T waves may also be seen



QRS duration 150 ms; QT/QTc 748/491 ms.

In many circumstances, urgent renal imaging is appropriate. Hydronephrosis suggests obstruction, a potentially reversible cause of acute renal failure. Bilaterally small kidneys strongly suggest chronic and irreversible disease. The most useful investigations in this situation are a plain radiograph of the kidneys, ureter and bladder (KUB) to look for calculi, accompanied by a renal and bladder ultrasound. An intravenous pyelogram is unlikely to be diagnostically useful in the presence of significant renal impairment, because the damaged kidneys are unable to concentrate the dye sufficiently for adequate visualization of the urinary tract. If a CT scan of the abdomen has been performed for other reasons it may provide useful diagnostic information about the kidneys.

Special investigations

In unexplained renal failure, special investigations assist diagnosis. Immunological tests (complement, antinuclear, antineutrophil cytoplasmic and antiglomerular basement membrane antibodies) and serum and urine electrophoresis are often helpful. Ultimately, the diagnosis is made only by renal biopsy. ◆

FURTHER READING

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Fluid and Electrolyte Problems

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Salt and water regulation

The perioperative management of a patient's fluid and electrolyte balance requires a basic understanding of the physiology of salt and water regulation. Water constitutes 50–70% of body fluids; two-thirds (28 litres) is in the intracellular compartment and one-third (14 litres) in the extracellular compartment. The extracellular fluid (ECF) is divided between the interstitial space (75%, 10.5 litres) and the intravascular space (25%, 3.5 litres).

Osmoregulation (water balance): the distribution of water between the fluid compartments is determined by hydrostatic pressure and osmotic pressure (osmolarity (mosmole/litre) or osmolality (mosmole/kg)).

Plasma osmolality = 2 × [Na] + [Glucose] + [Urea]

Differences between measured and calculated osmolality suggest the presence of osmolytes not routinely measured, such as mannitol and methanol, the latter being particularly important to consider in the unconscious patient in the emergency department. Plasma osmolality is determined almost entirely by water balance. Increases in osmolality are detected in the hypothalamus and result in the stimulation of the thirst drive (increased water intake) and release of antidiuretic hormone (ADH or vasopressin) from the posterior pituitary gland. ADH reduces water loss by acting on receptors in the collecting ducts of the kidneys to increase the number of water channels (aquaporin) on the collecting duct cells. By this and other intra-renal mechanisms (active sodium transport, counter-current exchange and low medullary blood flow) the kidney is able to produce urine as concentrated as 1200 mosmole/kg H_2O.

Volume regulation (sodium balance): extracellular volume is regulated by the renin–angiotensin–aldosterone system and atrial natriuretic peptide through their effects on sodium excretion. Renin is released from the juxtaglomerular apparatus in response to reduced plasma volume, renal ischaemia and sympathetic drive and converts angiotensinogen to angiotensin I. Angiotensin converting enzyme converts this to angiotensin II with resulting increased vascular tone, tubular sodium re-absorption and thirst. Angiotensin II also stimulates the secretion of aldosterone from the adrenal cortex. Aldosterone causes the tubules to retain sodium in exchange for potassium and hydrogen ions, which are lost.

The clinical approach

The stages to managing a patient's fluid and electrolyte status are:

- assess the patient's normal maintenance (background) fluid and electrolyte requirement
- correct pre-existing fluid and electrolyte deficits
- replace fluid and electrolyte losses during and following surgery
- adjust the type and quantity of fluids according to the patient's response and the presence of co-existing disease (e.g. cardio-pulmonary, renal disease).

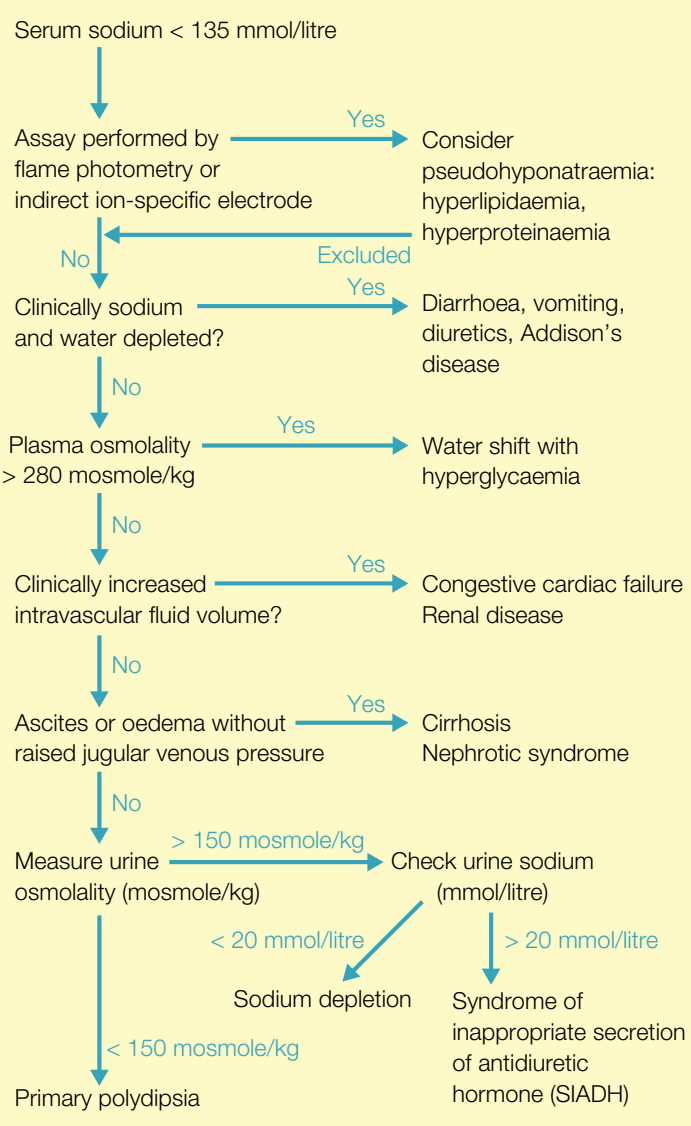
In all but the simplest of cases, the patient's response must be evaluated frequently and the replacement regimen adjusted accordingly. Changes in heart rate, blood pressure, capillary refill, skin turgor, urine output and jugular venous or central venous pressure must be interpreted alongside the results of laboratory data. In particular cases, it is helpful to quantify specific fluid losses by analysing the electrolyte content of nasogastric, diarrhoea or stoma losses. Although urine output is a useful gauge of central perfusion pressure and renal perfusion postoperatively, renal blood flow is regulated by opposing neurohormonal factors. Surgical stress tips the balance of these systems in favour of renal vasoconstriction and salt and water retention, and a degree of oliguria, irrespective of volume status, may last for days after surgery.

Specific electrolyte disturbances

Hyponatraemia

Hyponatraemia is a serum sodium level below 135 mmol/litre. Its cause can be established by combining measurements of serum osmolality, urine osmolality and serum creatinine with a clinical assessment of the patient's fluid status (Figure 1). Most UK laboratories use an indirect ion electrode method to measure sodium, therefore pseudohyponatraemia must be excluded by measuring osmolality or by measuring sodium using a blood gas analyser (a direct ion electrode method).

Evaluating hyponatraemia



1

The main symptoms of hyponatraemia (headache, nausea and vomiting, confusion, seizures and coma) and the side-effect of treatment (central pontine myelinosis) make the CNS of primary importance in hyponatraemia management. After 6–12 hours of hyponatraemia, an adaptive process in the brain reduces the number of osmotically active organic compounds in the brain cells. This minimizes the transcellular shift of water that would otherwise cause cerebral oedema and is complete by 72 hours. Consequently, rapid correction is appropriate when hyponatraemia is known to have developed acutely, but if there is any doubt about the duration of hyponatraemia the rate of correction of plasma or serum sodium must not exceed 1–2 mmol/litre/hour or 12–20 mmol/litre/24 hours. Patients with liver disease are particularly at risk.

The general management of hyponatraemia is as follows.

- Exclude a removable underlying cause.
- If ECF volume is reduced give isotonic saline.
- If ECF volume is normal or expanded, sodium is greater than 120 mmol/litre and the patient is asymptomatic, restrict fluid; if sodium is less than 120 mmol/litre or the patient is symptomatic, give isotonic saline or hypertonic saline; use loop diuretics, if necessary, to control ECF volume.

Although formulae help inform decisions about sodium replacement, they are often inaccurate, do not consider continuing losses, and must be used in conjunction with frequent laboratory assessment.

Na requirement (mmol) =
Total body water × Desired change in serum sodium

Hypernatraemia

Hypernatraemia (serum sodium greater that 145 mmol/litre) always indicates insufficient water in the body in relation to its solute content. Hypernatraemia in hospitals is most commonly caused by insufficient water intake, increased water loss and excess salt intake (intravenous or nasogastric). It develops if the patient is unable to perceive or communicate their thirst or is unable to retain ingested fluid (Figure 2).

Causes of hypernatraemia

Insufficient water intake

- No water available (e.g. lost at sea or on land)
- Inability to signal thirst to others
  - Infants
  - Intubated patients
  - Expressive dysphagia
  - Confusional states
  - Coma
- Unable to retain ingested water (e.g. vomiting)
- Hypodipsia

Increased water loss

- With sodium losses
  - Osmotic diuresis
  - Sweating
  - Diarrhoea/emesis
- Without sodium losses
  - Insensible (e.g. fever, hyperventilation (altitude))
  - Diabetes insipidus (e.g. central, nephrogenic)

Excess solute intake

- Accidental
- Deliberate: hypertonic or excess isotonic NaCl
- Iatrogenic: hypertonic $NaHCO_3$

2

Diabetes insipidus is associated with inappropriately dilute urine and may be caused by a reduction in ADH secretion (central diabetes insipidus) or a lack of responsiveness of the kidney to ADH (nephrogenic). It is diagnosed by a urinary osmolality less than 400 mosmole/kg H_2O. The causes of central diabetes insipidus include head injury, neurosurgery and CNS infections and tumours. Ethanol transiently blocks ADH release. Nephrogenic diabetes insipidus may be familial (ADH receptor and aquaporin-CD defects), drug related (e.g. lithium, demeclocycline), secondary to electrolyte disturbances (hypokalaemia, hypercalcaemia) or be associated with renal disease (e.g. polycystic kidney disease, myeloma).

The initial symptom of hypernatraemia is thirst. As serum sodium rises, patients develop nausea, confusion, coma and seizures. To protect the brain cells from injury, idiogenic osmoles are produced to reduce the shift of water out of the cells during hypernatraemia, but their metabolism takes time and too rapid correction of serum sodium risks cerebral oedema.

Management of the hypernatraemic patient begins with repletion of the intravascular volume with either colloid or isotonic saline. Once this has been achieved, correction of the total body water deficit begins. Although the extent of the water deficit can be estimated, continuing fluid losses must also be considered.

Water deficit (litres) =
{(serum sodium/140) – 1} × Total body water

About 30–50% of the water deficit should be replaced in the first 24 hours and the remainder replaced over the following 48–96 hours.

Hypokalaemia

Potassium is the major intracellular cation. Intracellular potassium levels are about 150 mmol/litre compared with 3.4–4.6 mmol/litre in plasma; this gradient is maintained by the Na/K pump. Acidosis decreases potassium uptake by cells and insulin and catecholamines activate the pump and drive potassium into cells. 90% of potassium is excreted in the urine (largely regulated by aldosterone) and the remainder in the stool.

Hypokalaemia may be the result of a shift of potassium into cells or a deficiency of intracellular potassium (Figure 3). Hypokalaemia increases the intracellular:extracellular potassium ratio causing hyperpolarization of cell membranes with neuromuscular, renal and endocrine sequelae. As well as the characteristic flattened T waves, depressed ST segments and U waves seen on the ECG, hypokalaemia enhances digitalis toxicity and can induce life-threatening ventricular dysrhythmias. Magnesium depletion can cause hypokalaemia, and when magnesium and potassium deficiencies coexist, correction of serum potassium is achieved only if magnesium stores are also replenished.

Causes of potassium depletion

Extrarenal
(Urine K < 20 mmol/day)
- Inadequate intake
- Copious perspiration
- Gastrointestinal losses
  - Diarrhoea
  - Laxative abuse
  - Villous adenoma

Renal
(Urine K > 20 mmol/day)
- Renal tubular acidosis
- Diabetic ketoacidosis
- Chloride depletion
  - Emesis/gastric suction
  - Diuretics
- Disorders of tubular function
  - Bartter's syndrome[1]
  - Gitelman's syndrome[2]
  - Liddle's syndrome[3]
- Mineralocorticoid excess
- Glucocorticoid excess
- Magnesium depletion
- Antibiotic therapy
- Leukaemia

[1]An inherited condition associated with normotension and hypokalaemic alkalosis. The primary defect may be defective chloride reabsorption or increased potassium tubular secretion

[2]Similar to Bartter's syndrome but associated with hypercalciuria

[3]A rare autosomal dominant condition that mimics a state of mineralocorticoid excess. Amiloride and triamterene, but not spironolactone, correct the hypokalaemia and hypertension

Potassium management depends on the underlying cause of the disorder. When a deficit exists, replacement should be achieved by oral supplementation or using potassium-sparing diuretics (e.g. amiloride). When intravenous replacement is necessary for life-threatening hypokalaemia (paralysis, ventricular dysrhythmias, digitalis toxicity) infusion rates of potassium 10–40 mmol/hour may be given, but only in the coronary care or critical care setting.

Hyperkalaemia

Hyperkalaemia may result from a shift of potassium from the intra- to the extracellular compartment or from the retention of potassium in the body (Figure 4). Defective urinary excretion of potassium has three main causes: an inadequate number of functioning nephrons; hypoaldosteronism; and defective tubular secretion of potassium. Although hyperkalaemia can cause paralysis, acidosis and hypotension, the primary concern is the increased risk of cardiac dysrhythmias heralded by characteristic changes on the ECG (flattening of P waves, widening of the QRS complexes, tenting of the T waves).

Aetiology of hyperkalaemia

Spurious
- Ischaemic venesection
- Haemolysis
- Abnormal erythrocytes
- Thrombocytosis
- Leucocytosis

Redistribution
- Acidosis
- Insulin deficiency
- β-adrenergic blockade
- Drugs
  - Arginine HCl
  - Succinylchloride
  - Digitalis toxicity
- Hyperkalaemic periodic paralysis
- Exercise
- Malignant hyperthermia

Renal
- Renal failure (severe)
- Aldosterone deficiency
- Addison's disease
- Enzymatic defects
- Hyporeninaemic hypoaldosteronism[1]
- Drugs
  - Prostaglandin synthase inhibitors
  - NSAIDs
  - Angiotensin-converting inhibitors
  - Heparin
  - Ciclosporin (cyclosporin)
  - Potassium-sparing drugs
- Tubular dysfunction
  - Acquired disorders
  - Pseudohypoaldosteronism

[1] Type IV renal tubular acidosis

Treatment of hyperkalaemia is indicated when serum potassium exceeds 6.5 mmol/litre, ECG changes are present or if the condition is likely to worsen rapidly. Management is initially aimed at minimizing the risk of cardiac toxicity with calcium preparations, then at shifting the potassium back into the cells (insulin/dextrose, sodium bicarbonate and β-agonists). It is then important to remove the cause of the hyperkalaemia and eliminate the excess potassium from the body with a cation exchange resin. In those with resistant hyperkalaemia, haemodialysis and peritoneal dialysis may be required. ◆

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Laboratory Tests of Renal Function

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The kidney's main function is to maintain normal composition of the extracellular fluid, which it does by producing urine. The kidneys of a healthy adult receive about 25% of the resting cardiac output (about 1300 ml/min). This large blood supply is channelled into the glomeruli, each of which filters blood into the Bowman's capsule of an individual nephron. There are about 1 million nephrons in each human kidney, which drain via the renal tubules into the renal pelvis and subsequently into the ureter.

The glomeruli filter 170–200 litres of protein-free ultrafiltrate fluid every 24 hours (50–60 times the normal plasma volume). However, up to 99% of the water is reabsorbed within the renal tubular network, resulting in a normal daily urine output of about 1500 ml, though this varies depending on changes in plasma volume or osmolality. The filtrate initially has the same crystalloid composition as plasma, but ion exchange and transport occur within the tubular system, which results in the composition of the fluid varying, depending on the needs of the body.

Normally, glucose is completely reabsorbed by the renal tubules and only minute quantities of protein appear in the urine. The breakdown products of protein metabolism, especially urea and creatinine, are almost exclusively excreted in the urine. The urine is the main route of elimination for water-soluble drugs and their metabolites, and the presence of oxidase enzyme systems in renal cells allows some drug metabolism to occur. The kidney also has endocrine functions and is an important site for the production of kinins and prostaglandins.

Assessment of renal function

The composition of blood and urine may reflect renal dysfunction and systemic disorders. Clinical evaluation of renal function should include an assessment of:

- concentration of non-protein nitrogen compounds in blood and urine
- glomerular filtration function
- secretory capacity of the renal tubules
- tubular ability to reabsorb water and electrolytes, as measured by urine concentrating ability.

No single test of renal function should be used or considered in isolation. All test results should be interpreted with reference to the patient's clinical history and examination.

Glomerular filtration rate (GFR)

The GFR is a measure of the clearance of substances from the bloodstream into the glomeruli, expressed in ml/min. It is related to the number of functioning nephrons. Most methods of measuring GFR involve the kidney's ability to clear marker substances. Depending on the substance, the renal clearance may be achieved by glomerular filtration, tubular secretion or a combination. In clinical practice, it is the volume of plasma cleared solely by glomerular filtration that is relevant.

If a substance is freely filtered by glomerular filtration, but is neither secreted nor absorbed by the renal tubules, then its plasma clearance represents the GFR. Plasma clearance of a substance may be calculated using the formula:

$$C_s = \frac{U_s \times V}{P_s}$$

where: C_s is clearance of the substance (ml/min); U_s is urinary concentration of the substance; V is urine flow rate (ml/minute); and P_s is plasma concentration of the substance. GFR is potentially the most useful marker of renal function, but accurate assessment is difficult in practice.

A number of exogenous substances are accurate markers of GFR, including inulin (the gold standard) and iohexol. The disadvantage of using exogenous markers is that they have to be administered by intravenous bolus, usually followed by an in-fusion to maintain steady-state plasma levels. During the infusion, accurately timed urine collections are obtained, making these tests labour-intensive and costly, and therefore usually restricted to use as research tools.

GFR may also be estimated using endogenous markers such as creatinine, urea and low molecular weight proteins (e.g. cystatin C).
Advantages of using endogenous markers are that they do not need to be injected and only a single blood test is required for the estimation.

Creatinine and creatinine clearance: creatinine is derived from creatine and creatine phosphate. Its production and renal excretion is constant and proportional to muscle mass. It is freely filtered by the glomerulus, but small amounts are also secreted by the proximal tubule. Thus, the GFR is overestimated by 5–10% in healthy individuals, but as renal function deteriorates, the contribution of secreted creatinine to overall clearance becomes more important. In addition, drugs such as cimetidine, trimethoprim and some cephalosporins interfere with the tubular secretion of creatinine thus increasing serum levels and decreasing clearance, without affecting GFR.

Despite these limitations, creatinine clearance is the simplest and most widely used method of assessing renal function. Nevertheless, it is important that urine should be correctly and accurately collected over 24 hours. The urine should be refrigerated during this period to avoid bacterial overgrowth and conversion of creatinine to creatine. A blood sample may be taken from the patient at any time during the collection period for plasma creatinine analysis.

The first and easiest test used in the assessment of renal function is usually measurement of plasma creatinine concentration. There is a wide range of normal values, reflecting the variation in muscle mass between individuals. Plasma creatinine levels are affected by a number of factors, including high-protein meals and concomitant administration of some drugs (see above). Therefore extrapolation of measured plasma creatinine levels to an estimate of GFR is difficult. Various formulae exist, the most widely accepted is that of Cockcroft and Gault:

Creatinine clearance in men =
(140 – Age) × Weight / (Plasma creatinine × 72)

Creatinine clearance in women =
(140 – Age) × Weight / (Plasma creatinine × 85)

Although incorporating the variables of age, gender and weight, these formulae have their limitations. For example, creatinine clearance is overestimated in patients who are obese or oedematous. As a rule of thumb, however, for every doubling of the plasma creatinine concentration, the GFR decreases by 50%.

Urea is the breakdown product of normal protein metabolism. In renal failure, urea is retained and its serum concentration rises. Dehydration also results in raised urea levels, but this does not necessarily reflect significant renal damage. Other factors influencing serum urea levels are shown in Figure 1. These variables can affect serum urea, therefore its measurement as an index of renal function has largely been supplanted by plasma creatinine estimation.

Factors influencing serum urea levels

Production
Increased by
- High protein diet
- Increased protein breakdown (e.g. infection, trauma, surgery)
- Glucocorticoid therapy
- Gastrointestinal bleeding
- Drugs (e.g. tetracyclines)
- Cancer

Decreased by
- Low protein diet
- Reduced catabolism (e.g. old age, hypothyroidism)
- Hepatic failure

Elimination
Increased by
- Raised glomerular filtration rate (e.g. pregnancy)

Decreased by
- Reduced renal blood flow (e.g. hypotension, dehydration)
- Glomerular disease
- Urinary obstruction

1

Plasma electrolytes: urine output and composition influence the plasma concentrations of sodium, potassium, bicarbonate and chloride. Thus, changes in plasma levels of these electrolytes may be indicators of renal function. However, the kidney also influences water balance and this must be taken into account when interpreting electrolyte results. For example, water overload is the most common cause of a low plasma sodium level in intensive care patients. On the other hand, sodium and bicarbonate retention may occur in severe illness, resulting in a low plasma chloride concentration.

Renal failure interferes with potassium excretion, resulting in hyperkalaemia. Hydrogen ion excretion is impaired, which may manifest as a low plasma bicarbonate and metabolic acidaemia.

Assessment of glomerular permeability

Healthy glomeruli largely prevent plasma proteins from entering the urine. Much of the protein that does cross the glomerulus is reabsorbed by the renal tubules, and as a result less than 150 mg/day protein is excreted via the kidneys. About 60% is derived from plasma proteins, the rest originates from the kidneys and lower urinary tract.

Urine dipsticks are the simplest and most common method of measuring urinary proteins. Urine dipsticks are sensitive to albumin and other negatively charged proteins, but are relatively insensitive to positively charged molecules, such as immunoglobulin light chains. A standard dipstick does not detect urinary proteins at a concentration less than 100–200 mg/litre (200 mg/day assuming daily urinary output of 2 litres).

Alternatives to dipstick testing involve analysis of collected urine. Overnight samples, first morning void, second morning void, random samples and spot samples have all been used. In these cases, the protein:creatinine ratio is used to correct for dilution effects. In the presence of stable renal function, a protein: creatinine ratio greater than 3.5 (mg/mg) indicates nephrotic-range proteinuria (defined as urine protein excretion over 3.5 g/day). However, the gold standard for quantifying proteinuria is the measurement of a 24-hour urine collection.

Interpretation of proteinuria should always be made with reference to renal function. As renal function deteriorates, less protein is available for filtration, and urinary protein loss falls. In the same way, low serum albumin levels result in reduced urinary albumin loss.

Assessment of tubular concentrating ability

Measurements of urine osmolality or specific gravity are used to assess the kidney's ability to conserve water by estimating the number of active particles in the urine.

Osmolality is considered a more useful measure of the kidney's concentrating ability than specific gravity because it measures the number of particles in the urine and is not greatly influenced by the presence of larger molecules (e.g. urea, glucose, proteins). The urine osmolality in normal subjects can vary from 50 to 1200 mosmole/kg depending on fluid intake, with a 'normal range' of 300–900 mosmole/kg.

The concentrating ability of the kidneys is usually assessed by an overnight fluid deprivation test and measurement of the osmolality of the first morning urine sample. A value over 850 mosmole/kg represents normal concentrating ability. In individuals with an absolute deficiency of antidiuretic hormone (ADH), or with an abnormal renal response to ADH (nephrogenic diabetes insipidus), urine osmolality seldom exceeds 300 mosmole/kg.

Specific gravity: urine specific gravity is a measure of the weight or density of dissolved particles in the urine relative to the density of water. Usually there is a close relationship between specific gravity and osmolality. However, the presence of large molecules, or of glucose or protein, upsets this relationship. For example, significant amounts of glucose in the urine (e.g. in diabetic nephropathy) increase urine density, though tubular concentrating ability may be preserved. Nevertheless, it is easy to drop a hydrometer into a urine specimen and determine its specific gravity, and this is sometimes used as a rapid assessment of urine concentration. The specific gravity of the plasma ultrafiltrate is 1.010, but the normal range for urine specific gravity is 1.003–1.035. However, the value may fall to 1.001 in patients with diabetes insipidus, and may be as high as 1.040–1.050 in patients who are excreting radiographic contrast medium.

Renal tubular acidosis (RTA) is an uncommon group of conditions that produce a metabolic acidosis in the presence of a normal anion gap. The acidosis results from renal tubular dysfunction such that chloride and hydrogen ions are retained at the expense of sodium and bicarbonate. These conditions are also referred to as hyperchloraemic acidoses. Ammonium chloride loading or fractional bicarbonate excretion tests are used in the investigation of RTA. The ammonium chloride loading test is performed to assess distal tubular RTA; the patient is given ammonium chloride, 100 mg/kg, and the urine pH measured hourly over 8 hours. In normal subjects, the urinary pH falls below 5.5 in at least one sample, whereas in cases of RTA, the pH seldom falls below 6.5. Fractional bicarbonate excretion is used in the assessment of proximal tubular RTA. Bicarbonate and creatinine concentrations are measured in urine and plasma and the fractional bicarbonate excretion is then calculated from the ratio of urine and plasma creatinine levels. In subjects with proximal RTA, the fractional bicarbonate excretion is high at 10–15%.

Urinalysis

Examination of the urine is an important step in the assessment of diseases of the urinary tract. Ideally a clean-catch midstream sample is used. Its appearance (colour, odour, turbidity) should be assessed, its specific gravity and pH determined, and it should be analysed with standard urinary dipsticks for the presence of blood, proteins, sugar and infection.

Appearance – the urine may appear darker than the usual straw colour, indicating a more concentrated urine or the presence of other pigments. For example, haemoglobin and myoglobin turn the urine a pink–brown colour. If the urine appears turbid, it may indicate the presence of infection or fat. Foaming of the urine on shaking suggests proteinuria.

Specific gravity and pH – the specific gravity provides an indication of the concentration of the urine. Urinary pH measurement is useful in patients with RTA or a history of renal stones.

Blood – the presence of red blood cells (RBCs) or free haemoglobin indicates renal or bladder disease. However, not all dipsticks can distinguish between intact erythrocytes and free haemoglobin. Therefore, any urine sample testing positive for blood should be examined microscopically for the presence of RBCs (more common than haemoglobinuria or myoglobinuria).

Proteins – standard dipsticks can detect urinary proteins at a minimum concentration of 150 mg/litre. The sticks are sensitive to albumin, but relatively insensitive to globulins or Bence-Jones proteins. If proteinuria is detected, a 24-hour urine sample should be collected and analysed for urinary protein excretion. The normal range depends on the laboratory method used, and may vary between laboratories. Most adults excrete 60–100 mg protein/day, but up to 200 mg is acceptable (300 mg/day in adolescents). The presence of proteinuria should always prompt further investigation, though postural proteinuria is accepted as a normal variant unlikely to progress to renal failure.

Microalbuminuria describes the excretion of 40–150 mg albumin/24 hours (i.e. above normal range, but below the level normally detectable by dipsticks). Microalbuminuria is an early indicator of diabetic nephropathy and it may also be a predictor of the development of nephropathy in other diseases (e.g. systemic lupus erythematosus). Kits are available to test urine samples for microalbuminuria.

Glucose – diabetes is the most common cause of glycosuria and patients who test positive for urinary glucose must be screened for the disease. However, glycosuria may also be found during pregnancy or as a result of renal tubular dysfunction.

Bacteriuria – detection of urinary nitrite indicates the presence of bacteria that degrade urinary nitrates. Leucocyte esterase in the urine indicates the presence of neutrophils. Used together, these tests are strongly suggestive of urinary tract infection if both are positive.

Microscopy – examination of the sediment from a spun sample of fresh urine normally shows the presence of a few RBCs, white blood cells (WBCs), renal cells, casts and possibly fat particles. However, an unspun, clean-catch sample is more suitable when examining for the presence of cells. More than 10 WBCs/ml^3 is abnormal in fresh urine, and indicates an inflammatory reaction within the urinary tract. Usually this represents a urinary tract infection, but sterile pyuria may be found in patients taking antibiotics or within 14 days of treatment. One or more RBCs/ml^3 of fresh unspun urine is abnormal and results in a positive dipstick test.

Casts are cylindrical bodies formed within the renal tubules and are composed mainly of renal glycoproteins. Their presence almost always indicates renal disease. They are described as hyaline, granular or cellular in appearance, depending on the material trapped inside the cast at the time of formation.

The presence of bacteria in the sediment of a clean-catch mid-stream specimen of urine is highly suggestive of infection. ◆

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Renal Failure and its Treatment

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In the UK, the annual incidence of end-stage renal failure is about 78/1,000,000 population. Many patients with acute renal failure present for anaesthesia or critical care. There are many aetiologies for renal failure, but the final pathways of loss of glomerular and tubular function are usually the same.

Acute renal failure defines an abrupt decrease in renal function sufficient to result in retention of nitrogenous waste. This accumulation leads to a range of disturbances, such as metabolic acidosis, hyperkalaemia, fluid balance problems and effects on other organs. It is associated with significant morbidity and mortality.

Chronic renal failure is usually characterized by a slow, but progressive, deterioration in measured renal function. Symptoms and signs tend to occur only when more than 60% of the total nephron mass is lost. Dialysis is not normally required until fewer than 10% of the nephrons are functioning.

Acute renal failure

Acute renal failure is a recent reversible or potentially reversible deterioration in renal function. It is a presenting feature in 1% of patients admitted to hospital and affects 2–5% of patients during their hospital stay. It is a major cause of death during acute illness especially in the ICU.

Causes

The causes of acute renal failure are generally multifactorial but are classified as prerenal, renal or postrenal (Figure 1). Prerenal and postrenal causes should be excluded as soon as possible because they are treatable but precipitate intrinsic renal disease if left uncorrected.

Causes of acute renal failure

Prerenal
Total body water depletion
- Haemorrhage
- Gastrointestinal losses
- Renal loss
- Skin loss

Volume redistribution
- Third spacing of fluid – isotonic transfer of fluid from the extracellular fluid to a non-functional interstitial compartment (e.g. pancreatitis, ascites)
- Increased vascular capacity (e.g. sepsis, anaphylaxis)

Decreased cardiac output
- Left-sided heart failure
- Right-sided heart failure
- Valvular heart disease
- Pericarditis, tamponade

Renal
Glomerular
- Primary (post-streptococcal, rapidly progressive glomerulonephritis)
- Secondary (systemic lupus erythematosus, vasculitis, endocarditis)

Tubulointerstitial
- Ischaemic (acute tubular necrosis)
- Nephrotoxin (aminoglycoside, radiocontrast)
- Allergic interstitial nephritis (drug induced)
- Interstitial nephritis (immune complex, non drug induced)
- Metabolic toxin (uric acid, calcium)
- Heavy metal (cis-platinum)

Vascular
- Atheroembolic
- Small vessel disease (scleroderma, malignant hypertension, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura)

Postrenal
- Obstruction in the urinary collection system

1

Prerenal causes result from renal hypoperfusion, usually from decreased intravascular volume. The decrease in renal blood flow leads to a fall in glomerular filtration rate (GFR). The kidney retains water and sodium to compensate, causing oliguria, and produces concentrated urine with a progressive inability to excrete nitrogenous waste. If left uncorrected, the reduction in renal blood flow damages the renal tubules and acute tubular necrosis develops. When this occurs, the kidney loses its ability to produce concentrated urine and the small volume of highly concentrated urine that was being produced becomes increasingly dilute.

Renal causes: intrinsic parenchymal renal disease is classified according to the site of injury (Figure 1). Glomerular disease is thought to be immunologically mediated and results in disrupted glomerular filtration. Continuing inflammation leads to glomerulus destruction.

Interstitial nephritis accounts for less than 10% of acute renal failure. It is a complex collection of inflammatory diseases. Drugs are the most common cause.

Acute tubular necrosis (ATN) accounts for 85% of renal causes of acute renal failure and 75% of all cases of acute renal failure. It is essential to differentiate between ATN and prerenal causes for correct management (Figure 2). The most common causes of ATN are renal hypoperfusion or ischaemia, chemical toxicity, trauma or sepsis. Nephrotoxins include analgesics (e.g. aspirin, non-steroidal anti-inflammatory drugs (NSAIDs)), aminoglycosides, immunosuppressive agents, contrast media and heavy metals. The thick ascending limb of the loop of Henle is particularly predisposed to injury because it is situated in the medulla, which receives only a small proportion of the total renal blood flow (in order that the concentration osmolality gradient is maintained). The active ion pumps in the loop of Henle are high oxygen consumers and the area is vulnerable to ischaemia.

Differentiating causes of acute renal failure

Test	Prerenal causes	Acute tubular necrosis
Urinalysis	Normal	Granular cell casts
Urine osmolality (mosmole/kg)	> 500	< 350
Urine sodium (mmol/litre)	10–20	> 20
Urine urea (mmol/litre)	> 250	< 150
Fractional sodium excretion	< 1%	> 1%

2

The tubular response to injury is not aetiology specific. The result is a rapid decline in renal function, which may require dialysis or haemofiltration. The two histological changes that can occur are:
- tubular necrosis with sloughing of the epithelial cells
- occlusion of the lumina by casts and cellular debris.

Other factors involved, in addition to the tubular obstruction, include backleak of filtrate across the tubular epithelia and a reduction in glomerular filtration. Histological changes may be patchy and appear mild compared with the severity of the resulting renal dysfunction.

Postrenal causes are always associated with obstruction (mechanical or functional) in the urinary collection system. Examples include bladder tumour, prostatic hypertrophy and ureteric stones. Ultrasound examination detects most cases.

Diagnosis

Diagnosis relies on a good history and examination, as well as laboratory tests and imaging.

History and examination indicate the likely cause of the renal failure. It is also important to review previous notes. The history should cover:
- nausea, vomiting or diarrhoea
- bleeding
- heart failure
- previous renal insufficiency
- oedema, hypertension or change in urine colour
- rashes
- what medications are being or have been taken?
- prolonged episodes of hypotension
- any radiocontrast dye?
- stones or other urinary obstruction
- nephrotoxic drugs (e.g. NSAIDs).

In a critical care setting, oliguria may be the first indicator of imminent renal failure. Physical examination is useful for assessing the volume status of the patient. Concentrated urine suggests prerenal renal failure. Signs of systemic disease should also be sought.

Urinalysis: laboratory tests begin with urinalysis (Figure 3). Protein +3 or 4 on dipstick testing suggests intrinsic renal disease with glomerular damage. Prerenal, ATN or postrenal causes of renal failure produce less protein in the urine. Microscopy can be used to examine the sediment from a centrifuged urine sample. Casts are formed from urinary Tamm-Horsfall protein, produced by tubular epithelial cells and reflect the content of the tubule.
- Hyaline casts are devoid of content, and are seen with dehydration, after exercise or associated with glomerular proteinuria.
- Red cell casts indicate glomerular haematuria (e.g. glomerulonephritis).
- White cell casts imply inflammation in the renal parenchyma (e.g. interstitial nephritis).
- Granular casts are composed of cellular remnants and debris.
- Fatty casts are usually associated with heavy proteinuria and nephritic syndrome.

In patients with prerenal and postrenal acute renal failure, the sediment usually lacks casts, cells or debris.

Results of urine analysis

	Urinary sediment	Proteinuria	Specific gravity
Prerenal	Generally benign sediment, few hyaline or granular casts	Trace	Increased
Intrarenal			
• Acute glomerulonephritis	RBCs with casts, WBCs with casts, granular casts, fatty casts	++++	Increased
• Acute tubular necrosis	Renal tubular cells and casts, course granular and pigmented granular casts	++	1.010–1.012
• Acute interstitial nephritis	RBCs, WBCs, WBC casts, renal tubular cells	++	1.010–1.012
Postrenal	Benign sediment	Trace	Increased early

3

Urine osmolality: the kidney can concentrate urine to a maximum osmolality of 1400 mosmole/kg. Dilute urine may have an osmolality as low as 30–60 mosmole/kg. The ability to produce concentrated urine depends on having intact, functioniong tubules. If there is tubular damage (e.g. ATN) the urine is relatively dilute, typically 300–350 mosmole/kg.

Urine sodium concentration: urinary sodium excretion reflects the ability of the nephron to retain filtered sodium (Figure 4). When the GFR is reduced, the tubule avidly reabsorbs sodium and water and sodium clearance is low. If the tubule is damaged, a high concentration of sodium passes into the urine. The fractional excretion of sodium (FENa) is the percentage of filtered sodium excreted in the urine:

$$\text{FENa} = \frac{\text{Urine sodium}}{\text{Urine creatinine}} \times \frac{\text{Plasma creatinine}}{\text{Plasma sodium}} \times 100$$

In prerenal failure and acute glomerulonephritis, when tubular function is retained, FENa is less than 1%. In disease processes affecting the tubule it is usually greater than 2%. Assessment of FENa can be misleading because some causes of ATN (e.g. dye-induced, rhabdomyolysis, haemolysis) may have a low FENa and patients with prerenal acute renal failure taking diuretics may have a high FENa.

Urine and serum diagnostic indices

	Prerenal	Renal	Postrenal
Urine sodium (mEq/litre)	< 20	> 20	> 20
Urine chloride (mEq/litre)	< 20	> 20	< 20
Fractional excretion of sodium	< 1%	> 2%	> 2%
Urine osmolality (mosmole/kg)	> 500	< 350	< 350
Urine/serum creatinine (mmol/litre)	> 40	< 20	< 20
Urine/serum urea (mmol/litre)	> 8	< 3	< 3

4

Serum creatinine and urea levels: creatinine is produced from the breakdown of muscle mass. The serum creatinine concentration is a function of the amount of creatinine entering blood from the muscles, its volume of distribution and rate of excretion. The first two factors are usually constant, therefore changes in serum creatinine are usually caused by changes in its rate of excretion.

Creatinine rises by 1–2 mg/dl/day in acute renal failure. Serum urea also rises but is a less reliable indicator of renal function because there are other causes of elevated urea (e.g. increased protein intake, gastrointestinal bleeding, enhanced catabolism). Other biochemical abnormalities in acute renal failure include metabolic acidosis, hyperkalaemia, hypermagnesaemia, hyperphosphataemia and hypocalcaemia.

Radiology: an intravenous pyelogram gives a good anatomical picture of the kidney, but no assessment of function. Ultrasound is highly portable and has no associated morbidity. Both investigations may identify or exclude obstruction to the renal tract and provide information about kidney size.

Prevention

Acute renal failure can often be prevented by attempting to maintain normal fluid balance, blood pressure and blood volume in patients at risk. These include patients who have undergone major surgery, burns or haemorrhage especially if they have some pre-existing renal impairment. If acute renal failure becomes established, accurate diagnosis is essential. Renal rescue therapy may avoid the onset of renal failure. Many cases of renal failure have a prerenal element and therefore renal blood flow and oxygen delivery must be optimized. Untreated prerenal failure precipitates ATN.

Maintenance of oxygen delivery – the first steps in preventing and treating prerenal failure are to exclude or treat hypoxia and optimize the circulating blood volume. This may require monitoring the right or left atrial pressure or other ways of assessing volume status. Low cardiac output states associated with normovolaemia may require inotrope therapy. Severe anaemia may impair renal oxygen delivery despite adequate renal perfusion.

Autoregulation – under normal circumstances, autoregulation determines that renal blood flow remains fairly constant over a range of mean arterial pressures. In disease states, autoregulation may be impaired and the renal perfusion pressure becomes more critical. Vasoconstrictors (e.g. noradrenaline) may increase urine output by increasing perfusion pressure. Noradrenaline also increases efferent arteriolar resistance more than on the afferent side, thus increasing the filtration fraction.

Furosemide (frusemide) infusion inhibits sodium reabsorption in the thick ascending loop of Henle by decreasing the activity of the Na^+-K^+-$2Cl^-$ cotransporter. It also stimulates vasodilator prostaglandins thereby increasing afferent arteriolar flow. However, there is little evidence that it prevents renal failure and it may increase the volume of urine produced with little or no effect on the failing kidney's ability to remove waste products. Increasing urine volume may decrease the need for haemofiltration or dialysis as a result of fluid overload.

Dopamine infusion increases the fractional sodium excretion and urine output, but not creatinine clearance. Its primary effect was thought to be an increase in renal blood flow mediated by dopamine receptors. However, it probably increases urine production by increasing cardiac output and therefore renal blood flow by its actions as an inotrope. In patients already receiving inotrope therapy it has no effect on renal blood flow. It has not been demonstrated to prevent the onset of acute renal failure. Side-effects include nausea, gastric stasis, inhibition of anterior pituitary hormones and depression of hypoxic drive.

Mannitol is thought to decrease tubular swelling, though there is little evidence. It is advocated by some in high-risk surgery (e.g. open heart surgery). Recent evidence suggests it may potentiate acute renal failure associated with radiocontrast administration.

Avoidance of nephrotoxins – nephrotoxic drugs (e.g. aminoglycosides, NSAIDs) should be avoided in all patients at increased risk of acute renal failure. This may include the elderly, those with pre-existing renal dysfunction and patients with circulatory impairment or hypotension.

Treatment

Renal blood flow and oxygen delivery should be optimized (see above) in all patients with acute renal failure, especially if the initial cause had a prerenal component. If there was an element of congestive cardiac failure, diuretics may be useful because they decrease afterload and so may increase renal perfusion. In liver failure, diuretics (e.g. spironolactone) or paracentesis may have a role.

There is no specific treatment for ATN, the most common renal cause of acute renal failure. All drugs with any degree of nephrotoxicity should be stopped. Nutritional and circulatory status should be optimized and sepsis treated. In some situations, oliguric ATN can be converted into non-oliguric ATN with diuretic therapy, which may have advantages regarding fluid balance and the requirement for dialysis or haemofiltration. There is little evidence that diuretic therapy influences long-term outcome despite non-oliguric ARF having a better outcome than oliguric renal failure.

Acute glomerulonephritis may respond to immunosuppressant drugs and/or plasmapheresis. In acute interstitial nephritis, removal of the offending allergen and treatment with corticosteroids may improve the outcome.

In postrenal failure, the obstruction to the flow of urine must be relieved. Treatment depends on the level of obstruction and varies from urinary catheter to percutaneous nephrostomy. There is often a secondary element of infection.

Renal replacement therapy

Renal replacement therapy may be required if conservative treatment fails. The three choices are peritoneal dialysis, intermittent haemodialysis and continuous haemofiltration/haemodiafiltration. Absolute indications for dialysis include:

- life-threatening hypoxia caused by fluid overload
- life-threatening systemic acidosis
- hyperkalaemia
- lethal drug overdoses that are better cleared by dialysis (e.g. lithium, theophylline)
- uraemia causing confusion, coma or pericarditis.

Relative indications for dialysis include:

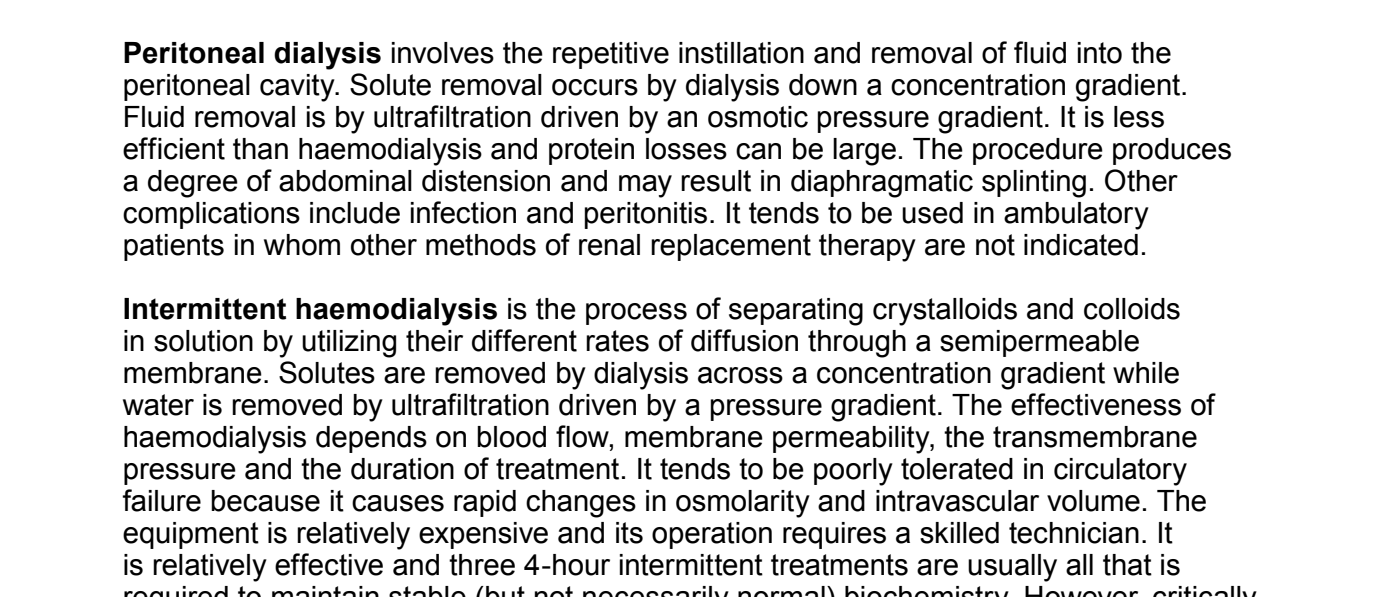
- blood urea nitrogen over 100 mg/dl
- platelet dysfunction causing bleeding
- fluid overload.

Peritoneal dialysis involves the repetitive instillation and removal of fluid into the peritoneal cavity. Solute removal occurs by dialysis down a concentration gradient. Fluid removal is by ultrafiltration driven by an osmotic pressure gradient. It is less efficient than haemodialysis and protein losses can be large. The procedure produces a degree of abdominal distension and may result in diaphragmatic splinting. Other complications include infection and peritonitis. It tends to be used in ambulatory patients in whom other methods of renal replacement therapy are not indicated.

Intermittent haemodialysis is the process of separating crystalloids and colloids in solution by utilizing their different rates of diffusion through a semipermeable membrane. Solutes are removed by dialysis across a concentration gradient while water is removed by ultrafiltration driven by a pressure gradient. The effectiveness of haemodialysis depends on blood flow, membrane permeability, the transmembrane pressure and the duration of treatment. It tends to be poorly tolerated in circulatory failure because it causes rapid changes in osmolarity and intravascular volume. The equipment is relatively expensive and its operation requires a skilled technician. It is relatively effective and three 4-hour intermittent treatments are usually all that is required to maintain stable (but not necessarily normal) biochemistry. However, critically ill patients may develop arrhythmias, increased intracranial pressure (ICP) and/or haemodynamic instability during intermittent therapies. This may be related to the significant extracorporeal blood volume or rapid fluid, electrolyte, or osmolality shifts during a 2–4-hour intermittent therapy.

Continuous renal replacement therapies have many advantages over intermittent therapies. The slow and continuous fluid and solute removal during continuous renal replacement therapy results in less haemodynamic instability and less acute changes in ICP. The basis of this treatment is haemofiltration, a convective clearance method to which haemodialysis may be added to improve the efficiency with which waste products are cleared. Blood may be taken from the arterial side and returned to the venous side (CAVH, continuous arterio-venous haemofiltration) using arterial pressure as the driving force for haemofiltration. Modern equipment tends to employ continuous veno-venous haemodialysis or diafiltration in which electric pumps remove blood from and return it to the venous circulation. Venous access is obtained in a large central vein using a cannula with two lumens (Figure 5).

Continuous venovenous haemodiafiltration circuit



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Whichever method is used, blood is taken to an extracorporeal circuit and the removal of solutes occurs by ultrafiltration. Fluid volume is replaced as required with a balanced electrolyte solution. Haemofiltration is effective at removing fluid but less so at removing waste solutes. Urea clearance is proportional to the filtration rate and blood flow. Dialysate can be passed countercurrent to blood flow to add a degree of dialysis and improve the efficiency of solute removal. With haemodiafiltration, urea removal is improved and its clearance becomes proportional to dialysate flow rate but independent of blood flow.

Possible problems

Anticoagulation – anticoagulants are required to prevent blood clotting in the filter and extracorporeal circuit. Heparin, low molecular weight heparin or epoprostenol are commonly used.

Dialysate solutions – acetate has now been replaced by lactate as the buffering agent used most commonly in dialysate solutions. They can both accumulate in patients with liver dysfunction, when their metabolism to bicarbonate is impaired. Under these circumstances, metabolic acidosis may worsen. The ideal buffering agent is bicarbonate, but it is unstable in solution and therefore more difficult to prepare.

Nutrition – ensuring adequate nutrition can be a problem, because amino acids are lost across filters. Patients require nitrogen and essential amino acids, preferably via the enteral route.

Drug clearance – the drug dose may require adjustment at the beginning of renal replacement therapy. Some drugs are cleared effectively by dialysis and haemofiltration depending on their molecular size, degree of protein binding and membrane adherence. Other drugs (e.g. ACE inhibitors) are not cleared at all.

ICU: there are no guidelines to indicate when supportive dialysis or haemofiltration should begin for patients with acute renal failure in the ICU. In most patients, the onset of acute renal failure represents a part of multi-organ dysfunction. Acute renal failure in the ICU is most commonly associated with ATN and therefore is potentially reversible, but the overall pathology is often overwhelming. Decisions regarding the commencement of renal replacement therapy must therefore take into account the whole picture and an experienced clinician must assess the likelihood of a successful outcome. Renal replacement therapy can complicate treatment, because of the potential hazards of dialysis catheter placement and the use of anticoagulants. However, by providing a mechanism for the easy removal of fluid it can solve fluid balance problems and 'create room' for enteral or parenteral nutrition.

Chronic renal failure

Symptoms and signs

Chronic renal failure is irreversible and may follow an episode of acute renal failure. It may result from any major cause of renal dysfunction, though the most common causes are glomerulonephritis and diabetic nephropathy. The progress of chronic renal disease is often slow, with symptoms and signs occurring only when more than 60% of the nephron mass is lost. As the disease progresses, anaemia and uraemia develop. Uraemia initially presents with malaise, lethargy and decreased mental acuity. Patients may experience nocturia as they lose their ability to produce concentrated urine. Plasma creatinine and urea concentrations rise in a non-linear way as GFR diminishes. To begin with, this rise is minimal, but once GFR is below 6 ml/min, the rise is rapid with systemic uraemia.

Neuromuscular symptoms of uraemia include twitching, peripheral and autonomic neuropathies, confusion, convulsions and ultimately coma. Anorexia, nausea, vomiting and diarrhoea are also common. Malnutrition leads to muscle wasting. Gastrointestinal ulceration and bleeding occur later in the disease process. 80% of patients develop hypertension due to increased renin–angiotensin activity, sodium and water retention and secondary hyperaldosteronism. Cardiomyopathy, ischaemic or hypertensive, and congestive cardiac failure occur leading to generalized oedema. Pericarditis can develop secondary to uraemia.

The skin is thin with poor healing. It may become pigmented and the patient may develop pruritus. Renal osteodystrophy and hyperparathyroidism, as well as osteomalacia, can occur. Normochromic, normocytic anaemia develops as a result of decreased erythropoietin production, shortened RBC survival and marrow depression. Hyperkalaemia and a chronic moderate metabolic acidosis usually signify end-stage renal failure.

Prognosis and treatment

Prognosis and treatment depend on the cause of the renal failure. Good control of blood glucose and arterial blood pressure reduces the rate of deterioration in GFR.

Diet – careful diet control is needed. Dietary protein must be reduced and calorie intake increased. Vitamins are necessary because of dietary restrictions. Dietary phosphorus is given to delay secondary hyperparathyroidism in early renal failure, but in later disease, phosphate-binding calcium salts are needed to achieve lower serum phosphate. Hypertriglyceridaemia is common and requires dietary control, because fibric acid derivatives can cause rhabdomyolysis.

Fluid and electrolyte balance – water intake is restricted if serum sodium is not in the normal range. Sodium is not restricted unless there is oedema or hypertension or congestive cardiac failure when diuretics can also be used.

Anaemia – erythropoietin and iron can be given.

Dialysis or transplantation is given if conventional therapy fails, or the underlying disease process is untreatable.

Anaesthesia

Effects on renal function

All general anaesthetic agents depress renal function. The type of procedure being undertaken, the duration of surgery, and the preoperative fluid status affect how much function is reduced. The changes to renal function are normally transient and resolve completely postoperatively.

Direct effects – toxicity may arise from volatiles as a result of alteration in renal concentrating capacity induced by fluoride ions. The link between halogenated anaesthetics and nephro-toxicity was established in 1970 and is related to free fluoride ions at a plasma concentration of 50 μmol/litre. It produces high output renal failure, which resolves after 10–20 days. Enflurane and sevoflurane may reach nephrotoxic levels but are eliminated so rapidly that the total amount of fluoride exposure is low.

Indirect effects – all anaesthetics reduce GFR and intraoperative urine flow. This is secondary to regional and systemic haemodynamic changes, alterations in the renin–angiotensin–aldosterone axis, and antidiuretic hormone release.

Anaesthesia in renal failure

The preoperative assessment should look for cardiovascular complications of renal disease, fluid and electrolyte balance and acid–base derangements. Autonomic neuropathy is associated with an increased risk of gastric aspiration and should be sought. Anaemia of renal failure seldom requires preoperative transfusion. Preoperative dialysis may be needed. Careful fluid balance is needed intraoperatively, with avoidance of potassium-containing fluids. A regional technique may be suitable.

Influence of renal disease on anaesthetic drugs

Changes in the pharmacokinetics of drugs in patients with renal failure result from changes in drug protein binding, altered drug elimination and altered cellular hepatic metabolism.

Intravenous anaesthetic agents: most anaesthetic agents are metabolized in the liver and excreted renally, and are considered safe in renal failure. Often the initial dose is decreased by 25–50% and the response noted as a guide to further treatment. Uraemia alters hepatic metabolism, increasing mixed function oxidase activity, therefore most drug metabolism is normal or increased in renal failure. Uraemia causes decreased plasma protein binding and CNS depression, therefore drugs causing further CNS depression should be avoided. Thiopental (thiopentone) causes prolonged anaesthesia in renal failure owing to the depressant effect of uraemia and decreased protein binding, leaving more unbound thiopental (thiopentone) available for effect. Propofol is safe, though dose reduction is advised because of the profound hypotension that can occur in renal failure patients. Etomidate may be a good alternative.

Opioids can be used; fentanyl is safe and has no active metabolites, but morphine does and should be avoided. Suxamethonium is safe if there is no hyperkalaemia or peripheral neuropathy. The rise in potassium is the same in renal failure as in normal renal function (0.5 mEq/litre).

Non-depolarizing muscle relaxants should be used carefully (Figure 6). Atracurium is a good choice because it is not eliminated renally. Its duration of action is the same in renal failure as in normal renal function. Pancuronium should be avoided and vecuronium used with care.

The dependence of non-depolarizing muscle relaxants on renal excretion for elimination

Elimination	Drug
60–90%	Pancuronium
25–60%	Tubocurarine
< 25%	Vecuronium, atracurium, suxamethonium, mivacurium

6

Inhalational agents: some volatile agents are degraded to renally excreted metabolites, which may have toxic effects. However, they do not rely on kidney function for reversal and so are considered safer in renal failure than intravenous agents.

Isoflurane has low peak fluoride levels and is safe, desflurane has no renal toxicity and halothane is not metabolized to fluoride. Enflurane and sevoflurane have the highest fluoride levels. Sevoflurane also degrades in soda lime to form compound A, which is nephrotoxic in rats. There is no evidence to support this in humans, and sevoflurane and enflurane are safe in renal failure.

Others: antihypertensives must be carefully titrated, because blood pressure can be labile in renal failure. Esmolol and labetalol are metabolized extrarenally and are safe to use. Sodium nitroprusside has a toxic metabolite, thiocyanate, which can accumulate in renal failure. Vasopressors may cause a decrease in renal perfusion. ◆

FURTHER READING

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Statistics

Anaesthesia
and intensive care medicine
on CD-ROM

Statistics

Ian Kestin

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Statistics are the tools used to describe and analyse numbers. The complete data set from a study may comprise many thousands of observations and it is impractical to give the full results in a published paper. Descriptive statistics are used to summarize this numerical information.

Types of data

There are three main types of data obtained in a research project and the type determines the methods used to describe and analyse the data.

Categorical (nominal) data: each of the subjects in the study is allocated to one of two or more mutually exclusive categories such as gender (male, female), blood group (A, B, AB, O), or social class. The categories have no ranking or numerical relationship to each other.

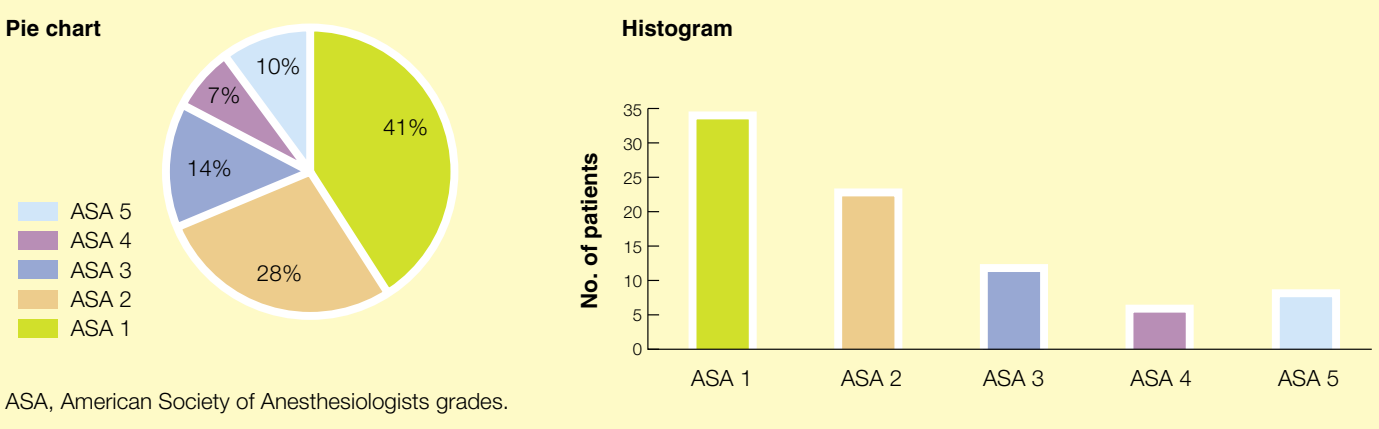
Ordinal data (ordered categories or ranked data): each of the subjects in the study is allocated to one of several mutually exclusive categories, and these categories have an intrinsic ranking or ordering. Examples are grades of oedema (mild, moderate, severe), or ASA scores (1–5). The categories may be numbered, but the numbering defines only the ordering of the categories, and does not 'scale' the relative magnitude of one category to another. For example, patients with head injuries are allocated using the Glasgow Coma Score (GCS) to one of 13 possible categories denoted by a whole number between 3 and 15. A patient with a GCS of 4 is worse than a patient with a GCS of 8, but is not 'twice as bad', whereas a patient with a weight of 80 kg is exactly twice as heavy as one with a weight of 40 kg. Misusing ordinal data by treating the numbers as if real measurements had been made is a common mistake.

Numerical data describe the actual numerical properties of the subjects. The measurements can be discrete or continuously variable. Discrete numerical data can take only certain values, usually integers (e.g. number of children, hospital deaths per year); continuously variable data can theoretically take any numerical value, but usually within a certain range (e.g. heart rate, weight).

Descriptive statistics

Descriptive statistics are required to summarize large data sets. Categorical data are easily described by histograms or pie charts; a visual illustration of the data clearly shows the frequency of the categories (Figure 1).

Two methods of illustrating the frequency distribution of categorical or ordinal data



ASA, American Society of Anesthesiologists grades.

1

Two essential properties describe ordinal or numerical data:

- the central location – where the bulk of the observations lie
- the variability – how closely the observations are clustered about the central location.

The central location of a series of observations is usually described using the mean, median or mode (Figure 2). Misuse of the mean is a common error, which properly should be used only with continuously variable numerical data. For ordinal data the median or mode must be used (e.g. it is wrong to quote a mean GCS of 7.5).

Common measures of central location

Measure of central location	Type of data	Definition
Mean	Continuously variable	Sum of all observations/number of observations
Median	Ordinal and numerical	The observation with half the observations above and half below (i.e. 50th percentile)
Mode	Ordinal and numerical	The most commonly occurring observation

2

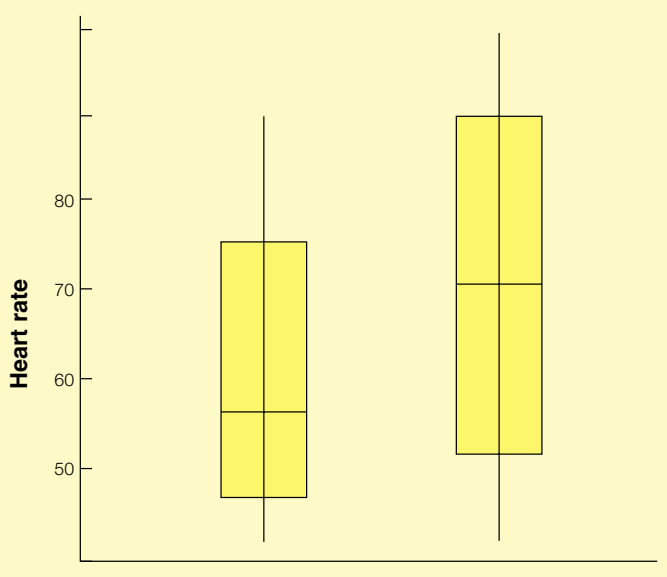
The variability can be described by the range, percentiles or the standard deviation.

The range gives the maximum and minimum values of the observations and is useful if there is some particular interest in the maximum or minimum response (e.g. the lowest respiratory rate recorded would be of clinical importance in patients given opiates). However, the range can give a misleading impression of the variability if there are single extreme results in the data.

A percentile is that observation which is greater than the appropriate percent of all the observations in the data set, so the 10th percentile is the observation that is greater than 10% of all the observations, the median is the 50th percentile, and the 90th percentile is the observation that is greater than 90% of the observations. Commonly used percentiles are the interquartile range (the 25th to 75th percentile), and the 2.5th to 97.5th percentile (containing 95% of the observations). Percentiles can be used for any type of data.

The standard deviation is applicable only to data that are continuously variable and normally distributed (see later). A common graphical way of summarizing information is the 'box and whisker' plot (Figure 3).

Box and whisker plot of heart rate after two different drugs



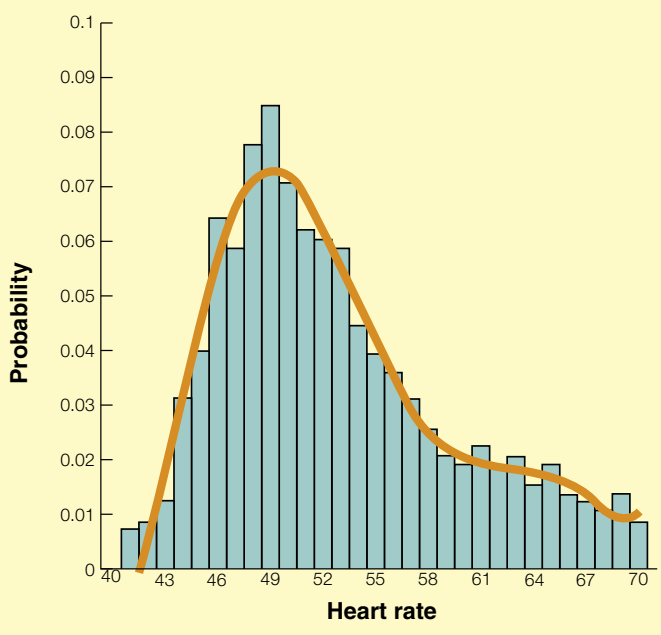
The horizontal line shows the median, the 'box' shows percentiles, commonly the 2.5th to 97.5th, and the vertical line shows the range of the sample data

3

Frequency distribution curves

A graph showing the probability of obtaining any particular observation is called a frequency distribution (Figure 4).

Frequency distribution

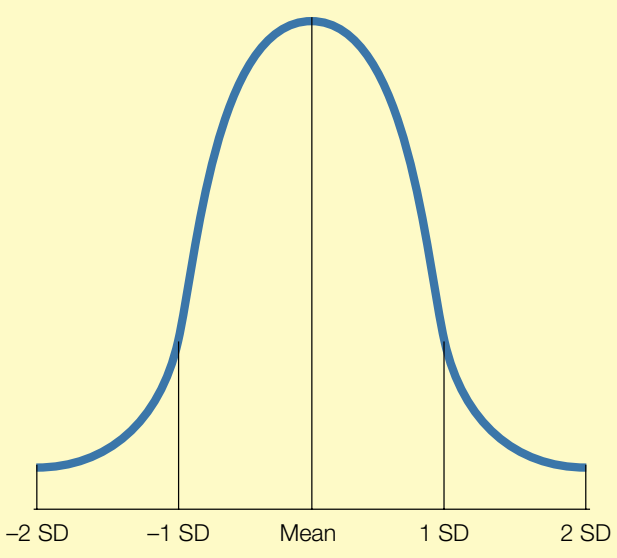


The heart rates of patients after an intravenous opiate have been measured. The probability of obtaining any given heart rate is shown by the histogram. As more patients are studied, the histogram can be replaced by a continuous curve

4

Normal distribution is a specific frequency distribution pattern that is common in biological data for which many statistical tests have been designed (e.g. t-test, analysis of variance). The central location can be described by the mean (which is the same as the mode and median), and the variability is described by the standard deviation. Multiples of the standard deviation about the mean always contain the same proportion of the observations (Figure 5). Not all symmetrical frequency distributions are normal (Figure 6).

Characteristics of a normal distribution



Calculation of sample parameters

Sample mean = $\Sigma_{x/n}$

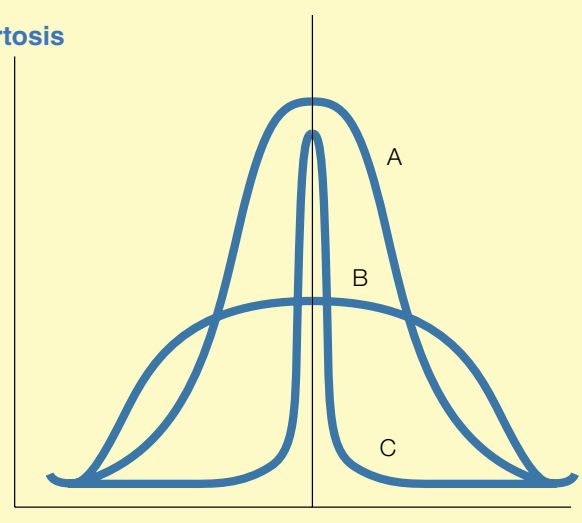
Sample standard deviation = $\sqrt{\frac{\Sigma(x - \bar{x})^2}{n - 1}}$

Mean ± 1 SD 67% of observations
Mean ± 2 SD 95% of observations
Mean ± 3 SD 99% of observations

SD, standard deviation

5

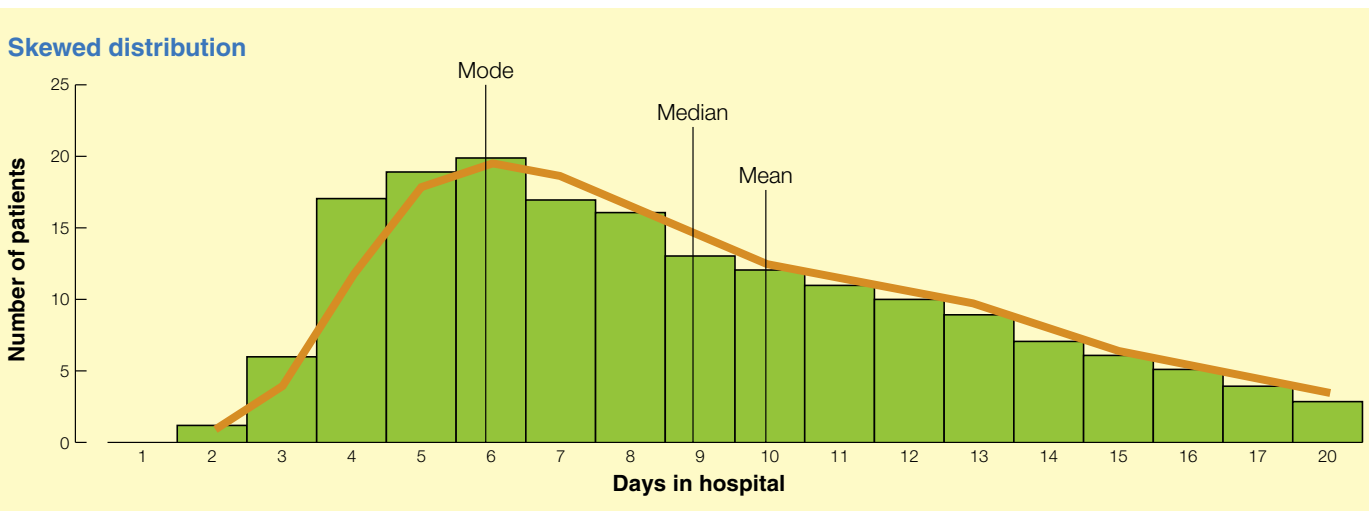
Kurtosis



Not all symmetrical frequency distributions are normal; the curve may be flatter or more peaked than the normal distribution. Plot A is a normal distribution. Plots B and C show symmetrical distributions that have a broader (platykurtic) or more narrow (leptokurtic) distribution than the normal distribution. A bimodal distribution is an extreme example of a platykurtic distribution

Skewed distributions are a common pattern in biological data, when the frequency distribution curve is not symmetrical (Figure 7). The frequency of hospital stay after an operation is commonly skewed most patients have similar lengths of stay, but some have complications and stay longer. This is an example of positively skewed data; negatively skewed data would be the reverse pattern and are less common. The mean, median and mode are all different for skewed data. If the single largest observation in the sample is increased, the mean increases, but the median and mode are unchanged; thus the median or mode are better indicators of the central location of a skewed distribution. As a rough estimate, if the standard deviation of a sample is more than half the mean, then the data are probably skewed.

Skewed distribution



Length of stay in hospital after surgery is an example of a positively skewed distribution. The mode is 6 days, the median is 9 days, and the mean is 10 days

Skewed data can often be mathematically transformed to conform to a normal distribution. Taking logarithms of a sample that is positively skewed usually produces a data set that is approximately normally distributed, and then techniques designed for the normal distribution can be used on the transformed data. The alternative is to use statistical tests designed for any data. If the data are transformed, care must be taken when reversing transformations back to the original units – confidence intervals can be reverse transformed, but not the standard deviation (the confidence limits will not be symmetrical about the mean). There are methods of testing if data conform to a normal distribution (e.g. the Shapiro-Wilk W test), and these ought to be carried out before using statistics designed for the normal distribution. Statistical techniques that use assumptions about the underlying distribution of the data (nearly always a normal distribution) are called parametric statistics. Techniques to describe and analyse data that make no assumptions about the underlying distribution of the sample or population data are called non-parametric statistics, and can be used on any type of data. Most of these tests are called rank sum tests; all the sample data are sorted in order and assigned a ‘rank’, and then the significance test compares the ranks of the data from different groups.

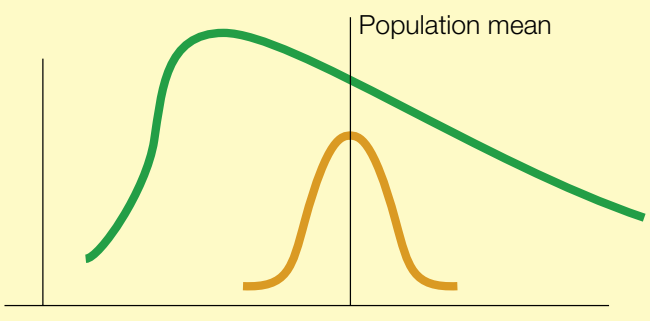
In practice, parametric statistics are reasonably reliable if used for continuously variable data that are not normally distributed provided the deviation is not too extreme. Parametric statistics should never be used for ordinal data, but non-parametric statistics can be used for all data, including the normal distribution. When the data are normally distributed, it is better to use the parametric tests specifically designed for the normal distribution.

Inferential statistics

Inferential statistics are used to infer properties about a wider population of subjects beyond those studied. These inferences are always made with some uncertainty because it is never known how representative the sample is. This uncertainty is measured by probabilities that measure the degree of confidence of the conclusions about the wider population.

The central limit theorem is the basis of much inferential statistics. This states that if several samples are taken from a population, then the means of these samples are distributed normally around the true population mean. The standard deviation of this normal distribution of the sample means is called the standard error of the mean (SEM). This is true even if the variable is not distributed normally in the population, provided that the samples are sufficiently large (Figure 8).

Central limit theorem



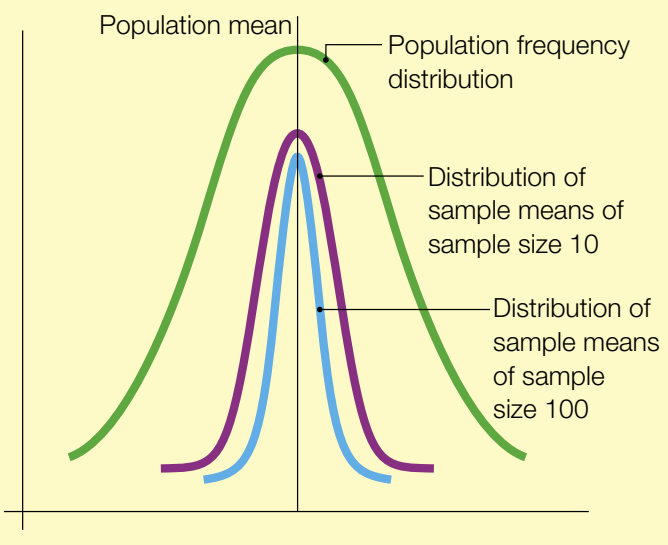
Frequency distribution of population

Distribution of means of samples size n from population. The SD of this distribution is the SEM. As n increases, the SEM decreases

The mean of samples taken from the population is distributed normally about the population mean.
SD, standard deviation; SEM, standard error of the mean

If the variable is distributed normally within the population (unlike Figure 8, where the population data are positively skewed), then we can further obtain an estimate of the SEM from the sample standard deviations (Figure 9).

Relationship of sample size and SEM



Standard error of the mean (SEM) = $s/\sqrt{n}$, where s is the standard deviation of the sample and n is the number of subjects in the sample

Using the properties of the normal distribution, an estimate of the true population mean can then be obtained from the sample mean. We can be 95% confident that the true population mean lies within the range

$$\bar{x} \pm (2 \times SEM)$$

where x is the sample mean. This range is called the 95% confidence interval for the true population mean. If we had 100 different samples, we could obtain 100 different estimates of this range; in about 95 of these, the true population mean would be within this range and in about 5 it would not lie within this range. In practice, we usually have only one sample, and we do not know if this is one of the 5% of occasions when the true population mean is outside the calculated range.

As n increases, the SEM decreases, and the 95% confidence intervals for the true population mean are narrower. Intuitively, large samples are more representative of the whole population, and the sample means of large samples are more closely clustered about the true population mean than those of small samples.

We have therefore used our sample and the central limit theorem to infer properties about the unknown parent population from which the sample was obtained. This introduces the concepts of assumptions (the assumptions that allow us to use the central limit theorem), of probabilities (the true population mean is 95% probable to lie within the calculated range) and of inferential errors (we make conclusions based on probability not certainty). Our application of statistics may be completely correct, but our conclusions can still be wrong!

Hypothesis testing

One of the main uses of statistics in medicine is to decide if the data from a clinical trial represent a real difference between treatments or could have arisen by chance – this is hypothesis testing.

For example, a clinical trial has been completed and the heart rates have been recorded in two groups of patients treated with drugs A and B. Our samples are drawn from two hypothetical populations; population A, all patients (similar to those in the study given drug A) who are or could be taking drug A, and population B, all patients (similar to those in the study given drug B) who are or could be taking drug B. We do not know how representative our samples are of these two populations. All statistical tests calculate a probability or confidence limits that the sample results could have been obtained if populations A and B did not differ. The logical stages in hypothesis testing are as follows.

- Form a null hypothesis. This states that the frequency distribution of heart rates in population A is the same as that in population B. The alternative hypothesis is that populations A and B have different frequency distributions.
- Choose the appropriate statistical test. In this case, we have continuously variable data that are usually normally distributed, so we can use a t-test.
- Obtain the *p* value. The statistical test uses the actual heart rates of our samples to calculate the probability (the *p* value) that we could have obtained our sample data if the null hypothesis were true (i.e. if the samples had been obtained randomly from a single population).
- Accept or reject the null hypothesis. Conventionally, a probability of 0.05 (5%) is chosen as the cut-off for the *p* value as sufficiently unlikely that we can reject the null hypothesis. This value is called the level of statistical significance, and can be chosen at a lower value (e.g. 0.01 or 1%) if we wish to make our conclusions less likely to be wrong. A higher value than 0.05 is seldom used. If *p* is less than 0.05, we conclude drugs A and B have different effects on the heart rate. If *p* is greater than 0.05, then there is a reasonable probability that we could have obtained these results because populations A and B are the same, and we conclude that drugs A and B do not have different effects. Both of these conclusions may be wrong. This pattern of reasoning is common to all clinical trials using inferential statistical tests for hypothesis testing for differences between groups in the study (Figure 10).

Choice of statistical test

The choice of statistical test is determined by the type of data and the number of groups; the most common statistical tests used in medical research are listed in Figure 11. In some studies, each subject in one group is uniquely paired with one in the other group(s). For example, if a variable is measured in the same individual before and after an intervention, then these two observations are related and the data are said to be paired (even if there are more than two groups). There are appropriate statistical tests that should be used for this type of data.

Logical steps in hypothesis testing and possible errors.

Form the null hypothesis

Choose a statistical test
Possible error: incorrect test chosen (e.g. one that is not applicable to this type of data)

Obtain a *p* value

Reject the null hypothesis if $p < 0.05$
Possible errors
- By definition, this decision will be incorrect on 5% of occasions (a Type I error)
- Poor study design. Samples show a real difference, but this is caused by bias – either because of poor study design or by chance, the samples differing in some important confounding factor, known or unknown

Accept the null hypothesis if $p > 0.05$, and conclude the treatments do not have different effects
Possible errors: there is a real difference in the treatments, but the study has failed to demonstrate this difference. This is a Type II error, and is more common than a Type I error. The most common cause of a Type II error is insufficient numbers of patients in the study

10

Multiple significance testing
If there are three or more groups in a study, it is tempting to test all the possible paired combinations to determine the differences between the various treatments (i.e. A versus B, B versus C, A versus C, etc). If all these combinations are tested with a statistical significance level of 5%, the risk of finding spurious differences by chance (a Type I error) increases considerably. The correct procedure is to use the appropriate statistical test for three or more groups (Figure 11). If we reject the null hypothesis, we conclude that there are differences between the three or more treatments used in the study, but we do not know which treatments differ.

Choice of statistical test is determined by the type of data and the number of groups

Type of data	Two groups	More than two groups
Categorical data (e.g. blood group)	Contingency tables	Contingency tables
Ordinal data (e.g. Glasgow Coma Scores)	Unpaired – Mann–Whitney test Paired – Wilcoxon rank sum test	Unpaired – Kruskall–Wallis test Paired – Friedman's test
Continuously variable data normally distributed (e.g. weight)	Unpaired – t-test Paired – paired t-test	Unpaired – Analysis of variance (ANOVA) Paired – paired ANOVA
Continuously variable data, not normally distributed (e.g. duration of hospital stay)	As for ordinal data, or transform the data to a normal distribution	As for ordinal data, or transform transform the data to a normal distribution

11

There are two ways round this problem. Special multiple comparison techniques (e.g. Scheffe F test, Duncan's test) can be used to determine the differences between the groups that limit the overall risk of a Type I error to 5%. Alternatively, a Bonferroni technique can be used. A decision is made on how many paired comparisons between groups are required, and each of the chosen paired comparisons is tested with a lower level of statistical significance (usually 0.05 divided by the number of comparisons). This works well if there are fewer than five comparisons, but above this, the technique becomes very conservative, and differences between groups do not achieve statistical significance even when the differences are large.

Contingency tables
Contingency tables are used to analyse categorical data. Usually the rows of the table are the different groups and the columns are the different categories to which the patients are allocated. Each cell in a table is the number of subjects from that group that have been allocated to that category (Figure 12).

A 2 × 2 contingency table

	Nausea and vomiting	No nausea and vomiting
Morphine	14	9
Ketorolac	3	17

The table compares the numbers of patients with nausea and vomiting after two different analgesic drugs

12

Contingency tables can be used for any number of groups and any number of observations about the groups for example, a study of the Glasgow Coma Scores of patients in 10 cities would be a 10 x 13 contingency table (10 cities, 13 possible GCS scores). There are problems with using large contingency tables; in the above example, only one city may be different and the other nine similar; the analysis may not detect this single difference. The logical process of hypothesis testing is exactly as before (i.e. a null hypothesis and an alternative hypothesis are formulated and a *p* value is obtained from the sample data). The test commonly used for contingency tables is called the chi-squared (χ^2) test. The number of expected patients if the null hypothesis were true is calculated for each cell and the difference between the observed and expected data in each cell is used to obtain the *p* value.

The following conditions must be observed when using contingency tables.
- The entries in each cell of the table must be the actual number of patients, not percentages.
- The χ^2 test calculates only an approximate *p* value and can be quite inaccurate with small samples; Fisher's exact test is a better choice.
- There are particular problems in 2 x 2 tables with small sample sizes. If the total in the table is less than 50, a modification of the χ^2 , called Yates' continuity correction should be used.

Repeated measurements
Many studies in anaesthesia involve making a series of observations over time on a single subject (e.g. the heart rate and blood pressure are measured in each patient for some time after administering a drug). This violates one of the assumptions of statistical tests that all the observations are independent of the others. This is clearly not the case in this experiment; if the heart rate is high at one measurement, then it is more likely to be high at subsequent measurements. This type of study can also generate enormous amounts of data, and multiple statistical comparisons are often made searching for statistical differences, increasing the risk of Type I errors. There are two methods of analysing this type of data.
- The simpler method is to use a 'summary measure' for the observations; the changes with time that have been measured in each patient are summarized in a single value used for the analysis. For example, if the systolic blood pressure and heart rate after induction of anaesthesia have been recorded, then examples of suitable summary measures for each patient could be the lowest systolic arterial pressure, the highest heart rate, the time to lowest blood pressure or the mean heart rate. The summary measures chosen depend on which clinical factors are most important. Summary measures can usually be analysed using simple methods.
- The alternative method is to use statistical tests designed for these data, such as analysis of variance for repeated measures. ◆

Statistics: Part 2

Ian Kestin

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Correlation and regression techniques are used to measure the relationships between two or more variables. For example, do they rise and fall together, are they inversely related (i.e. one decreases while the other increases), is the association linear, or is there no relationship at all?

- Correlation measures the degree of relationship between two independent variables.
- Regression mathematically expresses the dependence of one dependent variable on another independent variable. Regression is used to predict the dependent variable from the independent variable.

The common statistical techniques for correlation and regression measure linear relationships, but non-linear relationships can also be expressed mathematically.

Linear regression is expressed by the equation of a straight line

$$y = mx + c$$

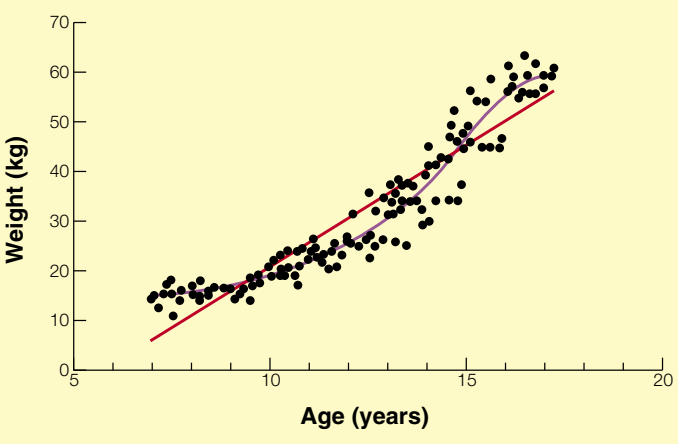
where: y is the dependent variable, x is the independent variable, m is the slope of the line and c is the intercept on the y axis.

Statistical programmes calculate m and c, the statistical significance of this linear relationship, and confidence limits for the true population values for m and c, provided certain assumptions are met:

- the possible values for y in the population for any given value of x should be normally distributed
- the variability of this normal distribution for y should be the same for all values of x
- the relationship is linear.

These assumptions can be tested mathematically, but it is usually sufficient to check the scattergram visually for any obvious deviations. If there is no scattergram, the reader cannot check if linear analysis is appropriate (Figure 1).

Non-linear regression



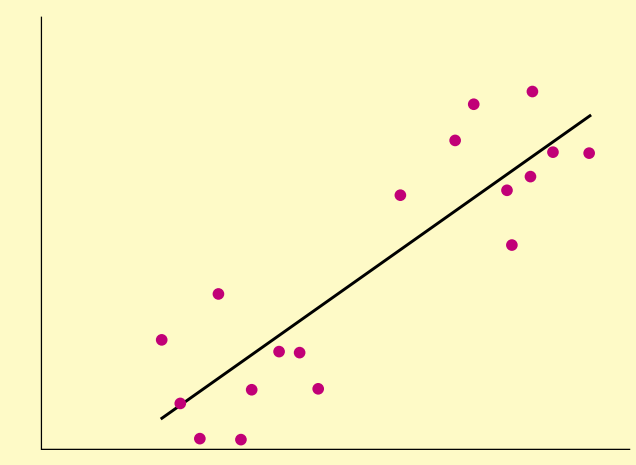
The ages and weights of 130 boys have been plotted and show a non-linear relationship because of the growth increase at puberty. A computer program would derive a highly statistically significant linear regression, though the relationship is better described as sigmoid. Accepting a linear regression equation just because it is statistically significant would miss important information in the data

1

Correlation

Correlation measures the degree of linear association of two independent variables. A common mistake is to assume that if two variables are correlated there must be a causal relationship. It is important to inspect the scattergram before using computer programs to obtain a correlation coefficient (Figure 2).

Errors in correlation



A statistically significant linear correlation in the whole sample can be calculated, but the data actually have a bimodal pattern, and within each subgroup there is no correlation of the two variables

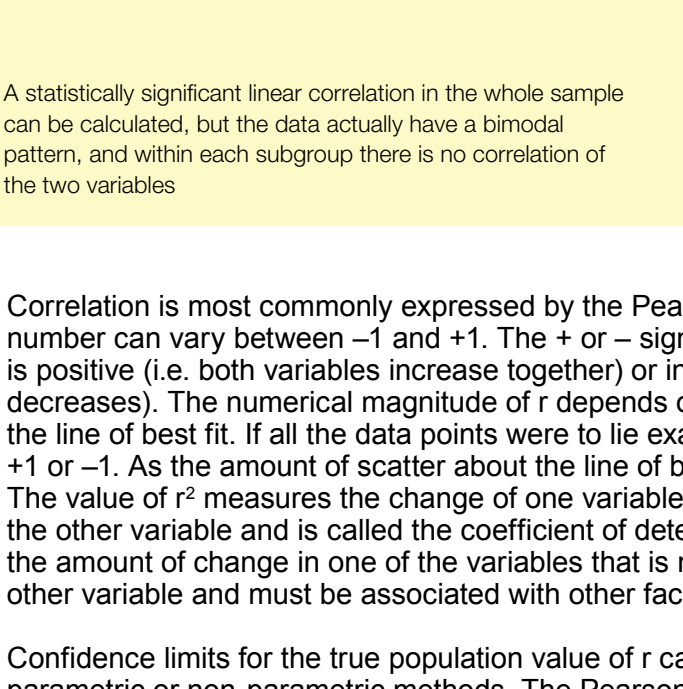
2

Correlation is most commonly expressed by the Pearson correlation coefficient, r. This number can vary between –1 and +1. The + or – sign conveys whether the relationship is positive (i.e. both variables increase together) or inverse (one increases as the other decreases). The numerical magnitude of r depends on the scatter of the points about the line of best fit. If all the data points were to lie exactly on a straight line, then r = +1 or –1. As the amount of scatter about the line of best fit increases, r approaches 0. The value of r^2 measures the change of one variable that is associated with change in the other variable and is called the coefficient of determination. The value of $(1–r^2)$ is the amount of change in one of the variables that is not associated with changes in the other variable and must be associated with other factors.

Confidence limits for the true population value of r can be calculated using either parametric or non-parametric methods. The Pearson correlation coefficient can be used for data that are continuously variable and approximately normally distributed in the population. If this assumption is incorrect then the alternative non-parametric method, the Spearman rank correlation coefficient, should be used. The two advantages of the Spearman non-parametric technique are that the strength of non-linear associations and the association between ordered categories can be measured.

Method comparison studies: any new method of measurement needs to be compared with the standard techniques. This is done by measuring the variable using the standard and new technique, and statistically analysing the paired measurements. The correlation coefficient has commonly been used for this purpose, but this is incorrect. If a new method is being compared with a standard method, and there is a constant bias to the new method compared with the standard, then the linear correlation coefficient will be +1 because there is perfect correlation, but complete disagreement, between the two measurements. The correct statistical technique to use is the Bland–Altman plot (Figure 3).

The Bland–Altman technique for a method comparison study



A new non-invasive method of measuring the arterial blood pressure (NIBP) is being calibrated using simultaneous intra-arterial measurements. The Bland–Altman plot has the systolic pressure measured invasively (IBP) as the x axis and the difference between the two measurements (NIBP–IBP) as the y axis. The mean difference (NIBP–IBP) is the bias, and the 95% confidence interval for the difference is the precision or limits of agreement for the two methods

3

Multiple regression analysis

The dependent variable can be expressed mathematically as a combination of any number of independent variables, either linearly or non-linearly, and this technique is 'multiple regression'. Logistic regression allows us to extend regression techniques to dependent or independent variables with categorical states (e.g. smokers/non-smokers, survived/dead).

It is common, especially in epidemiological studies, to find many possible factors associated with the prevalence of a disease. Some of these are independent causative risks and some are associated through other common factors. In the 1980s, smoking was found to be strongly associated with cervical cancer and proposed as a causative agent along with many other possibilities, including parity and alcohol consumption. It is now generally accepted that cervical cancer is commonly caused by a sexually transmitted virus, and these other correlated factors are more commonly present in women likely to acquire the virus. Stepwise logistic regression is a technique that mathematically includes those factors independently associated with the condition and removes from the equation those factors associated through some other common feature.

Meta-analysis and systematic reviews

Meta-analysis is a statistical technique used to combine the data from several studies of the same topic to reach a single conclusion. It is particularly useful if different studies report conflicting or equivocal results. There are various mathematical techniques for combining the data from different studies, and there is no single correct method. Like all statistical methods, accurate results are obtained only if the data and methods are used correctly. There have been some serious errors; for example, several studies in the 1980s demonstrated that intravenous magnesium reduced mortality after acute myocardial infarction, and a meta-analysis confirmed an important reduction in mortality. Subsequently, a large, single-centre study showed no beneficial effect of magnesium. A re-examination of the meta-analysis suggested a strong publication bias. Small studies showing a positive beneficial effect of magnesium had been published in journals, but small studies that showed no effect had not been published, probably because they had been rejected by the editors for insufficient power. The meta-analysis therefore included a biased selection of all the clinical trials of magnesium that were done and the conclusion was incorrect. To help avoid this problem in the future, a central register of all clinical trials has been suggested. This will enable reviewers to locate all the trials on a subject, published or not.

In a systematic review, the methods used to find all the published papers on the topic, the criteria used to assess the quality of the papers, and the techniques for combining and analysing the data, are all decided in advance and reported in detail in the published paper. Readers ought to be able to repeat the methods used by the authors with the same results. The two principal problems of conventional reviews are failure to find all the papers published on a topic (especially those in a foreign language) and bias in the reviewers. Some conventional reviews and editorials can be little more than disguised polemics.

Statistics and clinical trials

The general principles of clinical trials are described elsewhere. As well as describing and analysing the data obtained, statistical techniques have other uses in clinical trials.

Power analysis

An essential part of the design of any clinical trial is to reduce the risk of a Type II error as low as possible. A power analysis is a statistical technique to estimate the number of patients required to reduce the risk of a Type II error to an acceptable value. The calculations in a power analysis depend on the type of data (i.e. categorical, ordinal or continuously variable). The risk of a Type II error is called the β error; it should be 20% or less, and the power of the study is defined as $(1-\beta)$. For example, if β has been chosen to be 10%, the power of the study is 90%; with this number of patients, the study has a 90% probability of demonstrating any treatment difference if such a difference exists. The main determinants of the number of patients required in a study are:

- the magnitude of the difference between the treatment and control groups and the variability of the data (this information is usually unknown and is usually the purpose for doing the study, but estimates can be obtained from pilot studies, previously published work, or chosen by the investigators as the minimum difference of clinical importance to detect)
- the values chosen for α and β.

Large numbers of patients are needed if the difference between the treatment and control groups is small and the data are scattered widely about the poulation means.

Presentation of results

Confidence intervals are generally better than *p* values for reporting the results of clinical trials; both contain the same mathematical information, but confidence intervals better illustrate the conclusions and implications of the analysis. For example, if the 95% confidence interval for the difference between the treatment and control group includes zero, then the reader immediately knows the treatment may be ineffective or even harmful. Confidence intervals are particularly useful to indicate the true possible incidence of uncommon complications or side-effects after a trial in which there were few adverse events. Many authors report there were no complications in their study and recommend their technique as safe, without giving a thought to what the true incidence could be (Figure 4).

Upper 95% incidence for the true population incidence of a complication after a trial with n patients

Number of complications reported in a study of n patients	Upper 95% confidence limit for the true incidence of the complication in the population
0	3/n
1	5/n
2	7/n
3	9/n
4	10/n

If nothing goes wrong in a study of 50 patients, then the 95% confidence limit for the true incidence of adverse events is 6%, usually an unacceptable incidence of serious complications of a new technique or drug. A technique could not be recommended as safe from a small trial such as this

4

Number needed to treat (NNT) is the reciprocal of the absolute risk reduction of a treatment. It is a useful statistic for reporting clinical trials, combining both statistical and clinical information (Figure 5).

Incidence of stroke after 5 years in treated and untreated hypertensive patients

	Untreated hypertension; absolute risk of stroke	Treated hypertension; absolute risk of stroke	Relative risk	Relative risk reduction	NNT
Mild hypertension	0.015	0.009	0.6	0.4	167
Moderate hypertension	0.2	0.12	0.6	0.4	13

The number needed to treat (NNT) is the number of patients necessary to treat to prevent one stroke in that group. In both treated groups the incidence of stroke is reduced to 60% of that in the control group, but the baseline incidence of stroke in the patients with mild hypertension is much less. Because so many fewer patients with mild hypertension suffer strokes, many more must be treated unnecessarily to prevent one stroke than patients with moderate hypertension. In these patients, the cost and side-effects of treatment would be relatively more important

5

Design of clinical trials

Statistical techniques have been used to demonstrate the effects of bias in clinical trials. There have been four meta-analyses comparing those studies with adequate techniques to ensure the investigators were unaware of the treatment allocation (i.e. adequate 'blinding') with studies of the same topic in which the investigators probably could have discovered the treatment of the patients. All reported that there was an obvious exaggeration of the benefits of treatment in studies in which the investigators were inadequately blinded. The effects were similar but less marked if the trials had inadequate randomization of the subjects or if the patients were aware of the treatment allocation (*BMJ* 2001; **323:** 42–6). ◆

FURTHER READING

Altman D G. Practical Statistics for Medical Research. London: Chapman & Hall, 1991.

Technical skills

Anaesthesia
and intensive care medicine
on CD-ROM

Caudal Block

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The sacral hiatus, through which the caudal block is performed, is formed by the non-fusion of the 5th sacral vertebral arch and is covered by the sacrococcygeal membrane. In infants and young children, the sacral hiatus and the adjacent cornua are easily palpable because of the absence of the sacral pad of fat that usually develops at puberty. In adults, considerable anatomical variation exists, resulting in differences in size and shape of the hiatus that may make caudal block difficult. The sacral canal contains the dural and arachnoid sac, sacral nerves, blood vessels, lymphatics and areolar fat. The dural and arachnoid sac usually terminates at the level of S2 in adults but may extend to the level of S3 or S4 in infants.

Indications: caudal block is ideal for children because it is technically easier to perform than other approaches to the CNS. Single-shot caudal blockade can be used to provide analgesia for most outpatient surgical procedures below the level of the umbilicus, including surgery involving lower extremities, hip, pelvis, urogenital and perianal regions. In children, continuous caudal blockade has been used successfully for surgery to the upper abdomen and sites below the umbilicus. Excellent postoperative analgesia is obtained by infusing low-dose opioid, in combination with low concentrations of local anaesthetic.

The single-shot approach is most often used in adults for injection of a mixture of steroid and local anaesthetic to treat chronic pain conditions, particularly if the patient has had lumbar spine surgery. The caudal approach to the epidural space can offer a virtually straight course to the lumbar epidural space and for this reason it is commonly used to perform spinal endoscopy or to thread an epidural neuroplasty catheter to the desired lumbar level in patients with chronic low back pain with or without radiculopathy.

Technique: asepsis must be maintained throughout the procedure. With the patient in the lateral or prone position, the sacral hiatus is identified between the two sacral cornua. A line joining the sacral hiatus to the posterior superior iliac spines forms an equilateral triangle with its apex at the sacral hiatus. If difficulty is encountered in adults, lateral radiographic screening can be helpful.

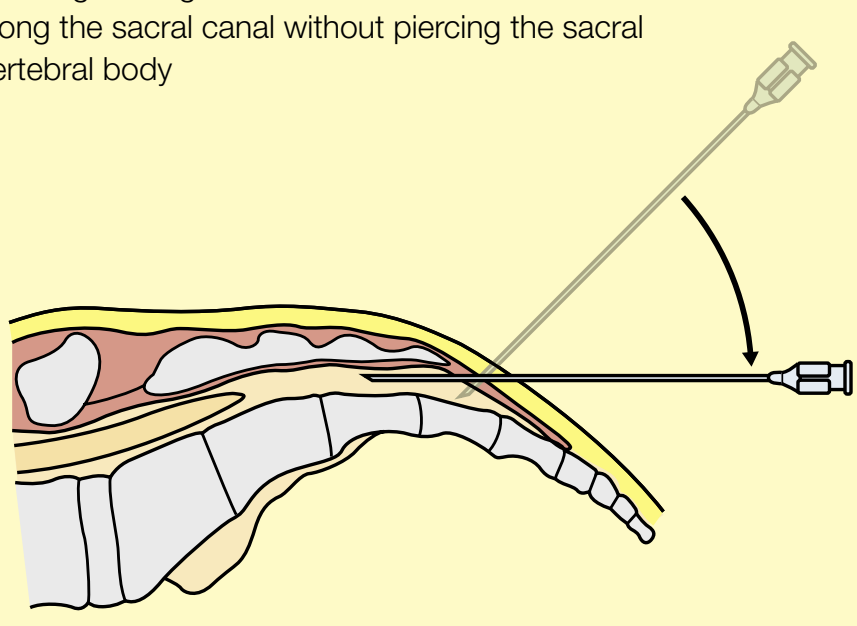
After infiltration of local anaesthetic, the caudal epidural space is entered using a 23 or 21 G needle. The needle must be placed in the midline and inserted at an angle of about 60° to the coronal plane, perpendicular to the other planes. The bevel of the needle should face anteriorly, allowing it to slide along the anterior sacral wall without piercing it. As the needle is advanced, a distinct loss of resistance is felt when the sacrococcygeal membrane is pierced. The needle is then lowered to an angle of about 20° (Figure 1) to ensure that all the bevel of the needle is in the caudal space. The advancement along the canal should be no more than necessary (the shortest distance to the dural sac is 19–34 mm in adults and less in infants). After negative aspiration for blood and CSF the local anaesthetic solution is injected slowly. If a Touhy needle is used, the bevel of the needle should face posteriorly before attempting to pass the epidural catheter.

The volume, dose and concentration of the local anaesthetic determine the quality, duration and extent of the block. Bupivacaine is the most commonly used agent but ropivacaine is being increasingly used because it is has a better toxicity profile with less motor blockade. The usual concentration is 0.25% bupivacaine or 0.2% ropivacaine. In children, 0.5 ml/kg of either drug results in an adequate sacral block; 1 ml/kg is used to block the lower thoracic nerves and 1.25 ml/kg to reach the mid-thoracic region. The total dose of bupivacaine or ropivacaine should not exceed 2 mg/kg. Additives such as opioids, clonidine and preservative-free ketamine prolong the duration of caudal anaesthesia. Several studies have shown that clonidine, 1–2 µg/kg, or preservative-free ketamine, 0.5 mg/kg, added to 0.25% bupivacaine or 0.2% ropivacaine can prolong analgesia two- or threefold. Clonidine can cause sedation, bradycardia and hypotension and is best avoided in day case procedures. The use of caudal opioids should be reserved for major surgery, when patients will be nursed in high-dependency units.

Potential complications of caudal block are infection, intravenous injection, intraosseous injection, dural puncture and venous air embolism.

Needle position for caudal block

A change of alignment is needed to advance the needle smoothly along the sacral canal without piercing the sacral vertebral body



Adapted from: Wildsmith J A W, Armitage E N eds. *Principle and Practice of Regional Anaesthesia.* Edinburgh: Churchill Livingstone, 1987.
By courtesy of the publisher.

1

Extradural Anatomy and Anaesthetic Techniques

Alice Gaynor
Adrian J England

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Adrian J England is Consultant Anaesthetist and Honorary Senior Lecturer at the Royal Free Hospital, London, UK. He has a primary interest in obstetric anaesthesia and co-ordinates the haematology section of the UK register of High Risk Obstetric Anaesthesia.

Regional blockade for pain relief during labour was first reported in 1900 by Kreis, using subarachnoid cocaine. Shortly afterwards, caudal anaesthesia became popular for surgery and in 1909 caudal extradural analgesia for labour was introduced. Sicard and Forestier described the loss of resistance technique for lumbar extradural needle insertion in 1921. This approach has a greater application for anaesthesia than the caudal route, though it was not popular for several years.

In the early 1940s, ureteric silk catheters were introduced into the caudal extradural space through a needle and by the mid-1940s, Tuohy had introduced the curved bevel needle to aid catheter insertion. By 1949, Tuohy's catheter technique had been modified for lumbar extradural blockade and extradural infusions were introduced in the 1950s. Extradural blockade for pain relief during labour started to increase in popularity in the 1950s and 1960s, particularly with the introduction of bupivacaine, a longer-acting local anaesthetic, and lately with the addition of opiates. Currently, in the UK, extradural analgesia is requested by about 30% of parturient women and is often used for postoperative analgesia.

Methods of investigation
Until the 1980s, extradural anatomy was largely described from post mortem findings and contrast-enhanced radiographs. Now epiduroscopy and superfine fibreoscopy allow direct visualization of the extradural space and spinaloscopy allows visualization of the subarachnoid space. CT and MRI allow investigation of anatomy without distortion from instrumentation, and the cryomicrotome differentiates finer details.

Extradural region and surrounding structures

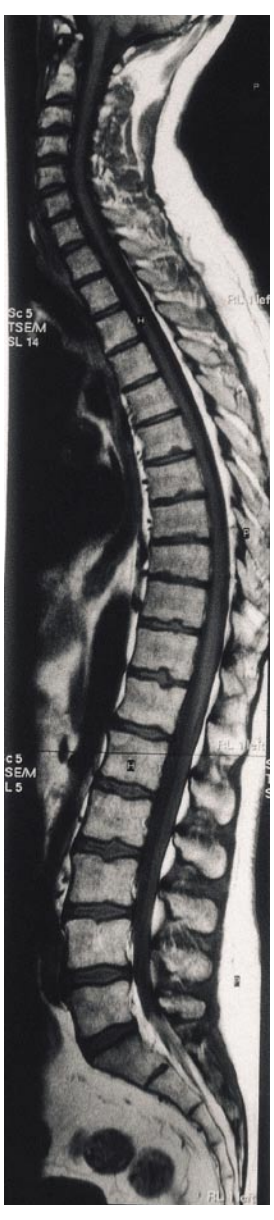
Boundaries and shape: the extradural space extends from the foramen magnum, at the base of the skull, to the tough sacrococcygeal membrane covering the sacral hiatus. It lies between the dural sac and the vertebral canal in the cervical, thoracic and lumbar regions. In adults the dural sac terminates opposite the middle third of the second sacral vertebra and below this extends the extradural space.

In a neutral, supine position, the spinal column forms a thoracic kyphosis, with T8 as the most posterior aspect (not T4 as previously postulated) and a lumbar lordosis, with L4 the most anterior vertebra. This gives the extradural space an S shape when viewed in sagittal section (Figure 1).

The vertebral canal is widest in the lumbar and cervical regions, narrowing in the thorax. Its diameter ranges from 16 mm (sagittal) by 30 mm (coronal) in the lower lumbar and upper cervical regions to 14 mm by 16 mm in the mid-thoracic region giving it the contour of an elongated, flattened hourglass.

In the cervical and thoracic spine, the vertebral canal is oval, giving the extradural space a crescent shape, but in the lumbar region the vertebral canal is triangular and the extradural space deepens into the posterior sulcus.

There is a marked variation in sacral canal anatomy between individuals. The sacrococcygeal membrane is absent in about 10% of adults; the distance from the upper limit of the sacrococcygeal membrane to the dura ranges from 34 mm to over 80 mm; and the volume of the caudal space ranges from under 10 ml to over 25 ml.

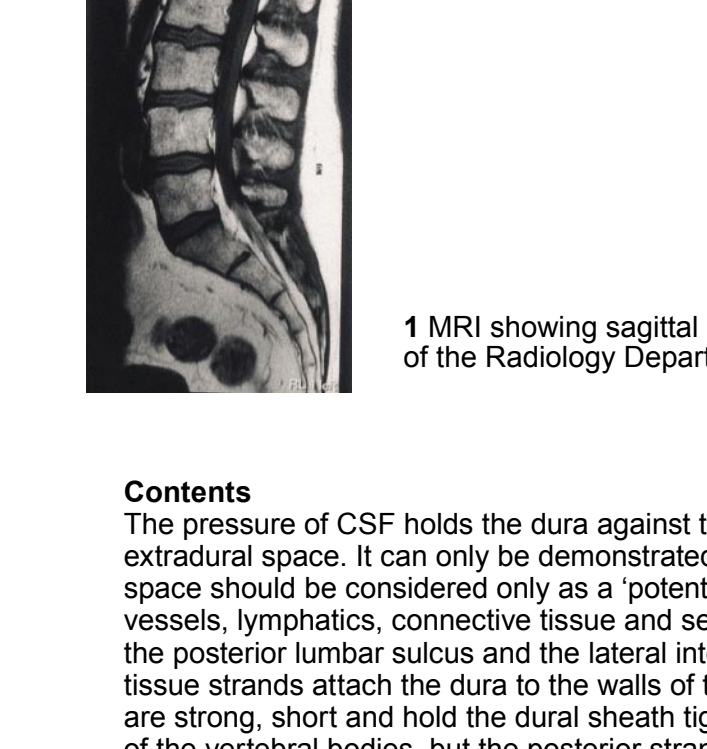


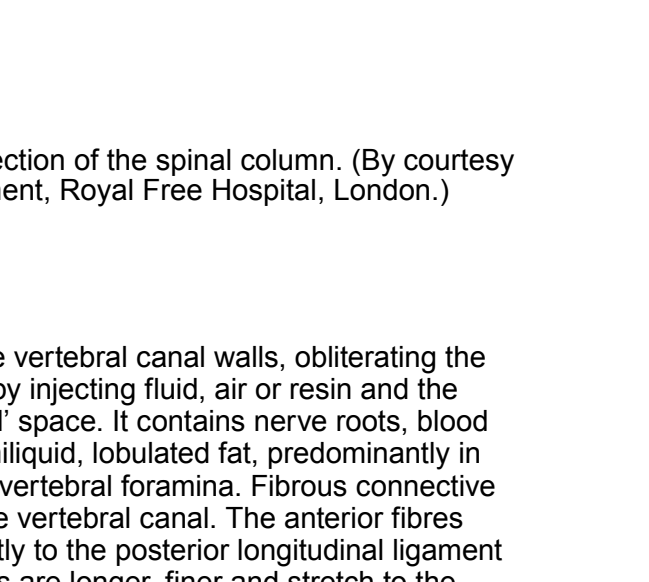
1 MRI showing sagittal section of the spinal column. (By courtesy of the Radiology Department, Royal Free Hospital, London.)

Contents
The pressure of CSF holds the dura against the vertebral canal walls, obliterating the extradural space. It can only be demonstrated by injecting fluid, air or resin and the space should be considered only as a 'potential' space. It contains nerve roots, blood vessels, lymphatics, connective tissue and semiliquid, lobulated fat, predominantly in the posterior lumbar sulcus and the lateral intervertebral foramina. Fibrous connective tissue strands attach the dura to the walls of the vertebral canal. The anterior fibres are strong, short and hold the dural sheath tightly to the posterior longitudinal ligament of the vertebral bodies, but the posterior strands are longer, finer and stretch to the laminae. Controversy surrounds the potential width of the posterior extradural region. Estimates vary with measurement technique,position, and changes in arterial, venous, CSF, abdominal and thoracic pressures. The distance between the ligamenta flava and the dura in the lumbar region varies from less than 2 mm to 8 mm and in the thoracic and cervical regions the 'potential' extradural space is even smaller.

Plica mediana dorsalis: the presence of a physical barrier such as a dorsomedian connective tissue band attaching the dura to the posterior vertebral laminae, or a fold of dura, have been postulated. These would provide a plausible explanation for the development of the unilateral blockade that is sometimes observed during extradural analgesia. Some human epiduroscopy studies have visualized a structure, but there is a wide variation in its reported appearance, ranging from a few strands of connective tissue to a complete membrane. A unilateral filling defect following injection of contrast into the extradural space has also been demonstrated using CT. However, this evidence for a barrier remains controversial. These invasive techniques require cannulation of the extradural space, which could distort its anatomy, or may induce changes within the space, therefore these findings may represent an artefact. Other epiduroscopy studies have not reported the membrane. Investigations that do not require instrumentation of the extradural space, such as unenhanced CT or MRI, and anatomical studies (Figure 2) using the cryomicrotome have failed to demonstrate it. Also, inadvertent segmental or unilateral analgesia following extradural blockade is usually correctable by resiting the catheter. If a structural barrier was present then subsequent catheters should also cause segmental or unilateral blockade. Alternative explanations include extradural fat in the posterior sulcus causing an occasional filling defect, but not causing a complete structural barrier. Unilateral or segmental extradural blockade could be caused by the migration of the extradural catheter to the anterolateral extradural space with unilateral spread of local anaesthetic.

Transverse section of the second lumbar interspace





Photograph and line drawing showing a transverse section through the second lumbar interspace, revealing the cauda equina within the dural sac and posterior and anterolateral deposits of fat within the extradural space. Note the deep posterior sulcus between the ligamenta flava, with no evidence of a posterior fold of dura mater or midline fibrous band. The posterior longitudinal ligament with the longitudinal veins of the internal venous plexus are clearly defined, lying anterolaterally. (By courtesy of Dr J Salisbury, Department of Histopathology, King's College Hospital, London.)

Anterior, lateral and posterior borders: the posterior longitudinal ligament forms the anterior relation of the extradural space throughout its length. This extends across the posterior surface of the vertebral bodies and contains longitudinal fibres adherent to the posterior aspect of each vertebral disc and to the adjacent margins of the vertebral bodies. The laminae of the vertebral arches within the ligamenta flava make up the posterior border of the vertebral canal, with the vertebral pedicles and intervertebral foramina lying laterally.

Ligamenta flava: these two fibro-elastic bands lie anterior to the vertebral laminae and posterolateral to the extradural space. The midline sulcus between them forms the apex of the extradural space. They are thin in the cervical region, becoming progressively thicker towards the lumbar region where they measure between 12 mm and 22 mm wide and between 2 mm and 5 mm thick and their medial margins oppose at less than 90°.

They contain vertically running fibres that stretch from the lower half of the anterior surface of the laminae above to the posterior surface of the upper margin of the laminae below and extend laterally to the intervertebral foramina where they join the capsule of the articular facet joint. In the midline they are generally separated by fat and a few small veins, but may be fused in some areas.

Interspinous ligaments run obliquely between the spinous processes of adjacent vertebrae. Anteriorly, they splay out from the sagittal plane and merge with the posterior fibres of the ligamenta flava at the vertex of the midline sulcus. Posteriorly they are continuous with the tough supraspinous ligament. In the cervical region they fuse with the supraspinous ligament to form the strong and thick ligamentum nuchae, which extends from the spine of the seventh cervical vertebra to the occipital protuberance.

Dural sheath is a continuous cylinder of fibrous tissue of varying thickness, marking the internal border of the extradural space. It is lined by the thin arachnoid mater and contains CSF, the spinal cord and the nerve roots before they leave the spinal canal. It bulges slightly at the lower cervical and lower thoracic regions and runs inside the vertebral canal from the foramen magnum to the lower border of the second sacral vertebra. When viewed by MRI the dural sheath appears attached to the posterior longitudinal ligament at the level of the intervertebral disc anteriorly but to the periostium of the lamina posteriorly. This creates a 'saw tooth' appearance to the posterior extradural fat when viewed in a sagittal plane (Figure 1).

The adult spinal cord ends, as the conus medullaris, at the lower border of the first lumbar vertebra. Below this the nerve roots form the cauda equina. In adults, the dural sac terminates opposite the middle third of the second sacral vertebra.

Between the dura and arachnoid mater lies another potential space, the subdural space. This extends a short distance down the nerve roots and contains a thin film of serous fluid, which may communicate with lymph and venous channels.

Spinal nerve roots lie inside the dural sheath and pass through the anterolateral extradural space. Anterior and posterior spinal nerve roots cross the subarachnoid space and perforate the dura independently. Invested by a dural cuff, the two roots unite at the intervertebral foramen forming the spinal nerve root.

In the cervical and thoracic regions the nerve roots follow a short lateral course in the spinal canal, but in the lumbar region they form the cauda equina and run vertically, tightly packed inside the dura, before leaving the spinal cord through the appropriate intervertebral foramina.

Venous and arterial systems: the internal venous plexus drains the vertebrae, spinal cord and meninges. It is a system of valveless longitudinal veins mostly in the anterolateral part of the extradural space. These vessels divide to allow the passage of the nerve roots and form segmental veins which connect with the systemic circulation through the lateral sacral veins in the pelvis; lumbar veins in the abdomen; azygous and intercostal veins in the thorax and vertebral veins to the cerebral sinuses in the cervical region.

In late pregnancy, the gravid uterus compresses the abdominal aorta and almost completely occludes the inferior vena cava when supine, even with a lateral tilt. This leads to an engorged extradural venous plexus, which displaces the dura from the posterior border of the vertebral bodies. The dural sac becomes compressed anteriorly, but the posterior extradural space is not affected.

Segmental arteries, arising directly from the aorta and vertebral arteries, supply medullary feeder branches, which pass through the intervertebral foramina at each level and supply the spinal cord through locally perforating radial arterioles. There is a marked variation in arterial supply within the spinal cord. Generally, three arterial trunks extend the length of the spinal cord, a midline anterior spinal artery lying in the anterior median fissure and two smaller, paired, posterior spinal arteries. The segmental arteries also supply the spinal nerve roots by dividing into small anterior and posterior radicular arteries that travel with the nerve roots and sometimes anastomose with the large anterior spinal artery or the smaller posterior spinal arteries. Often the artery of Adamkiewicz, a single large anterior radicular artery that usually arises from one of the lower left intercostal or upper lumbar arteries, is present. This provides the main blood supply to the lower section of the anterior spinal artery, and is responsible for the blood supply to the lower spinal cord.

Extradural blockade

Extradural cannulation is normally achieved with the spine flexed because this widens the gap between the vertebral laminae, allowing easier passage of a Tuohy needle. The lateral position causes a scoliosis, which distorts the midline anatomy. A sitting position prevents this deformity, but substantially raises hydrostatic pressure within the CSF, potentially increasing the risk of inadvertent dural puncture.

Lumbar approach: the triangular shape of the posterior extradural space in the lumbar region renders this the most suitable site for extradural cannulation. At this level, regional blockade can provide analgesia across the lower thoracic, lumbar and upper sacral dermatomes and is suitable for procedures involving the lower limbs and lower abdomen.

The shortest distance from the skin to the posterior extradural midline sulcus in the lumbar region is at the L3/4 interspace and is usually 4 to 5 cm). This is the safest recommended level to attempt epidural or subarachnoid needle insertion. Historically, Tuffier's line, running between the iliac crests, was believed to be at L4, but cadaveric and radiographic studies show wide variations. Misidentification of vertebral level may result in cord damage if the conus terminates below the instrumented space.

The distance between the posteromedial border of the ligamentum flavum and the dura at the L3/4 interspace varies from less than 2 mm to 8 mm. If a needle-through-needle technique is used for combined subarachnoid/extradural blockade using a midline approach a spinal needle extending 10 mm beyond the tip of the Tuohy needle will usually penetrate the dura.

Caudal approach: for regional blockade the caudal extradural space is approached through the tough sacrococcygeal ligament covering the sacral hiatus. It is popular for sacral and perineal anaesthesia, though volumes of local anaesthetic solution in excess of 20 ml are usually necessary for an adequate block in adults. Recent MRI has shown the shortest distance from the sacrococcygeal membrane to the dura is 34 mm, therefore a 25-mm-long 23 G needle can be safely used without risk of dural puncture.

Thoracic and cervical approach: the thin, crescent shape of the extradural space and the proximity of the spinal cord to the ligamentum flavum increase the risk of spinal cord trauma with instrumentation at these levels. This risk may be reduced by adopting a paramedian approach. Thoracic extradural blockade may provide useful analgesia following upper abdominal or thoracic surgery and the cervical extradural space may be cannulated for the treatment of chronic pain.

Midline and paramedian approaches: to facilitate instrumentation of the extradural space, the spine is flexed to open the spaces between the vertebrae. With the midline approach, the needle is inserted between two spinous processes and advanced in a slightly cephalad direction, between the two ligamenta flava. With the paramedian approach, the needle is inserted at right angles to the skin, 1–1.5 cm lateral to the spinous process and advanced perpendicularly to the lamina then redirected cephalad and medially towards the midline sulcus, stepping off the lamina before passing through the ligamentum flavum. The end-point is identified using a loss of resistance technique. The advantages of the paramedian approach are listed in Figure 3.

Advantages of the paramedian approach

- It is easier to teach
- Vertebral flexion need not be so marked for instrumentation
- Catheter insertion is easier
- The catheter is more likely to run cephalad
- The catheter is less likely to coil in the anterolateral space
- Nerve root irritation by the catheter is less likely
- Fewer inadvertent dural punctures
- Fewer inadvertent bloody taps
- Fewer segmental or unilateral blocks
- It is the approach of choice for thoracic extradural cannulation

Acknowledgements
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Insertion of a Chest Tube to Drain Pneumothorax

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Intercostal chest tube drainage with an underwater seal is a simple and effective method of eliminating air from the pleural space. It is undertaken as an elective or urgent procedure. Emergency chest drainage for tension pneumothorax is undertaken using a wide-bore cannula in the second intercostal space (mid-clavicular line) of the affected side. Knowing when and how to place an intercostal chest drain safely is a valuable skill for all doctors.

When to insert a chest drain

Not all pneumothoraces require chest tube drainage. The average rate of absorption of air in the pleural space occurs at about 1%/day. Expectant management is a reasonable option for patients who are not compromised, with a small and non-progressive spontaneous pneumothorax. Chest drain insertion is required for patients with moderate to large spontaneous pneumo-thoraces and pneumothoraces associated with trauma.

Patients with a history of multiple pneumothoraces or who have undergone previous thoracic surgery may have adhesions. As a result, areas of lung can adhere to the chest wall. Under these circumstances, chest drain insertion by an inexperienced person may lead to inadvertent lung perforation. If difficulty is anticipated, expert advice or assistance should be sought.

Preparation and positioning

All the necessary equipment should be available before scrubbing up (Figure 1). To alleviate the patient's anxiety, it is helpful to explain the procedure, benefits and risks. The patient is then positioned lying, shoulder elevated and undressed to the waist with the arm abducted at 90° (Figure 2). The arm may be held behind the head, but this often results in a slow downwards drift as the patient becomes tired or experiences pain. Absorbent pads are placed under the patient to prevention soiling of the clothes or bed.

Equipment required for chest drain insertion

- Sterile gown and gloves
- Antiseptic solution
- Sterile gallipot for antiseptic solution
- Sponge-holding forceps
- Swabs
- Sterile disposable drape
- 10 ml syringe
- 21G needle
- l0 ml 1% lidocaine (lignocaine)
- Scalpel with a No. 11 blade
- Roberts clamp
- Chest drain (the standard size is 28F)
- No. 2 silk stitch on a hand-held needle
- Drain bottle (primed with saline)
- Sterile connecting tubing

Opinions vary on the ideal size for a chest tube. It is influenced by the size and build of the patient. Its aim is to drain air. The flow in a chest tube is governed by the Fanning equation that relates turbulent flow to the fifth power of the radius of the tube. If the flow in the tube is not sufficient to drain the air leak, then the lung will not expand fully. Therefore, the largest tube that can fit comfortably within the intercostal space should be used

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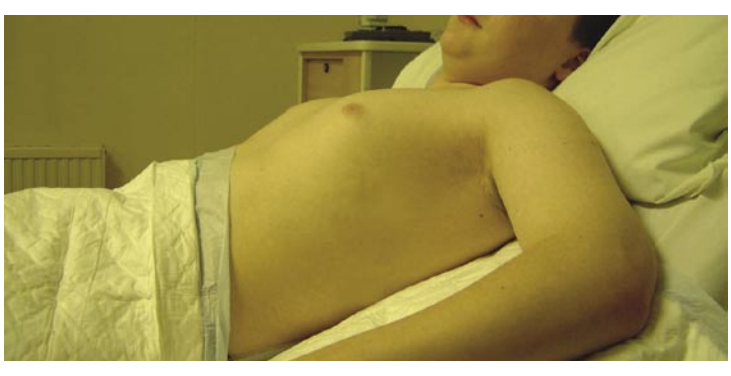


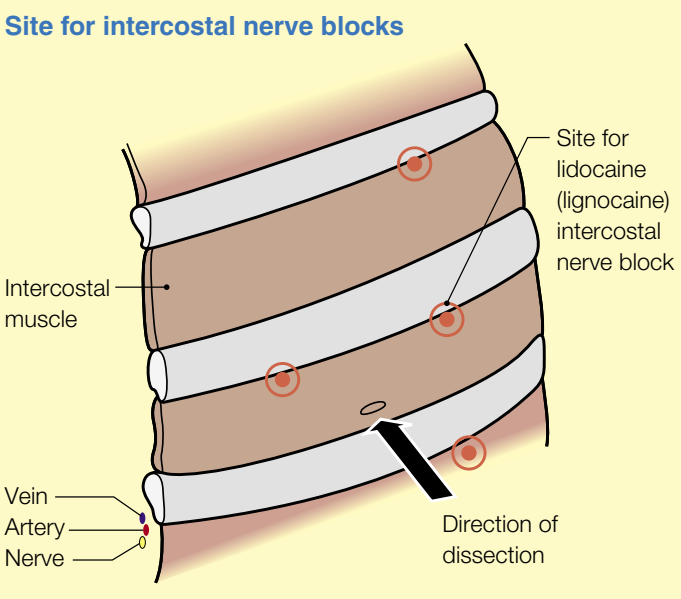
2 Position for chest drain insertion.

How to insert a chest drain

The position of the skin incision depends on which intercostal space the chest drain is introduced through. The triangle (or more correctly quadrangle) of safety is bounded posteriorly by the posterior axillary line, anteriorly by the lateral border of pectoralis major and overlies the 3rd to 5th intercostal spaces. Usually the 4th intercostal space is chosen, just anterior to the midaxillary line.

The surgical field is prepared with a generous coat of antiseptic solution and the intended spot marked by palpation; the antiseptic leaves an imprint as it dries. A small hole is cut in the centre of a sterile paper drape which is applied to the chest wall, such that the antiseptic imprint lies within the centre of the hole. About 1–2 ml of 1% lidocaine (lignocaine) is then injected to create a transverse wheal to demarcate the length and position of the skin incision. The tip of the scalpel blade is used to make a skin incision large enough to admit the operator's index finger comfortably. Blunt dissection can proceed painlessly through the subcutaneous fat up to deep fascia without the need for lidocaine (lignocaine). Once the deep fascia is reached, the intercostal space becomes distinctive. Further lidocaine (lignocaine), 8 ml, is used to create a field block by injecting multiple intercostal nerves. The needle is advanced to identify the rib immediately superior to the chosen intercostal space and 'walked' down the rib until soft tissue is felt. The needle is then angled 45° upwards and the syringe aspirated to ensure that the tip does not lie within the vessels of the neurovascular bundle before injecting 1% lidocaine (lignocaine), 2–3 ml. Using the same method, a further 2 ml is injected in the targeted intercostal space to block the intercostal nerve anteriorly and also in the intercostal nerve of the space above and below the targeted intercostal space (Figure 3).

Site for intercostal nerve blocks



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When the intercostal block is effective, the Roberts clamp (a heavy duty, serrated large artery forceps) is used with gentle but firm pressure to spread the intercostal muscles apart. Dissection occurs superiorly, starting at the inferior aspect of the targeted intercostal space (to avoid the neurovascular bundle). The Roberts clamp should enter the pleural cavity easily once the deep fascia and muscle layer has been negotiated; a gush of air is normally audible at this point. The jaw of the Roberts clamp is opened to dilate the puncture site, followed by the index finger to dilate a tract into the pleural space. This is an important step. The tip of the finger detects any adherent lung tissue. If all is well, the tract is dilated in the process to admit a 28F chest drain comfortably. If this manoeuvre is not performed satisfactorily, it can become difficult to find the tract for the chest drain because the tissues retract to seal the path made by the Roberts clamp.

Once satisfied that no lung tissue is adherent to the chest wall, a 28F drain is introduced into the pleural space without a trocar. To direct the drain to an apical or basal position, thoracic surgeons may leave the trocar engaged in the drain but with its sharp tip usually more than 2.5 cm (1") away from the tip of the chest tube to facilitate the initial direction of the chest tube. The drain and trocar can then be angled upwards within the thorax to achieve an apical position or directed posteroinferiorly to achieve a basal position. Once the first 5 cm (2") of the drain are directed within the thoracic cavity, the trocar is withdrawn. The drain is advanced continuously until a change in resistance is felt as the tip abuts the pleural apex or base of the diaphragm. Occasionally, pain is experienced in the neck and shoulder as the tip of the drain impinges on the apex. Withdrawal of the drain by 2.5 cm (1") ensures a perfectly apical position and alleviation of pain. At this point, make a mental note of the distance marker at skin level.

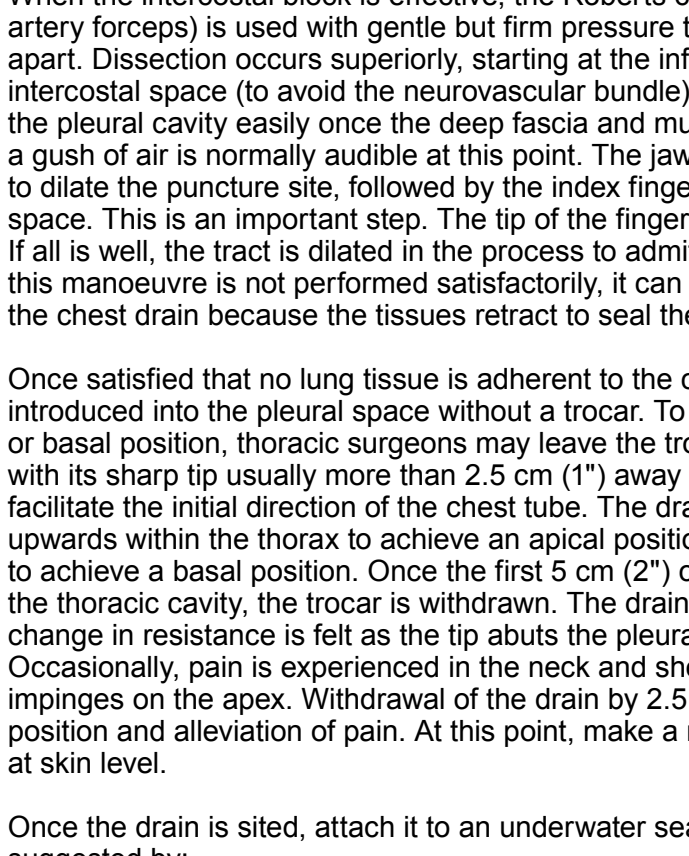
Once the drain is sited, attach it to an underwater seal. Entry into the thoracic cavity is suggested by:

- fogging of the tube
- a respiratory swing
- bubbling on coughing.

The drain is then sutured with a No. 2 silk suture as a horizontal mattress suture, with a double throw to secure the initial tie (Figure 4). Check that the distance marker on the skin has not changed before tying a knot around the tubing to secure the chest drain. It is important to ensure that the tension on the knot is sufficient to indent the chest tube to ensure that the drain does not displace. This suture also acts as a purse string to secure the wound after chest drain removal. It is standard practice to obtain a chest radiograph following chest drain insertion to:

- ensure that the drain lies within the thoracic cavity
- evaluate the position of the drain
- ensure that the lung re-expands
- screen for complications (such as a new effusion from intra-thoracic bleeding).

Securing the chest drain



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Complications

Perforation of the lung is a potential complication of chest tube insertion. It usually occurs when a chest drain is forcibly inserted with the trocar fully engaged, such that the point sticks out from the tube. Warning signs are bleeding and a brisk air leak. Laceration to the intercostal artery can result in impressive haemorrhage. If this occurs, fluid resuscitation and clamping of the drain to tamponade the bleeding is warranted. Both these complications require consultation with a thoracic surgeon and usually necessitate surgical exploration. ◆

Intravenous Regional Anaesthesia

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Intravenous regional anaesthesia (IVRA) was first described by August Bier in 1908. He observed that when local anaesthetic was injected between two tourniquets into a limb, a rapid onset of analgesia occurred in the area between the tourniquets and a slower onset occurred beyond the distal tourniquet. The technique did not become popular until the 1960s when it was reintroduced by Holmes.

Today, the technique is slightly modified, using either a single or a double tourniquet at one site and injecting local anaesthetic as distal as possible to the cuff. The double tourniquet is used to increase safety and to reduce tourniquet pain in the awake patient, but there is potential for confusion and accidental deflation of the wrong cuff, which may lead to toxic systemic levels of local anaesthetic.

IVRA is technically staightforward and does not require specific anatomical knowledge. Published series report successful anaesthesia in 96–100% of patients with a low incidence of side-effects. It is a reliable, simple and safe method of providing anaesthesia for minor surgical procedures to the extremities if it is administered by experienced clinicians. The advantages and disadvantages of IVRA are listed in Figure 1.

Advantages and disadvantages of intravenous regional anaesthesia

Advantages

- Speed of onset and rapid recovery
- Reliability (in the absence of local infection and with adequate equipment)
- Muscle relaxation
- Technical simplicity

Disadvantages and complications

- Poor postoperative analgesia
- Limited time of surgical anaesthesia (< 90 minutes)
- Difficulty in providing a bloodless field
- The potential of systemic local anaesthetic toxicity
- Nerve damage secondary to direct compression by the tourniquet
- Compartment syndrome and loss of limb (very rare)

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Mechanisms of action: local anaesthetic diffuses into the small veins surrounding the nerves and then into the vasa nervorum and capillary plexus of the nerves, leading to a core to mantle (centripetal) conduction block in the nerves involved. Local anaesthetic then diffuses into the small nerves in the skin, blocking their conduction. The tourniquet produces ischaemia which contributes to the analgesic action of the local anaesthetic by blocking nerve conduction and motor endplate function. 20 minutes after tourniquet application there will be analgesia to pinprick without the additional injection of local anaesthetic. However, the speed of onset and the density of anaesthesia are greater with injection of local anaesthetic.

Indications: IVRA is used for surgical interventions on the hand, forearm or elbow, which will not exceed 1 hour. These include manipulation of forearm fractures, excision of wrist ganglia and palmar fasciotomy. IVRA is particularly useful for tendon grafting because it enables the surgeon to observe movement and tension of the grafted tendon (after deflating the tourniquet) before closing the wound (continued anaesthesia with a wrist block). IVRA can also be used for surgery on the foot, ankle or lower leg, for example for removing plates, screws and foreign bodies. Surgery on the elbow or knee is poorly tolerated using IVRA.

Contraindications are mainly related to tourniquet use. Absolute contraindications include sickle cell disease, Raynaud's disease and scleroderma, allergy to local anaesthetics and patient refusal. Relative contraindications include severe hypertensive or peripheral vascular disease, local infection, and skeletal muscle disorders or Paget's disease (local anaesthetic may spread to the systemic circulation via venous channels in bone).

Procedure

Before the procedure the patient should be:

- starved for 6 hours
- monitored closely (standard monitoring applied)
- placed on a tipping trolley
- have consented after explanation of the procedure.

The equipment required for IVRA includes:

- pneumatic tourniquet, a pressure gauge, checked for leak before the procedure
- Esmarch bandage or Rhys-Davis exsanguinator
- local anaesthetic solution
- resuscitation equipment and drugs.

IVRA of the arm: a 22 G cannula is placed intravenously as distal as possible in the arm to be anaesthetized. Venous access is established in the opposite arm to allow administration of fluids or drugs if necessary. The double tourniquet (two tourniquets each 6 cm wide or a single one 14 cm wide) is applied on the arm with generous layers of padding, ensuring that no wrinkles are formed and the tourniquet edges do not touch the skin.

The arm is exsanguinated either by using the Esmarch bandage or a Rhys-Davis exsanguinator. If this is impossible, exsanguination can be achieved by elevating the arm for 2–3 minutes while compressing the axillary artery. The distal tourniquet is inflated to at least 100 mm Hg higher than the patient's systolic blood pressure (250–300 mm Hg). The proximal tourniquet is inflated to the same pressure. After ensuring inflation, the distal cuff is deflated.

Before injecting local anaesthetic it must be confirmed that no radial pulse is palpable. The local anaesthetic is then injected slowly. A standard volume for injection into the upper limb is 40 ml, which can be increased to 50 ml in a fit, large adult. If the injection is too rapid the venous pressure may exceed the tourniquet pressure and the local anaesthetic solution may escape into the systemic circulation.

Surgical anaesthesia is usually achieved within 15 minutes. The distal tourniquet, which overlies part of the anaesthetized arm, can then be inflated and the proximal one deflated to relieve tourniquet pain.

The cuff should not be deflated until 20 minutes after local anaesthetic injection because systemic toxic doses of local anaesthetic may occur. It is thought that after 20 minutes, 30% of the injected drug is fixed within the tissues and is unavailable for immediate release into the systemic circulation. Cuff deflation should be performed in cycles with deflation/inflation times of less than 10 seconds until the patient no longer exhibits signs of systemic toxicity (e.g. tingling of the lips, tinnitus, drowsiness). Severe signs of systemic toxicity include bradycardia, hypotension, ECG abnormalities, fitting and loss of consciousness. Maximum blood levels of local anaesthesia occur within 10 minutes of cuff deflation. Therefore, the patient should be monitored closely for 30 minutes following tourniquet release. With lidocaine (lignocaine), 2.5–3 mg/kg, and cuff deflation after 10 minutes, blood levels have been reported to be less than 2 μg/ml.

If severe CNS intoxication occurs, baseline resuscitation guidelines should be followed. Emergency drugs (e.g. thiopental (thiopentone), propofol) must be readily available and 100% oxygen should be administered.

IVRA of the leg: the basic technique is the same as for the arm but the dose and volume of local anaesthetic has to be doubled for IVRA of the leg, which is associated with an increased potential for local anaesthetic toxicity. The tourniquet pressure must be higher in the leg (350–400 mm Hg), to occlude blood flow in the femoral artery. This may increase the occurrence of tourniquet pain. Tourniquets may be applied to the thigh (two tourniquets about 9 cm wide) or one at the calf (below the head of the fibula) and one at the thigh. The latter is for safety in case of distal cuff failure and is not usually inflated.

Choice of drugs

Many local anaesthetic drugs, with or without additives, have been used for IVRA, but it is commonly felt that 0.5% prilocaine, 3–6 mg/kg, is the drug of choice because it has less systemic toxicity and is partially taken up in the lungs before reaching the systemic circulation. The usual dose is 40 ml (200 mg) without adrenaline (epinephrine). However, the manufacturers have ceased production of 0.5% prilocaine. 1% prilocaine remains available and is licensed for IVRA, though its stability is not guaranteed if diluted. In the USA, prilocaine is unavailable and 0.5% lidocaine (lignocaine), 3 mg/kg, is used. If IVRA is applied to the leg a larger volume must be injected (up to 100 ml). Prilocaine can be used undiluted (maximum recommended dose is 400 mg in adults) but lidocaine (lignocaine) is commonly diluted to lower concentrations (e.g. 0.2% to 0.25%).

Prilocaine can cause methaemoglobinaemia (up to 6% of haemoglobin) but this is usually clinically insignificant.

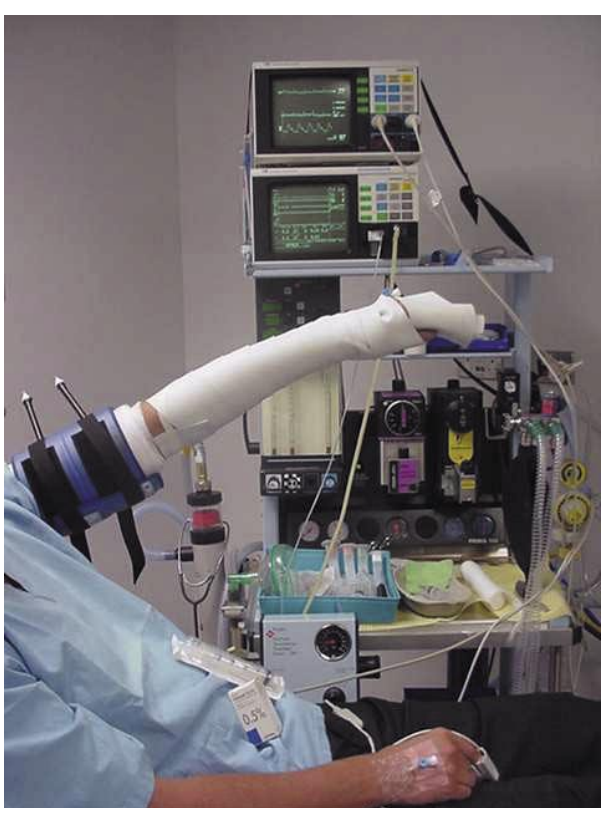
Other local anaesthetic agents have been used but are not superior regarding analgesia or onset time of block. Severe toxic reactions and death have been observed with bupivacaine and its use is contraindicated. In one study, 0.2% ropivacaine was intraoperatively as effective as 0.5% prilocaine but postoperative analgesia was prolonged; no side-effects were reported.

Additives to local anaesthetics have not been consistently shown to have an effect during IVRA but may increase the length of postoperative analgesia, probably because of a systemic effect following tourniquet release. The reported enhancement of IVRA with pethidine, 1 mg/kg, may reflect intrinsic local anaesthetic activity of the drug.

Experiments with the addition of muscle relaxants produced marked muscle relaxation but did not augment analgesia.

Ketamine alone appears to provide good sensory analgesia but some patients lost consciousness and exhibited the typical features of ketamine anaesthesia after tourniquet release.

Many other drugs have been studied, but only the addition of clonidine, 150 μg, an α_2-agonist, or the non-steroidal anti-inflammatory drugs ketorolac, 20 mg, and tenoxicam, 20 mg, to the local anaesthetic solution appeared to be effective in prolonging postoperative analgesia and relieving tourniquet pain. Guanethidine and calcium-channel blockers have been evaluated only in the context of chronic pain management.



2 Intravenous regional anaesthesia of the arm showing use of two cannulae: a, double tourniquet; b, Esmarch bandage; c, full resuscitation equipment and monitoring.

Local Anaesthesia for Awake Tracheal Intubation

Nick Woodall

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Intubation under local anaesthetic is widely recognized as a cornerstone in the management of the difficult airway. However, the variety of local anaesthetic techniques available leads to confusion and often gives the impression that intubation under local anaesthesia is difficult. This article attempts to clarify the situation. Readers are referred to more detailed texts for a discussion of the indications for awake intubation.

Preparation
Patients require psychological preparation, this is best provided by an explanation of the indication for intubation under local anaesthesia and a description of what they should expect. Premedication or sedation is useful for anxious patients. Patient co-operation is essential, over-sedation is a dangerous substitute for adequate local anaesthesia.

If nasotracheal intubation or fibre-optic endoscopy is planned, topical nasal vasoconstrictors (e.g. xylometazoline spray, cocaine) reduce bleeding. Systemic pre-treatment with anticholinergic agents reduces secretions and increases the intensity, speed of onset and duration of topical local anaesthesia. Glycopyrrolate, 5 µg/kg, can be given 10–15 minutes before administration of local anaesthetic at a time when oxygen and routine monitoring is being attached.

Anaesthesia of the upper airway

Topical anaesthesia of the upper airway is required whatever method is used to provide anaesthesia of the pharynx, larynx and trachea.

Nasal anaesthesia
Cocaine as a 4% solution, 80 mg (2 ml), is a commonly used topical local anaesthetic for the nasal mucosa because it is also a vasoconstrictor. However, toxic side-effects and myocardial ischaemia have been reported following small doses. The maximum recommended dose of cocaine is 1.5 mg/kg.5% lidocaine (lignocaine) combined with phenylephrine as co-phenylcaine is an alternative. If this is unavailable, 4% lidocaine (lignocaine), 80 mg (2 ml), applied to the nasal mucosa as a spray or on cotton-wool tipped swabs produces satisfactory analgesia of reasonable duration.

Oral analgesia
4% lidocaine (lignocaine) spray, 80 mg (2 ml), is suitable for oral analgesia. The patient should swirl the solution around the mouth and then gargle with it. The gag reflex may be initiated by stretch receptors in the tissues of the oropharynx or by mucosal stimulation, therefore complete abolition is difficult with surface anaesthesia alone. However, additional 10% lidocaine (lignocaine) spray, 100 mg, directed into the posterior oropharynx at the back of the tongue to the left, right and in the midline usually provides satisfactory conditions for fibreoptic endoscopy or laryngeal mask insertion. 10% lidocaine (lignocaine) stings when applied to mucous membranes, therefore a dilute local anaesthetic solution should be applied first.

Anaesthesia of the lower airway

Following anaesthesia of the mouth, topical anaesthesia of the lower airway may be used alone or supplemented with nerve blockade.

Topical anaesthesia
Nebulization is a simple method of producing airway anaesthesia. However, nebulization is time consuming and the resultant airway anaesthesia often requires supplementation. This technique may be useful to obtund airway reflexes before another form of local anaesthesia if coughing needs to be avoided or minimized. Concentrated local anaesthetic solutions are needed in high doses because only about 15% of a nebulized drug reaches the airway. 10% lidocaine (lignocaine), 6 mg/kg, is effective and peak plasma lidocaine (lignocaine) concentrations have been found to be less than one-fifth of the level regarded as toxic (5 mg/litre) following nebulization of this dose.

Transendoscopic administration: anaesthesia of the pharynx, larynx and trachea may be produced by the direct application of local anaesthesia under vision using a fibrescope. Trans-bronchoscopic administration provides a straightforward and reliable method of producing airway anaesthesia, which avoids many of the complications or contraindications associated with injections. Though the doses of lidocaine (lignocaine) given by this route tend to be high, a total dose of up to 9 mg/kg appears to be safe when given by the transbronchoscopic route. Much of the local anaesthetic swallowed is metabolized in the liver before it reaches the systemic circulation, but lower doses must be used in the presence of severe liver disease.

Following topical anaesthesia of the mouth or nose the endoscope is advanced into either orifice until the posterior aspect of the tongue or the epiglottis can be seen (protection for the endoscope is essential to prevent damage by the teeth if the oral route is chosen). From a distance, local anaesthetic is sprayed on to the back of the tongue. If the epiglottis is not seen, the endoscope is advanced further until it is visible overlying the glottis. The epiglottis and glottis are sprayed in turn until the vocal cords cease reacting to local anaesthetic administration. The endoscope is then advanced closer to the larynx and additional local anaesthetic is delivered through the vocal cords to the lower airway until coughing ceases. When this has been achieved, the passage of an endoscope into the trachea is usually well tolerated.

Heavy contamination of the airway with blood, sputum or vomit may obscure the view rendering the spray-as-you-go method difficult.

Translaryngeal or transtracheal administration produces satisfactory conditions for fibreoptic, retrograde or blind intubation techniques when combined with topical upper airway anaesthesia. Local anaesthetic injected into the airway through the cricothyroid membrane or between the tracheal rings precipitates a brief but intense bout of coughing, dispersing local anaesthetic throughout the airway and producing anaesthesia of the trachea and a significant degree of anaesthesia of the laryngeal inlet and epiglottis.

The cricothyroid membrane is most easily located and recognized. Infiltration of the skin and subcutaneous tissues with local anaesthetic containing a vasoconstrictor provides analgesia and reduces bleeding at the puncture site. A cannula or needle is then inserted through the anaesthetized area into the airway. During insertion this should be directed backwards and slightly caudad to avoid vocal cord trauma. Entry into the airway is confirmed by aspiration of air via the needle.4% lidocaine (lignocaine), 80–160 mg (4 ml), is then rapidly injected and the needle removed. Injection at end inspiration results in the rapid upward spread of lidocaine (lignocaine), whereas injection at end expiration produces more effective anaesthesia of the lower airway.

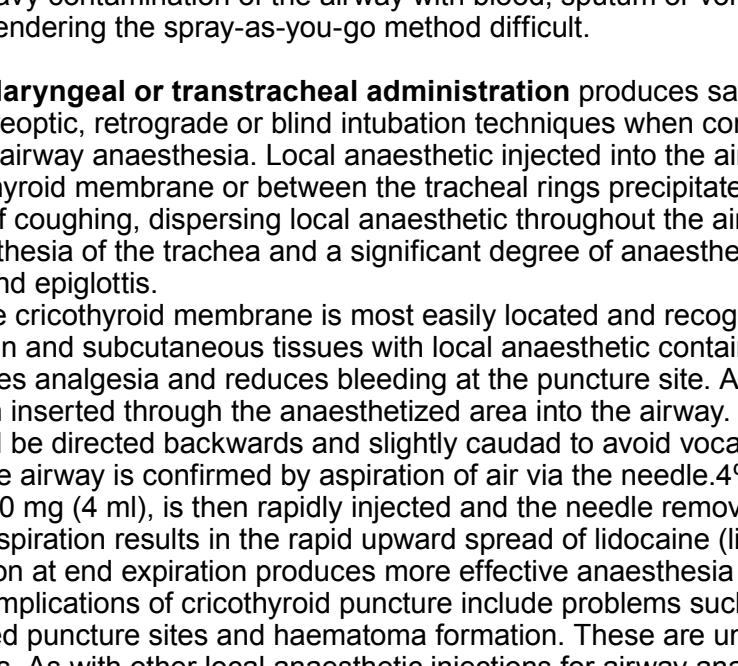
Complications of cricothyroid puncture include problems such as broken needles, infected puncture sites and haematoma formation. These are uncommon and seldom serious. As with other local anaesthetic injections for airway anaesthesia, local infection or the presence of a coagulopathy may contraindicate its use.

Nerve block
Nerve blocks produce intense analgesia of part of the airway, they require small volumes of local anaesthetic and induce little coughing. However, they are often difficult to perform on patients with airway problems owing to limited mouth opening or restricted neck movement.

Glossopharyngeal nerve block: the glossopharyngeal nerve supplies sensation to the posterior third of the tongue, the anterior surface of the epiglottis, the lateral pharyngeal wall and the inferior surface of the soft palate. It passes behind the anterior pillar of the tonsillar fossa to send branches to the tongue and pharynx. Bilateral glossopharyngeal nerve block combined with topical oropharyngeal anaesthetic may abolish the gag reflex permitting direct laryngoscopy. This intensity of analgesia is seldom required for fibreoptic intubation unless it is necessary to pass a double-lumen tube under local anaesthesia.

To perform a glossopharyngeal nerve block, the tongue is displaced medially with a laryngoscope blade or a spatula (Figure 1). Surface analgesia is provided by the topical application of lidocaine (lignocaine), following which a 20 G spinal needle is inserted to a depth of 5 mm into the base of the anterior pillar of the tonsil, at the level of the skin reflection on to the tongue. Following aspiration, 2% lidocaine (lignocaine), 40 mg (2 ml), is injected slowly.

Site of glossopharyngeal nerve block



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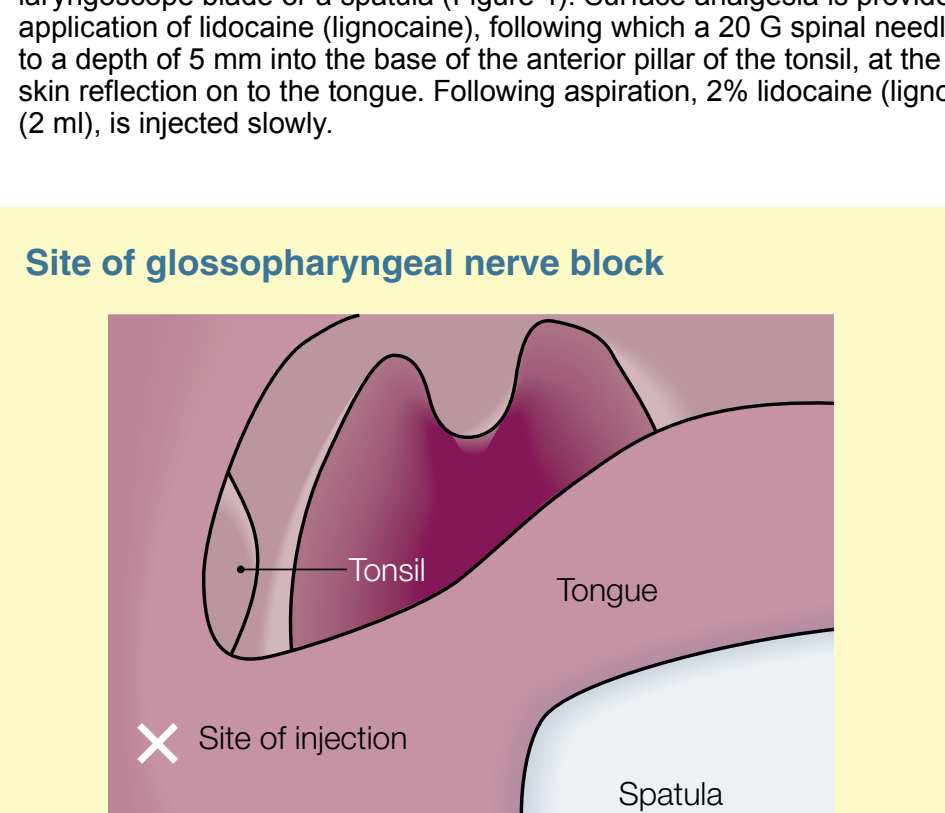
Superior laryngeal nerve block: the superior laryngeal branch of the vagus nerve supplies sensation to the undersurface of the epiglottis and the larynx above the level of the vocal cords. It can readily be blocked as it passes anteromedially between the greater horn of the hyoid bone and the superior cornua of the thyroid cartilage as it passes medially along the thyrohyoid membrane which it pierces to provide sensation to the larynx (Figure 2).

The hyoid bone is found directly above the thyroid cartilage where it can be rocked between the thumb and index finger of one hand. The lateralmost part of the hyoid bone, the greater horn, lies extremely close to the carotid artery. The superior laryngeal nerve may be blocked by ‘walking’ a 25 G needle inferiorly off the greater horn and injecting 2% lidocaine (lignocaine), 2 ml subcutaneously, superficial to the thyrohyoid membrane following negative aspiration of blood.

Superior laryngeal nerve block and cricothyroid puncture



Source: Cousins M J, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anaesthesia and Management of Pain.* 3rd ed. Philadelphia: Lippincott-Raven, 1998.

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Lower Limb Nerve Blocks

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Lower limb blocks have been perceived to be difficult to learn. In fact they are easy to perform; the nerves are large and simple to locate, there are fewer absolute contraindications than for central neuroaxial block and the rate of complications is low. Clinical experience rapidly increases success rates and successful outcomes will reinforce the impetus for their widespread use.

Patients and their anaesthetists want to avoid severe postoperative pain. In the case of surgery for hip and knee replacement, the debate on how to reduce postoperative pain usually revolves around the merits of central regional blocks versus general anaesthesia. Many surgeons comment on the increased requirement for urinary catheterization and a perceived delay in the throughput on a list if regional blocks are performed. An insensate limb (including the non-operated limb) is also at risk of pressure area trauma. Anaesthetists may withhold regional blocks for fear of central neurological damage, post-dural puncture headache or if anticoagulant drugs have been given for prophylaxis of deep venous thrombosis or thromboembolism.

The obvious solution is to carry out the local anaesthetic block on the affected limb only. Historical methods, necessitating a search for paraesthesiae and deposition of large volumes of dilute local anaesthetic with patchy effectiveness have largely been abandoned with the widespread availability of specifically designed low-power nerve stimulators. The large nerves supplying the lower limb are straightforward to locate. A relatively low volume of high-concentration local anaesthetic deposited in this way may produce effective analgesia for up to 72 hours. The patient retains the use of the unblocked limb to move around the bed or for early mobilization as opposed to being 'tethered' to the bed by a patient-controlled analgesia system or an epidural infusion, and urinary catheterization is avoided in many patients.

For surgery below the knee, especially in younger patients, it is unnecessary to produce a dense surgical block of both lower extremities with spinal or epidural anaesthesia when perhaps only the hallux is being operated on. In the foot and ankle, the nerves are superficial and blocks are simple to perform even without a nerve stimulator.

Nerve-blocking techniques are an ideal supplement to light general anaesthesia and can also be used as 'rescue' from failed epidural anaesthesia, for preoperative analgesia or for treatment of patients in recovery, when either the surgical procedure is more extensive than expected or the pain experienced by the patient is unexpectedly severe.

Patients are becoming better informed and more critical in the discussion of the choice of anaesthetic technique. Some patients reject epidural or spinal anaesthesia outright but will accept a peripheral nerve block. The popularity of nerve-blocking techniques is growing and increasingly patients will have experienced successful nerve blocks before and ask for them again.

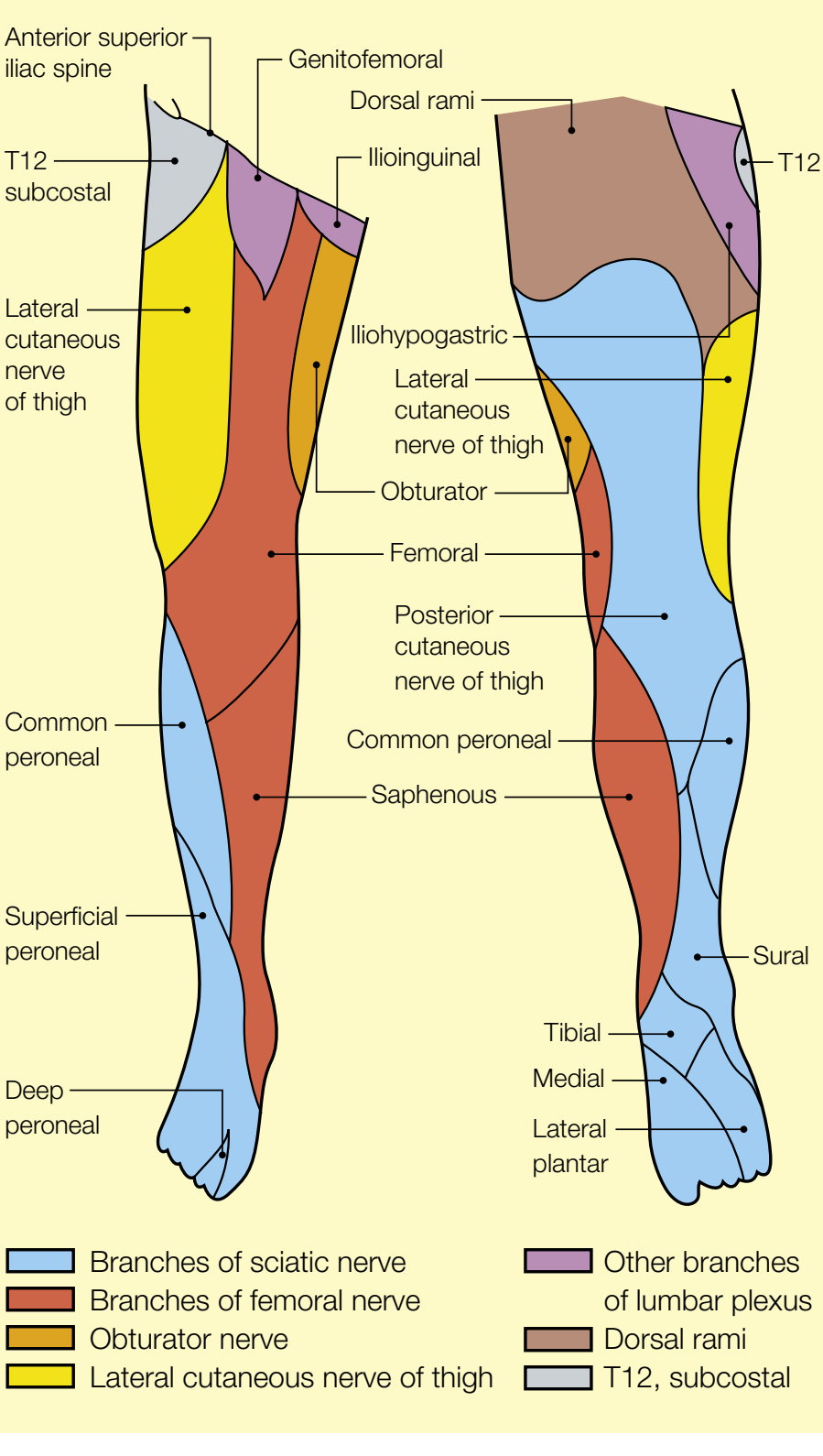
General requirements

It is always important to check with the surgeon exactly what the proposed surgery entails. The site of the main surgical procedure might be blocked but the tourniquet pain or a requirement for bone graft may lie outside the blocked area. A light general anaesthetic might cover this eventuality but it should be checked.

Anatomy

When hip surgery is included, the innervation of the lower limb involves dermatomes T12–S5 (Figure 1). The T12 ventral ramus, the subcostal nerve, travels obliquely downwards until its terminal portion supplies the area of the greater trochanter. The anterior primary rami of lumbar roots 1 to 4 form nerves in a lumbar plexus, which then pass through the body of the psoas muscle. In sequence, from superior to inferior, the nerves are iliohypogastric, ilioinguinal, genitofemoral, lateral cutaneous of thigh, obturator and femoral. The femoral branch of the genitofemoral supplies a small patch of skin on the upper thigh over the femoral triangle, which is compressed by a high thigh tourniquet. The sacral plexus receives the anterior primary rami of sacral nerve roots 1 to 5 and contributions from lumbar roots 4 and 5 as the lumbosacral trunk (separate and medial to the lumbar plexus). The sciatic nerve is formed from these roots and from its origin two distinct bundles may be seen. The tibial nerve is the larger of the two and runs down via the popliteal fossa to the posterior aspect of the medial malleolus where it divides into the medial and lateral plantar nerves. The common peroneal nerve, is about half the size of the tibial nerve, and runs lateral to the tibial nerve through the popliteal fossa round the head of the fibula to terminate as deep and superficial peroneal nerves. The two trunks forming the sciatic nerve constitute the largest nerve in the body (about 20 mm).

Sensory innervation of the lower limb



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Specific clinical indications

Hip surgery

Joint replacement: the main sensory innervation of the hip is from the lumbar plexus, but the subcostal nerve T12, should also be covered by infiltrating along the iliac crest with 10–15 ml of relatively dilute local anaesthetic (e.g. 0.25% bupivacaine).

Lumbar plexus block offers a proximal block of most of the major nerves (femoral, obturator and lateral cutaneous nerve of thigh) that supply the hip region. The plexus is deep-seated, adjacent to vascular structures and close to epidural and intrathecal spaces; therefore, though complications are unusual, a high index of suspicion should be maintained. A 100–150 mm stimulator needle is introduced 30–40 mm from the midline and advanced perpendicular to the skin in all planes. The caudal edge of the transverse process is level with the cephalad edge of the spinous process of the same vertebra. The L3 transverse process is the easiest to use because it is the longest and thinnest of the lumbar transverse processes, allowing the block to be performed as far away from the epidural and intrathecal spaces as possible, and with a reasonable space between it and the adjacent transverse processes. When the transverse process is contacted the needle is 'walked off' usually above the process and advanced a few more millimetres until a pulse-synchronous muscle twitch is obtained in the thigh. This occurs on average at 90 mm from the skin surface.

Large volumes of local anaesthetic, 30–50 ml, are needed for a complete block, but they are associated with an increased risk of epidural and intrathecal spread. To avoid this risk, lower-volume block can be used as a supplement to a light general anaesthetic or to extend analgesia following a spinal anaesthetic.

Sciatic nerve block – the hip joint receives an articular branch from the sciatic nerve, but blocking it increases the risk of pressure area damage to the heels. The therapeutic block may also be confused with surgical trauma caused to the nerve at operation and less drug can be used for the lumbar plexus block.

Fractured neck of femur: the block required does not have to be as proximal as for hip replacement surgery. The procedure can sometimes be performed as a percutaneous procedure and is of relatively short duration. An injection adjacent to the femoral artery can spread up under the inguinal ligament and block the nerves of the lumbar plexus; femoral, obturator and lateral cutaneous nerve of thigh. The block is often referred to as the 3-in-1 block. In clinical use, large volumes (35–50 ml) are required to block the higher portions of the plexus reliably, but in combination with sedation or supplementary analgesia even lower-volume techniques offer a viable alternative to spinal anaesthesia. Individual nerve block may also be used or the 'missing components' of the 3-in-1 block can be added.

Femoral nerve block – the technique to block the femoral nerve, and with larger volumes to produce the 3-in-1 block, is to introduce the block needle 10 mm lateral to the femoral artery, a sufficient distance below the inguinal ligament to allow a 45° angle of approach to the nerve. In heavily built or obese patients it may be easier to approach from 20–30 mm below the ligament to allow this 45° slope, but the nerve should not be blocked too low because it commonly divides at a high level. It usually lies at a shallower depth than the artery, but it is variably placed, sometimes even behind it, and the nerve stimulator is more or less essential for a successful surgical block.

Fascia iliaca compartment block of femoral, obturator and lateral cutaneous nerve of thigh by an injection below the fascia iliaca at the junction of the lateral one-third and medial two-thirds of the inguinal ligament is easy to perform in children because their tissue planes are much looser. A double 'pop' is felt, as first the fascia lata and then the fascia iliaca are penetrated. The situation in adults is less clear, but because the fascia is attached to the capsule of the hip joint this might improve the chance of local spread to the area of surgery.

Lateral cutaneous nerve of thigh – missed block of the lateral cutaneous nerve of thigh is common and can be corrected by direct block 20 mm below the anterior superior iliac spine with a push through the fascia lata with a distinct 'pop'. The nerve is blocked with 10–15 ml of solution and no subcutaneous swelling should be seen. Alternatively, the nerve may be blocked in the canal under the inguinal ligament with injection made just above it, with a double 'pop' through fascia lata and iliaca as for fascia iliaca compartment block.

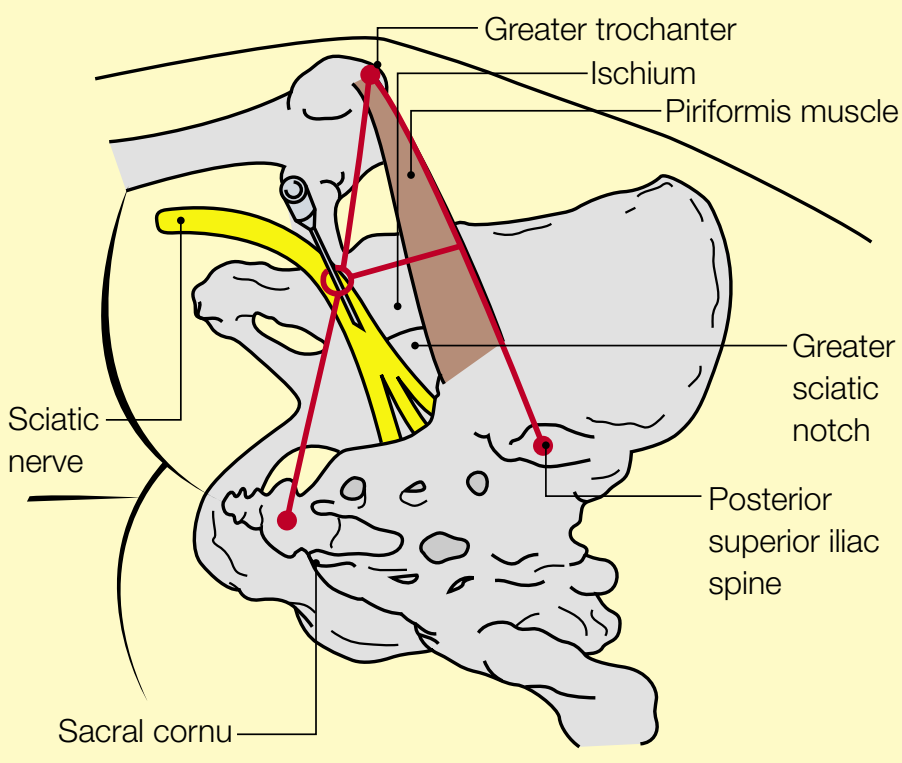
Obturator nerve block is easy to perform, contrary to some textbook descriptions. The heel of the leg to be blocked is put on to the opposite lower leg or knee and a needle introduced above the most prominent adductor muscle tendon directed slightly upwards, backwards and at about 10–15° lateral to the sagittal plane until a pulse-synchronous muscle twitch is obtained in the adductor muscles. The needle can be walked off the inferior pubic ramus into the obturator canal if bone is contacted. Block of T12 fibres should also be performed as described above.

Knee surgery

Femoral, sciatic and obturator nerve block is required for complete surgical block of the knee. Individual nerve blocks are probably a better choice than a 3-in-1 block because the placement of relatively small quantities of concentrated local anaesthetic gives a long period of anaesthesia, for example up to 72 hours with 0.75% bupivacaine on the femoral or sciatic nerves, or 12 hours with lidocaine (lignocaine) or prilocaine. The technique may therefore be contraindicated in day surgery. Surgical techniques are improving and arthroscopic-assisted anterior cruciate ligament repair or unicompartmental replacement of the medial tibial and femoral surfaces only do not justify long-duration block and may prevent discharge within 24 hours, which is usual for these techniques in fit patients.

Sciatic nerve block – the sciatic nerve is large and relatively easy to locate. The two simplest and most logical approaches are the classical 'Labat' method performed in the lateral position and the supine 'Raj' technique carried out with the patient's leg flexed to 90° at the hip and knee. The lateral approach is less easy to landmark and the anterior approach requires a 150 mm approach to a structure that is as little as 30 mm under the skin posteriorly. The insertion point for the needle for the 'Labat' sciatic notch method is a hand's breadth below the midpoint of a line between the posterior superior iliac spine and the greater trochanter, whereas in the supine method it is halfway between the greater trochanter and the ischial tuberosity (Figure 2).

Landmark anatomy for somatic blockade



Adapted from: Bridenbaugh P O, Wedel D J. The Lower Extremity: Somatic Blockade. In: Cousins M J, Bridenbaugh P O eds. *Neural Blockade.* Philadelphia: Lippincott-Raven, 1998.

Alternative techniques include intra-articular local anaesthetic with or without an opiate or local infiltration, however, they require a tourniquet, which precludes their use as sole anaesthetics. Intravenous regional anaesthesia is theoretically possible but not often performed owing to the high volumes required, the lack of analgesia after tourniquet release, and tourniquet discomfort in the conscious patient.

Foot and ankle surgery

Blocks may be carried out proximally (as described above), at knee level, at the ankle or by metatarsal or digital block. The lower leg and foot receive the terminal branch of the femoral nerve, the saphenous nerve, which closely follows the long saphenous vein, and the two main branches of the sciatic nerve, the common peroneal and tibial nerves. Block of these nerves at knee level is a good choice for major foot and ankle surgery.

Saphenous block at the knee is achieved by infiltrating along the inner aspect of the knee from tibial tubercle to the medial border of the tibia; 5–8 ml of local anaesthetic is sufficient. The saphenous vein is a good landmark, if it is visible, because the nerve lies just medial to it.

Sciatic nerve (common peroneal and tibial nerve) block at the knee is carried out in the popliteal fossa. The direct posterior approach is probably the most straightforward; the needle passes through subcutaneous tissues and fat only before the nerve is located at a depth of 20–30 mm. The patient either lies prone or an assistant holds the leg up vertically to allow access for a nerve-stimulating needle. The sciatic nerve, or its two branches if it has already divided, are lateral to the popliteal artery in the upper part of the popliteal fossa. Both branches of the nerve should be located and blocked with 5–10 ml of local anaesthetic. The pulse-synchronous muscle twitch found with the tibial nerve portion is plantar flexion of foot and hallux and that of common peroneal stimulation is eversion and dorsiflexion of the foot.

Ankle block: to anaesthetize the foot completely, five nerves (saphenous, sural, tibial, deep and superficial peroneal) must be blocked. However, surgery is often limited to part of the foot only and therefore it is uncommon to have to block all five nerves. The nerves may be blocked at any point in their course according to surgical requirement and general convenience. The technique is simple to perform and there are few complications. Three nerves are relatively superficial and a subcutaneous infiltration from just behind the lateral malleolus, across the anterior aspect of the ankle, to the saphenous vein in front of the medial malleolus blocks them all.

The saphenous nerve is usually blocked at the level of the medial malleolus, superficially and around the saphenous vein. The territory supplied by this nerve is a strip along the medial border of the foot and the medial side of the arch of the sole.

The sural nerve is blocked as it runs behind the lateral malleolus and its territory is a strip along the lateral border of the foot as far as the little toe.

The superficial peroneal nerve supplies the dorsum of the foot except for the cleft between the first and second toes (deep peroneal).

The deep peroneal and tibial nerves can be blocked close to arteries, the dorsalis pedis on the dorsum of the foot and the tibial artery behind the medial malleolus, respectively. The tibial nerve is blocked halfway between the point of the malleolus and the heel. The disadvantage of blocking at these points is that there is limited space available to deposit local anaesthetic, and so the block is of limited duration. It may also be risky to compromise the arterial supply to the foot in patients in whom peripheral arterial disease may have been the indication for surgery such as debridement or amputation of ischaemic toes and ulcers.

A mid-tarsal block is an alternative block for the tibial nerve. In addition to the subcutaneous infiltration for blocks of saphenous, sural and superficial peroneal nerves, 5–10 ml of local anaesthetic is deposited just distal to the retinaculum below the medial malleolus. At this point, the tibial nerve will already have divided into the medial and lateral plantar nerves and the space is much less restricted than the area around the tibial artery, therefore pressure on or trauma to the arterial supply is unlikely. The deep peroneal nerve can be blocked at mid-tibia to avoid injection on the dorsum of the foot. The needle is inserted about 60 mm above the skin crease at the ankle and 10 mm lateral to the sharp anterior edge of the tibia. The needle is advanced until the tibia is contacted, then 3–5 ml local anaesthetic is injected after withdrawing sufficiently to avoid subperiosteal placement.

Metatarsal and digital block can be performed in a manner analogous to hand blocks. They are all that may be required for minor toe surgery (e.g. nail bed ablation). The advantage of the metatarsal block in this circumstance is that it is still applicable even if surgery extends proximal to the area covered by digital nerve block or if the area to be operated on is infected. These blocks are best avoided in patients with digital ischaemia: in particular, no adrenaline (epinephrine) preparation must be used.

Refinements and developments

Although it is possible to produce extended analgesia from 'single-shot' blocks, the total volume of anaesthetic required may be high, though complications of local anaesthetic toxicity are uncommon in clinical practice. An elegant solution is to place a catheter next to the nerve or into the nerve plexus. Equipment is available so that the standard nerve stimulator can be used for nerve location and once the pulse-synchronous muscle twitch end-point is reached a catheter can be passed via the cannula pre-positioned over the stimulator needle. The initial blocking dose can then be given in divided doses and further doses can be given for postoperative analgesia or a local anaesthetic infusion delivered.

Better systems are being developed, so that the catheter can deliver the nerve location current. Another development is an insulated Tuohy-type needle which avoids the intermediate step of placing a cannula to pass the catheter and potentially increases accuracy.

Local anaesthetic drugs that have reduced toxicity in overdose (e.g. ropivacaine, L-bupivacaine, both of medium to long duration of action) have recently become available. Their place in peripheral nerve block is not yet clear, because most of the early investigations have focused on obstetric epidural analgesia, but the potential to use relatively larger doses for the major nerve blocks offers a significant advantage over standard bupivacaine. Ropivacaine also offers the possibility of separating motor and sensory effect so that extended analgesia may be possible with minimal motor block.

Tests of Pulmonary Function

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Pulmonary function tests provide objective measurements that are essential tools in the investigation of respiratory disease. They are used to screen for and define respiratory impairment, to quantify its severity, and to monitor the course of disease and its response to treatment. They may also be used as part of preoperative assessment and risk stratification. Simple tests, such as spirometry and peak expiratory flow rate, may be performed readily at the bedside. More complex tests of pulmonary gas exchange, such as carbon monoxide transfer factor and flow volume loops, require the facilities of a lung function laboratory.

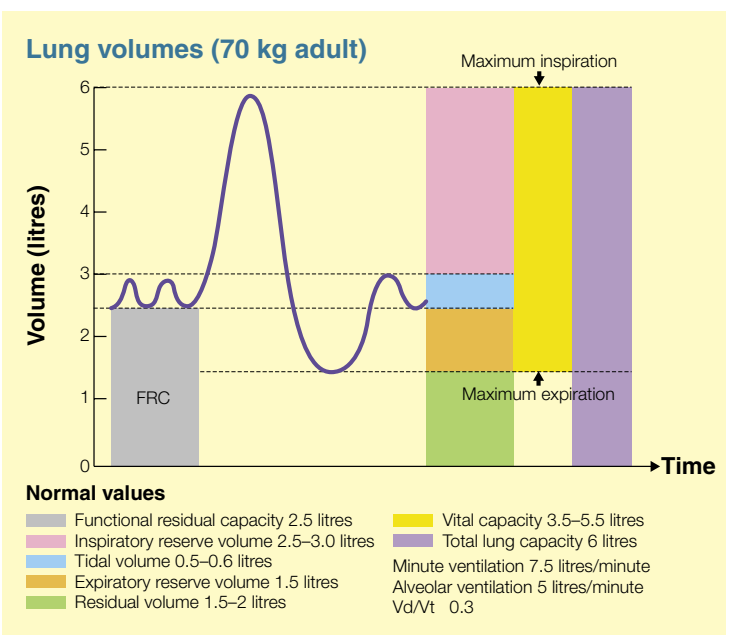
Normal values depend on the patient's height, age, gender and ethnic group. Population studies of healthy never-smoking subjects have produced reference equations for predicting the mean normal values for an individual. The patient's test result may be compared with the mean reference value and predicted range, which includes 90% of the population, or expressed as a percentage of the population's mean reference value (percent predicted). Pulmonary function tests should not be interpreted in isolation and should be considered in the context of all relevant clinical information.

Standards in interpretation of lung-function tests: most tests of pulmonary function require patient cooperation, therefore test quality is an important factor in interpreting results. Variability is greater than with most other clinical tests because of the inconsistency of patients' efforts; about 5% of ambulant patients are unable to cooperate. The European and American Thoracic Societies have published standards to minimize variability in the performance and interpretation of these tests.

Measurements are made in the erect or sitting posture and it is conventional to present respiratory volumes at body temperature and pressure saturated (BTPS). As measurements are made under conditions of ambient temperature and pressure, saturated with water vapour (ATPS), a correction is required to convert the measured volume into the volume occupied at 37°C (BTPS).This results in approximately a 10% increase in volume.

Spirometric tests

Spirometers measure expired lung volume (Figure 1). Dry bellows spirometers such as the vitalograph (Figure 2) are convenient for bedside use. They are designed to record a single vital capacity expiration using a bellows attached to a pen and a recording chart that plots expired volume against time. Electronic spirometers (Figure 3) are increasingly used, which incorporate a handheld pneumotachograph and are lightweight and portable. In intubated patients an estimate of vital capacity may be obtained with the moving plane respirometer (Figure 4). Whatever device is used, it should be calibrated regularly against a standard volume to ensure accurate measurements.



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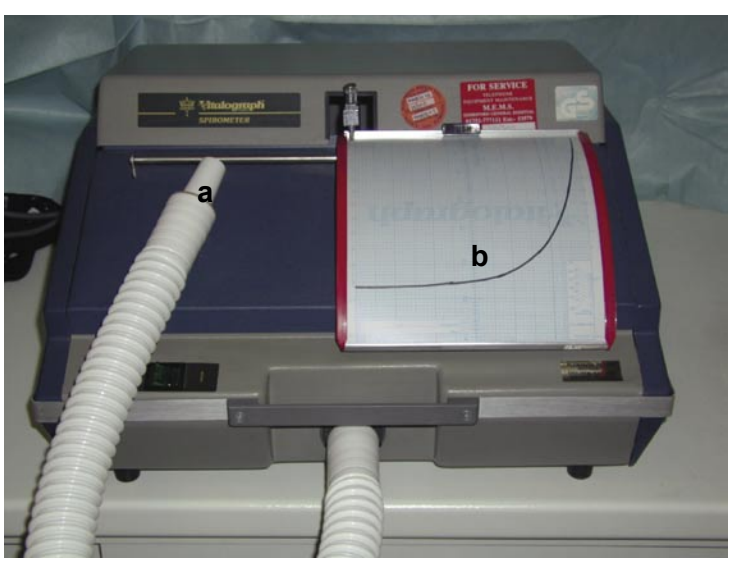
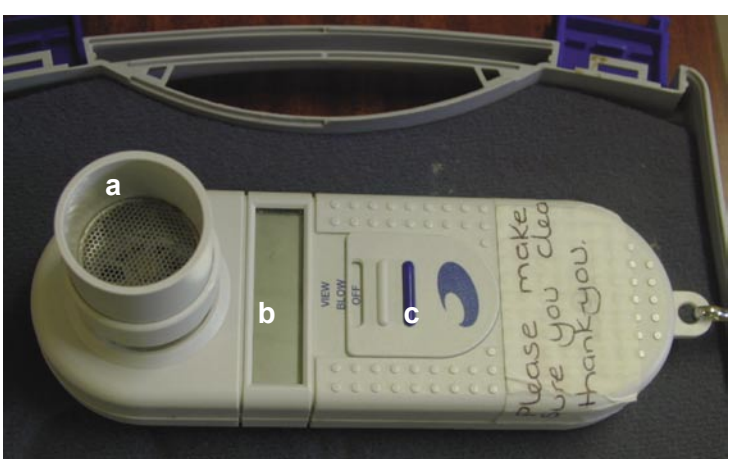


2 Vitalograph. **a** Mouthpiece, **b** spirometer trace.



3 Hand-held electronic spirometer. **a** Mouthpiece, **b** display, **c** reset button.

4 Wright's respirometer. Large outside scale measures in 0.1-litre divisions. Small inner scale measures in 1-litre divisions.

Residual volume cannot be exhaled, therefore spirometers measure only vital capacity and its subdivisions. Measurement of residual volume, total lung capacity and functional residual capacity can be undertaken only with techniques such as helium dilution or body plethysmography.

In standard spirometric evaluation, the subject takes a maximal inspiration followed by a forced expiration for as long as possible into the spirometer. When using the dry bellows spirometer it is important to ensure that expiration continues until all air has been expired from the lungs and not to stop when the record chart stops moving after 5 seconds. This is particularly important in patients with severe airflow limitation who may have a prolonged expiration time. Figure 5 shows the typical expiratory spirometry obtained in normal, obstructive and restrictive lung disease.

Vital capacity (VC) and forced vital capacity (FVC)

VC is the maximum volume of air expelled from a starting point of maximum inspiration to residual volume. It is termed FVC when obtained from a maximum effort expiration and slow VC following a normal effort expiration. In the normal subject, slow VC equals FVC, but in airways obstruction, slow VC is consistently larger than FVC, owing to airway collapse reducing forced expiration.

VC or FVC may be reduced by:

- reduced lung compliance (e.g. lung fibrosis)
- chest deformity (kyphoscoliosis)
- muscle weakness (myopathy, Guillain–Barré, high spinal cord injury)
- airways obstruction (in chronic obstructive pulmonary disease (COPD) air trapping occurs, causing increased residual volume and reduced VC).

A reduced VC, which falls by more than 10% when the patient is supine suggests diaphragmatic weakness. A VC greater than 10–15 ml/kg is required to sustain spontaneous ventilation and can be a useful bedside measurement to indicate the need for ventilatory support or to predict successful weaning from ventilation. In the ICU, VC measurements are of greatest use in patients with neuromuscular disease (e.g. Guillain–Barré syndrome). Measurement of VC depends on technique and effort, which limits its use in most patients with acute respiratory failure because they are dyspnoeic and unable to comply.

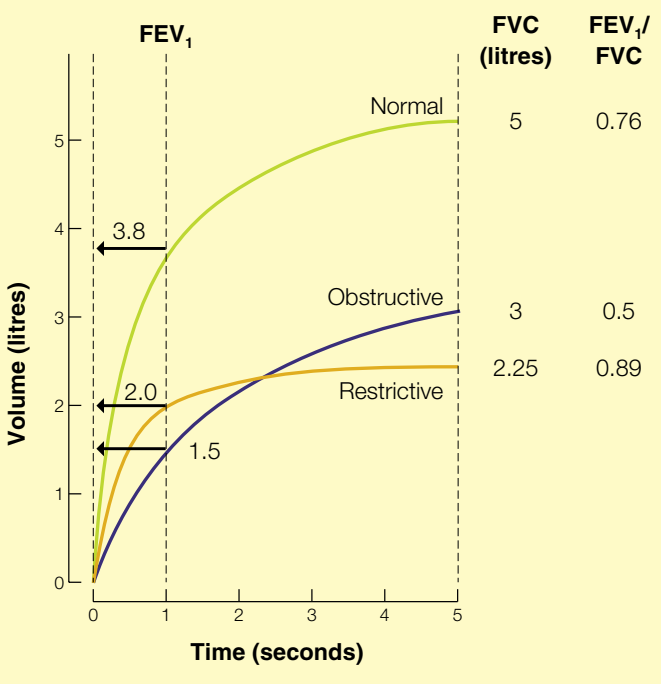
Forced expiratory volume in 1 second (FEV_1)

FEV_1 is the volume of air expelled in the first second of forced maximal expiration after a full inspiration. FEV_1 is reduced by obstruction of the airways, loss of lung recoil and, rarely, by severe weakness of the respiratory muscles. FEV_1 is a more reproducible measurement than FVC, particularly in airflow obstruction, and is used to quantify intrathoracic airway obstruction and assess response to bronchodilators. In COPD, FEV_1 grades the severity of disease and is an important predictor of prognosis. However, FEV_1 is not particularly sensitive in detecting early or mild obstruction and there is poor correlation between FEV_1 and dyspnoea in COPD. A reduced FEV_1 may also reflect a reduction in total lung capacity (TLC), which occurs in restrictive lung disease (e.g. pulmonary fibrosis) or following pneumonectomy.

FEV_1: FVC ratio

In normal subjects during a forced expiratory manoeuvre, at least 75% of the air is expelled in the first second. In patients with obstructive lung disease, the FEV_1 falls proportionally more than the FVC, therefore the ratio of FEV_1:FVC falls. In restrictive lung disease, the FEV_1 and FVC are reduced in the same proportion and the FEV_1:FVC ratio remains normal or even raised, reflecting accelerated lung emptying (Figure 5).

Spirometry in normal, obstructive and restrictive lung disease



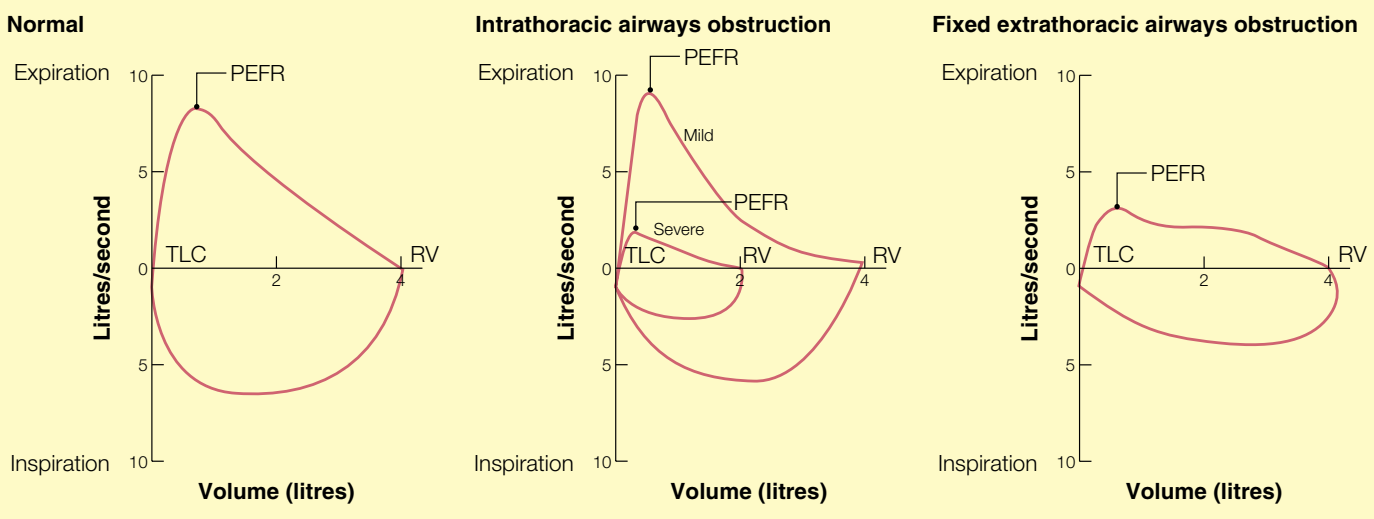
FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

5

Tests of maximum flow

During a forced expiration at any lung volume, increasing effort at first increases flow but a plateau is reached at most lung volumes when expiratory flow cannot be increased regardless of effort. Above a critical level, the increased alveolar pressure resulting from increased effort is exactly counterbalanced by compression of large intrathoracic airways, limiting further increase in flow. Thus, expiratory flow measurements are not dependent on maximum effort apart from the peak expiratory flow. The maximum expiratory flow rate that can be achieved is reduced as lung volume drops, producing the characteristic expiratory flow volume curve (Figure 6). The highest expiratory flow rate is achieved at TLC and is termed the peak expiratory flow rate (PEFR). In contrast, maximum inspiratory flow is proportional to the negative pleural pressure generated and is effort dependent.

Flow volume loops



PEFR, peak expiratory flow rate; TLC, total lung capacity; RV, residual volume.

In patients with severe airway obstruction, expiratory flow cannot be increased with any effort, even at rest (expiratory flow limitation) and during exercise, end expiratory volume increases (dynamic hyperinflation). Peak expiratory flow occurs at full lung inflation and in normal subjects the maximum value obtained is effort dependent because flow limitation does not occur.

In the lung function laboratory, expiratory (and inspiratory) flow measurements are made with a rapid-response pneumotachograph. This measures flow from the small pressure drop that occurs across a fixed resistance using a sensitive pressure transducer.

Flow volume loop

The flow volume curve is obtained by asking the subject to inhale to TLC, then producing a forced maximum effort expiration to residual volume followed immediately by a maximum effort inspiration back to TLC. Flow is plotted against lung volume between TLC and residual volume to produce the characteristic flow volume loop (Figure 6). The maximum expiratory flow rate at various lung volumes, including 75%, 50% and 25% VC, is commonly reported. The maximum mid-expiratory flow (MMEF) is the flow recorded during the middle half of forced expiration (between 75% VC and 25% VC) and is a sensitive indicator of obstruction in the smaller peripheral airways. Flow volume loops are commonly used to supplement spirometry because they provide additional information. In particular, distinctive patterns represent the presence of intra- or extra-thoracic obstruction (Figure 6). The expiratory flow volume curve is abnormal in patients with mild obstructive airways disease even when measurements such as FEV_1 are within normal limits.

Peak expiratory flow rate (PEFR)

At the bedside, PEFR may be measured with a simple hand-held device. Wright's peak flow meter is a constant pressure, variable orifice device, able to measure peak flow rates up to 1000 litres/min. A fixed baffle in the meter directs exhaled air to strike a moveable vane. The vane reaches its furthest excursion according to the PEFR and is held there by a ratchet. A simpler, cheaper version consists of a cylindrical tube, and a piston, which is blown along its length proportionate to the peak flow. Subjects are asked to take a full inspiration to TLC then to blow out forcefully into the peak flow meter, which is held horizontally. The lips must make a tight seal round the mouthpiece and the best of three attempts is recorded. In normal subjects, the value of PEFR depends on effort and the calibre of the large central airways. In airway disease, PEFR is reduced by obstruction in small or large airways. Although PEFR is used for monitoring the course of asthma, reduction in PEFR is not specific to airway obstruction. Restrictive lung disease and respiratory muscle weakness may be associated with a reduction in PEFR, and a diagnosis of airways obstruction has to be confirmed with spirometry.

Transfer factor for carbon monoxide (TLCO)

The efficiency of gas exchange by the lungs can be assessed from the uptake of inhaled carbon monoxide (CO), which is limited by the rate of diffusion from alveolar space into the erythrocyte. CO has a high affinity for haemoglobin, such that the blood in the alveolar capillary never becomes saturated with CO and the capillary CO tension can be assumed to be zero. This simplifies the calculation of diffusing capacity for CO, which is expressed as the quantity of CO taken up per unit of time per unit of partial pressure of CO. Originally termed the diffusing capacity (CO diffusion in the lungs: DLCO), it has been realized that in addition to the molecular diffusion of CO across the alveolar capillary barrier, the chemical combination of CO with haemoglobin is a rate-limiting step (this explains why TLCO changes with haemoglobin). Therefore, the term transfer factor (CO transfer in the lung: TLCO) was introduced and is used interchangeably with DLCO.

TLCO is estimated by inhaling a known quantity of CO and measuring the change in CO concentration over a measured time. This is typically undertaken during a 10-second breath-hold at TLC or during a period of re-breathing. An insoluble gas, such as helium, is also inhaled and the lung volume to which the inhaled CO is diluted is measured from the change in concentration of the insoluble gas. This volume is termed the alveolar volume (VA). The coefficient of gas transfer or specific gas transfer (KCO) is the TLCO expressed per unit of alveolar volume (KCO = TLCO/VA). DLCO is reported in North America and expressed in ml/min/mm Hg. In Europe, the term TLCO is used with the units mmol/min/kPa.

TLCO measurement is influenced by the alveolar oxygen tension (PAO_2) because of the competition between oxygen and CO for haemoglobin binding sites. Measurements are usually made with an FiO_2 (fraction of oxygen in inspired air) of 18% and variations in PAO_2 between subjects can be ignored. Changes in haemoglobin concentration have a significant influence, with a 4% fall of TLCO per 1 g drop in haemoglobin. Values obtained in the pulmonary function laboratory may be corrected to a reference haemoglobin of 14.5 g/dl with a standard equation.

When interpreting the TLCO, the following fundamental relationship should be considered:

Gas exchange capacity (TLCO) =
Alveolar volume (VA) x Efficiency (KCO)

TLCO may be reduced from a reduction in alveolar volume, a reduction in the efficiency of gas exchange or a combination. A low KCO is characteristic of emphysema, interstitial lung disease (fibrosis) and pulmonary vascular disease. Pulmonary hypertension and pulmonary embolism are associated with reduced KCO with a preserved VA. The increase in alveolar volume associated with emphysema results in a marked reduction in KCO. In extrapulmonary restriction (e.g. chest wall disease), TLCO is slightly reduced while KCO is increased owing to the reduction in VA but reflecting the normal underlying lung. In asthma, TLCO may be slightly elevated, while alveolar haemorrhage is associated with marked elevations in TLCO owing to the presence of extravascular haemoglobin which binds CO. TLCO measurements are also used in assessing a patient's predicted tolerance of lung resection, with a predicted value over 50% being desirable. Following pneumonectomy, the TLCO falls according to the amount of lung resected, while KCO is preserved or increased.

Typical changes in lung-function tests

Condition	VC	FEV_1	FEV_1/VC	TLCO	KCO	Notes
Asthma	→	↓	↓	→	↑	FEV_1 increased after bronchodilator
Emphysema	↓	↓↓	↓↓	↓	↓↓	Increased VA results in marked decrease in KCO
Pulmonary fibrosis	↓	↓	↑ or →	↓↓	↓	VA reduced SaO_2 may fall on exercise due to diffusion limitation
Chest wall restriction	↓	↓	→	↓	↑	VA reduced but KCO increased as underlying lung normal
Respiratory muscle disease	↓	↓	→	↓	↑	10% fall in VC from erect to supine posture suggests diaphragm weakness
Alveolar haemorrhage	↓	↓	→	↑	↑↑	Increased KCO returns to normal after 48 hours

FEV_1, forced expiratory volume in 1 second; KCO, gas transfer coefficient; SaO_2, oxygen saturation in arterial blood; TLCO, transfer factor for carbon monoxide;
VA, alveolar volume; VC, vital capacity

Patterns of lung-function tests in respiratory disease

When diagnosing a patient with respiratory symptoms, the results of the range of pulmonary function tests need to be considered. Figure 7 (above) summarizes the typical changes that occur to the standard lung-function tests in a number of common conditions.◆

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Principles of Intravenous Drug Administration

Johan F Coetzee

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Circulating drugs are removed by distribution to peripheral tissues and by excretion and metabolism. Thus, bolus doses exert transient effects and repeated doses are required for continuous effects. However, repetitive boluses produce peaks and troughs in blood concentration and therefore varying effects. The most efficient method of maintaining a desired drug effect is by continuous infusion to achieve constant blood concentrations.

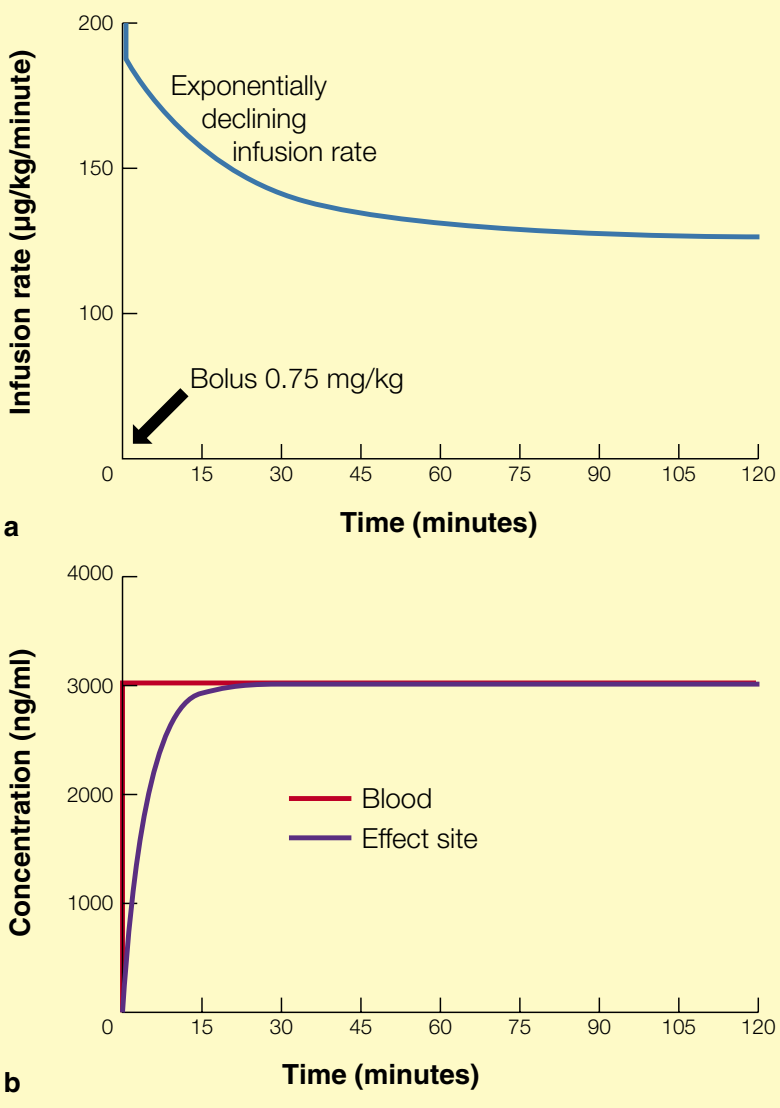
Achieving steady-state drug concentrations in blood

The behaviour of drugs subject to first-order kinetics can be represented by multicompartmental models, typically comprising a central compartment that receives and excretes drug, and from which distribution occurs into one or two large peripheral compartments. In 1968, Kruger-Theimer indicated how pharmacokinetic models can be used to design efficient dosage regimens. This Bolus, Elimination, Transfer (BET) regimen, comprises three components (Figure 1).

- Administer a **B**olus dose calculated to fill the central (blood) compartment.
- Admininster a constant-rate infusion equal to the **E**limination rate.
- Simultaneously, administer an infusion that compensates for **T**ransfer to the peripheral tissues. This infusion is initially rapid and declines asymptotically towards the elimination rate as the tissues absorb drug. Mathematical details can be obtained from textbooks on pharmacokinetics.

A simplified approach to approximate the exponentially declining infusion is by a series of manually stepped-down constant infusions. This is exemplified by the ‘10, 8 and 6’ dose regimen for propofol (Figure 2).

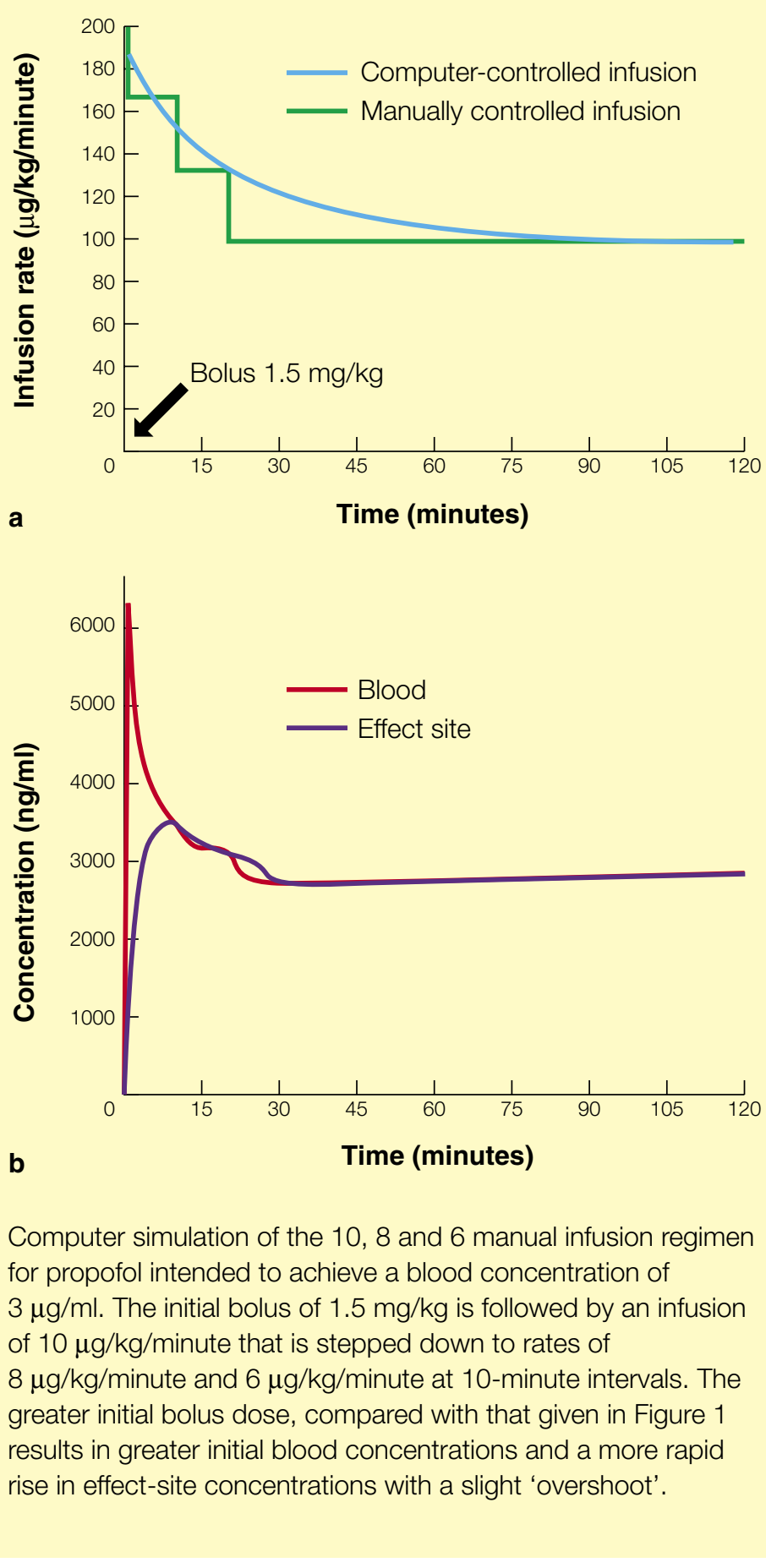
Achieving a constant blood concentration of propofol using a BET regimen



Computer simulation of propofol administered by a **B**olus, **E**limination and **T**ransfer (BET) dose regimen to achieve and maintain a constant blood concentration of 3 µg/ml.
a Administration of a bolus dose at time zero, calculated to establish the initial targeted concentration. This is followed by an infusion, which is initially rapid and then declines asymptotically to the maintenance rate. **b** The theoretical blood and effect-site concentrations. Note how the effect-site concentrations lag behind those in the blood. It is possible to achieve a more rapid rise in effect-site concentrations towards the targeted concentration at the cost of greater blood concentrations and therefore a greater likelihood of side-effects.

1

The 10, 8 and 6 manual infusion regimens



Computer simulation of the 10, 8 and 6 manual infusion regimen for propofol intended to achieve a blood concentration of 3 µg/ml. The initial bolus of 1.5 mg/kg is followed by an infusion of 10 µg/kg/minute that is stepped down to rates of 8 µg/kg/minute and 6 µg/kg/minute at 10-minute intervals. The greater initial bolus dose, compared with that given in Figure 1 results in greater initial blood concentrations and a more rapid rise in effect-site concentrations with a slight ‘overshoot’.

2

Target-controlled infusions (TCI) by computer
Using a pharmacokinetic model, a computer performs a simulation, continuously calculating the ‘patient’s’ expected drug concentration and administers the BET infusion, adjusting the pump speed, typically at 10-second intervals. By specifying an appropriate target concentration, the anaesthetist uses the device in a similar fashion to a vaporizer. There are differences between predicted and actual concentrations, but these are not of great consequence, provided the true concentrations are within the drug’s therapeutic window, within which the clinician may adjust the targeted concentrations, according to patient response. Measured/predicted errors of about 30% are clinically acceptable. These devices simplify intravenous drug administration by relieving the clinician of tedious calculations and by eliminating errors. Furthermore, computer-assisted TCI allow more accurate dosing, maintenance of stable drug concentrations (and therefore stable effects) and ability to make proportional changes (Figure 3). In order to use TCI, clinicians need to associate blood drug concentrations with expected effects; this is a familiar exercise for anaesthetists who relate alveolar anaesthetic partial pressures of inhaled anaesthetics to drug effect. Similarly, the concept of minimum effective plasma concentration (EC_{50}) is identical to that of minimal alveolar concentration for inhaled agents. Target-concentration guidelines for different intravenous drugs and drug combinations are available from standard textbooks. It must be borne in mind, however, that as with inhaled anaesthetics, no one targeted concentration will suit all patients. Patient pharmacokinetics and pharmacodynamics are influenced by age, cardiac output, coexisting disease, smoking, concurrent drug administration, body temperature and intensity of noxious stimulation. These factors must be considered when choosing target concentrations, and dose should be titrated according to clinical signs.

Advantages of BET dose regimens

- Rapid achievement of desired blood concentrations
- Avoidance of high peak concentrations that occur with a manually delivered bolus and therefore a reduced risk of side-effects
- More accurate dosing and therefore:
  - better haemodynamic control
  - reduced drug consumption
  - more rapid recovery
  - less postoperative depression
- Ability to maintain stable concentrations and therefore stable effects
- Ability to make proportional changes
- Use is similar to that of a vaporizer. Titrate to effect

Added advantages of computer-assisted BET infusions
- Elimination of calculation errors
- Compensation for any interruption to the infusion
- Easy to assess the relationship between drug concentration and effect
- Display of effect-site concentrations
- Prediction of time to recovery (context-sensitive decrement time)
- Possibility of targeting the effect site (analogous to targeting end-tidal partial pressures of volatile anaesthetics)

3

The *Diprifusor* (AstraZeneca, Macclesfield, UK) is a TCI device dedicated to propofol administration. It is anticipated that commercially available TCI technology will expand to include other drugs such as opioids and other hypnotics. TCI can be applied to any drug that exhibits first-order kinetics and should be applicable to those with narrow therapeutic indices, for example certain antibiotics, cytostatics and, anti-epileptics. Various computer programs may be downloaded from the Internet (e.g. http://pkpd.icon.palo-alto.med.va.gov/) and several TCI pumps (e.g. STELPUMP, STANPUMP and RUGLOOP from the Universities of Stellenbosch, Stanford and Ghent, respectively); others are screen-based simulators (PK-SIM). These programs provide useful educational and research tools that enable clinicians to experiment with dose regimens and to represent the expected results graphically, thereby developing familiarity with intravenous drug administration and encouraging dosing according to pharmacokinetic and pharmacodynamic principles.

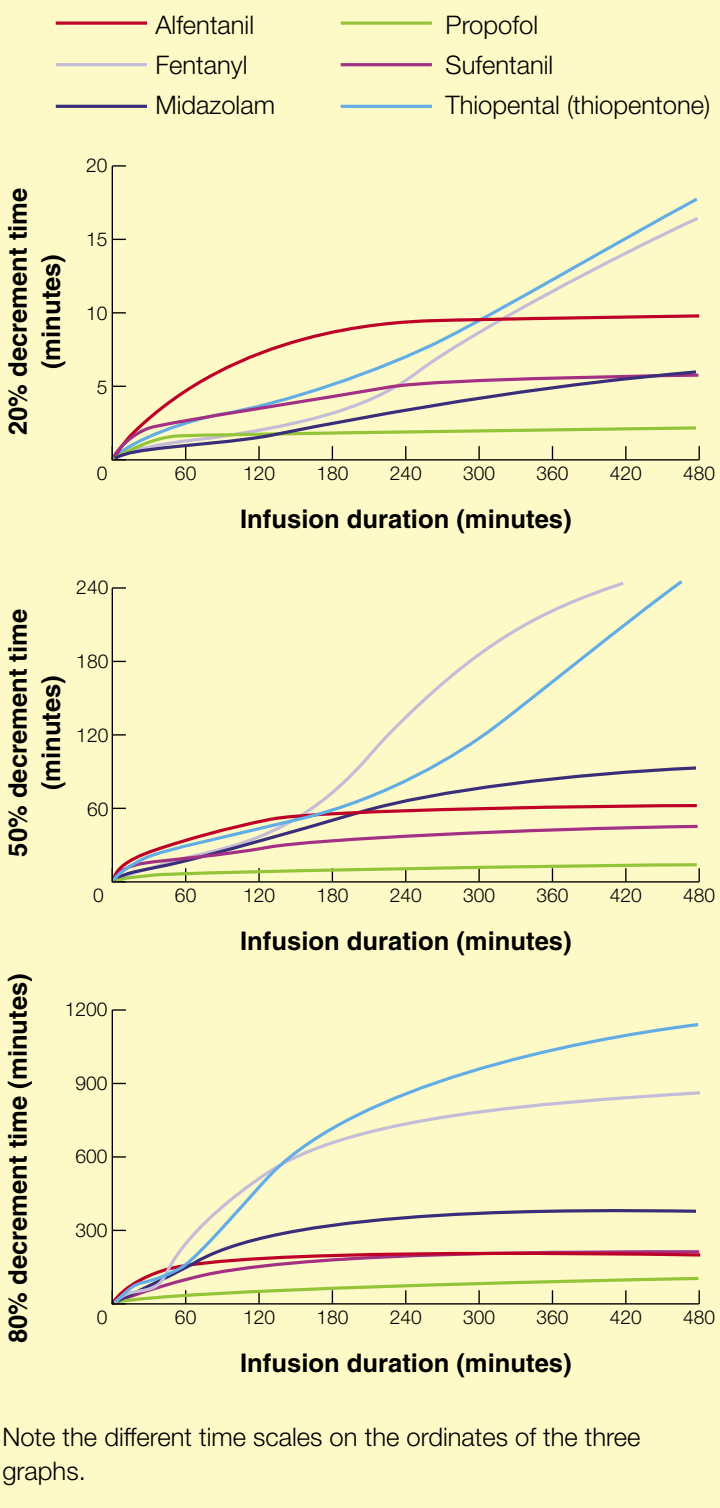
Furthermore, pharmacokinetic simulations can be used to develop manually adjusted BET infusion regimens that approximate the continuously changing infusions provided by computer control. Nomograms for devising manually adjusted infusion regimens are available in the literature.

Recovery after intravenous infusions

Prolonged infusions can lead to prolonged recovery times. A method for quantifying this phenomenon is to calculate the times required for blood concentrations to decrease by a fixed fraction after maintaining constant concentrations for various infusion durations. These are termed 'context-sensitive' decrement times ('context sensitive' referring to the infusion duration) (Figure 4). Note that propofol and sufentanil have context-sensitive 'half-times' (50% decrement times) that increase gradually with infusion duration. In contrast, the context-sensitive half-times of thiopental (thiopentone), fentanyl and midazolam are markedly dependent on infusion duration and become inordinately prolonged after infusions that last longer than 1 hour. Clinically, 50% concentration decrements of propofol and the three opioids often represent recovery from moderate clinical effects, however, there are also circumstances in which a 20% or an 80% plasma-concentration decrease is required for recovery. In Figure 4, conservative dosing, achieving blood concentrations that require only 20% decrements for recovery, leads to rapid recovery times, even after prolonged infusions. In contrast, when large concentration decrements are required for recovery (80%), context-sensitive recovery times show steep increases even after brief infusions.

Figure 4 illustrates that sufentanil is a good choice for opioid administration by infusion, having short, predictable context-sensitive half-times. The new opioid, remifentanil is rapidly hydrolysed by tissue esterases so that the 50% and 80% context-sensitive decrement times are 3 and 12 minutes, regardless of infusion duration because there is virtually no accumulation of drug in peripheral compartments. The protracted decrement times of fentanyl may be used to provide postoperative analgesia by administering infusions during prolonged surgery, attaining concentrations at which moderate analgesia is achieved without excessive respiratory depression (2–3 ng/ml).

Computer simulations of the context-sensitive decrement times of various hypnotics and opioids



Note the different time scales on the ordinates of the three graphs.

4

The rate at which drug concentration decreases after an infusion, is determined by the rate at which it is irreversibly removed from the body, as well as the rate of redistribution to peripheral tissues. Recovery after an infusion therefore has little relevance to the elimination half-life of a drug because the elimination half-life does not take redistribution into account. For example, propofol and sufentanil have long elimination half-lives but short context-sensitive half-times. Note that context-sensitive decrement times are not represented by a single number: they are a continuum of time values that are a function of infusion duration and can be represented by a graph. Considering that decrement times depend on the concentrations achieved as well as the dose history, it is often difficult for clinicians to anticipate patients' time to recovery. A useful feature of TCI is continuous calculation and display of expected times to recovery, should the infusion be stopped, assisting the clinician to ascertain when to reduce or terminate the infusion. A hydraulic model has been used to explain context-sensitive recovery times, in which the heights of fluid levels in interconnecting cylinders represent drug concentrations in various compartments. This analogy is identical to the model used by Mapleson to represent the uptake and elimination of inhaled anaesthetics.

Relationship between drug concentration and effect

Most drugs exert their effects at a distant site and the circulation transports drug molecules to their site of action. Whereas steady-state blood concentrations correlate with drug effects, when blood concentration is changing, or has recently changed, there is a time-lag between changing blood concentrations and changing effects. This phenomenon is illustrated in Figures 1 and 2. Limited space precludes a detailed discussion of the relationships between blood and effect-site concentrations; the time-related hysteresis between dose and effect is described in the further reading.

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Spinal Anaesthesia

William Harrop-Griffiths

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There are few, if any, techniques in anaesthesia that can match the effectiveness, elegance, economy, simplicity and safety of spinal anaesthesia. Its popularity has waxed and waned since its inception in 1898 but its use in anaesthesia and analgesia is likely to increase.

Anatomy
The spinal cord terminates at about the level of the first lumbar vertebra (L1) in the adult human. However, it is important to note that there is variation and that the end of the cord is below L1 in about 40% of patients. Beyond its termination, nerves continue to their exit points from the vertebral canal as a sheaf of nerves called the cauda equina (see page 108). The spinal cord and cauda equina are bathed in CSF contained by the arachnoid mater, a gossamer-thin membrane closely applied to the inside of a more substantial layer called the dura mater. The subarachnoid space ends at the level of the second sacral vertebra (S2).

The spinal anaesthetist aims to place drugs in the CSF so that they can act on the cauda equina and spinal cord. Spinal anaesthesia at the thoracic, and even cervical, level is recorded, but its use is not standard practice. Access to the subarachnoid space is usually attempted below the L1 level to avoid direct mechanical damage to the spinal cord by the spinal needle. It is thought that the nerve roots comprising the cauda equina are difficult to skewer with a needle. It has been suggested that the L3/4 interspace is the “highest that all good anaesthetists should aim for spinal insertion”.

Technique
The patient should receive a full explanation of the risks and benefits of the technique. Ideally, the patient should be treated in an environment that contains trained assistance for the anaesthetist, full resuscitation equipment and the facilities necessary for the performance of a general anaesthetic. Secure intravenous access should be gained. The patient should be placed in a position that increases the palpable spaces between the spinous processes. Usually, this is achieved by the patient flexing his or her spine in the lateral or sitting position.

The technique should be aseptic. Local anaesthetic should be injected subcutaneously and through the interspinous ligament into the space between the spinous processes. A spinal needle, usually at least 9 cm in length, is inserted in the midline and passed, often with a slightly cephalad angulation, until the characteristic feeling of the passage of the needle through the ligamentum flavum and dura mater is felt. The trochar of the needle is removed and a free flow of CSF is awaited before injection. It is common, though not mandatory, to aspirate CSF into the syringe at the beginning and end of the injection to confirm that the entire dose of drug is delivered into the CSF. The needle is then withdrawn.

A paramedian or lateral approach (i.e. using an entry point lateral to the midline) may be used if there are difficulties in accessing the subarachnoid space by the midline approach.

Recent modifications to include the passage of an epidural catheter at the same time as spinal injection (combined spinal-epidural) may involve the placement of a Tuohy or other epidural needle in the epidural space and the subsequent passage of a spinal needle through the epidural needle. A longer spinal needle is needed for this technique so that it emerges about 1 cm beyond the end of the epidural needle. Alternatively, purpose-designed epidural needles with separate channels or orifices may be used to facilitate this technique.

The placement of a subarachnoid catheter to allow the provision of continuous spinal anaesthesia suffered a setback with the withdrawal of small spinal catheters in the USA. The drugs used for spinal anaesthesia are listed in Figure 1.

Local anaesthetics and adjuncts commonly used for spinal anaesthesia and analgesia

Local anaesthetics	Drugs used to prolong block	Opioids	Alternative analgesic drugs
Bupivacaine	Adrenaline (epinephrine)	Fentanyl	Ketamine
Lidocaine (lignocaine)	Phenylephrine	Morphine	Neostigmine
Tetracaine	Clonidine	Diamorphine	
		Pethidine	

Factors affecting block height (Figure 2): the term baricity in this context describes the specific gravity of a spinal injection relative to that of the CSF. A hyperbaric solution is heavier than CSF and will fall with gravity, and is often termed a ‘heavy’ solution. A hypobaric solution will rise against gravity. An isobaric solution will neither fall nor rise. Local anaesthetic solutions can be rendered hyperbaric by the addition of glucose and hypobaric by the addition of sterile water. Unadulterated local anaesthetic solutions (e.g. 0.5% and 0.75% bupivacaine) are effectively isobaric and the height of the block after their injection is dependent largely on the mass of drug injected. The final block height after the injection of hyperbaric and hypobaric solutions depends, to an extent, on the patient’s position. For instance, injection of a modest amount of hyperbaric solution in the sitting position will lead to a so-called ‘saddle block’, (i.e. a block of the sacral roots; the parts of the body that come into contact with a horse’s saddle). If a hyperbaric solution is injected and the patient is laid supine shortly after injection, the block height is likely to approximate to the root value of the most dependent part of the thoracic kyphosis (i.e. the mid-thoracic dermatomes). Adjusting the patient’s position after injection of a hyperbaric solution may encourage or limit spread. If a higher block is required, the patient can be turned to the head-down position. If no further cephalad extension of the block is required, the patient can be turned to a head-up position, being mindful of the potential this position has for leading to hypotension. The response to hypotension in a patient who has just undergone spinal anaesthesia with a hyperbaric solution should not include placing the patient head-down; this encourages further cephalad spread of the block.

Hypobaric solutions can be injected into a patient in the prone jack-knife position to encourage a sacral block or in the patient with, for instance, a fractured neck of femur, while lying on the unaffected side, encouraging a more unilateral block of the affected, uppermost hip. Positional changes after about
5 minutes have little value as the local anaesthetic is thought to be ‘fixed’ by this time, although the maximum block height after spinal anaesthesia can take 20 minutes to achieve.

Relation of factors to block height

Factors affecting block height
- Baricity of solution
- Patient position
- Mass of drug
- Direction of lateral bevel of spinal needle
- Gender
- Patient height (minor effect)
- Age (minor effect)

Factors not affecting block height
- Barbotage (the repeated injection and aspiration of solution during a spinal injection)
- Patient weight
- Rate of injection
- Coughing or straining
- Added vasoconstrictor

Physiological effects
The injection of local anaesthetics into the CSF causes blockade of the nerves of the cauda equina and the spinal cord. The degree and extent of the block depend on the mass of the drug, its concentration, its baricity and the position of the patient. Rather than the segmental block seen in epidural anaesthesia, spinal blockade affects all nerves at, and distal to, the maximum dermatomal height of the block. Nerve types are blocked in the traditional order, thus small nerve fibres serving the sympathetic nervous system, pain and temperature are blocked before touch and motor fibres. The use of low concentrations of local anaesthetic is thought to be able to produce a degree of ‘differential block’, leading to a spinal block that provides analgesia without significant impairment of motor function. This form of block is popular for the initiation of analgesia in labour.

Opioid drugs given on their own or in combination with local anaesthetics act on the opiate receptors in the spinal cord. Other drugs (see below) may be added to modify the baricity of the injectate or the duration of the block.

The physiological impact of a spinal block is proportional to its dermatomal height. Blockade of the sympathetic nerves arising from the mid-thoracic and upper thoracic segments causes significant venous pooling and results in hypotension. A spinal block to T10 has minimal cardiovascular impact. A block to T6 causes a decrease in arterial blood pressure in the order of 25%, and a block to T4 decreases it by about 30%. The cardiac sympathetic (cardio-accelerator) nerves have root values of T1–T4. Blockade of these nerves causes bradycardia and worsens hypotension.

Unopposed parasympathetic activity in the gut can cause hyperperistalsis with blocks above T5, which are therefore associated with nausea and vomiting.

In patients with significant lung disease, progressive blockade of intercostal muscles may give rise to dyspnoea. Extension of the block to the mid-cervical segments (C3–C5) affects the function of the phrenic nerves. Extension of the local anaesthetic through the foramen magnum allows it to bathe the hindbrain and causes unconsciousness, often called a ‘total spinal’.

Use of spinal anaesthesia
Spinal anaesthesia is safe and effective but consideration must be given to the following factors.
- Surgery should be on the lower abdomen/pelvis or on the lower limb.
- A single-shot spinal may have a duration of only 60–90 minutes. Continuous spinal anaesthesia may be used to prolong the block for operations longer than this.
- Contraindications are listed in Figure 3.
- The risk of headache should be considered (see below).
- Thought should be given to the provision of analgesia after the block has worn off.

The addition of opioids to the spinal injection may prolong analgesia for up to 12 hours. The use of a combined spinal-epidural will allow analgesia via an epidural catheter for a prolonged period.

Contraindications to spinal anaesthesia

Absolute
- Patient refusal may lead to legal action for assault
- Increased intracranial pressure may cause coning and death
- Severe coagulopathy may cause epidural haematoma or subarachnoid bleed

Relative
- Local sepsis may lead to epidural abscess or meningitis
- Systemic sepsis may lead to epidural abscess or meningitis
- Moderate coagulopathy (includes anticoagulent therapy) may cause epidural haematoma or bleeding
- Hypovolaemia may cause marked hypotension
- Mild coagulopathy (includes anticoagulant therapy) may cause epidural haematoma or subarachnoid bleed
- Neurological disease (e.g. multiple sclerosis may lead to deterioration – there is no convincing evidence to suggest that spinal anaesthesia causes a significant deterioration in chronic neurological conditions such as multiple sclerosis)

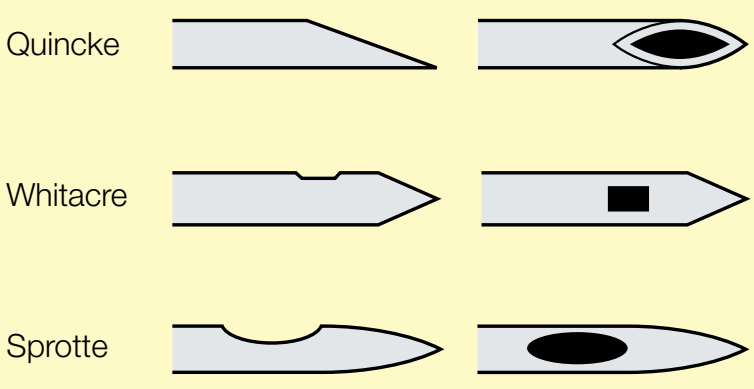
Complications
Hypotension: can be a desirable side-effect or an undesirable complication, depending on the clinical situation. It is customary to ‘preload’ patients undergoing spinal anaesthesia with moderate to large volumes of crystalloid or colloid in an attempt to minimize hypotension. Doubt has been cast on this approach and many anaesthetists now agree that “the solution to pharmacological vasodilation is pharmacological vasoconstriction”. The author will continue to use moderate preloading in patients not at risk of volume overload until the adverse effects of this practice are proven beyond reasonable doubt. However, it is mandatory to have access to vasoconstrictor drugs when administering spinal anaesthetics. The choice of drug is seldom critical. Ephedrine is popular for obstetric anaesthesia because of its beneficial effects on ovine placental blood flow. This is also logical because the hypotension is often a combination of vasodilatation and bradycardia, making a combined α- and β-adrenoceptor agonist a good choice. Methoxamine and metaraminol are also effective vasoconstrictors. Bradycardia should be treated with an anticholinergic drug, most popularly atropine. The occasionally dramatic hypotension seen with spinal anaesthesia to mid-thoracic levels makes the technique an unwise choice in patients with heart valve stenosis or a limited stroke volume for other reasons.

Post-dural puncture headache (PDPH): the incidence of PDPH is proportional to the size of the hole in the dura. Spinal needles in common use range from the large 18 G and 22 G needles used by physicians for diagnostic lumbar punctures to the 25 G, 27 G and 29 G needles favoured by anaesthetists. However, the shape of the hole may also be important. Spinal needles that have a conical tip (e.g. Whitacre, Sprotte) are less likely to cause PDPH than similar sized needles with a traditional cutting (Quincke) tip (Figure 4) because the conical tipped needles divide, rather than cut, the dural fibres. Similarly, a cutting bevel lined up with the longitudinal dural fibres is thought to be associated with a lower incidence of PDPH than a bevel cutting across the fibres (Figure 5).

The young suffer a higher incidence of PDPH than the old, and females fare worse than males, pregnant ones even more so. Multiple dural punctures are associated with a higher incidence of PDPH than a single puncture. The passage of a subarachnoid catheter, even though it necessitates the production of a relatively large hole in the dura, may enjoy a lower incidence of PDPH than an equivalent sized hole made for a single injection. The reasons are poorly understood, though oedema of the dural edges may be implicated. Traditionally, patients were not allowed to mobilize for some hours after spinal anaesthesia because this was thought to decrease the incidence of PDPH. This dogma is now being questioned.

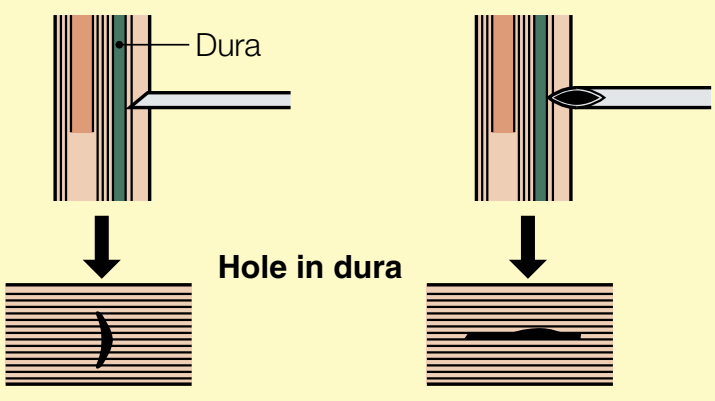
The management of PDPH includes bed rest, adequate hydration, good analgesia and, if severe or prolonged, an epidural blood patch.

Common tip designs for spinal needles



4

Number of fibres cut by different shaped needles



If the bevel of a spinal needle with a Quincke tip is aligned parallel with the fibres of the dura, fewer fibres are cut as shown on the right.

5

Failure: spinal anaesthesia is a simple procedure and, with training and experience, access to the CSF should be achievable in all but a few patients.

Neurological damage to the spinal cord or cauda equina can be caused by direct needle trauma or administration of neurotoxic drugs. Neurological damage is rare, and it should be noted that neurological damage from such conditions as anterior spinal artery syndrome can occur during general anaesthesia in the absence of spinal or epidural techniques. Anterior spinal artery syndrome comprises damage to motor nerves in the anterior part of the spinal cord due to inadequate blood supply from its nutrient artery, the anterior spinal artery. When seen, this rare condition is usually associated with a combination of widespread atherosclerotic disease and sustained hypotension.

Rare complications

- Infection of the meninges is a potential risk of spinal anaesthesia but convincing reports of its occurrence are rare.
- The use of spinal opioids may be associated with late respiratory depression. Cephalad spread of CSF containing opioid drugs gaining access to the respiratory centre located superficially in the floor of the fourth ventricle may cause delayed and potentially fatal respiratory depression. Doubt has recently been cast on whether the incidence of this complication is any higher or more significant than the risk of respiratory depression with opioids given by the intravenous or intramuscular routes. The risk of late respiratory depression with spinal opioids increases with increasing age, and the concomitant administration of opioids or CNS depressants by any other routes.
- There have been occasional reports of short-term deafness or cranial nerve dysfunction after spinal anaesthesia. Very rarely, sudden cardiac arrest may occur with no apparent cause in young adults undergoing spinal anaesthesia.

Spinal Anaesthesia and Spinal Cord Trauma

Felicity Reynolds

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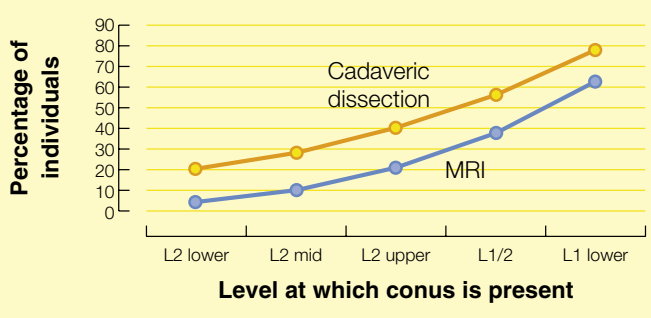
Spinal anaesthesia is simple to perform and in the field of obstetric anaesthesia it avoids the mortal risks associated with general anaesthesia and epidural blockade. As the local anaesthetic dose requirement for intrathecal anaesthesia is one-tenth that for epidural, the risk of total spinal blockade is minimized, while accidental intravenous injection is less likely and less dangerous. However, complications such as headache and nerve damage are more significant. Headache was so common in the obstetric population that it deterred many from using spinals until the reintroduction of atraumatic needles. Since then, spinal anaesthesia has exploded in popularity. In consequence, other sources of morbidity are of crucial importance.

The subarachnoid space deserves our respect. It contains not only the spinal cord, but also nerve roots that are devoid of the dural covering that protects them in the epidural space. This puts them at greater risk from neurotoxic injury and from trauma. Every injectate must be screened with care and every spinal needle inserted gently with control; paraesthesiae on needle insertion may presage prolonged symptoms.

More serious than nerve root damage is spinal cord damage. The conus medullaris, the tapering lower end of the spinal cord, is not at a constant segmental level. Although widely supposed to end at the lower border of the body of L1 in adults, in 1894 it was shown to reach L2 in 27% of men and 43% of women. Further studies of cadavers and adult MRI scans showed that the conus may reach the lower border of L2 in 2–20% of individuals, and L1/2 in 37–57% (Figure 1). Thus, choosing L1/2 for spinal insertion should be out of the question, while even the L2/3 space is unwise, but a genuine L3/4 is safe, other than in children or in the presence of a tethered cord (a rare congenital abnormality).

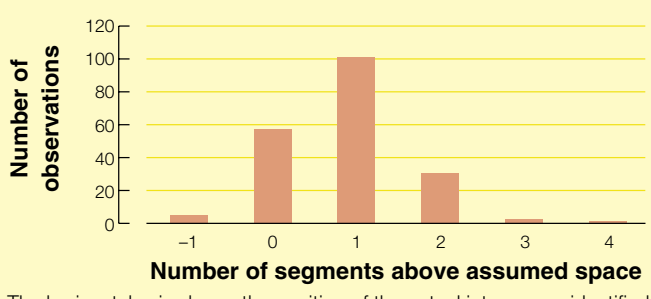
Proportion of adults in whom the cord would be present at each spinal level



Cumulative data, derived from: Reimann A F, Anson B J. *Anatomical Record* 1944; **88:** 127–38 and Saifuddin A *et al. Spine* 1998; **23:** 1452–6. Reproduced with permission from the publishers of *Anaesthesia*.

1

Identification of lumbar interspaces by Oxford anaesthetists



The horizontal axis shows the position of the actual interspace, identified by MRI, relative to the assumed space, in 200 observations. Data from: Broadbent C R *et al*. *Anaesthesia* 2000; **55:** 1122–6. Reproduced with permission from the publishers of *Anaesthesia*.

2

Medical students and preregistration house officers are recommended to use L4/5 for lumbar puncture, to avoid damage to the spinal cord. Anaesthetists, who have become accustomed to a relative freedom of choice with epidural insertion, may have become incautious with spinal needles, while some textbooks have condoned the selection of spaces as high as L1/2. Even experienced anaesthetists are inaccurate in identifying lumbar segmental levels, with 68% of chosen spaces being higher than assumed by anything up to four segments (Figure 2). Experience does not improve accuracy, because in the absence of universal radiological screening, there is no feedback. Thus, you are more likely than not to select a space that is higher than you think, which is erring on the side of danger. To identify the interspace, Tuffier's line is more widely used than the twelfth rib, or counting down from the vertebra prominens or up from the sacrum. Although Tuffier's line usually crosses the midline at L4/5, it may be as high as L3/4. Its accuracy can be improved, but only slightly, by palpating both iliac crests, rather than by dropping a perpendicular from one towards the midline. Obesity reduces the accuracy of interspace identification by any of the methods.

Does such inaccurate identification of lumbar interspaces really matter for spinal insertion? Yes it does. During the 1990s a number of cases of conus damage following spinal anaesthesia were reported, and many more are *sub judice*. The damage appeared to follow needle insertion alone; avoiding injection after painful insertion did not remove the risk. Patients suffered from persistent pain, paraesthesiae and sometimes numbness, usually unilateral, in dermatomes L4/5–S1, foot drop and in some cases disorders of micturition. On MRI scan an area of high signal on T2 was visible on the same side as the clinical lesion. This was variously reported as suggestive of a small syrinx, haematoma or infarct. Recovery was slow or partial. In most cases anaesthetists believed they had used L2/3, but L1/2 was probably selected. Using as a defence that a practice is condoned by a textbook may not be safe if the recommendation is not logical. Most, but not all, cases have followed the use of atraumatic needles, but these are so widely used that this is not evidence of their inherent danger.

Setting out to use any space above L3 for spinal anaesthesia, as for diagnostic lumbar puncture, is inadvisable, because of our inaccuracy and the variability of the position of the conus. A space in the lower lumbar region should therefore be our aim. Bear in mind the following:

- atraumatic spinal needles have at least 1 mm of blind tip beyond the hole
- from L1/2 the needle tip may reach the conus in about 60% of individuals
- from L2/3 it can reach the conus in 4–20%
- women are at greater risk than men
- Tuffier's line is not reliable
- the space you choose is probably higher than you think
- a spinal needle should not be inserted above the L3 spinous process. ◆

Upper Limb Nerve Blocks

Martin J Herrick
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The brachial plexus forms the entire somatic nerve supply to the upper limb except for the intercostobrachial and medial brachial cutaneous nerves, derived from T2, which supply the medial upper arm. The brachial plexus extends from the lateral aspect of the cervical vertebrae to the axilla, passing between the anterior and middle scalene muscles over the first rib, where it lies immediately behind the subclavian artery. Here it forms three trunks – upper, middle and lower. Below the clavicle, the plexus surrounds the axillary artery as three cords – medial, lateral and posterior.

The prevertebral fascia extends the length of the plexus and encloses the nerves with the subclavian then axillary artery to form a neurovascular bundle in a continuous sheath.

Figure 1 lists the prerequisites for regional anaesthesia.

Preparation for regional anaesthesia

- Explanation of procedure and risks, and obtaining consent
- Fasting
- Monitoring
  - blood pressure
  - ECG
  - pulse oximetry
- Intravenous access
- Resuscitation facilities
- Skilled technical support
- Aseptic technique
- Time
  - 15 minutes minimum for set-up and block
  - 45 minutes for anaesthesia (axillary block)

1

Nerve stimulation
Nerve stimulation facilitates nerve localization without generating painful paraesthesiae.

- The polarity of the needle should be negative to minimize the current required for stimulation.
- The stimulus frequency should be 2 Hz.
- An initial current of 1 mA is adequate. Higher currents may cause painful muscle twitches.
- When using needles with the whole bevel uninsulated, the needle tip is within 2 mm of the motor nerve when the muscle twitches at 0.5 mA (0.3 mA for those with only the bevel tip uninsulated).

Intraneural injection is unlikely if no muscle twitch occurs at 0.2 mA and the twitch ceases within 0.5 seconds after injection of 0.5 ml local anaesthetic. Resistance to injection should be minimal and the injection should be painless or generate only mild pressure sensation.

Brachial plexus block

The features of the three most common techniques for brachial plexus block, interscalene, subclavian perivascular and axillary, are outlined in Figure 2. With any of these techniques, a catheter can be inserted to provide prolonged analgesia. All approaches achieve sympathetic nerve block of the arm, while sympathetic block of the head, with Horner's syndrome, accompanies over 50% of procedures above the clavicle.

Although some anaesthetists use large volumes of 0.5% bupivacaine alone, apparently with a very low incidence of toxic reactions. 0.5% levobupivacaine or ropivacaine are less cardiotoxic alternatives. A mixture of 0.5% bupivacaine and 1% prilocaine reduces the toxicity potential and, in theory, promotes a quicker onset. Block duration averages 8–12 hours.

Three commonly used approaches to brachial plexus blockade

	Interscalene	Subclavian perivascular	Axillary
Blocks	C4–C6/7 roots	Upper/middle trunks ± lower trunk	Medial and lateral cord/ulnar and median nerves
Misses	C8–T1 roots	Lower trunk (in 10%)	Musculocutaneous nerve Posterior cord/radial nerve
Good for	• Shoulder • Upper arm	• Arm • Hand (? except ulnar)	• Ulnar forearm/hand • Continuous infusion • Children
Poor for	• Hand • Respiratory impairment	• Surgery on little finger • Coagulopathy • ? Emphysema	• Radial forearm
Local complications	• Phrenic nerve block • Subarachnoid block • Epidural block • Vertebral artery injection	• Pneumothorax • Haemothorax direct dural cuff • Subclavian artery puncture	• Phrenic nerve block • Recurrent laryngeal nerve block • Axillary artery puncture
Dose	• 0.5 ml/kg up to 40 ml	• 0.5 ml/kg up to 40 ml	• 50–60 ml

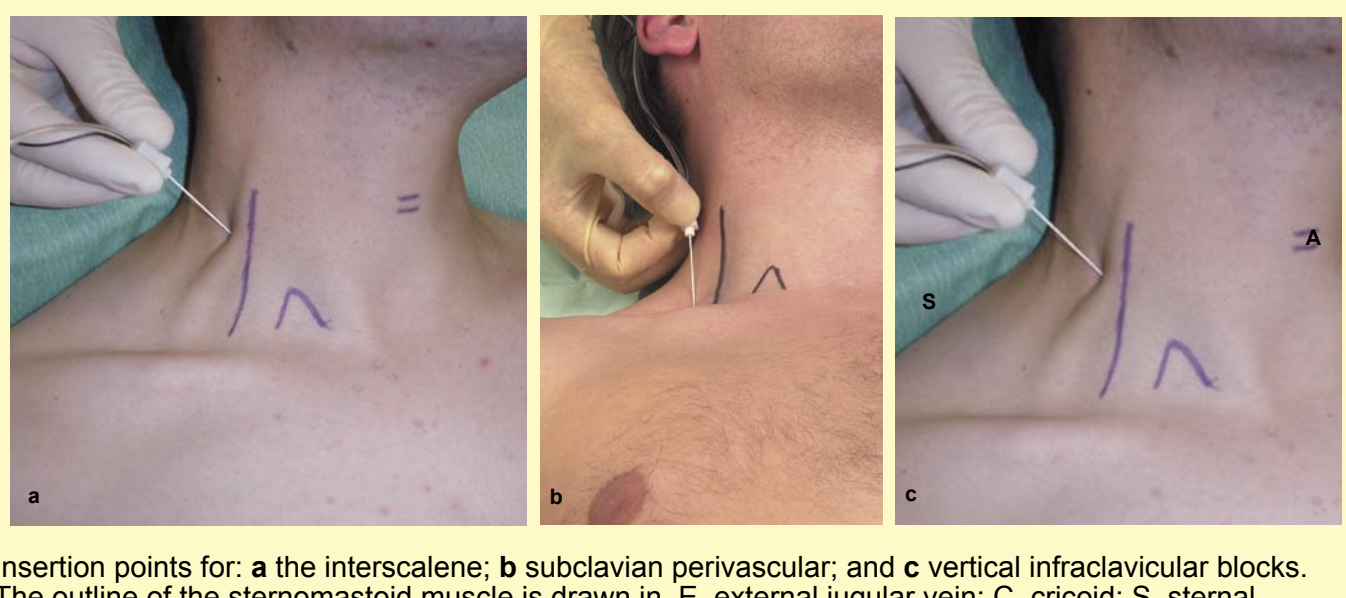
2

Interscalene block
Technique: the lateral border of the clavicular head of the sternomastoid muscle is identified at the level of C6, level with the cricoid cartilage. Palpating laterally, the shallow interscalene groove is identified at the same level. The external jugular vein usually crosses the groove at this point.

A 25-mm needle is inserted perpendicular to the skin and advanced medially, caudally and dorsally (Figure 3). With this angulation, the needle inserts on the transverse process of the vertebra if the roots are missed. The brachial plexus is usually only 1–2 cm deep at this point.

Using paraesthesiae to identify the plexus, sensation must be elicited below the shoulder; and, using muscle stimulation, a twitch should be evoked in the upper arm muscles. If nerve roots are not located, the needle reaches the lateral process of C6 (Chassaignac's tubercle) and is 'walked' anteriorly.

Landmarks are easily identified without special positioning, which is useful in patients with painful conditions. Caudal spread of local anaesthetic is encouraged by head-up positioning or digital pressure proximal to the injection site.



Insertion points for: **a** the interscalene; **b** subclavian perivascular; and **c** vertical infraclavicular blocks. The outline of the sternomastoid muscle is drawn in. E, external jugular vein; C, cricoid; S, sternal notch; A, acromion.

3

Complications: direct, horizontal insertion risks penetration of vertebral vessels, or the epidural or subarachnoid spaces through the intervertebral foramen. Phrenic nerve block (almost 100%) may be a hazard in patients with chronic pulmonary disease, though the risk is less than expected in those with emphysema (possibly because the diaphragm is already splinted by hyperinflated lung).

Subclavian perivascular block
Subclavian perivascular block, a supraclavicular approach to the brachial plexus, is an interscalene block, but it anaesthetizes the three trunks of the plexus as they cross the first rib.

The first rib runs approximately anteroposteriorly at the point where it is crossed by the trunks of the brachial plexus between the scalene muscles. The rib therefore acts as a 'backstop' to the advancing needle. As the lower trunk may lie under the subclavian artery, the medial antebrachial and ulnar nerves are the most commonly missed. This block is therefore unsuitable for surgery confined to the medial side of the limb.

Technique: the insertion point is in the inferior part of the interscalene groove, posterior to the subclavian artery (palpable in only 50% of patients). A 50-mm needle is aimed directly caudally (Figure 3). There must be no medial angulation to avoid the needle passing the medial edge of the first rib and entering the pleura. The plexus is usually 2–3.5 cm below the skin. If paraesthesiae are used to identify the plexus, clear sensation must be elicited below the shoulder. Using muscle stimulation, a twitch should be evoked in muscles below the elbow. If the needle inserts on the first rib, it should be redirected anteriorly or posteriorly.

Complications: pneumothorax may occur, but is less likely with subclavian perivascular block than with the classical supraclavicular approach, in which the risk is 2–25%. It may not become apparent for 8–12 hours. Emphysematous bullae at the apex of the lung are contraindications to this approach.

If the subclavian artery is punctured, it is difficult to apply pressure. This block is therefore not recommended in patients with bleeding diatheses.

Phrenic nerve block is less common with this approach than with interscalene brachial plexus block.

In children under 12 years of age, the first rib is not fully calcified, and may not prevent the needle penetrating pleura.

Axillary block
The axillary approach is technically easier for beginners, and is associated with fewer major complications. It is also the easiest approach for catheter insertion, which facilitates prolonged analgesia and sympathetic blockade following major reconstructive surgery.

Technique: with the patient's arm abducted to 90°, a finger is placed over the pulsation of the axillary artery in the groove between the pectoralis major and latissimus dorsi muscles. A 25-mm needle is inserted adjacent to the fingertip and towards the apex of the axilla. The position of the needle tip may influence the scope of the block (Figure 4).

Axillary block requires a high volume of local anaesthetic. Applying digital pressure distal to the injection site encourages proximal spread. The musculocutaneous nerve leaves the sheath above the axilla, and is usually missed unless an additional 7–10 ml of local anaesthetic are injected into the coracobrachialis muscle.

Relationship of the needle to the axillary artery for preferential nerve block

Nerve preferred	Needle relationship to artery	
Median	Lateral	(above)
Ulnar	Medial	(below)
Radial	Posterior	(behind)

4

Identification

- Nerve stimulation: the success rate is higher (85–95%) if separate branches are located and individually blocked.
- Transarterial: depositing local anaesthetic behind and in front of the artery has a high success rate (90–99%).
- Click: a click is felt on passing through the perivascular sheath, accompanied by transmitted pulsation from the artery. It has a success rate of 50–80%.
- Paraesthesiae: the risk of nerve damage may be higher.

Vertical infraclavicular block

Infraclavicular approaches have not been widely accepted because it is difficult to determine the exact insertion point and the angle of advancement. However, the vertical infraclavicular block is an improvement. The insertion point lies immediately below the clavicle at the mid-point between the anterior surface of the acromion and the suprasternal notch. The stimulating needle is advanced directly posteriorly (i.e. vertically in the supine patient) until flexion or extension of the wrist or fingers is obtained (Figure 3).

Pleural puncture, though apparently inevitable, is highly unlikely provided that:

- the insertion point is not medial to that described
- there is no medial angulation while advancing
- the needle is no longer than 50 mm.

It is usually easy to define the landmarks, even in obese patients; and the patient's arm may rest on the abdomen during the procedure, which is more comfortable following trauma.

Theoretically, there is a higher chance of blocking all the nerves, but a large volume of local anaesthetic (50 ml) is required, because at this point the sheath is at its broadest in the sagittal plane.

As yet there are few studies evaluating the effectiveness and the risks of vertical infraclavicular block compared with more conventional approaches.

Intercostobrachial and medial brachial cutaneous block

The intercostobrachial and medial brachial cutaneous nerves supply the skin on the medial side of the upper arm, an important fact to remember if an upper arm tourniquet is applied. They are blocked by subcutaneous infiltration over the axillary artery. Because this block is required only for the duration of surgery, 1% prilocaine or 1% lidocaine (lignocaine) is ideal. However, the dose of 3 ml, which is often quoted, is inadequate; 10 ml over the artery, extending to the anterior corner of the axilla under pectoralis major and to the posterior axillary fold, allows comfortable tourniquet use for 90 minutes.

Nerve blocks at the elbow

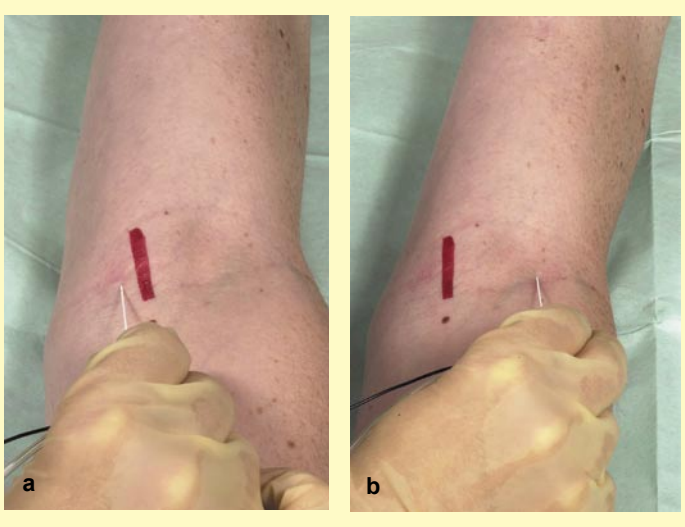
Nerve blocks at the elbow may augment an incomplete brachial plexus block and, using 0.5% bupivacaine, they can last for 12 hours or more. Except for ulnar nerve block for surgery to the little finger, they are not used as sole anaesthesia because:

- there are six nerves potentially requiring blockade, including sthe three cutaneous nerves of the forearm
- nerve distribution of the hand is variable with wide overlap
- there is no anaesthesia for an upper arm tourniquet.

Ulnar nerve passes between the medial epicondyle and the olecranon, in a tunnel formed by the two heads of flexor carpi ulnaris. It is blocked 2 cm proximal to this in order to minimize the risk of pressure neuropathy. Using a 25-mm stimulating needle, flexion of the little and ring finger or adduction of the thumb is sought. Wrist flexion should be ignored because this may be due to direct muscle stimulation. Only 3–4 ml of local anaesthetic is required.

Median nerve usually lies 1 cm medial to the brachial artery at the level of the intercondylar line (Figure 5). It is 0.5–1 cm deep to the bicipital aponeurosis. A 25-mm needle is inserted in a slightly cephalad direction until a 'pop' is felt as the aponeurosis is punctured. Flexion of the wrist or fingers indicates proximity to the nerve and 6–8 ml of local anaesthetic is injected.

Radial nerve may be blocked at the intercondylar level, in the groove between the biceps and brachioradialis muscles(Figure 5). If too distal, it is possible to block the deep (muscular) and miss the superficial (sensory) branches. The nerve is 2–3 cm deep and overlies the lateral epicondyle. Using a 50-mm stimulating needle, finger or thumb extension are sought. Direct muscle stimulation may cause wrist extension, which should be ignored. A local anaesthetic dose of 8 ml is sufficient.



5a Median and **b** radial nerve blocks anterior to the left elbow, showing insertion points at the intercondylar line. The surface marking of the brachial artery is drawn on the skin of the cubital fossa.

Nerve blocks at the wrist

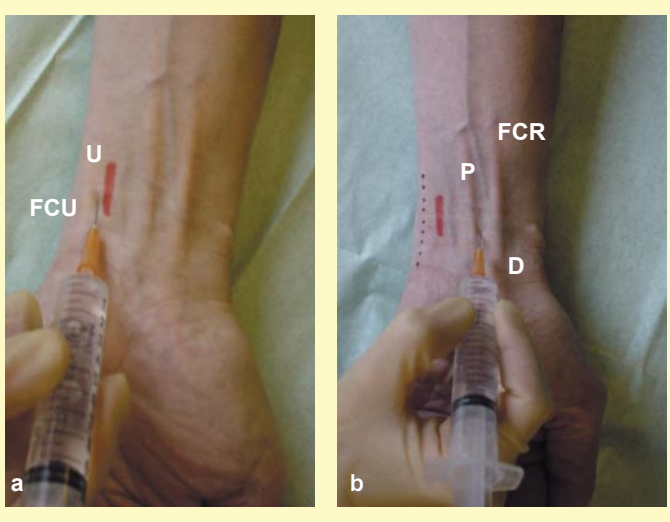
Nerve blocks at the wrist may be used for surgery on the distal palm or fingers, provided that a forearm tourniquet is suitable (the lower muscle mass reduces ischaemic tourniquet pain) and the maximum surgical time is 1 hour, because of the absence of anaesthesia for the tourniquet. Such nerve blocks are particularly suitable for day case surgery, because full arm control is maintained. Using 2% lidocaine (lignocaine), the onset of block is 5 minutes.

All three nerves are blocked 2 cm proximal to the distal skin crease of the wrist. Nerve stimulation is seldom successful. Consequently, the median and ulnar nerves are located by paraesthesiae using a 25 G needle. This makes the blocks unsuitable for anaesthetized patients or, arguably, for augmenting an incomplete brachial plexus block.

The nerve supply to the hand is variable. Furthermore the deep tissues of the hand do not reflect dermatomal distribution. The radial nerve is almost entirely cutaneous, while the ulnar nerve supplies deep tissues extending to the thenar eminence.

Ulnar nerve lies between the tendon of flexor carpi ulnaris and the ulnar artery (Figure 6). The needle is advanced with slight cephalad angulation until the patient feels paraesthesiae in the little or ring fingers. The needle is then withdrawn 1 mm and 3 ml of local anaesthetic slowly injected.

Median nerve is located deep to the flexor retinaculum, between the tendons of flexor carpi radialis and palmaris longus (Figure 6). In the absence of palmaris longus, the nerve is found 1 cm. to the ulnar side of flexor carpi radialis. The needle is advanced with slight cephalad angulation through the flexor retinaculum until the patient feels paraesthesiae in the thumb or index finger. After withdrawing 1 mm, 3 ml of local anaesthetic is injected. Because the superficial palmar branch arises proximal to the wrist, a further 3 ml of local anaesthetic is deposited subcutaneously.



6a Ulnar and **b** median nerve blocks of the left wrist. U, ulnar artery; FCU, flexor carpi ulnaris; FCR, flexor carpi radialis; P, palmaris longus; D, distal skin crease.

Superficial radial nerve divides 7 cm above the wrist. Using a 23 G long-bevelled needle, a subcutaneous weal of 6–8 ml of local anaesthetic is placed in a transverse line from the palmar edge of the radial styloid to the mid-dorsum of the wrist, taking care to avoid intravascular injection.

Day case surgery

The potential to avoid general anaesthesia, and thus minimize sedation and nausea postoperatively, makes regional anaesthesia attractive for day case surgery. Furthermore, it provides excellent postoperative analgesia. Selection guidelines for day surgery should be maintained, because failure of the block may necessitate general anaesthesia.

The techniques with lower risks include axillary brachial plexus block, wrist block and intravenous regional anaesthesia. Higher approaches to the brachial plexus are associated with more serious complications. With the interscalene brachial plexus block, complications are unlikely to occur more than 4 hours after the block is performed. This block is therefore excellent for major arthroscopic surgery of the shoulder as a day procedure. Pneumothorax resulting from other supraclavicular approaches may be delayed by up to 12 hours and these approaches may therefore be more appropriate for 23-hour stay procedures.

FURTHER READING

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Anaesthesia for Bronchoscopy, Tracheal and Airway Surgery

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Flexible bronchoscopy is usually carried out under conscious sedation and topical local anaesthesia. The Academy of Medical Royal Colleges has published relevant procedural guidelines for flexible bronchoscopy.

Rigid bronchoscopy is performed to aid the diagnosis and management of transbronchial and pulmonary pathology, and, particularly in children, for the removal of inhaled foreign bodies. It is usually carried out under general anaesthesia.

Preoperative assessment: it is important to assess cardio-respiratory physiology, airway considerations, neck mobility and a history of smoking. Chest radiography for airway and pulmonary pathology is mandatory. Other investigations are clinically determined.

Induction: if the airway is patent, intravenous induction is used. Neuromuscular blockade is achieved with a drug chosen for an appropriate duration of action.

Bronchoscopy causes a profound vasopressor response that must be controlled, usually by short-acting opioids, short-acting intravenous β-blockade or magnesium sulphate. Remifentanil infusion combined with propofol or sevoflurane can provide good cardiovascular stability and rapid recovery.

Position: the patient is supine with the head resting on a single pillow. The eyes and vulnerable teeth or bridgework should be protected. As the bronchoscope is advanced it is usually necessary to extend the patient's neck.

Ventilation and airway management: the two ventilatory strategies used during bronchoscopy are a Sanders' injector or intermittent positive-pressure ventilation (IPPV) via the ventilating side-arm of the bronchoscope.

The injector uses a high-pressure oxygen supply to release a jet of oxygen from a needle at the operator end of the bronchoscope. This creates a Venturi effect, entraining atmospheric air, and provides an inspiratory gas mix of oxygen-enriched air. Using this technique it is essential that there is free passage of air from the upper airway, to enable entrainment of air and to allow passive expiration, thereby avoiding volutrauma.

The ventilating bronchoscope has a glass window or a rubber diaphragm to enable passage of instruments, and a side arm that can be connected to an anaesthetic circuit. Ventilation can be managed with an appropriate gas mix including a volatile anaesthetic agent. This technique is most commonly used in children and babies, hand ventilating via a T-piece.

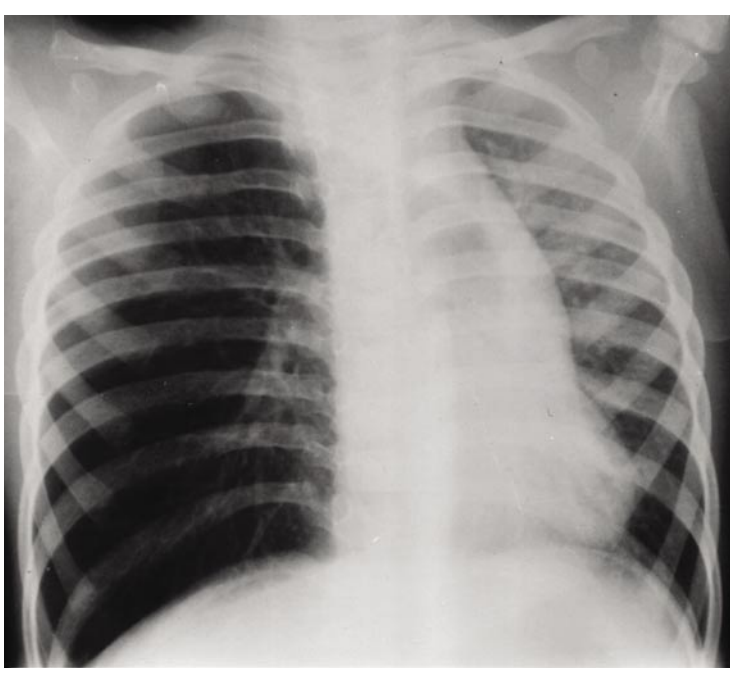
Maintenance of anaesthesia: the use of a Venturi injector necessitates an intravenous technique for maintenance of anaesthesia. Propofol is widely used and its rapid offset makes it an ideal agent in most cases. Whether intermittent boluses, infusion, or target-controlled infusion is used depends on individual preference. When a ventilating bronchoscope is used, a volatile agent can be used for maintenance of anaesthesia. Rapid emergence is desirable, therefore sevoflurane or desflurane are preferred.

Postoperative management: unless bronchoscopy is to be followed by a surgical procedure, a rapid emergence is desirable with airway reflexes and cough being restored. This allows secretions and blood to be cleared effectively.

Interventional bronchoscopy

Inhaled foreign body

An inhaled foreign body is most common in children under 3 years of age. It is not infrequent in the obtunded (e.g. in alcoholism) and may also occur in senile dementia. It may present in a number of ways from acute upper airway obstruction, to a more insidious presentation with a chronic cough, recurrent respiratory tract infections and unilateral wheeze, depending on where the foreign body lodges. Radiological examination may be normal, may reveal a radio-opaque foreign body or may show unilateral hyperinflation due to obstruction (Figure 1). An inhalational induction is traditional because IPPV may blow the foreign body distally into the smaller airways, or may cause a ball-valve effect, resulting in distal air trapping. The alternative school of thought is that any foreign body that requires bronchoscopic removal is impacted and unlikely to be displaced with IPPV. Intravenous induction, paralysis with suxamethonium, and passage of the bronchoscope provides the fastest, safest means to secure the airway. This approach relies on having a skilled bronchoscopist present at induction.



1 Plain chest radiograph of a 6-year-old child showing hyperinflation of the right lung caused by obstruction of the right main bronchus by a foreign body.

After removal, laryngeal stridor may develop because of repeated instrumentation of the airway. Intravenous dexa-methasone, 600 μg/kg/day in 4 divided doses, and nebulized adrenaline (epinephrine), 5 ml of 1:10,000, repeated every 2–4 hours, are normally sufficient to provide relief. In severe cases, re-intubation and a period of postoperative ventilation may be necessary.

Bronchoscopic stent insertion and tumour debulking

In critical stenosis, a tracheal stent can be sited, as palliation, or until definitive surgery is undertaken. Laser, diathermy and cryotherapy are used to debulk tumours obstructing the airway. Induction of anaesthesia may result in complete obstruction. The patient is preoxygenated, and anaesthesia induced cautiously by intravenous or inhalational means. Each technique has advantages and disadvantages. When an adequate depth of anaesthesia has been reached the airway should be assessed and ventilation taken over. It is essential that a skilled bronchoscopist is present: this may be the only way to relieve the obstruction if the airway is lost.

For laser resections, precautions must be taken to avoid airway fires .
- Use as low an inspired oxygen concentration as possible.
- Nitrous oxide should be avoided.
- Short bursts of laser should be used.
- All personnel should be trained in the use of the equipment.

Tracheal surgery

Tracheal surgery was first performed in the 1950s, and subsequent advances in anaesthetic and surgical practice have made increasingly radical resections possible. It may be possible to excise more than half the trachea. The challenges for the anaesthetist are:
- airway compromise
- airway sharing
- airway transection
- postoperative airway oedema.

Tracheal surgery requires close communication between anaesthetist and surgeon, and a planned strategy to deal with the airway and ventilation.

Indications: tracheal resection is indicated for stenotic or obstructive lesions of the trachea. Most commonly, these are benign strictures following intubation, or tracheostomy. The different causes of tracheal pathology are summarized in Figure 2.

Aetiology of tracheal pathology

Intrinsic tumours
Primary
- Malignant (adenoid cystic carcinoma, squamous cell carcinoma)
- Benign (neurofibroma, chondroma, chondroblastoma, haemangioma, pleomorphic adenoma)

Secondary
- Direct extension (thyroid, larynx, lung, oesophagus)
- Metastasis (lung, breast, lymphoma)

Inflammatory lesions
- Post-intubation
- Post-traumatic
- Post-infectious
- Burns
- Connective tissue diseases (systemic lupus erythematosus, Wegener's granulomatosis, amyloidosis)

Extrinsic lesions (NB not treated by tracheal resection)
- Goitre
- Vascular compression

Miscellaneous
- Sarcoidosis, osteoplastica tracheopathia, idiopathic

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Preoperative assessment: in addition to cardiorespiratory assessment a full assessment of the site and extent of the stenosis is made. CT is the most useful investigation. In addition, pulmonary function tests provide functional information about the stenosis. It is important to assess neck movement because the neck is extended and flexed intraoperatively.

Induction: a selection of small tracheal tubes must be available, including uncuffed and armoured tubes. A surgeon must be ready with a rigid bronchoscope in case of obstruction. Intra-arterial monitoring should be established before induction, along with ECG, pulse oximetry and capnography. In cases of severe stenosis, induction should be performed cautiously, as described above. If the stenosis is less severe, intravenous induction can be performed safely and the bronchoscope inserted when the patient is paralysed.

Bronchoscopy is performed to assess the site and extent of the lesion and to assess the amount of healthy trachea proximal and distal to the lesion. Intubation is then performed. The tip of the tracheal tube should be above the lesion, unless the lesion is so proximal that the tube cannot be secured, in which case it should be passed beyond the stenosis.

Position: the position of the patient depends on the site of the lesion and the surgical approach. For high and mid tracheal lesions a collar incision is used with or without an upper sternotomy. The patient is placed supine with the neck in full extension. Before the anastomosis can be performed, the neck must be flexed to approximate the two ends. For low tracheal lesions the approach is via a right posterolateral thoracotomy incision, with the neck flexed. For carinal lesions a right posterolateral thoracotomy incision may be used, though a median sternotomy, or a clamshell incision may be chosen.

Ventilation and airway management

Many different ventilatory strategies have been used to deal with the problems associated with tracheal surgery. The site and extent of the lesion, and the preferences of the anaesthetist and the surgeon determine the technique used.

Manual jet ventilation: a Venturi injector can be used via a tracheal tube, bronchoscope, or small catheter to deliver oxygen and entrained air to the distal airway. This technique can be used for the entire procedure, but it is more often used during the period when the trachea has been transected, and the anastomosis created. To facilitate this, a small catheter is passed via the tracheal tube into the distal airway, to which the Venturi injector is connected.

Using this technique, the surgeon has good access to the surgical field, however, there are a number of disadvantages. Blood and debris can be sprayed across the surgical field or entrained into the distal airway. Manual jet ventilation often results in large tidal volumes, especially if too large an injector is used, causing volutrauma. If there is no route for egress of gas, barotrauma can result. Both of these are more likely if the catheter tip has migrated distally.

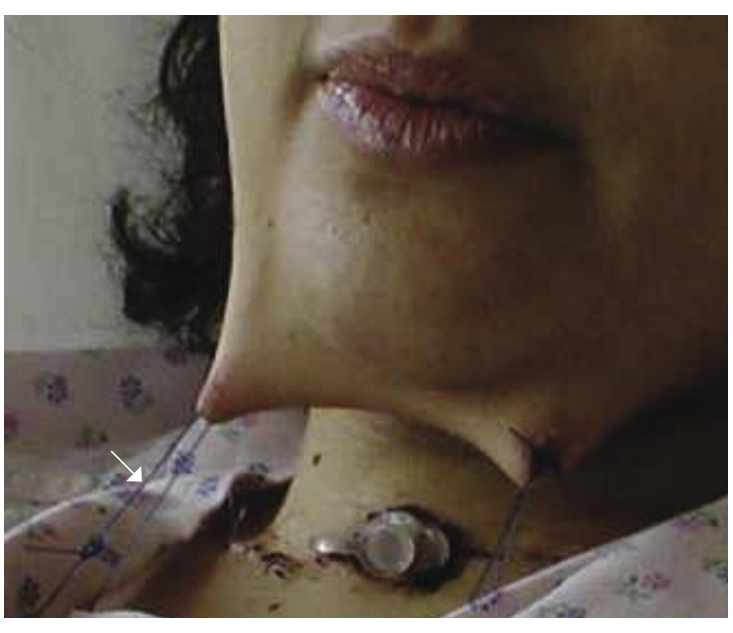
Mechanical jet ventilation may be used to provide a more controlled environment. There are several benefits to mechanical jet ventilation. Inflation pressures are lower than with conventional ventilation, but mean airway pressures are similar, which should decrease barotrauma and improve gas exchange through lung recruitment. It provides an unobstructed surgical field (as only a small catheter is passed into the distal airway), there is minimal lung expansion, or mediastinal movement, thus providing the surgeon with a quiet field, and because there is constant outflow of gas there is little chance of entrainment of blood or debris into the distal airways. However, if there is no route for free egress of gas from the lungs barotrauma will occur.

IPPV and distal tracheal intubation is the most commonly used technique. The trachea is intubated above the lesion. Once the trachea is opened the tracheal tube can be pushed across the lesion into the distal airway, or the surgeon places a sterile tracheal tube into the open distal trachea and the old tracheal tube is withdrawn into the proximal trachea. The diseased segment of trachea can be excised around the tracheal tube. To fashion the anastomosis it may be necessary to remove the tracheal tube for short periods of time. To facilitate these short apnoeic periods, ventilation should be with 100% oxygen during this part of the operation. When the posterior wall of the anastomosis is complete and the sutures are in place, the distal tracheal tube can be removed, the proximal tracheal tube carefully advanced across the anastomosis, and the anastomosis completed.

Other techniques: tracheal resection performed with the patient breathing spontaneously throughout the procedure has been described. However, there are many problems with this including the development of ventilatory acidosis, intraoperative coughing and aspiration of blood and debris into the distal airway.

Cardiopulmonary bypass appears to be a good way to ensure gas exchange and avoid the problems described above. However, it prolongs the procedure, has its own problems and is unnecessary. Systemic anticoagulation can cause bleeding, especially when the surgery is difficult.

Postoperative management
The anastomosis is protected from excessive traction. Guardian sutures are placed between the chin and the upper chest wall (Figure 3). This holds the neck in about 35° of flexion. They are left for 7–10 days, and is surprisingly well tolerated.



3 Guardian suture (arrowed) and minitracheostomy.

Several factors may compromise the postoperative airway. The trachea is oedematous and contains a vulnerable suture line. There may be a degree of soiling of the distal airway. The aims of early postoperative management are listed in Figure 4. ◆

Aims of early postoperative management

Early extubation
Positive-pressure ventilation and direct pressure from tracheal tube or its cuff may compromise the blood supply to the suture line

Clearance of secretions
- Humidification
- Physiotherapy
- Fibre-optic bronchoscopy
- Minitracheostomy

Decrease tracheal oedema
- Maintain a head-up position
- Nebulized adrenaline (epinephrine) and steroids (Note: these drugs may compromise anastomotic healing)

4

Anaesthetic Equipment for Thoracic Surgery

John W W Gothard
Tariq Hoth

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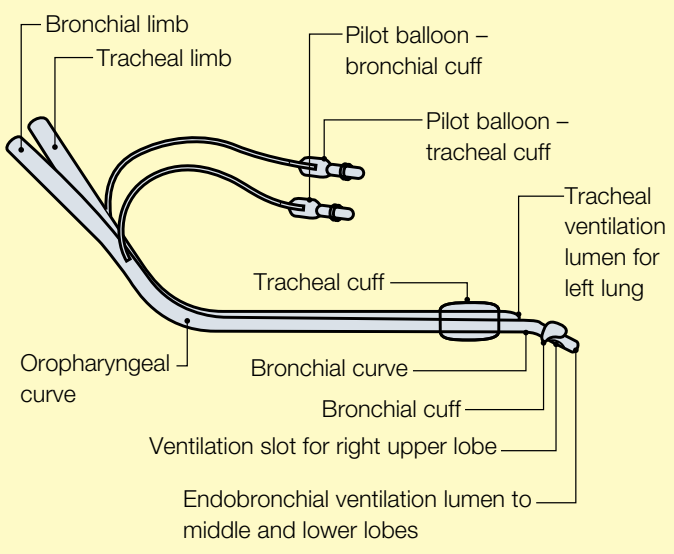
In 1931, Gale and Waters were the first to describe endobronchial intubation in clinical practice. Magill developed right and left single-lumen endobronchial tubes. Little changed until the introduction of the double-lumen endobronchial Carlens tube in 1949. This was initially used for differential broncho-spirometry but was adapted and used for selective ventilation during thoracic surgery; it is still used in some centres. It has a carinal hook, which in theory prevents placement of the tube too far distally but can also make laryngeal intubation difficult. Robertshaw, a Manchester anaesthetist, developed his own pattern of left and right double-lumen endobronchial tube in 1962. This design omitted the carinal hook of the Carlens tube and incorporated larger D-shaped lumina. The right-sided Robertshaw tube included a ventilation slot in the bronchial cuff to accommodate the early take-off of the right upper lobe from the main bronchus on this side.

In current practice, selective one-lung ventilation during thoracic surgery is most commonly achieved with a double-lumen endobronchial tube. These tubes also prevent spill-over of blood and infected secretions from one lung to another. Bronchial blockade can also be used to separate the lungs and there has recently been a resurgence of interest in this technique.

Double-lumen endobronchial tubes

Double-lumen tubes are similar to the original Robertshaw tube (Figure 1). In the UK, the two most widely used tubes are the Robertshaw (Phoenix Medical) and the Bronchocath (Mallinckrodt). Many other manufacturers (e.g. Rusch, Portex, Sheridan) also make double-lumen tubes.

Basic pattern of a right-sided double-lumen endobronchial tube



From: Gothard J W W. *Anaesthesia for Thoracic Surgery*. 2nd ed. Oxford: Blackwell Scientific Publications, 1993

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Robertshaw tubes are available in four sizes ranging from large to extra-small. Bronchocath tubes are available in French gauge sizes of 35, 37, 39 and 41, with a small 28 tube for left endobronchial intubation only. Modern versions of both types of tube are disposable. The Robertshaw tube is made of rubber with a smooth outer coating, and the Bronchocath tube is made of polyvinylchloride (PVC). Both tubes are made in right and left forms, shaped to allow placement in the appropriate bronchus (Figure 1). There are two pilot balloons that allow inflation of tracheal and bronchial cuffs. The bronchial pilot balloons and cuffs are blue for easy identification. The right-sided Robertshaw tube has a ventilation slot built into the bronchial cuff. The equivalent Bronchocath tube has a ventilation slot distal to an eccentrically placed bronchial cuff. In general, the ventilation slot of the Robertshaw tube is larger than that of an equivalent size of Bronchocath tube and there is evidence that right upper lobe ventilation can be achieved more reliably with the Robertshaw tube.

Type and size of tube

It is preferable to use a left-sided double-lumen tube where possible. In UK practice, a right-sided tube is used if lung resection is to be undertaken on the left. In most other instances, including video-assisted thoracic surgery, a left-sided tube is used to obviate the problem of right upper lobe ventilation.

The size of tube selected and the insertion depth depend on the height, weight, body build and gender of the patient. Cohen has stated (see Further Reading) that a 37 FG tube can be placed in most women, while a 39 FG tube is used in the average man. However, the problem is not quite so simple. Bronchocath tubes are long and not designed to be inserted to 'the hilt'. Robertshaw tubes are designed to be inserted so that the bite-block (above which the tracheal and endobronchial portions separate) is approximately at the level of the patient's teeth. Even with this design feature, a large Robertshaw tube can easily be advanced too far in a large patient with a short neck so that an upper lobe is occluded. It has been suggested that a double-lumen tube should be inserted to a depth of 29 cm (from the teeth) in men and women 170 cm in height and that this depth should be increased 1 cm for each 10 cm increment in height of the patient.

The solution to these problems is to use a fibre-optic bronchoscope to check the position of the double-lumen tube.

Placement and position check

Double-lumen tubes are inserted into the airway using standard laryngoscopy with the tip of the tube pointing anteriorly/upwards. Once past the vocal cords the tube is rotated to the appropriate side and advanced until it is in place. The tracheal cuff is then inflated and the seal checked. The tracheal limb of the tube is then opened to air, via the upper suction cap, and the appropriate catheter mount clamped, leaving only the bronchial limb ventilated. The bronchial cuff is then inflated with the minimum amount of air to ensure cuff seal. Any gas leak should be eliminated from the intubated bronchus. This is detected as gas passing up the open tracheal limb. It should be remembered that bronchial rupture has been reported with double-lumen tube insertion, particularly on the left side.

Correct positioning of the tube is confirmed by auscultation and observation of chest movements. Particular attention should be paid to the ventilation of the upper lobe zones, which can easily be obstructed by a misplaced tube. In addition, the above checks should be repeated after positioning the patient for surgery. Double-lumen tubes are also known to migrate intraoperatively because they soften at body temperature and if the airway is handled surgically. An increased airway pressure or change in flow/volume loop configuration may warn of this occurrence before arterial desaturation.

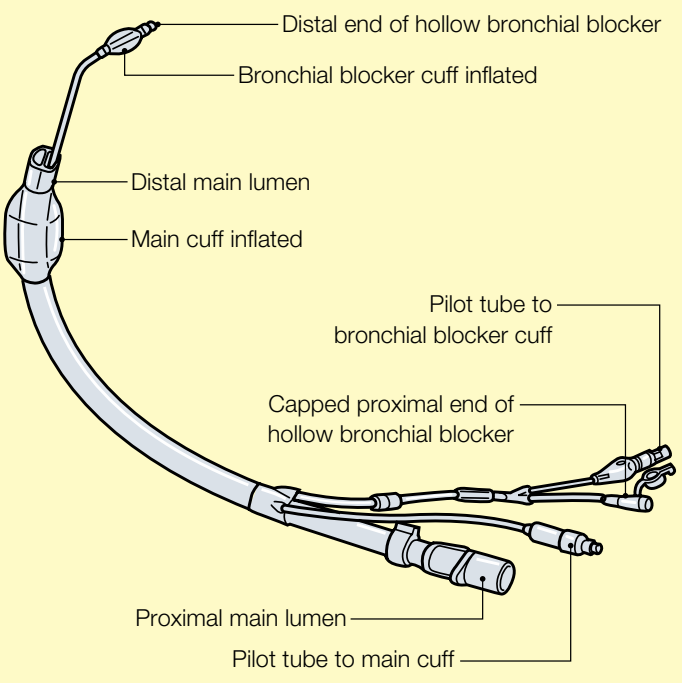
Bronchial blockade

Bronchial blockers have been used intraoperatively for many years to block individual lobes and to facilitate one-lung ventilation by blocking a main bronchus. Several devices, including Fogarty embolectomy catheters and urinary catheters, have been used as improvised bronchial blockers. There has been a renaissance in interest in using bronchial blockade over the last decade, particularly in Japan and North America. This has led to the development of a combined tracheal tube and bronchial blocker, the Univent tube, and the commercial availability of single endobronchial blockers such as that developed by Arndt.

The Univent tube

The Univent tube comprises a tracheal tube with a bronchial blocker (Figure 2). It was introduced into clinical practice by Inoue in 1982 and is probably the most commonly used blocker.

Univent tube – combined tracheal tube and bronchial blocker



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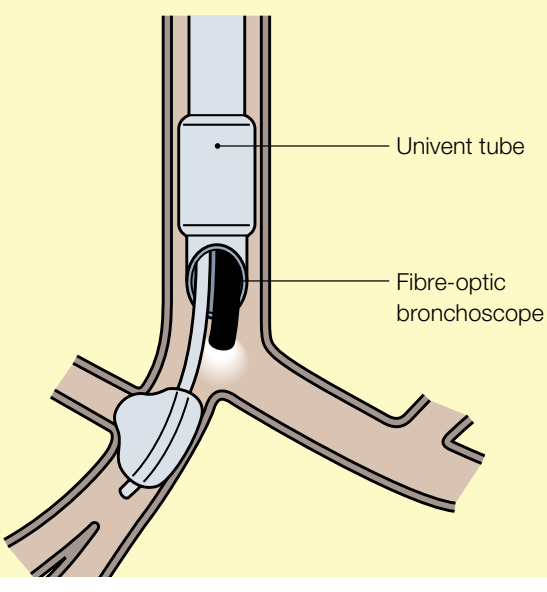
The tube is made in a variety of sizes. It comprises a tracheal tube with a moveable blocker inserted through the anterior wall. The tube is placed in the trachea in the usual way and the blocker advanced, preferably under fibre-optic bronchoscopic control, to block the appropriate main or lobar bronchus (Figure 3). This blocker has the advantage that individual lobes can be blocked, but other potential advantages seem theoretical (Figure 4).

Bronchial blockade of the right upper lobe achieved with a Univent tube under fibre-optic bronchoscopic control



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Advantages and disadvantages of the Univent tube

Advantages
- Lobar blockade possible
- Ease of use for difficult intubation
- Facilitates easy suction of secretions
- Eliminates tube change if ventilation required postoperatively

Disadvantages
- Less versatile than double-lumen tube
- Blocker can migrate
- More expensive than double-lumen tube
- Inflation/deflation of lung more difficult

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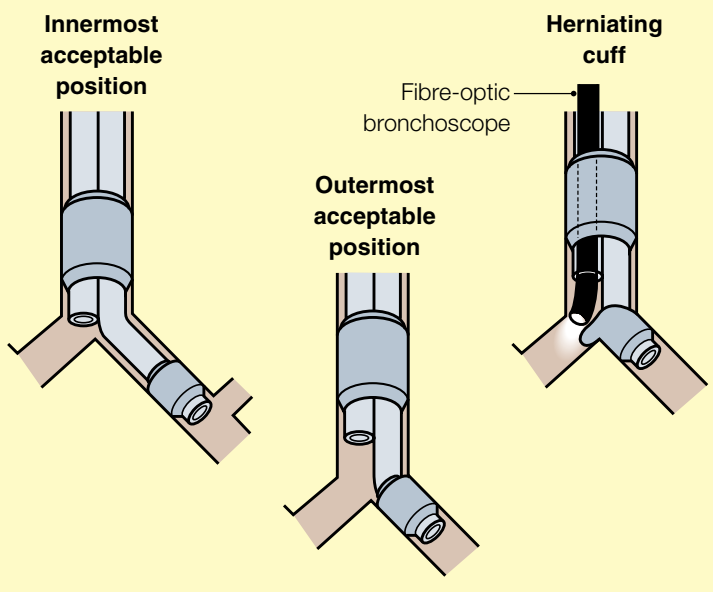
Fibre-optic bronchoscopy

Fibre-optic bronchoscopes and multi-purpose fibre-optic anaesthetic laryngoscopes (e.g. Olympus LF-2) are readily available. Therefore, it is easy to perform routine direct-vision assessment of endobronchial tube and bronchial blocker placement. The introduction of robust paediatric fibre-optic bronchoscopes (e.g. Olympus LF-P) allows this to be carried out with the smallest tubes.

The fibre-optic bronchoscope can be used at the utset of a procedure to aid in a difficult laryngeal intubation or it can be used to 'rail-road' an endobronchial tube into the appropriate bronchus under direct vision. More often it is used to check the position of double-lumen tubes following blind placement (Figure 5). Some authors consider this step to be mandatory.

Fibre-optic bronchoscopy used to check the position of a left-sided double-lumen tube



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A previously placed double-lumen tube is checked by first passing the fibre-optic bronchoscope down the tracheal lumen to ensure a clear view of the non-intubated bronchus (i.e. no cuff herniating across the carina). It is then passed down the bronchial lumen to ensure that the left upper lobe is not obstructed or, alternatively, that the ventilation slot in a right-sided tube is opposed to the right upper lobe orifice. These checks should be repeated if the tube is repositioned and after the patient has been turned into the lateral thoracotomy position. Fibre-optic bronchoscopy may also become necessary if ventilation problems occur intraoperatively. It is essential to maintain and observe full monitoring of the patient during fibre-optic bronchoscopy.◆

FURTHER READING

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Slinger P. Fiberoptic Positioning of Double-lumen Tubes. *J Cardiothoracic Anesthesia* 1989; **3:** 486–96.

Interpreting the Chest Radiograph

Ian J Runcie

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A system for looking at the film

Identification: check name and side marker are present.

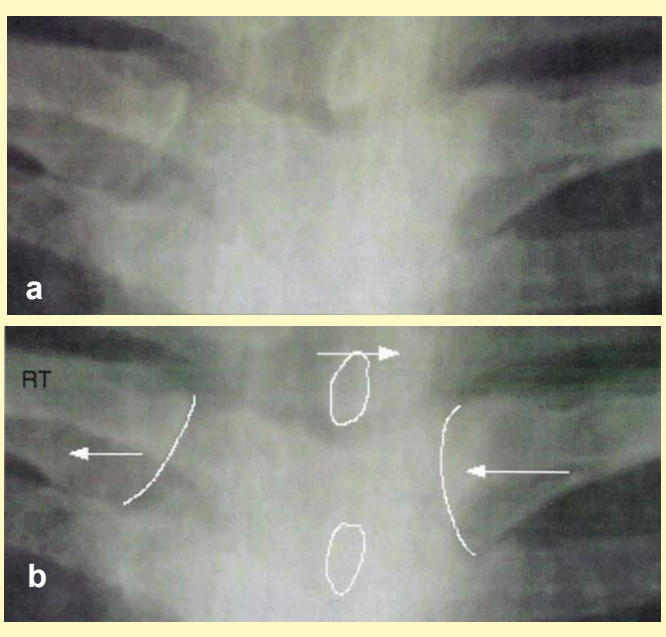
Film quality: an indication of how precise is the information on the film.

Penetration – a good film allows the localization of one or two thoracic disc spaces.

Inspiration – following good inspiration the diaphragm is normally at or near the level of the posterior 10th rib. The right diaphragm is usually higher than the left.

AP or PA, supine or erect – the radiographer should mark how the film has been taken. AP films have the scapula and magnified heart projected over the lung fields and heart size cannot be assessed. Most portable and all supine films are AP. Supine films show less of the lung fields and the mediastinum appears wide: it is pointless trying to decide if a patient has an aortic dissection on a supine film. Interpretation of a film of a patient with a marked kyphosis suffers from similar difficulties.

Centring – allow for rotation before evaluating mediastinal and tracheal shift by examining the relationship between the medial ends of the clavicle and the posterior spinous process. The side to which the patient is rotated usually becomes more translucent (black). But there are exceptions and marked degrees of rotation are required to produce significant changes in radiographic density (Figure 1).



a Patient rotated towards her right. **b** The medial ends of the clavicles and the spinous processes are outlined with their apparent direction of movement. The mediastinum and trachea being anterior structures move in the same direction as the clavicles.

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Bones: start checking from the outside (i.e. humeri, shoulders, clavicles). Note if there are any secondaries, fractures or arthritis. Is the spine straight?

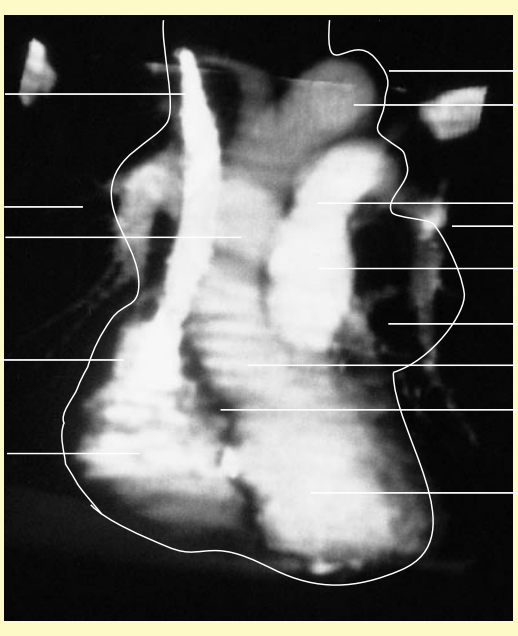
Ribs – look through the heart to where the ribs meet the spine. Check the lateral chest wall and the anterior end of each rib. Compare the two sides all the time. Many prefer to examine each rib as a whole but it is possible to miss one unless care is taken.

Soft tissues: briefly examine the muscles of the chest wall and note any surgical emphysema. The trachea should be central or it may be pushed slightly to the right of the midline in patients with aortic dilatation. Note the size, shape and position of the mediastinum and hila. Note any discrepancy of height in the diaphragm and examine the area below.

Lung fields: compare the two sides by mentally dividing them into six parts (i.e. right and left upper mid and lower zones). Go back to the difficult areas: apices, costophrenic angles, hila and through the heart. There is a lot of lung behind the heart. Note the position and thickness of the horizontal fissure which normally extends out from the centre of the right hilum.

Mediastinum

Cardiac shadow (Figure 2) – on a PA film the maximum width of the heart shadow compared with the maximum width of the combined lung fields approximates the cardiothoracic (CT) ratio. It is normally below 50% but can be up to 60% in elderly patients. The true CT ratio is the sum of maximum distances from the centre of the heart shadow to each heart edge over the maximum external bony thoracic wall.



2 A three-dimensional CT cardiac angiogram showing the approximate outline of the cardiac shadow. The anterior portions of the right atrium and right ventricle have been removed.

Assessment of chamber size is best done by echocardiography but the classic chest radiograph signs of left atrial enlargement are accurate (double right heart border, infilling of the concavity between the aortic knuckle and the pulmonary artery and splaying of the carina).

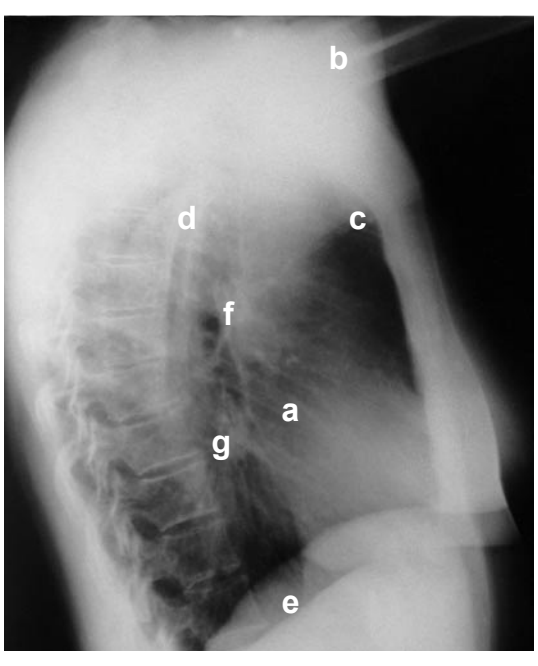
The hila are central mediastinal structures and the hilum on the side to which rotation has occurred may become obscured by the heart shadow. The anatomy of the pulmonary vessels is such that the left hilum is the higher. If this is reversed or if they are at the same level there is likely to be some collapse.

The diaphragm is normally at the level of the 10th posterior rib but the position is variable and its height depends on several factors, including the radiographic technique. It is a thin structure (3 mm) and if it appears to be thicker than this then the gas apparently delineating its lower surface is probably in the gut.

Lung fields should be of similar density. The basal arteries should look notably thicker and longer than those to the upper zones. The horizontal fissure should be at the level of the right hilum and is normally very thin. Bronchial walls, if seen at all, should be thin and restricted to the perihilar regions. Any measurable thickness indicates peribronchial thickening.

Only gross cases of vascular redistribution, plethora, air trapping and bronchiectasis are likely to be diagnosed with certainty. Low flat diaphragms may indicate emphysema but can also be produced by a massive breath in. About 10% of patients with pulmonary emboli have normal chest radiographs.

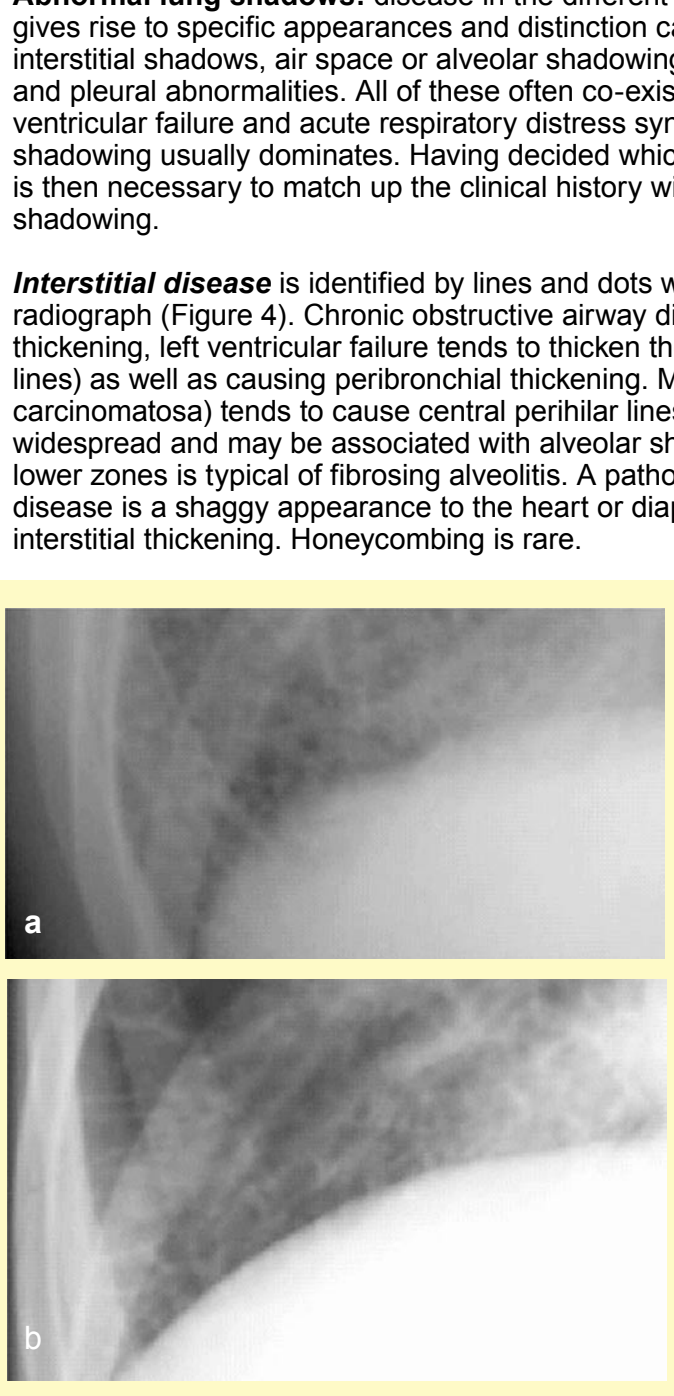
The lateral radiograph is sometimes helpful in the further localization of pathology (Figure 3). It may identify small effusions or basal pneumonia not seen on frontal chest radiographs. Good knowledge of the anatomy as seen on the lateral view is helpful in interpreting the frontal view. Posteriorly the lung is darkest just above the diaphragm. If not, there is probably some basal pathology, either an effusion or posterior consolidation. The shadows of the humeri, glenoids and scapulas can occasionally be misinterpreted. Look at the diaphragms. Note that you can see almost the whole length of the right one but not the anterior end of the left where it comes up against the heart.



3 Normal lateral chest radiograph. **a** Oblique fissure; **b** humerus; **c** soft tissue of arm; **d** scapulas (anterior borders); **e** inferior vena cava (posterior border); **f** hila; **g** confluence of pulmonary veins.

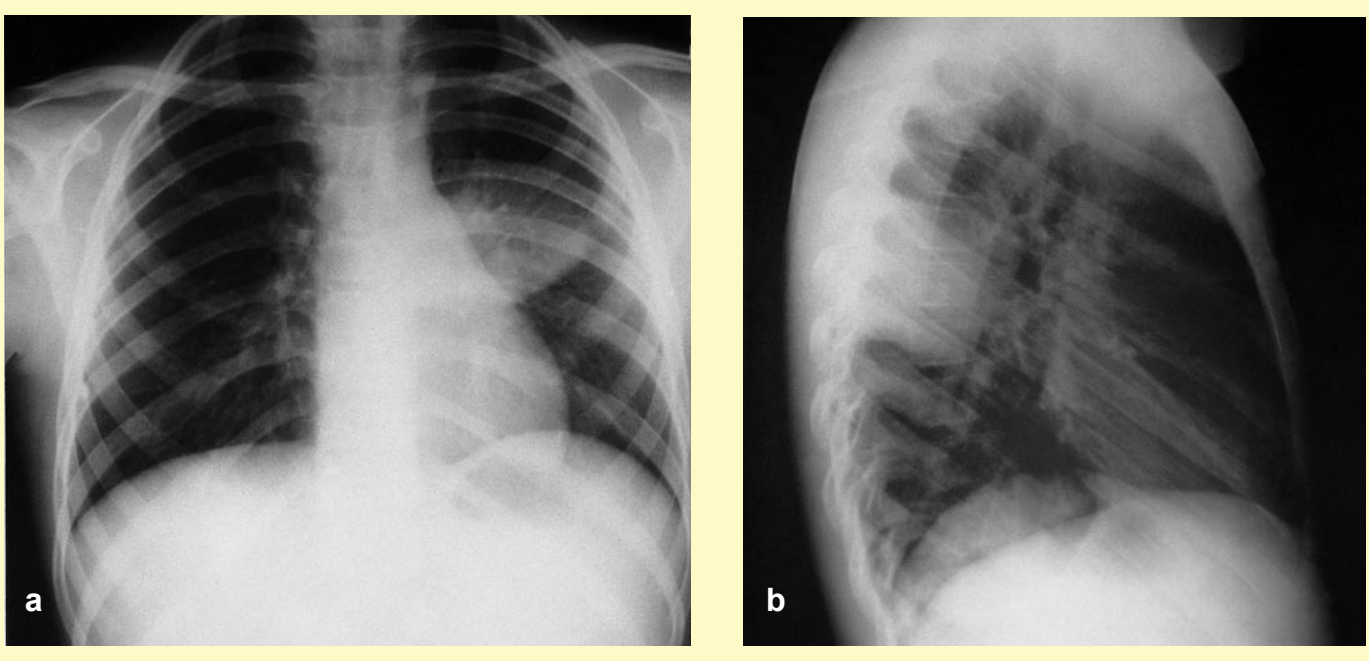
Abnormal lung shadows: disease in the different anatomical divisions of the lung gives rise to specific appearances and distinction can usually be made between interstitial shadows, air space or alveolar shadowing (often called consolidation) and pleural abnormalities. All of these often co-exist for example in pneumonia, left ventricular failure and acute respiratory distress syndrome (ARDS), but one type of shadowing usually dominates. Having decided which of these you are looking at, it is then necessary to match up the clinical history with the type and distribution of the shadowing.

Interstitial disease is identified by lines and dots with variable distribution on the radiograph (Figure 4). Chronic obstructive airway disease (COAD) causes peribronchial thickening, left ventricular failure tends to thicken the peripheral interstitium (Kerley B lines) as well as causing peribronchial thickening. Malignant involvement (lymphangitis carcinomatosa) tends to cause central perihilar lines. Drug reactions are often widespread and may be associated with alveolar shadowing. A reticular pattern in the lower zones is typical of fibrosing alveolitis. A pathognomonic appearance of interstitial disease is a shaggy appearance to the heart or diaphragm caused by adjacent interstitial thickening. Honeycombing is rare.



Two patients with interstitial shadowing. **a** Fibrosing alveolitis with the typical shaggy diaphragm. **b** Interstitial pulmonary oedema showing Kerley B lines. Note the relatively sharp diaphragm.

Alveolar shadowing – 'fluffy' shadows tending towards coalescence and fading away at the edges except where bounded by a fissure. Any shadowing with a sharp edge at a fissure or with a clear lobar or segmental distribution must be alveolar (Figure 5). Soft tissue borders adjacent to the shadowing are lost but any air-containing spaces in the shadowing are outlined and air bronchograms are a characteristic feature. Distribution of the alveolar shadowing is helpful. A lobar distribution suggests pneumonia. Central positioning suggests left ventricular failure or fluid overload. Widespread and changing alveolar shadowing may indicate opportunist, including fungal, infection.



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a Consolidation adjacent to the upper left heart border; the heart border remains visible. This means that the consolidation must be posterior. **b** The consolidation is posterior, overlying the vertebral bodies. The consolidated segment is below the level of the oblique fissure and therefore must be in the apical segment of the lower lobe. If it were above the oblique fissure it would be in the posterior segment of the upper lobe.

Pleural fluid causes loss of the costophrenic angles and a homogeneous basal shadow with a concave upper border on the erect view; there may be thickening of the horizontal fissure. Smaller amounts of fluid may be seen on the lateral view in the posterior costophrenic recess.

Masses – check the size and whether they are well or ill defined. Ill-defined, spiculated masses are usually primary tumours. Note any other lesions and any adjacent pathology (e.g. collapse or overlying rib destruction). Thick walled cavitation suggests an abscess or tumour. Multiple cavities suggest abscesses or infarcts. Note whether a peripheral lesion is pulmonary or pleural. A lung lesion adjacent to the chest wall has a concave border. Check the bones to exclude secondaries.

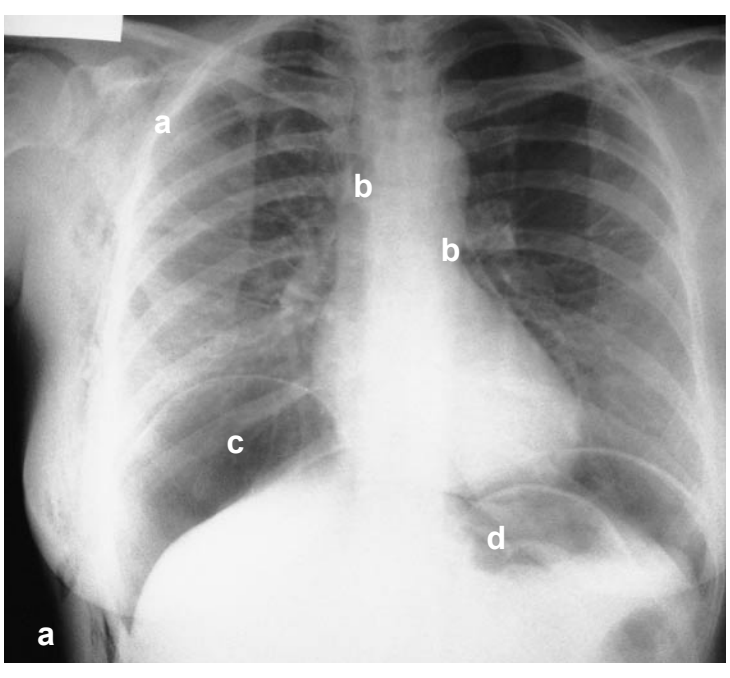
Emphysema produces bullae, low flat diaphragms (below the anterior 7th rib), lack of peripheral vessels and an increase in the branch angles of the arteries. Other pathology (e.g. left ventricular failure) may be difficult to identify.

The ICU film

The problems associated with supine and portable films are exacerbated by the condition of the patients in ICU. Patients are usually unable to cooperate and their lungs are often poorly compliant, causing unusual appearances to familiar pathologies. The information gained from a single ICU film may be limited. This may be counterbalanced by the availability of serial, usually daily, films allowing the progression of changes to be recognized.

Abnormally placed gas

The appearances of surgical emphysema and pneumo-mediastinum (recognized by air outlining the upper mediastinal structures) may indicate the presence of an unrecognized pneumothorax or possibly a pneumoperitoneum (Figure 6).



6 Patient with a massive pneumoperitoneum in whom the gas has tracked up behind the crura into the mediastinum and out through the thoracic inlet to cause surgical emphysema. **a** Surgical emphysema; **b** air in mediastinum; **c** diaphragms; **d** bowel wall.

Pneumothorax in the supine ICU patient seldom conforms to the classic appearance of a thin apical or upper zone line with no lung markings peripherally. A white line may be seen adjacent to the mediastinum or roughly parallel to the chest wall, or parts of the mediastinum may appear 'sharper' than usual. There may be no radiological evidence of a pneumothorax and a high degree of suspicion is necessary.

Pneumopericardium is recognized by the presence of air completely surrounding the heart shadow. It is usually benign except for the rare cases of tension but may point to the presence of serious pathology (e.g. fistulas, infection).

Pleural fluid

Pleural fluid in the supine or semi-erect patient lies over the posterior chest wall and does not have the familiar clear-cut upper edge. Usually a veil of increased density is seen in the lower parts of the lung fields. It may be distinguished from alveolar shadowing because the basal pulmonary vessels may be seen, and by the lack of an air bronchogram. However, the two pathologies often coexist. Ultrasound shows effusions well and can be used to guide drains if necessary. The sudden appearance of an effusion in a patient without fluid overload may suggest a haemothorax. Loculated effusions may show as well-defined masses or thickening of fissures and should raise suspicions of an empyema or bleeding. A fluid level going straight across the lung field on an erect film indicates fluid and air in the pleural space.

Alveolar shadows

Alveolar shadows can be associated with infection, pulmonary oedema, aspiration, contusion and ARDS.

Infections – a lobar or segmental distribution suggests lobar pneumonia. More diffuse shadowing in an immunocompromised patient suggests opportunist infection, including fungi. Persistent upper zone shadowing in association with cavitation and fibrosis may indicate tuberculosis. Cavitation anywhere could mean specific organisms (e.g. tuberculosis, *Staphylococcus, Pneumococcus*). Multiple 1–2 cm cavities suggest septic emboli.

Lung oedema is diffuse if linked with left ventricular failure, fluid overload and freshwater drowning. It may be localized following aspiration and linked to other changes (e.g. atelectasis).

Contusion may be localized to the site of injury and show progression for some days following the injury. Pulmonary haemorrhage can be diffuse and indistinguishable from pulmonary oedema.

ARDS can mimic almost any other acute condition. Radio-logically it is best identified by its relentless progression from central pulmonary alveolar shadowing to more generalized and persistent coverage of the whole lung.

Atelectasis varies from complete collapse of a lung as evidenced by massive mediastinal shift to the side of the collapse to small often temporary white lines in subsegmental atelectasis. It is seldom associated with demonstrable mucus plugging. The appearances of lobar collapse are discussed on page 375.

Lines

Radiographers should be informed if the chest radiograph is required for a specific line or tube because they may be able to vary the technique and may repeat the film automatically if the line is not shown well. Regarding line insertion, ultrasound measurements have shown that raising the patient's feet produces just as much jugular vein dilatation as tipping the patient head down.

A tracheal tube should be at least 5 cm above the carina because flexion or extension of the head can move it by as much as 4 cm. A small pneumomediastinum or surgical emphysema is not uncommon following the insertion of a tracheostomy tube.

On the chest radiograph a subclavian line can be expected to be entering the subclavian vein at the lateral edge of the first rib, the brachiocephalic vein at the sternoclavicular joint and the superior vena cava at the first anterior intercostal space. Common malplacements are upwards into the jugular vein and across the midline into the opposite brachiocephalic vein. A medially placed deviation at its lower end may indicate placement into the right ventricle. Rarely, the catheter can enter the azygos vein or the internal mammary vein, producing a localized kink near the superior vena caval origin.

Pneumothorax is the most common complication of line insertion. Complete malposition into the mediastinum is uncommon; it rapidly results in mediastinal widening and loculated pleural effusions.

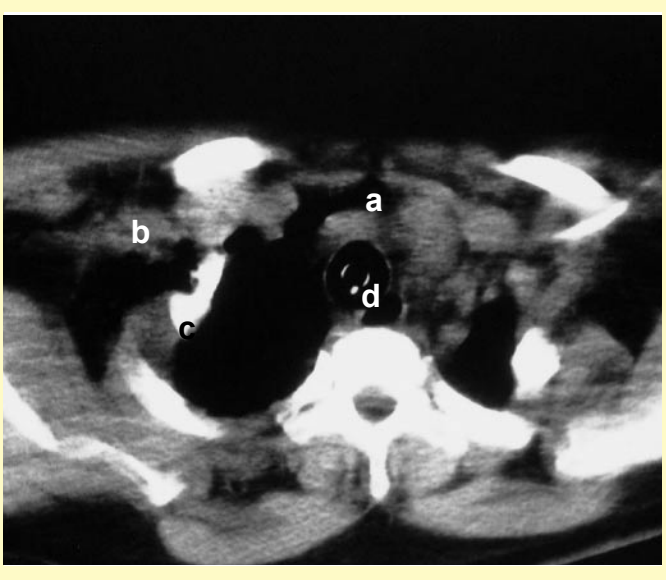
A line that shows a small kink or a gentle deviation at its distal end may be up against the vessel wall with the potential of erosion. This particularly applies to pulmonary artery occlusion catheters in the relatively thin pulmonary arteries in the presence of pulmonary hypertension. The rare complication of catheter breakage should be dealt with as soon as possible, preferably by an interventional radiologist. Such large emboli can drift peripherally with time and can erode vessels rapidly, particularly in the pulmonary circulation.

Most pacemaker wires are inserted into the subclavian vein and directed into the apex of the right ventricle. A lateral view shows the distal end of the correctly placed wire coursing anteriorly. The course of the wires should be smooth on both the AP and lateral views and any localized kinks are suspicious. The most common site of wire fracture is between the clavicle and the first rib, usually well seen on the frontal view. Myocardial perforation can occur at the time of insertion. This may be seen as the tip of the wire being outside the cardiac silhouette but may not be obvious in the plane of a single film and is best identified by echocardiography. The pacemaker can continue to work satisfactorily in this situation.

Nasogastric tubes have holes along their distal 10 cm and need to be well into the stomach to stop gastro-oesophageal reflux occurring via these holes. They can enter the bronchial tree but bizarre-looking 'malplacements' are usually caused by the presence of a hiatus hernia rather than by oesophageal rupture.

CT (Figure 7) is useful in ICU patients, but requires planning and involves a demonstrable risk. The following are easily identified and localized: effusions, drains, pneumothoraces, pulmonary parenchymal disease including emphysematous changes and interstitial disease, tumours including secondaries, and pulmonary emboli up to second or third branch level. ◆

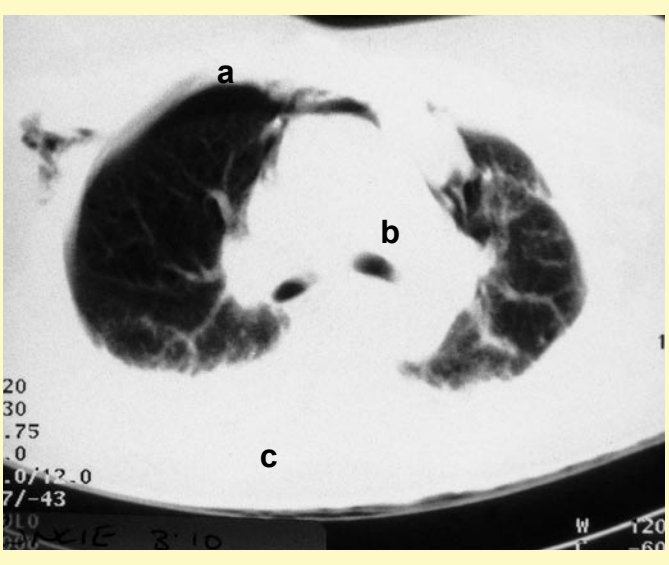
CT of trauma patient



Bone window level through lung apices.

a Pneumomediastinum; **b** surgical emphysema;

c flail segment; **d** tracheal tube.



Lung window level through main bronchi.

a Pneumothorax; **b** pneumomediastinum;

c lung contusion.

Pathophysiology of Respiratory Disease and its Significance to Anaesthesia

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Many patients with respiratory disease present for anaesthesia. The patient's current status, in relation to their best personal baseline symptoms, quality of life and spirometry values, should be determined. If patients are at their best level, it is unlikely that they will be greatly improved by pre-surgical modification of therapy. However, recent exacerbations of airway disease, pulmonary infection or an increase in sputum production should be treated aggressively and new symptoms must be investigated.

Clinical examination should elicit signs of airway obstruction (inspiratory and expiratory), tachypnoea, dyspnoea or the use of accessory muscles, a 'barrel' chest and cyanosis. In patients ASA III or higher, or with dyspnoea, arterial blood gases should be measured in addition to non-invasive oximetry to determine the presence of elevated resting $PaCO_2$ levels. A recent chest radiograph is mandatory and in patients with borderline cardiopulmonary function, particularly with non-homogeneous pulmonary pathology, a CT scan may direct care.

Cardiac co-morbidity is common in patients with respiratory disease. ECG is mandatory and echocardiography should be performed in patients with advanced pulmonary disease to assess right ventricular function and the degree of secondary pulmonary hypertension. New or recent exacerbations of chest pain require specialist cardiological assessment. Guidelines for cardiac risk stratification in patients undergoing non-cardiac surgery have been published and should be incorporated into preoperative risk evaluation and the process of informed consent.

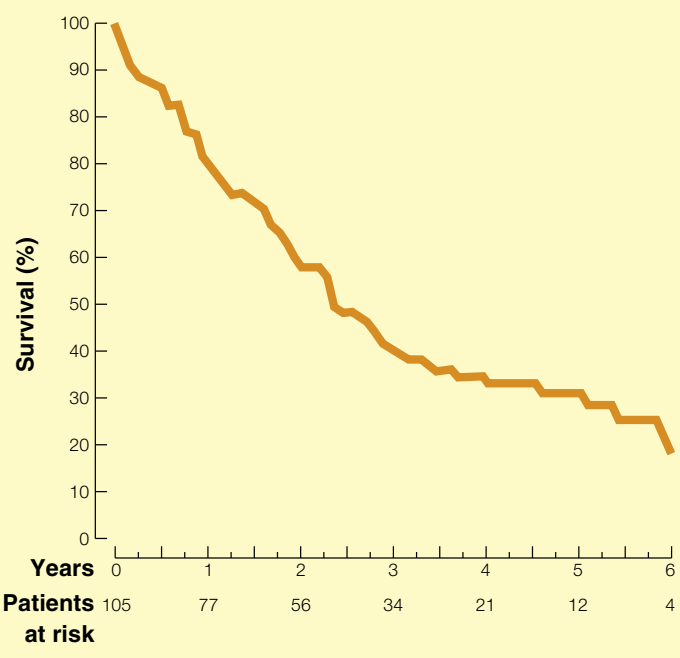
Chronic obstructive pulmonary disease (COPD)
Patients with COPD have alveolar emphysema and chronic airway inflammation. Patients with predominantly emphysematous changes exhibit lung hyperinflation with moderate derangement of gas exchange, while those with more severe airway inflam-mation are more likely to develop severe hypoxaemia, CO_2 retention and secondary pulmonary hypertension.

Emphysema results in increased lung compliance, decreased elastic recoil and closure of small airways in expiration, thus increasing both functional residual capacity (FRC) and residual volume (RV). Effort-independent expiratory flow limitation results, though inspiratory flow rates may be normal, and is exacerbated by airway constriction or oedema and mucous plugging. Chronic bronchitis (large airways) and bronchiolitis (terminal bronchioles) result in airway obstruction due to mucus, airway oedema or mucous gland hypertrophy, smooth muscle contraction and fibrosis induced airway distortion. Large airway changes have little effect but chronic bronchiolitis causes increased airway resistance, both in inspiration and expiration, resulting in locally reduced ventilation, reduced V/Q ratios and alveolar collapse leading to characteristic hypoxaemia of chronic airway inflammation.

Effect of anaesthesia: patients with severe COPD are at risk of exacerbation of V/Q mismatch under anaesthesia. Airway closure occurs at higher lung volumes and airway resistance is increased. Controlled ventilation is usually required but increases physiological dead space and may lead to inadvertent gas trapping in emphysema patients. Expiratory time should be set to allow for prolonged exhalation. Bronchodilator properties of volatile agents have little effect in COPD. Hypoxaemia is relatively uncommon in the ventilated patient with chronic bronchitis but may be a feature of induction and emergence. In such patients, continuous positive airway pressure in the recovery phase may be beneficial. Coughing and effective physiotherapy must be facilitated by effective postoperative analgesia.

Outcome: patients with COPD are two to five times more likely to suffer postoperative pulmonary complications, depending on the severity of disease. Patients with FEV_1 less than 1 litre are at high risk and likely to require high level postoperative care, especially if they exhibit resting CO_2 elevation (> 6.5 kPa) and FVC is less than 50% of that predicted. A recent study of patients with severe COPD (FEV_1 < 1.2 litre, FEV_1/FVC < 75%) undergoing non-cardiothoracic surgery revealed 6.6% mortality but disappointing survival rates (53% at 2 years, 30% at 4 years) – lower than longitudinal studies of COPD patients without surgery (Figure 1).

Long-term survival of patients with severe COPD



Observed survival rates in 105 patients (53 general, 52 regional or local). The higher mortality, compared with COPD without surgery, was thought due to effects of anaesthesia and surgery, or the underlying disease for which surgery was requried.
Reproduced from Wong *et al*., *Anesth Analg* 1995; **80:** 276–84 with permisssion

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Perioperative interventions: there is little specific information on the efficacy of widely practised preoperative therapy. Patients who are not at their best baseline level should undergo aggressive preoperative optimization and surgery should be deferred until this is achieved. Data from the 1970s suggested that combinations of bronchodilators, antibiotics, physiotherapy, smoking cessation and corticosteroids could reduce the incidence of postoperative pulmonary complications in COPD patients.

Currently, combined nebulized inhaled β_2-agonists and ipratropium bromide are recommended, with additional inhaled steroids (e.g. budesonide) if there is a reversible airway component. A short course of systemic steroids may be effective in patients who do not achieve best personal baseline with bronchodilator therapy, although this potential benefit must be balanced against the risk of administering preoperative steroids. Causative organisms in pulmonary infection should be identified and directed antibiotic therapy instituted. Empirical antibiotic therapy in patients with increased sputum production is often recommended but remains controversial.

Intensive preoperative chest physiotherapy has been shown to reduce the incidence of postoperative complications in COPD patients, particularly in those who produce considerable sputum. Nutritional status is often poor in COPD and short-term benefits can be gained with preoperative supplements, even for 2 weeks.

Asthma
Asthma pathophysiology combines increased airway smooth muscle contraction, airway wall inflammation and oedema and mucous plugging due to increased production of tenacious mucus. Air flow resistance is consequently increased and maximum expiratory flow rates decrease. Pulmonary hyper-inflation occurs with an increase in FRC and RV.

Anaesthesia: asthmatic patients should be free of wheezing, be near to their best value peak flow rate and at least 80% of predicted values. Patients who are unstable or poorly compliant with therapy should be admitted for a period of supervised nebulized therapy. In brittle or resistant asthmatics, short courses of systemic steroids may be administered preoperatively and current evidence suggests that this is not associated with an increase in complications, particularly wound infections.

Volatile agents decrease airways resistance in asthmatics and halothane has been used therapeutically for this. Among the agents in widespread use, isoflurane has been most extensively investigated and has favourable bronchodilator properties. Well prepared, known asthmatics infrequently cause major difficulties and the incidence of clinically significant bronchospasm is less than 10%. More dangerous is the previously unrecognized asthmatic who unexpectedly develops severe acute asthma perioperatively. The American Closed Claims Project reported that, in 40 such patients, of whom 33 had died or sustained neurological damage, 50% had no history of asthma.

The principles of management of a severe asthma attack include nebulized and intravenous bronchodilators, cortico-steroids and volatile anaesthetic agents and cardiovascular support. In severe cases, adrenaline (epinephrine) infusions may be required to break the bronchospasm and both ketamine and high-dose magnesium sulphate have been used. Ventilation must ensure adequate oxygenation but severe gas trapping, with resultant haemodynamic compromise, must be actively avoided. Slow respiratory rates (6–10/minute) with prolonged expiratory times should be used and intermittent disconnection from the ventilator, to allow the lung to fall to its equilibrium volume, is valuable if haemodynamic compromise occurs. Some permissive hypercapnia is expected and desirable in these patients.

Upper respiratory tract infection (URTI)
Clinical studies of the implications of URTI have been performed almost exclusively in children, and, in view of an increased risk of adverse anaesthetic events (cough, laryngospasm or other airway obstruction, breath holding or desaturation), have advised postponement of elective surgery for up to 6 weeks following severe URTI. A 2-week delay is commonly advised for mild infections. In adult practice, evidence on the implications of URTI for anaesthesia is almost non-existent. URTI increases upper airway irritability, which correlates well with symptoms, for up to 15 days, suggesting that a 2-week delay and resolution of symptoms is advisable before elective surgery. New or increased production of purulent sputum in patients with underlying respiratory disease usually warrants antibiotic therapy. There is no information on the impact of mild, presumably viral, infections in patients with, or without, respiratory disease before anaesthesia; the prudent approach is to delay elective surgery. In more urgent surgery, the priority of surgery is likely to override concern about mild URTI.

Smoking
Smoking is associated with pathophysiological changes in the cardiovascular and respiratory systems that have significant implications for anaesthesia. In the airway, there is impaired clearance and increased production of mucus. Narrowing of small airways results in airway closure and increased ventilation–perfusion (V/Q) mismatch. Increased irritability and reflex sensitivity occurs in upper and lower airways. Cardiovascular implications include an increase in oxygen demand through nicotinic activation of the sympathoadrenergic system, as well as decreased oxygen supply to tissues due to increased carboxyhaemoglobin (COHb) levels and raised coronary vascular resistance. COHb levels of 5–15% may be encountered in smokers (normally 2% or up to 4% in city dwellers). Standard transmission type pulse oximeters interpret COHb as oxygenated haemoglobin (and may overestimate peripheral oxygen saturation (SpO_2) in smokers) and fail to reflect the left shift of the oxygen-haemoglobin dissociation curve that is induced by COHb.

Many studies have investigated perioperative complications in smokers. Pulmonary complications represent the major area of perioperative morbidity – smokers are 2–6 times more likely to suffer from atelectasis and pneumonia. Hyper-responsive airways render smokers more vulnerable to laryngospasm and bronchospasm, and coughing, in combination with impaired mucus clearance, may impact on pain-control requirements and adversely affect wound healing. Recent data suggest that continued smoking by patients at risk of coronary disease (> 65 years) increases the incidence of transient myocardial ischaemic events under anaesthesia.

Given the short half-lives of both nicotine (0.5–1 hour) and COHb (4 hours), a period of preoperative smoking cessation lasting 12–16 hours should normalize both levels. Smoking cessation of at least 8 weeks is required to reduce the risk of pulmonary complications in smokers. Paradoxically, the risk may be increased, due in part to short term changes in the balance of mucus production and clearance, during this interval period. A much longer period, at least 6 months, is required before complication rates approach those of non-smokers and the longer the period of abstinence, the better.

Cystic fibrosis (CF)
CF is characterized by airway mucous gland hyperplasia and the production of abnormal mucus that encourages bacterial growth. Most CF patients are colonized with *Pseudomonas aeruginosa*, which inflicts a course of recurrent infective exacerbation and remission. Repeated bacterial infection, atelectasis and mucous plugging eventually lead to cystic bronchiectasis and necrotizing pulmonary disease.

Anaesthetic implications: patients with CF present for disease- related procedures (pneumothorax, nasal polyps, insertion of vascular or enteral feeding access) and for unrelated procedures. While elective surgery is often performed in hospitals with CF units, an increasing adult population of CF patients may present to general hospitals for both simple and emergency surgical procedures. Survival data demonstrate increased survival with over 50% of CF patients alive at 25 years. Children born with CF in the 1990s are likely to survive up to four decades, regardless of the impact of advances in gene therapy.

Patients with CF exhibit increased intrapulmonary shunt and gas trapping. Total lung capacity and residual volume are increased while FEV_1 and FVC are both reduced. PaO_2 is often mildly reduced and $PaCO_2$ is usually normal. PaO_2 less than 7 kPa or $PaCO_2$ over 6.5 kPa usually reflects advanced disease with 2-year mortality from CF of about 50%.

Intraoperative management is often straightforward, particularly if patients are not suffering an infective exacerbation. Patients should perform physiotherapy exercises immediately before the procedure. Tracheal intubation is preferred for all but the shortest procedures and allows for tracheobronchial suction which should be performed regularly during the procedure. Controlled ventilation, usually with short-acting muscle relaxants is routine, and although reversal of neuromuscular blockade must be complete, pharmacological reversal may be undesirable in some patients owing to unpredictable effects on the tenacity of respiratory secretions. In advanced disease, the authors transfer patients sedated and ventilated to the recovery room where they undergo aggressive physiotherapy and tracheobronchial toilet for a variable period (e.g. 0.5–2 hours) during stabilization before extubation. Postoperative analgesia must allow effective coughing and regional techniques should be considered. The risk of respiratory depression with opiates is counterbalanced by the facilitation of coughing and physiotherapy in patients at risk of severe postoperative pain. ◆

Post-thoracotomy Analgesia

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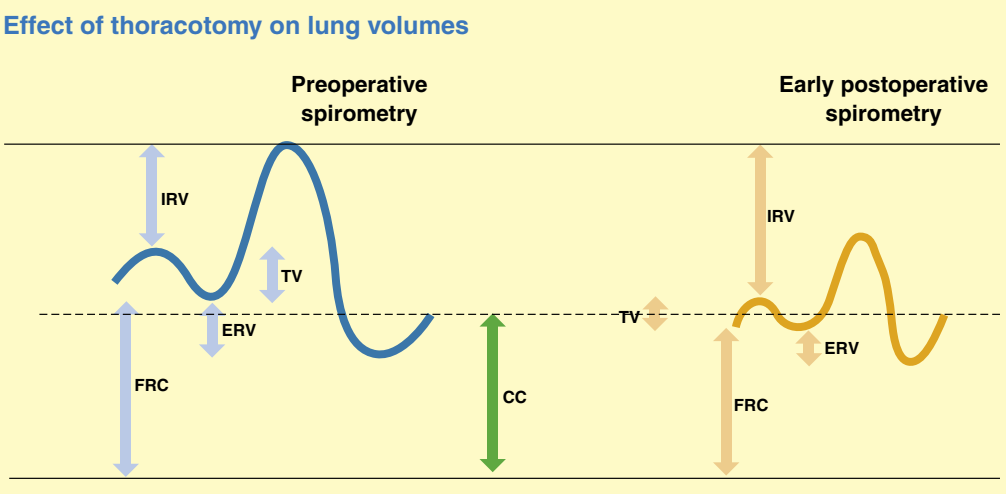
A posterolateral thoracotomy usually involves about seven somatic dermatomes. The pain of a thoracotomy has been described as among the most severe of the many iatrogenic causes. Movement, including breathing and coughing, exacerbates the pain. Adequate postoperative analgesia is important for humanitarian reasons and to reduce the incidence of pulmonary and other morbidity occurring in patients undergoing thoracic surgery.

Normally, active tidal inspiration is followed by passive expiration. However, in a post-thoracotomy patient with inadequate analgesia, active tidal inspiration is followed by contraction of the expiratory muscles to limit further distraction of the injured skin, muscles, ligaments and bone. This active expiration results in a reduction in the functional residual capacity, usually to below the closing capacity, leading to airway closure and atelectasis. Splinting the chest, as a result of involuntary muscle contraction, reduces the inspiratory reserve volume and coughing becomes less effective. These spirometric changes (Figure 1) contribute to the development of postoperative atelectasis and sputum retention, which may progress to potentially fatal chest infection.

Effect of thoracotomy on lung volumes



FRC, functional residual capacity;
TV, tidal volume;
CC, closing capacity;
IRV, inspiratory reserve volume;
ERV, expiratory reserve volume

1

The techniques used to provide post-thoracotomy analgesia are summarized in Figure 2. However, in practice there are two widely used techniques:
- systemic opioids ± nerve block ± non-steroidal anti-inflammatory drugs (NSAIDs)
- epidural analgesia.

There is evidence that well-prepared patients experience less postoperative pain and most patients benefit from a clear explanation of what to expect postoperatively. When choosing post-thoracotomy analgesia the following must be considered:
- planned procedure (pneumonectomy versus pleurectomy)
- surgical technique (open versus thoracoscopic)
- patient's physiological reserve, co-morbities and preference
- resources available including hospital infrastructure and anaesthetic expertise.

Methods of post-thoracotomy analgesia

Opioids	**Local anaesthetic**
Intramuscular	Intercostal
Intravenous	Paravertebral
Patient-controlled analgesia (PCA)	Intrapleural
Epidural	Subcutaneous
Spinal	Spinal
Non-opioid	**Mechanical**
Non-steroidal anti-inflammatory drugs	TENS (transcutaneous electrical nerve stimulation)
Paracetamol	Cryoanalgesia

2

Systemic opioids ± nerve block ± NSAIDs
Opioids: systemic opioids have a narrow therapeutic window in the context of reducing pulmonary complications post-thoracotomy. Without analgesia, patients experience considerable pain, expire actively and splint their chest wall, coughing and sighing are suppressed and the probability of developing atelectasis is high. Titrated systemic opioids moderate pain, reduce chest wall splinting, enable passive expiration and involuntary sighing and therefore facilitate effective coughing. The likelihood of developing atelectasis is reduced. Additional systemic opioids further reduce pain but increase sedation, reduce coughing and sighing and thereby increase the likelihood of atelectasis developing. Maintaining this narrow therapeutic window is made more difficult by the fivefold patient-to-patient variability in opioid requirements and the well-known reduction in opioid requirements with time. Patient-controlled analgesia (PCA) systems are widely used. PCAs are effective because patients usually prefer some pain to excessive sedation. Post-thoracotomy, the analgesia provided by a PCA is seldom adequate and additional strategies are often used.

NSAIDs: the addition of NSAIDs improves analgesia but increases the potential for side-effects, particularly in this predominantly elderly population with a high incidence of renal dysfunction and peptic ulcer disease.

Paravertebral blocks: the thoracic paravertebral space is wedge- shaped. It is bounded medially by the intervertebral bodies and discs, anterolaterally by the parietal pleura, and posteriorly by the transverse processes and costotransverse ligaments. The paravertebral space contains the dorsal rami, rami communicantes, the sympathetic chain and the intercostal nerves. Paravertebral blocks can be achieved by single injections, repeated injections or catheter-facilitated paravertebral infusions. Paravertebral catheters can be placed percutaneously or under direct vision by the surgeon. Paravertebral blocks are usually contraindicated in patients with an empyema, paravertebral tumour or a skin infection at the site of needle insertion. Relative contraindications include haemostatic abnormalities and patients who have had a previous thoracotomy.

Technique – at an appropriate level, using aseptic precautions, a Tuohy needle is inserted 2.5 cm lateral to the superior aspect of the relevant spinous process and then advanced perpendicular to the skin, in all planes, until contact is made with the transverse process, usually at a depth of 2–4 cm. If contact is not made with bone at the expected depth, the Tuohy needle is fanned superiorly and inferior in the sagittal plane, to detect inadvertent advancement between two transverse processes, before advancing the needle further. After contact with bone is made the needle is walked, rostrally, off the transverse process and advanced until loss of resistance is felt, after confirming no blood on aspiration, an appropriate dose of local anaesthetic is given and, if required, a catheter sited. Paravertebrals are easier to insert than epidurals and are probably safer. However, in about 10% of patients they do not work and in the others the effect is variable.

Epidural analgesia
Meta-analysis has shown that the administration of local anaesthetic containing epidural solutions via a thoracic epidural to patients undergoing upper gastrointestinal surgery results in a significant reduction in pulmonary complications. The post-thoracotomy analgesia produced by a combination of local anaesthetic and opioids administered via a thoracic epidural is excellent (gold standard) and is now widely used. However, patient selection is important because of the possibility of spinal cord injury. The risk of spinal abscess can be reduced by meticulous asepsis and avoiding thoracic epidurals in patients with local or systemic sepsis. The risk of spinal haematomas can be reduced by avoiding thoracic epidurals in patients with haemostatic abnormalities detected by:
- obtaining a personal and family bleeding history
- inquiring about exposure to drugs effecting haemostasis
- measuring the platelet count and performing clotting studies.

Controversy remains about whether thoracic epidurals should be inserted in awake or anaesthetized patients. Many operators, including the authors, think it is safer to insert thoracic epidurals in conscious patients. This also allows confirmation of correct placement before surgery. For thoracic epidurals the use of a mixture containing a lipid-soluble, segmentally acting, opioid (e.g. fentanyl) is logical because this almost eliminates the risk of sudden late respiratory depression caused by the rostral spread of opioid in the CSF. Numerous different epidural mixtures have been studied but the most widely used solutions contain fentanyl, 4 μg/ml, in 0.125% bupivacaine. The excellent somatic dermatomal analgesia produced by thoracic epidural analgesia is often marred by severe ipsilateral shoulder pain. Disruption or irritation of the mediastinal or diaphragmatic pleura and/or pericardium result in visceral pain conducted via the phrenic nerve referred to the ipsilateral shoulder. Treating this referred pain is difficult. Phrenic nerve infiltration with lidocaine (lignocaine) is effective but of limited duration and may compromise ventilation. However, patients receiving thoracic epidural analgesia and phrenic nerve block experience almost no post-thoracotomy pain.

Patients receiving thoracic epidural analgesia should be assessed at least hourly. If patients are not monitored on a high dependency unit they should receive high dependency nursing on the ward. All patients receiving hydrophilic opioids epidurally should undergo continuous respiratory function monitoring. Slow rostral spread of hydrophilic opioids in the CSF may result in sudden delayed respiratory depression. ◆

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Preoperative Assessment for Thoracic Anaesthesia

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Thoracic surgical procedures are associated with significant morbidity and mortality. Major postoperative respiratory complications (e.g. pneumonia, atelectasis, respiratory failure) occur in up to 20% of patients and account for most of the overall 3–4% mortality. Recent advances in care result in few patients being rejected by the anaesthetist as thoracic surgical candidates on the basis of preoperative pulmonary disease. In each patient a risk/benefit assessment should form part of the process of informed consent. For the general approach to preoperative assessment see *Anaesthesia and Intensive Care Medicine* **2:4:** 124. Specific preoperative assessment and optimization of cardiac and pulmonary function are vital. Medical optimization may involve pre-admission for physiotherapy, antibiotic or supervised bronchodilator therapy, cardiovascular stabilization and even nutritional support before surgery.

Cardiac assessment
History, examination, assessment of functional status and ECG should identify patients at high risk. Routine specialized cardiac screening is not indicated or cost effective. Patients require further investigation if they exhibit major or intermediate risk predictors (Figure 1).

Clinical predictors of increased perioperative cardiovascular risk

Major predictors
- Unstable coronary syndromes (recent myocardial infarction with evidence of ischaemia, unstable or severe angina)
- Decompensated congestive cardiac failure
- Severe valvular disease
- Significant arrhythmia (high-grade A-V block, supraventricular arrhythmias with uncontrolled ventricular rate, symptomatic arrhythmias with underlying heart disease

Intermediate risk predictors
- Mild angina
- Previous myocardial infarction
- Compensated or previous congestive cardiac failure
- Diabetes

Minor risk predictors
- Advanced age
- Abnormal ECG
- Cardiac rhythm other than sinus
- History of stroke
- Uncontrolled systemic hypertension

Modified from American College of Cardiology (ACC)/American Heart Association (AHA) Task Force Report on guidelines for perioperative cardiovascular evaluation for non-cardiac surgery, 1996.

1

Thoracic surgical patients with ischaemic heart disease may undergo optimization of medical therapy, angioplasty, with or without stenting, or coronary artery surgery. In those who require both coronary artery surgery and pulmonary resection, combined procedures can be undertaken but it is usual to delay the thoracic procedure for 4–6 weeks after cardiac surgery. The impact on outcome of angioplasty and/or coronary stenting in such patients is not known; modification of anticoagulant therapy to facilitate surgery may increase the risk of cardiac complications.

Patients who have suffered recent myocardial infarction (MI) should not undergo elective surgical procedures for 6 months. However, thoracic surgery for malignant disease is a relative emergency and surgery for pulmonary resection can be undertaken with acceptable risk 6 weeks after MI.

Severe valvular heart disease is a high risk predictor of perioperative cardiac events, but data on outcome are limited. Valve surgery should be advised on standard cardiological criteria, regardless of the need for thoracic surgery, and should ordinarily precede the thoracic procedure. The presence of valve disease increases the risk, but even if severe, this risk should not necessarily be prohibitive.

Assessment of respiratory function
An ASA Class I or II patient with full exercise capacity does not require special cardiorespiratory screening before thoracic surgery. ASA Class III patients, or those with limited exercise capacity, require more critical preoperative assessment, especially if substantial pulmonary resections are planned. No single respiratory function test has sufficient sensitivity or specificity to predict outcome following pulmonary resection. Slinger has recently advocated anaesthetic assessment combining elements of respiratory mechanics, gas exchange and cardio-pulmonary performance in prethoracotomy patients (Figure 2).

Prethoracotomy respiratory assessment

Respiratory mechanics	Cardiopulmonary reserve	Parenchymal function
ppo FEV_1 > 40% *	VO_{2max} > 15 ml/kg/min *	*ppo* D_LCO > 40% *
MVV, FVC, RV/TLC	Stair climb > 2 flights	PaO_2 > 8.3 kPa
	6 minute walk	$PaCO_2$ < 6.3 kPa
		Exercise SpO_2 fall < 4%

* most valid test

This 'three legged stool' concept has been proposed as a reasonably simple approach to anaesthetic assessment in thoracotomy patients. Of the parameters listed, *ppo* FEV_1 > 40%, *ppo* D_LCO% > 40% and VO_{2max} > 15 ml/kg/min represent thresholds below which patients face increased risk.
Source: Slinger & Johnston, *J Cardiothorac Vasc Anesth* 2000; **14:** 202–11, with permission. For abbreviations see text

2

Respiratory mechanics – British Thoracic Society (BTS) recommendations highlight the screening value of simple spirometry and suggest that no further respiratory function tests are required if, for a lobectomy, the post-bronchodilator forced expiratory volume in 1 second (FEV_1) is over 1.5 litres or, for a pneumonectomy, is over 2 litres, provided there is no evidence of interstitial disease or unexpected disability due to dyspnoea.

In more formal respiratory function testing, parameters that correlate with postoperative outcome include FEV_1, maximal voluntary ventilation (MVV), forced vital capacity (FVC) and residual volume to total lung capacity ratio (RV/TLC), when expressed as a percentage of predicted volumes (corrected for age, gender and height), and particularly if postoperative values, based on the percentage of functioning lung tissue removed, can be predicted. The most valid single test for post-thoracotomy respiratory complications is predicted postoperative (*ppo*) FEV_1 percentage, calculated as preoperative FEV_1 % x (1 – % functional lung tissue removed/100). The percentage functional lung tissue removed is calculated by dividing the total lung tissue into segments (19) and assessing the number of functioning segments to be removed. Quantitative pulmonary perfusion scans can also be used to define the amount of functional tissue to be removed.

In terms of postoperative morbidity, *ppo* FEV_1% values over 40% predict a low risk of postoperative morbidity, values below 30% predict an extremely high risk and values of 30–40% define an intermediate risk group for which data are inconclusive.

Lung parenchymal function – preoperative arterial blood gas (ABG) analysis is routine in most patients undergoing thoracic surgery. Traditional alert values (PaO_2 < 8.3 kPa, $PaCO_2$ > 6.3 kPa) are commonly cited as risk factors but there are no large or prospective studies correlating ABG values with outcome. Elevated $PaCO_2$ values are generally considered to place patients at higher risk but no stratification is available and it is unclear at what level of $PaCO_2$ this risk might become prohibitive.

The most useful predictive test of gas-exchanging capacity is the diffusing capacity for carbon monoxide (D_LCO) and *ppo* values can be obtained by applying the same equation as for *ppo* FEV_1% above. A *ppo* D_LCO% below 40% predicts an increase risk of postoperative respiratory and cardiac complications, and a value over 40% indicates patients at low risk.

Cardiopulmonary performance – stair climbing (the number of steps climbed without stopping) is a simple test of cardiopulmonary reserve. The ability to climb three or more flights of stairs is associated with low perioperative mortality; inability to climb two flights reflects increased risk. Stair climbing provides a broad indicator of cardiopulmonary reserve but is not standardized.

Formal exercise testing is the gold standard for assessment of cardiopulmonary reserve and maximal oxygen consumption (VO_{2max}) correlates with postoperative morbidity (Figure 3). Patients with VO_{2max} values below 15 ml/kg/min require further assessment including consideration of *ppo* VO_{2max} values.

Preoperative VO_{2max} values and risk assessment in thoracic surgery

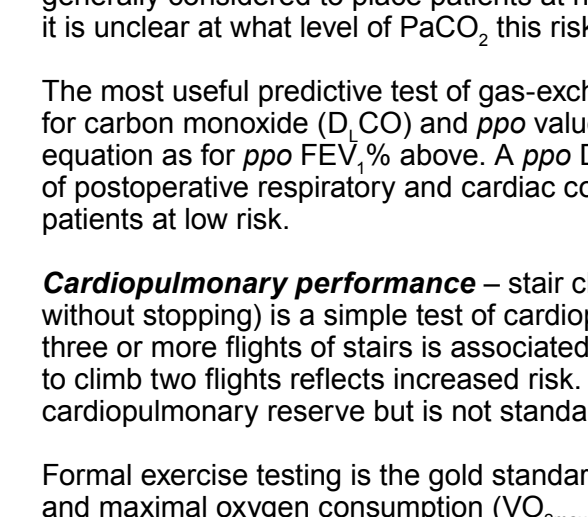
VO_{2max} (ml/kg/min)	Prediction
> 20	Favourable, low mortality, tolerate pneumonectomy
15–20	Acceptable risk benefit, may tolerate pneumonectomy
10–15	High risk, needs further assessment, limited resection
< 10	Very high risk, probably inoperable

3

Formal VO_{2max} testing is expensive and labour intensive. The 6-minute walk test correlates well with VO_{2max} in patients with severe pulmonary disease, and the inability to walk 200 m has been associated with poor outcome in those undergoing lung volume reduction surgery for emphysema. The shuttle walking test, a standardized and externally paced walking test, may correlate better with VO_{2max}. The inability to complete 25 shuttles strongly suggests a VO_{2max} below 15 ml/kg/min.

Oximetry values may also predict outcome. Resting peripheral oxygen saturation (SpO_2) below 90% and a reduction in SpO_2 of 4% or more during exercise predict major morbidity and prolonged stay in intensive care following pneumonectomy.

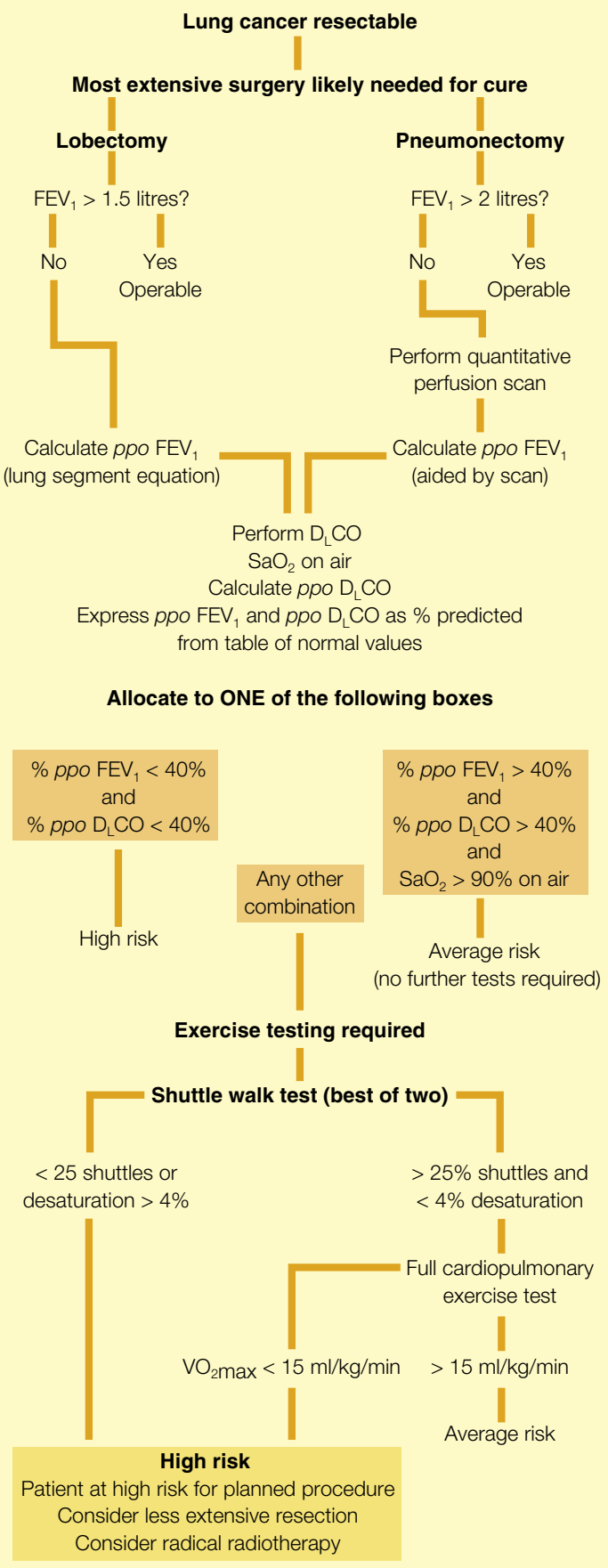
Ventilation–perfusion (V/Q) lung scans are sometimes performed in the preoperative assessment, particularly if pneumonectomy is planned. They accurately define areas of functioning or nonfunctioning lung (Figure 4).



4 CT scan showing severe emphysema and carcinoma of the left lower lobe bronchus. Pulmonary function tests were extremely unfavourable but V/Q scan revealed almost no perfusion to the left lung. Reassessment incorporating V/Q data conferred operability and the patient underwent an uncomplicated left pneumonectomy.

Algorithms for preoperative assessment
The use of assessment pathway algorithms in prethoracotomy patients has been reported. Prospective clinical evaluation of one algorithm, in 137 patients undergoing lung resections, resulted in a 50% reduction in complications, with the same percentage of inoperable patients (< 4%). Figure 5 is modified from the recommendations of the BTS Working Party (2001). The details are not important for examination candidates but it is important to recognize that these algorithms can be used to provide consistency in clinical evaluation and that there is evidence of improved outcome from this protocol-driven approach. Risk assessment and the limits of operability should be regularly reassessed to take account of new advances. BTS recommends that their guidelines be reviewed in 5 years. ◆

Algorithm for selection of patients suitable for resection for lung cancer



See text for abbreviations

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Principles and Practice of Thoracic Anaesthesia

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Most lung resections are carried out for the surgical treatment of primary malignant tumours (Figure 1). 80% of primary lung tumours are inoperable at presentation, therefore only about 3000 of these operations are performed annually in the UK. Mortality for pulmonary resection remains relatively high at 5% for pneumonectomy and 2.9% for lobectomy and therefore preoperative assessment of these patients is important.

Thoracic surgical results from 47 UK centres (1999–2000)

	Numbers	Deaths
Lung resection for primary malignant tumours		
Pneumonectomy	779	39 (5.0%)
Lobectomy/bilobectomy	2208	63 (2.9%)
Video-assisted thoracoscopic surgery (VATS) for pulmonary/pleural disease		
Lung biopsy	506	6 (1.2%)
Bullae	56	2 (3.6%)
Lung volume reduction surgery (unilateral)	50	3 (6.0%)
Lung volume reduction surgery (bilateral)	15	1 (6.7%)
Pneumothorax (various procedures)	735	6 (0.8%)
Pleural biopsy	499	5 (1.0%)
Pleural biopsy and chemical pleurodesis	932	18 (1.9%)
Pleurectomy	84	2 (2.4%)
Pleurectomy and drainage of empyema	154	4 (2.6%)

Adapted from: The database of The Society of Cardiothoracic Surgeons of Great Britain and Ireland

1

The appropriate management of anaesthesia and one-lung ventilation facilitates surgery and is likely to improve outcome. Recently there has been an increase in the number of thoracic procedures carried out using video-assisted thoracic surgery (VATS). These procedures almost all require one-lung ventil-ation at times and the observed physiological changes and principles of management are similar to those during pulmonary resection.

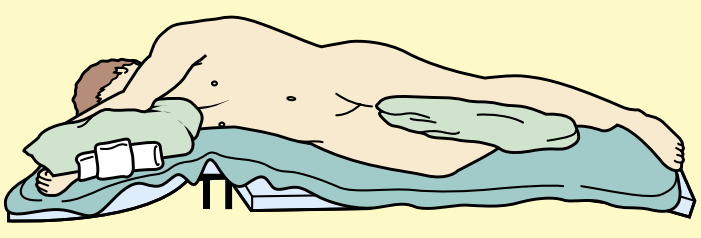
Thoracotomy and pulmonary surgery

Positioning the patient

Most pulmonary resections are undertaken with the patient in a lateral position. Following induction of anaesthesia, intubation, insertion of intravascular lines and confirmation of the side of surgery, the patient is turned into the lateral position. Several devices can be used to stabilize the patient on the operating table (Figure 2). The lower shoulder is pulled through anteriorly, allowing the flexed lower arm to be tucked under the pillow supporting the head. The upper arm is extended and placed over the head, taking care not to stretch the brachial plexus. Some surgeons who use a more anterior muscle-sparing incision, prefer to place the upper arm in a padded arm support attached to the head of the operating table.

The lateral thoracotomy position

The patient is stabilized by a comfortable mattress. Note the 'bridge' raised in the operating table, directly below the chest, to aid surgical access



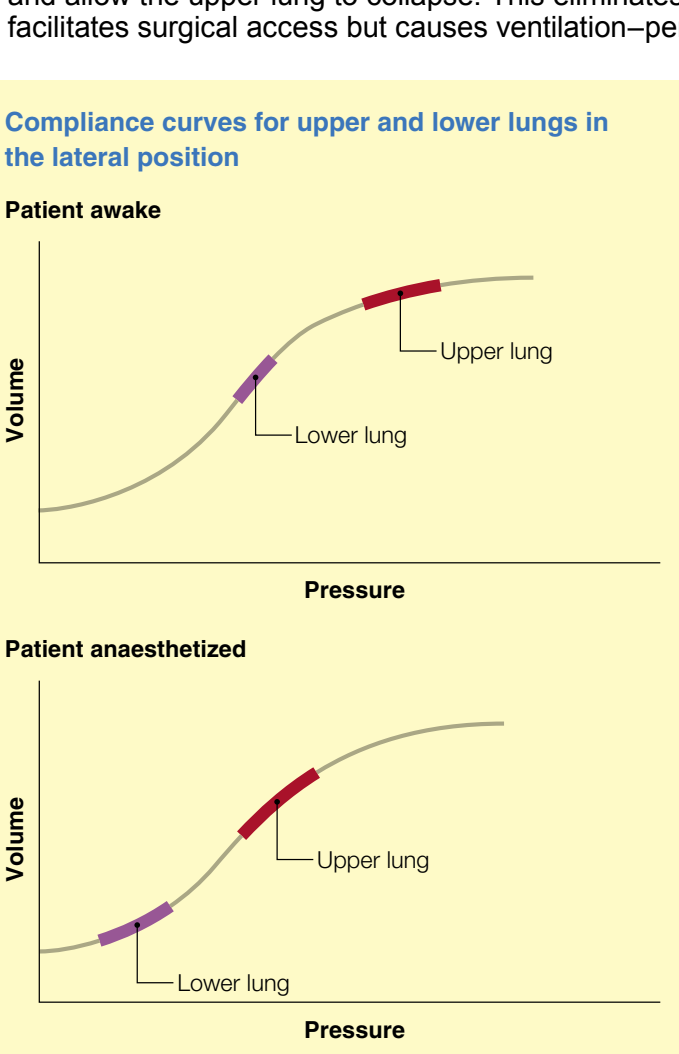
From: J W W Gothard. *Anaesthesia for Thoracic Surgery.* Oxford: Blackwell Scientific Publications, 1992

2

Stability of the pelvis is achieved by flexing the lower leg at the hip and knee while the upper leg, padded with a pillow, is kept relatively straight. Further stability may be achieved with chest and pelvic supports. Once the patient is positioned and all vulnerable areas padded, a warm-air convective heating blanket is applied to minimize heat loss during surgery.

Physiological consequences: in the awake patient there is little or no additional ventilation–perfusion mismatch in the lateral position. An increase in perfusion to the lower lung, caused by the effect of gravity on the low pressure pulmonary circulation, is matched by increased ventilation because this lung is on the steep part of the compliance curve (Figure 3). During anaesthesia the situation changes. In the spontaneously breathing patient there is a reduction in inspiratory muscle tone (particularly the diaphragm) and a decrease in the volume of both lungs with a reduction in functional residual capacity (FRC). The non-dependent upper lung therefore moves to the steeper part of the compliance curve and receives more ventilation. Paralysis and intermittent positive-pressure ventilation (IPPV) are used during thoracotomy to overcome the problems of the open pneumo-thorax created by surgery. The compliance of the non-dependent lung is further increased in this situation. In practice, it is usual to selectively ventilate the lower lung (one-lung ventilation; OLV) at this point and allow the upper lung to collapse. This eliminates the preferential ventilation and facilitates surgical access but causes ventilation–perfusion mismatch.

Compliance curves for upper and lower lungs in the lateral position



From: Yentis S M, Hirsch N P, Smith G B, eds. *Anaesthesia and Intensive Care A–Z.* 2nd ed. Oxford: Butterworth–Heinemann, 2000

3

Anaesthesia

The principles of anaesthesia for thoracic surgery are the same as those for any major surgery. Anaesthesia is usually induced intravenously. The choice of agent is seldom important. Patients presenting for lung resection are unlikely to have a co-existing airway problem and therefore a non-depolarizing neuromuscular blocking agent can be used to facilitate intubation and IPPV. A long-acting agent (e.g. pancuronium) is suitable for most operations but it is equally acceptable to use short-acting agents and give incremental doses as required. Special consideration must be given to patients with muscle weakness caused by myasthenia gravis or the myasthenic syndrome. Occasionally patients presenting for palliative VATS have an airway problem relating to tracheal or bronchial compression or an endobronchial tumour but patients undergoing lung resection are more likely to present as a 'difficult intubation' on the basis of conventional criteria.

Anaesthesia can be maintained with volatile agents delivered in an air/oxygen gas mixture or an oxygen/nitrous oxide mix. Alternatively, anaesthesia can be maintained intravenously with propofol, possibly in combination with remifentanil.

Hypoxic pulmonary vasoconstriction (HPV)

HPV is a homeostatic mechanism whereby pulmonary blood flow is diverted away from hypoxic or collapsed areas of lung. It might be expected to improve oxygenation during OLV, but *in vitro* experiments have shown that volatile agents inhibit HPV though *in vivo* studies have failed to demonstrate gross inhibition. Although volatile agents depress HPV directly, they also enhance it by reducing cardiac output. Therefore, HPV response is apparently unchanged in the presence of volatile agents during thoracotomy and OLV. Handling the lung also reduces HPV.

Potent inhaled anaesthetic agents (e.g. isoflurane) are not contraindicated during OLV and may be desirable because of their bronchodilator properties and ease of use. Significant inhibition of HPV is more likely with halothane, which should be avoided.

Intravenous agents (e.g. propofol) do not inhibit HPV and should improve arterial oxygenation during OLV. Evidence in the literature supports this contention, but it is inconclusive. Therefore, in patients with poor arterial oxygenation during OLV, it might be worth changing to a total intravenous technique.

Analgesia

If opioid drugs are to be used postoperatively it is logical to use the same drugs intraoperatively. If epidural analgesia is to be used postoperatively it should be established before surgery.

Monitoring

Monitoring and vascular access for major pulmonary surgery should be comprehensive (Figure 4). Pulmonary artery catheters can be placed in the lung contralateral to surgery only if radiological screening facilities are available. This is unnecessary in routine clinical practice. Transoesophageal echocardiography is not used during routine thoracic surgery but it may be used in the management of high-risk patients in the future.

Ventilation

Endobronchial tubes or bronchial blockers are inserted immediately following induction of anaesthesia or after preliminary bronchoscopy. Use of these devices to achieve lung separation and collapse of the lung on the operative side is described elsewhere.

Monitoring requirements for major pulmonary surgery

Electrocardiogram (ECG)

Pulse oximetry

End-tidal gas analysis
- Carbon dioxide trace particularly useful during one-lung ventilation (OLV)

Flow/volume loop
- Useful during OLV

Invasive arterial pressure measurement
- Arterial blood gas analysis invaluable during OLV

Nasopharyngeal temperature
- Heat loss significant during thoracotomy

Urinary catheter
- Appropriate for long procedures
- Consider if epidural analgesia is used or if renal function poor

4

Management of OLV: pulmonary blood flow continues to the upper lung during OLV, creating a true shunt where there is blood flow to the alveoli but no ventilation. This shunt is the main cause of hypoxaemia during OLV, though the alveoli with low ventilation–perfusion ratios also contribute. Venous admixture or shunt increases from a baseline of about 10% during two-lung ventilation to 20–30% during OLV.

OLV should be established so that it inflates the lung adequately but also minimizes intra-alveolar pressure and prevents diversion of pulmonary blood flow to the upper lung. This is not easy to achieve. High frequency jet ventilation for thoracic surgery provides ventilation at low airway pressures (see *Anaesthesia and Intensive Care Medicine* **3:6:** 204). Despite its potential advantages it is not in widespread use and this article discusses conventional IPPV.

It is reasonable to use an inspired oxygen concentration (F_IO_2) of 50% initially. When OLV is established this can be increased to 100%, if required. This cannot affect the true shunt in the upper lung but can improve oxygenation via the alveoli with low ventilation–perfusion ratios in the lower lung.

There is increasing evidence that over-inflating the single lung (volutrauma) can be detrimental and lead to acute lung injury. Deflation and inflation of the lung on the operative side with the potential for ischaemia or reperfusion injury has also been implicated in lung damage. The use of low tidal volumes improves outcome in ventilated patients with acute respiratory distress syndrome and this may also apply to OLV. Pressure- limiting ventilation is also likely to be beneficial. Limiting ventilation (Figure 5) can lead to carbon dioxide retention, but some permissive hypercapnia is preferable to lung trauma.

Guidelines for one-lung ventilation (OLV)

- Inspired oxygen concentration of 50–100% (Increase if oxygen saturation < 90%)
- Normal inspired:expired ratio (1:2) (Increase expiratory phase if gas trapping likely)
- Consider pressure-limiting ventilation
- Use small tidal volumes (e.g. 6–7 ml/kg)
- Allow permissive hypercapnia
- Use positive end-expiratory pressure
- Avoid over-inflation (volutrauma)

5

Hypoxia during OLV – it is difficult to predict which patients are likely to become hypoxic (arterial oxygen saturation less than 90%) during OLV. Patients with poor lung function are sometimes accepted for lung resection on the basis that their diseased lung is contributing little to gas exchange and this can be confirmed by ventilation–perfusion scanning. Conversely, patients with normal lung function are more likely to be hypoxic during OLV, presumably because an essentially normal lung is being collapsed to provide surgical access. A recent study found that the most significant predictors of a low arterial oxygen saturation during OLV were a right-sided operation, a low oxygen saturation during two-lung ventilation before OLV and a high (or more normal) forced expiratory volume in 1 second (FEV_1) preoperatively.

Once hypoxia occurs it is important to check the position of the endobronchial tube and readjust it if necessary. A high inflation pressure (more than 30–35 cm H_2O) indicates that the tube is displaced. It may be helpful to analyse a flow/volume loop or at least manually re-inflate the lung to get a feel for the compliance. If a tube is obstructing a lobar orifice only one or two lobes are being ventilated at most and hypoxia is likely. Suction and manual re-inflation of the dependent lung may also be helpful at this stage.

Other measures to improve oxygenation include increasing the inspired oxygen concentration, introducing positive end-expiratory pressure (PEEP) to the dependent lung or supplying oxygen to the upper lung via a continuous positive airway pressure (CPAP) system (thereby reducing the shunt). The introduction of PEEP to the lower lung with CPAP (100% oxygen) to the upper lung has also been described but this lowers cardiac output and thus oxygen delivery.

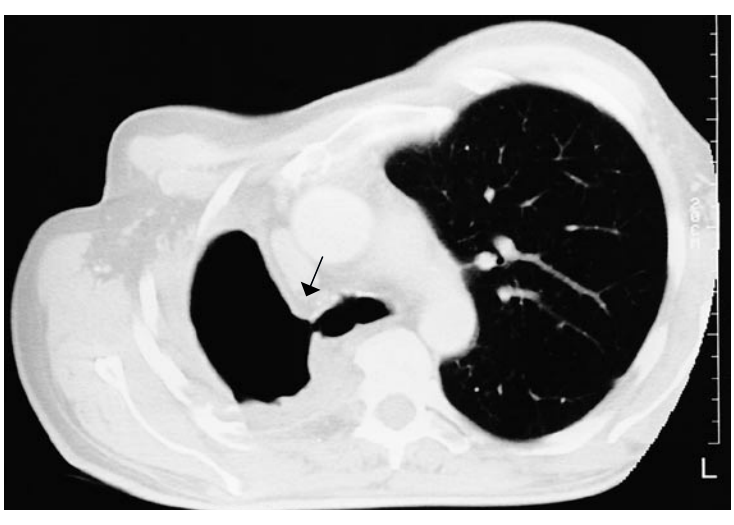
Chest drainage
Pleural or chest drainage is an essential part of the management of the thoracotomy patient. Chest drains allow the escape of air, blood or fluid from the pleural space to facilitate re-expansion of remaining lung and elimination of mediastinal shift. Drainage tubes inserted at operation are connected to an underwater seal drain, which acts as a one-way valve. Two chest drains are commonly inserted following lung resection (other than pneumonectomy). Low pressure, high volume suction is usually applied to the outlet of the drainage bottle to facilitate egress of air.

Air leak does not occur after pneumonectomy and therefore chest drainage is not mandatory. The chest can be closed without a drain if the surgeon is confident that there is no significant bleeding. If this approach is taken, air is aspirated from the pneumonectomy space to centralize the mediastinum once the patient has been turned into a supine position. Some surgeons leave a basal chest drain in for the first 24 hours following pneumonectomy. This drain is clamped but connected to an underwater seal drainage bottle. The clamp is released for about 2 minutes every hour to allow any accumulated blood to drain. Suction is never applied to a pneumonectomy drain because it pulls the mediastinum across and severely impedes or totally obstructs venous return.

Termination of anaesthesia and early postoperative period
Once chest drains are in place any remaining lung is suctioned and carefully re-inflated, keeping the pressure low. As chest wall closure is completed residual neuromuscular blockade is reversed and anaesthesia lightened. After a straightforward pulmonary resection it is usual to re-establish spontaneous respiration and extubate the patient in the operating theatre, or soon afterwards in a recovery area. This is best achieved with the patient in a sitting position. After complex or difficult surgery (e.g. lung resection combined with excision of chest wall) it may be prudent to ventilate the patient for a few hours postoperatively.

Specific procedures

Bronchopleural fistula
A bronchopleural fistula is a direct communication between the tracheobronchial tree and the pleural cavity (Figure 6). Causes include dehiscence of a bronchial stump following lung resection, trauma, inflammatory lesions (e.g. tuberculosis) and neoplasms. In developed countries, bronchopleural fistula has classically been described in relation to pneumonectomy. Its incidence following pneumonectomy is now low in specialized centres but its anaesthetic management remains an examination topic.



6 CT scan showing a chronic bronchopleural fistula following pneumonectomy. The mediastinum is pulled across towards the side of surgery (a normal finding), but there is also a clear communication between the bronchial stump and the thoracic cavity on the side of the pneumonectomy.

Bronchopleural fistula can occur at any time following pneumonectomy but usually occurs 3–15 days postoperatively. Hospitals accepting major trauma patients may admit patients with traumatic rupture of the major airways after high-speed traffic accidents. These injuries are a form of bronchopleural fistula and usually require surgical repair.

Bronchopleural fistula after pneumonectomy: the patient usually presents with symptoms related to infected space fluid flowing into the remaining lung. Acute onset with a large fistula presents with severe dyspnoea, with the patient coughing up brownish infected space fluid. Signs of cardiorespiratory failure are also apparent as a result of hypoxia and septicaemia. A chest radiograph confirms the diagnosis, showing loss of pneumonectomy space fluid and consolidation or increased shadowing in the remaining lung. Initial management includes general resuscitation. Oxygen is administered and an intravenous infusion commenced. The patient should be sat up to prevent any further spill-over of space fluid and a chest drain inserted on the pneumonectomized side to remove remaining fluid (suction should not be applied). When surgical repair is to be undertaken, the patient is transported to theatre in the sitting position, with the drain unclamped but with the drainage bottle below the patient.

Anaesthetic management: classically a post-pneumonectomy bronchopleural fistula should be isolated with an endobronchial tube placed in the remaining lung before IPPV is commenced. To secure the airway before the administration of a muscle relaxant two methods were advocated: awake endobronchial intubation using local analgesia of the upper respiratory tract; and an inhalational induction and intubation under deep inhalational anaesthesia. These techniques should be mentioned by an examination candidate but in practice both techniques are fraught with problems, particularly in these debilitated patients. Most thoracic anaesthetists use a conventional intravenous induction, following pre-oxygenation, with the patient in a sitting position and the drain open. An endobronchial tube can then be inserted safely in the main bronchus under fibre-optic bronchoscopic control after administration of suxamethonium. IPPV to the isolated lung can then be commenced and the patient positioned for surgery.

Video-assisted thoracic surgery (VATS)
VATS has been widely adopted for many procedures (Figure 1). A small, but important, group of patients also undergo lung volume reduction surgery for emphysema with the use of this technique. VATS is less invasive than open thoracotomy and is carried out through a series of ports inserted through the chest wall. It is vital to collapse the lung on the side of surgery for these procedures and therefore the use of endobronchial tubes and OLV is increasing to facilitate this surgery. There is usually less postoperative pain than after open thoracotomy and length of hospital stay may be reduced.

Anaesthetic techniques are similar to those used for lung resection. The operation is usually carried out with the patient in a lateral position, occasionally with the upper arm elevated in an arm rest.

It is essential to let the lung down before access ports and telescopes are introduced. Patients presenting for VATS may have abnormal lungs, particularly those scheduled for lung volume reduction surgery.

Lung collapse or deflation on the operative side can usually be achieved with a left-sided endobronchial tube, because this type of surgery does not breach the airway. Lung collapse during OLV is slow in the presence of marked emphysema and several techniques have been used to promote this. Some centres insufflate carbon dioxide into the pleural cavity. The gas is delivered at a low pressure and low flow (2 litres/minute) but presents a small risk of gas embolism. Others promote the idea that continued use of 50% nitrous oxide in oxygen as the inspired gas will promote lung collapse. The authors do not take any specific measures to promote lung collapse apart from ensuring that the lung is not partially ventilating via a leak around the cuff of the endobronchial tube. They occasionally apply gentle suction to the lung, although with marked emphysema this is relatively ineffective. Once the surgeons have visualized the space and divided adhesions, lung collapse is usually well enough established to allow definitive surgery to proceed.

For most VATS, OLV can be managed as described above for lung resection. Lung volume reduction surgery may be carried out bilaterally, therefore the second stage of the operation is carried out while the patient survives on the previously operated (and transiently damaged) lung.

The principles of OLV (Figure 5) also apply to general VATS. It is more important with lung volume reduction surgery to limit inflation pressure and to increase the expiratory phase of ventilation (I:E ratios of 1:3 or even up to 1:5) to prevent hyperinflation. PEEP is generally contraindicated for similar reasons. These limitations of ventilation almost certainly lead to hypercapnia but this is well tolerated in these patients. Gross over-inflation of the lung can lead to reduced venous return and cardiovascular collapse. If this is suspected, the patient should be disconnected from the ventilator to allow the ventilated lung to collapse and reduce intrathoracic pressure.

After most VATS the patients can be extubated in the normal way. Following lung volume reduction surgery it is desirable to establish spontaneous respiration as soon as possible to prevent exacerbation of air leaks and further trauma to the stapled or sutured lungs. The authors usually replace the endobronchial tube with a tracheal tube at the end of surgery and wean the patient from ventilation in the ICU over the ensuing few hours. It is mandatory to establish epidural analgesia to facilitate this. ◆

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Radiographic Appearance of Lobar Collapse

Ian J Runcie

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Collapse or atelectasis is a reduction in the volume of an area of lung. There are three radiographic signs of lobar or segmental collapse.

Changes in density – are usually a late sign.
- The collapsing area may appear denser owing to approx-imation of the vessels within it.
- The surrounding lung may appear less dense owing to compensatory emphysema, usually identified by increased spaces between vessels compared with the other side rather than an obvious increase in blackness. A comparative vessel count is often useful.

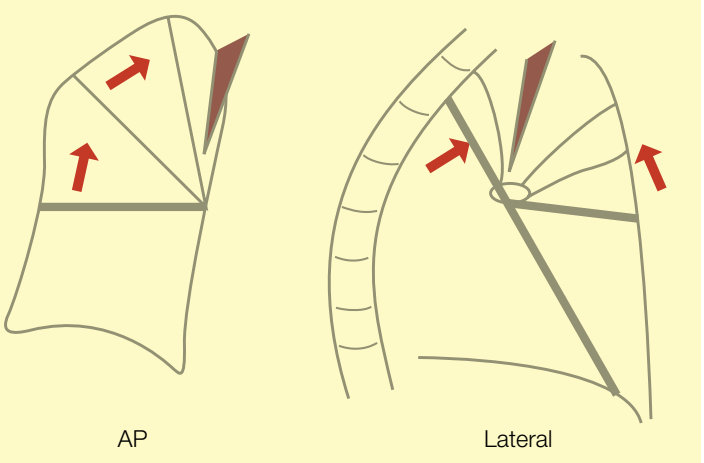
Changes in position – the hilum, mediastinum and diaphragm may shift towards the site of the collapse. Fissures show characteristic movement.

Borders adjacent to collapsed airless lung may be lost.

The following descriptions are of isolated lobar collapse. In practice there is often some associated consolidation or pre-existing disease (e.g. fibrosis) that alters the appearance. The appearances described below are only a guide to interpretation in practice.

Total collapse
Total collapse of a lung gives a whiteout on the affected side because of the airless lung and movement of the mediastinum and hemi-diaphragm to fill the space. Ribs on the affected side move closer. The other lung shows compensatory emphysema and may appear to cross the midline.

Right upper lobe collapse
The horizontal fissure moves from the horizontal towards the vertical and the upper end of the oblique fissure moves forward (Figure 1).



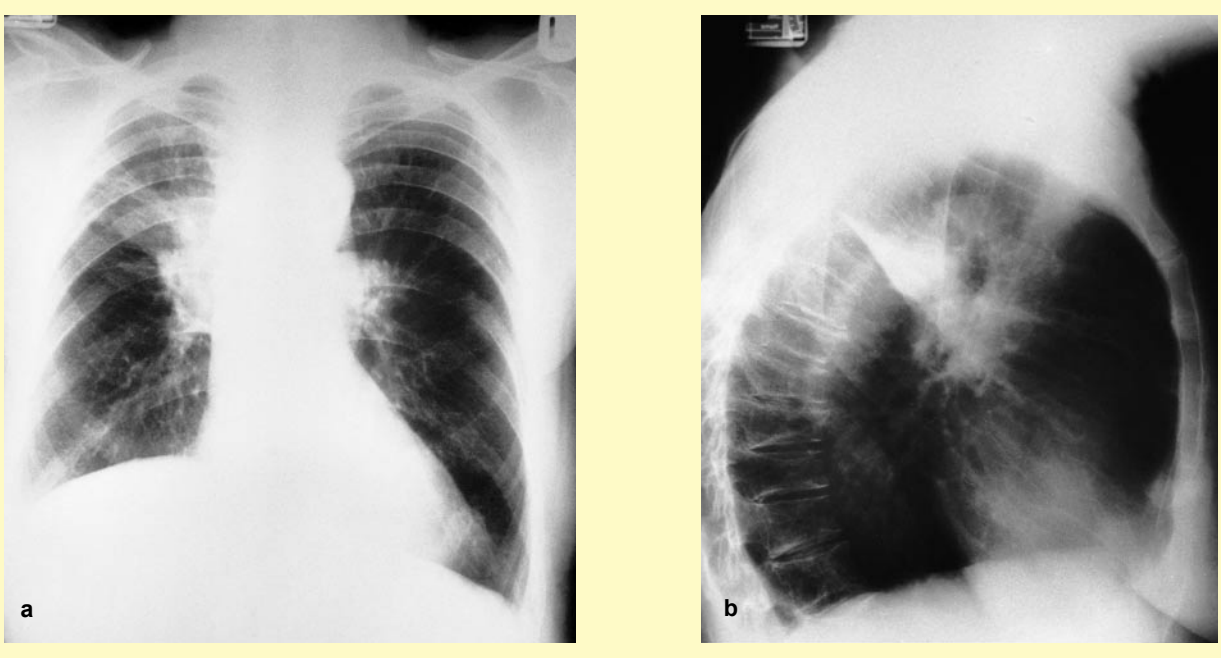
1

Changes in density
- Right upper lobe vessels move closer (Figure 2) and just before total collapse a density appears alongside the superior mediastinum.
- Compensatory emphysema occurs in the mid and lower zones.

Changes in position
- The horizontal fissure pivots on the hilum. Its lateral and anterior ends moving upwards. The upper half of the oblique fissure moves anteriorly. In severe collapse, the two meet up against the superior mediastinum. The trachea moves to the right.
- The right hilum is elevated and more prominent. Tenting may occur.

Borders – in severe collapse, the upper mediastinal border may be lost.

Tenting of the diaphragm is often a feature of upper lobe collapse or fibrosis, particularly following tuberculosis. If seen as a new feature it may be diagnostic of upper lobe collapse. It is caused by the elevation of the hilum pulling on the pulmonary ligament and accessory fissures. The pulmonary ligament is a strand of fibrous tissue between the hilum and the diaphragm.



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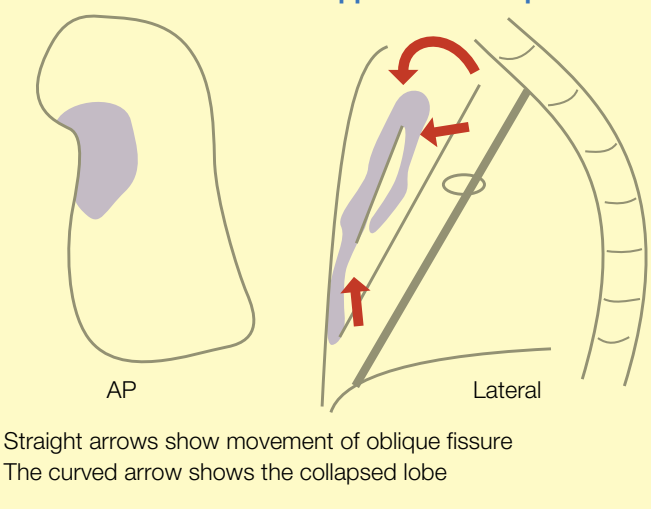
Example of right upper lobe collapse. **a** There is crowding of vessels in the right upper lobe (x) plus some increase in density which **b** shows to be caused by associated consolidation immediately superior to the oblique fissure in the posterior segment. The anterior segment is not consolidated. The consolidation demonstrates the anterior position of the oblique fissure. The normally positioned left oblique fissure can be seen more posteriorly (y). **a** The PA view shows the hila at the same level. Normally the right hilum is slightly below the left.

Left upper lobe collapse
The oblique fissure moves forwards (Figure 3) and comes to lie close to the anterior chest wall. In severe collapse the anterior part of the lobe moves posteriorly away from the anterior chest wall. The lower lobe then comes over the top of the collapsed lobe and comes to lie against the anterior chest wall. On the frontal view, the fissure is not seen but the collapsed lung may become evident against the upper mediastinum.

Changes in density
- The vessels in the left upper lobe approximate and a density appears around the aortic knuckle (PA view). The anterior part of the chest becomes increasingly denser (lateral view).
- Compensatory emphysema occurs in the left lower lobe.

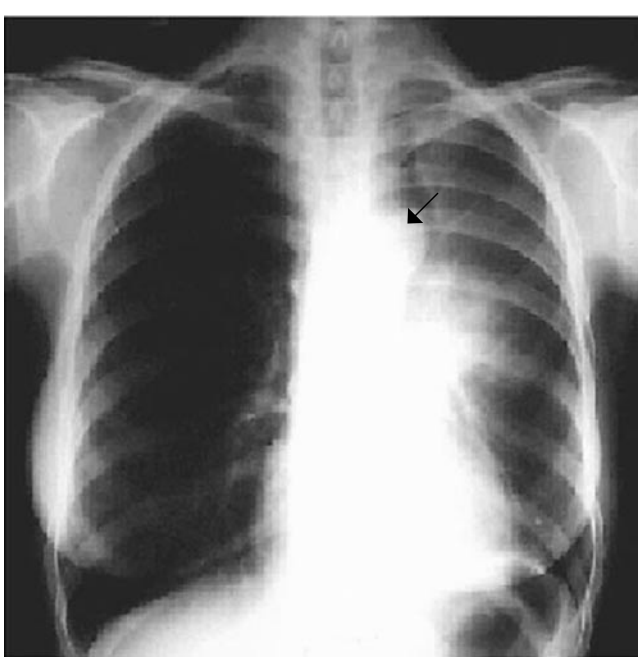
Changes in position – the fissure moves as shown in Figure 3.
The trachea moves left. As the left lower lobe expands, the diaphragm and the left hilum may elevate, and tenting may occur.



3

Borders – as the lobe collapses it rests against the aortic knuckle which lies anteriorly. As it loses air and becomes dense the aortic knuckle disappears. If the collapse advances further, the knuckle may be seen again, outlined against the lower lobe.

Figure 4 shows advanced left upper lobe collapse.



4 Advanced left upper lobe collapse. The collapsed lobe is closing down onto the hilum, becoming denser and causing the veil-like shadowing around the hilum. Note that there is no shift of the mediastinum, trachea, hemi-diaphragm or hilum. Nor is there any obvious compensatory emphysema. There is no pre-existing lung disease and the left lower lobe is sufficiently large and flexible to fill the available space. It is large enough to have come round medial to and above the collapsing lobe, causing the lucency around the aortic knuckle (arrow) and allowing this structure to be clearly seen.

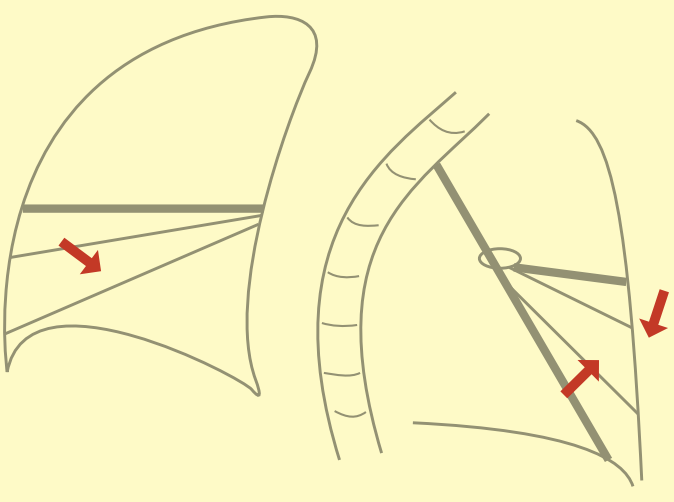
Right middle lobe collapse
The horizontal fissure and lower half of the oblique fissure approximate. The horizontal fissure is the more mobile. The collapsed lobe comes to lie against the heart border.

Changes in density – because the lobe is small, compensatory emphysema is seldom seen. There may be a vague density against the heart border (PA) better seen on the lateral view as a clear wedge-shaped opacity.

Changes in position – fissure movement is shown in Figure 5. It is best seen on the lateral view. On a PA film, if the horizontal fissure is not seen, any other changes may not be recognized.

Borders – in the late stages, the right heart border may be lost (Figure 6).

Lower lobe collapse
The pattern is similar on both sides (Figure 7). The oblique fissure moves backwards and medially. The fully collapsed lobe becomes a wedge of tissue lying up against the posterior mediastinum. The middle and upper lobes expand to fill the space lateral and anterior to the collapsing lobe.



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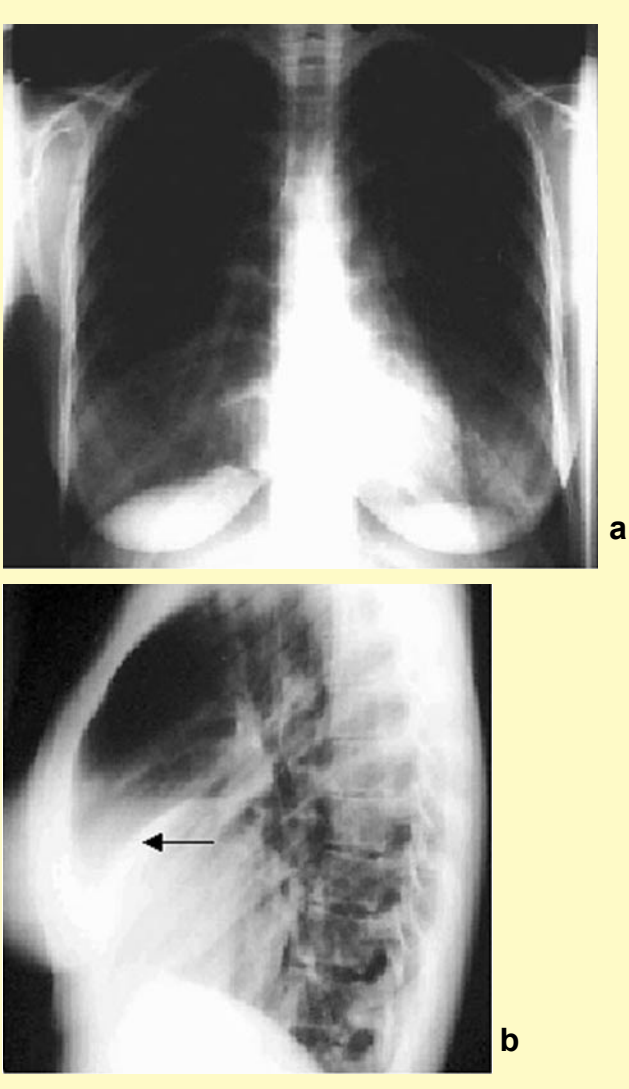
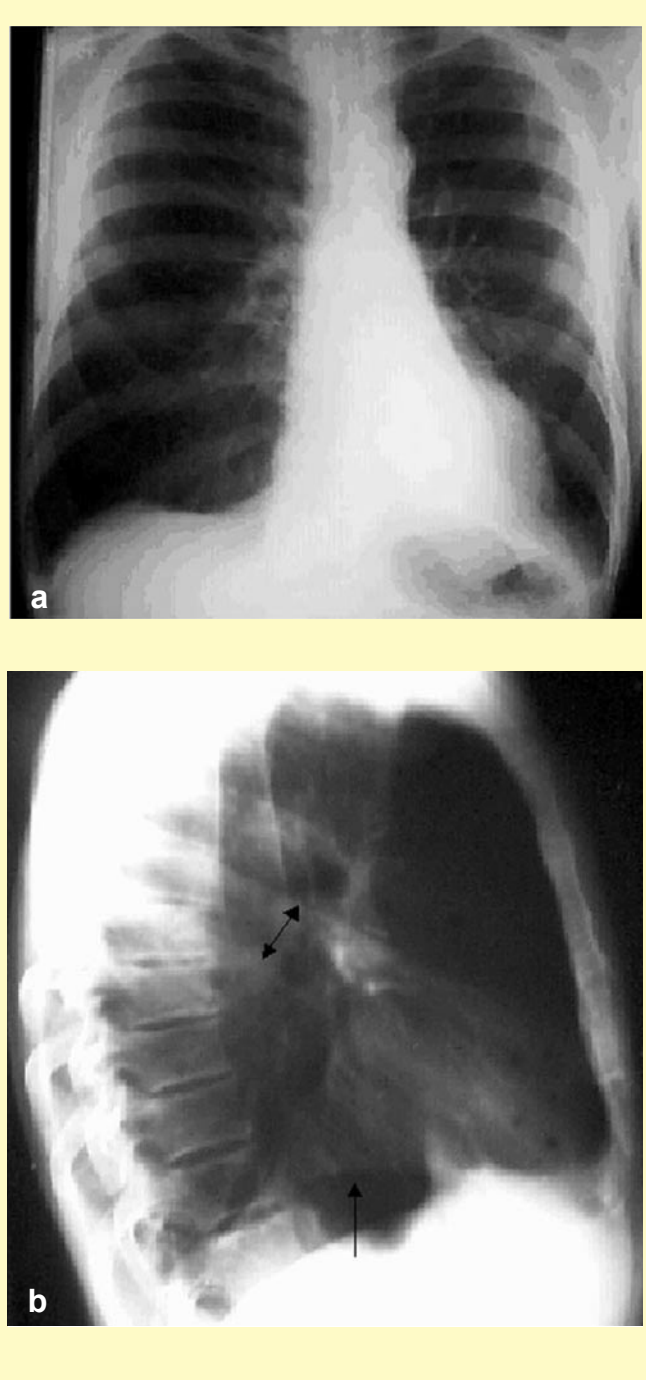


6

Example of middle lobe collapse. **a** There is loss of the right heart border. The horizontal fissure cannot be seen. **b** On the lateral view the horizontal fissure and the oblique fissure have approximated to each other leaving the middle lobe as a linear density overlying the heart shadow (arrowed).



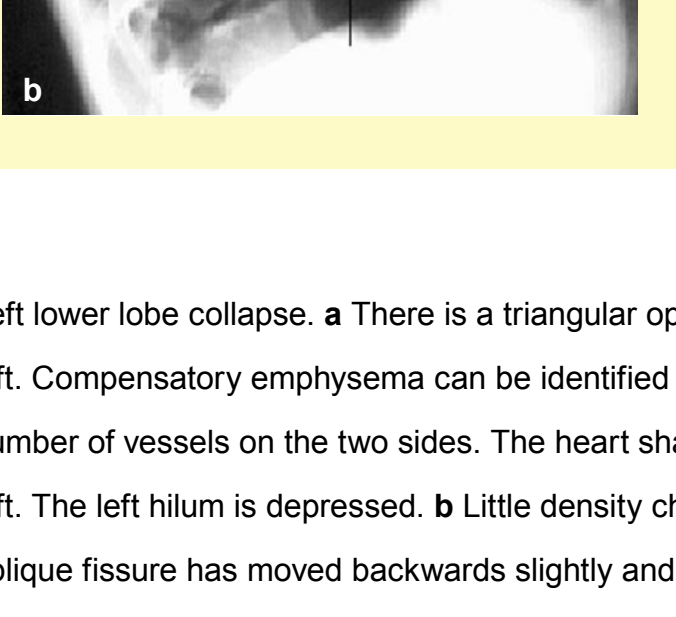
7

Left lower lobe collapse. **a** There is a triangular opacity behind the heart on the left. Compensatory emphysema can be identified on the left by comparing the number of vessels on the two sides. The heart shadow has moved slightly to the left. The left hilum is depressed. **b** Little density change can be identified. One oblique fissure has moved backwards slightly and can be seen behind the hilum. The other can still be seen in front of the hilum (double arrow). The posterior part of the left diaphragm cannot be identified though the stomach bubble (arrow) shows where it should be. Its anterior part can be identified in front of the little diaphragmatic ‘tent’ near to the inferior insertion of the oblique fissure. The right hemi-diaphragm can be clearly seen. This must mean that there is a considerable increase in the density of the collapsing lung, possibly with some associated consolidation.

Changes in density

- As the lobe moves posteriorly it becomes increasingly dense on the lateral view. On the AP view it may be seen as a wedge shape (through the heart shadow on the left).
- Compensatory emphysema occurs in right upper lobe.

Changes in position – the oblique fissure moves backwards (Figure 8). On the right the horizontal fissure may move in a similar way to right middle lobe collapse but the lung underneath it becomes less, rather than more, dense. There is movement of the heart shadow towards the side of the collapse and the hemi-diaphragm may elevate, especially if there is pre-existing lung disease limiting the compensatory emphysema. The hilum becomes depressed.



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Lingular collapse

Lingular collapse is often involved in upper lobe collapse, but the lingula may collapse on its own. Features are identical to right middle lobe collapse except that there is no horizontal fissure. On the frontal view the only evidence may be a subtle loss of the left heart border.

Plate atelectasis or linear collapse

Areas of subsegmental collapse appear as lines of variable thickness. Plate atelectasis is often temporary and seen postoperatively or it may be long-standing and fibrotic, in which case it may be referred to as scarring. ◆

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Respiratory Emergencies

Kenneth M Sim

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Optimal gas exchange in the lung is achieved through matched distribution of ventilation and perfusion, with free diffusion of oxygen and carbon dioxide across the alveolar–capillary membrane. Acute interruption of the processes necessary to sustain gas exchange is rapidly life threatening. The causes may be multiple (Figure 1) and the pathology complex, but the ability to recognize and manage respiratory emergencies represents the sharp end of anaesthetic practice.

Respiratory emergencies may be encountered inside or outside hospital, in patients of all ages, and in circumstances that vary with regard to available equipment and support personnel. Appropriate management requires an ordered approach and the application of resuscitation principles promoted in the teaching of advanced trauma and cardiac life support.

- Assess the presenting condition of the patient.
- Administer supplemental oxygen.
- Use available techniques and equipment to establish effective ventilation.
- Consider requirements for advanced airway management including emergency intubation techniques.

Causes of respiratory emergencies

Trauma
- Mechanical disruption, foreign body, haemorrhage
- Pneumothorax, haemothorax
- Thermal injury

Infection
- Croup, bronchiolitis, epiglottitis
- Pneumonia

Neoplastic
- Tumour obstruction or compression

Perioperative respiratory events
- Obstruction or interruption of the ventilatory pathway
- Irritable airways with bronchospasm
- Barotrauma and pneumothorax
- Pulmonary oedema
- Anaphylaxis

Inflammatory
- Asthma
- Acute lung injury

Neurological
- High spinal cord transections
- Ascending polyneuropathy
- Brainstem lesions

Chemical
- Inhalational injury
- Carbon monoxide, cyanide toxicity
- Drug intoxication
- Aspiration pneumonitis

Vascular
- Pulmonary embolism and infarction
- Superior vena caval obstruction
- Pulmonary oedema

1

Respiratory obstruction

Airway oedema, inflammation and foreign body inhalation are examples of conditions leading to acute respiratory obstruction. Patients with these conditions have a marked increase in the work of breathing, with clinical features including intercostal recession, paradoxical respiratory efforts and stridor. Obstruction of the upper airway results in an inspiratory, or combined inspiratory and expiratory, wheeze. Obstruction below the level of the cords is generally associated with expiratory wheeze. Signs of deterioration include:

- hypoxia – associated with restlessness and increasing distress
- fatigue or deteriorating conscious level
- diminishing respiratory sounds.

These findings indicate that complete obstruction may be imminent and senior assistance is required urgently. Management options are limited to confirming the diagnosis and relieving or bypassing the obstruction. The methods are dictated by circumstance, experience and equipment.

If time allows, the patient should be transfered to theatre where the contents of the difficult airway trolley and skilled assistance improve management. More than one anaesthetist should be present. An experienced surgeon should be on site, ready to establish a surgical airway. Options to be considered include intravenous or inhalational induction of anaesthesia with direct laryngoscopy or fibre-optic bronchoscopic intubation either awake or with adjunctive transtracheal jet ventilation.

In practice, blood, oedema and lack of cooperation are impediments to awake intubation. An obstructed upper airway is a relative contraindication to transtracheal jet ventilation because a limited expiratory pathway and stacking of breaths can result in barotrauma. Anaesthetic techniques that maintain spontaneous breathing are generally safer than the use of muscle relaxants with positive pressure ventilation by mask. The view at laryngoscopy can be improved by using the McCoy laryngoscope. Intubation may be more easily achieved over a gum elastic bougie.

As in all difficult airway situations, it is important to consider alternative plans of action should the preferred option fail. Temporary control with a laryngeal mask or Combitube airway may be possible, but in a deteriorating emergency situation it is important to proceed without further delay to cricothyrotomy or tracheostomy.

Adjunctive airway management techniques should be practised in elective conditions. Simulator training can enhance the selection of appropriate choices in emergency airway care.

Close observation of the patient must continue after control of the airway has been achieved. Sustained high negative intrathoracic pressures can result in mechanical damage to the alveolar–capillary membrane. Pulmonary oedema as a sequel to upper airways obstruction has been reported in adults and children.

Asthma

Asthma is an inflammatory disease characterized by broncho-constriction, oedema of the airway wall and mucous plugging of the small airways. Severe acute asthma refers to a prolonged exacerbation of asthmatic symptoms unresponsive to usual medical treatment. Airway narrowing causes imbalance of ventilation and perfusion, lung hyperinflation, and increases the work of breathing which results in respiratory muscle fatigue. If therapy is delayed or inadequate, acute respiratory failure develops.

Severe acute asthma may present with slow onset in those with longstanding unstable asthma or in fulminant form in response to environmental triggers. Features of life-threatening asthma include agitation, exhaustion and altered mental state. Shortness of breath affects the ability to speak in sentences. A history of severe attacks, previous tracheal intubation or intensive care indicates a high risk of complications, including death.

Initial treatment

Initial treatment is based on the administration of high dose β_2-agonists, high flow oygen and systemic corticosteroids. Salbutamol and terbutaline are equally effective and should be given by the inhaled route initially. In hospital, delivery should be via an oxygen-driven nebulizer. The initial dose in those over 5 years is salbutamol, 5 mg, or terbutaline, 10 mg. The dose should be halved in those under 5 years of age. The clinical response is measured by following trends in heart rate, respiratory rate and peak expiratory flow. Nebulized β_2-agonists should be continued until significant clinical improvement is seen or serious side-effects, such as tachycardia or dysrhythmia occur. Nebulized ipratropium bromide can be added if the initial response to treatment is poor, but should not be considered first-line therapy. Oxygen saturation should be maintained above 92% with humidified high flow oxygen by face mask.

The anti-inflammatory action of corticosteroids in asthma has a delayed onset over several hours, therefore systemic corticosteroids should be given early in adequate doses. The dose recommended in adults is hydrocortisone, 100–200 mg intravenously. Classically, nebulized corticosteroids were thought to have no place in the initial management of severe acute asthma but recent work suggests that they may have a complementary role. Empirical antibiotic therapy is not recommended.

Circulation

Severe acute asthma can have a significant effect on cardio-vascular function. Lung hyperinflation affects venous return and the position of the interventricular septum and can adversely affect left ventricular filling and emptying. Pulsus paradoxus, a feature of severe acute asthma, refers to the significant reduction in arterial systolic pressure measured during inspiration. Sweating and fluid losses from the respiratory tract compound these circulatory effects and thus action to maintain circulating volume is required. Volume loading with 20–30 ml/kg body weight of a crystalloid solution may be necessary.

Investigations

A chest radiograph is unnecessary in the initial investigation of acute asthma unless the diagnosis is in doubt, for example if a foreign body is suspected. Arterial blood gas analysis is generally performed but is not predictive of outcome. Hypercapnia and respiratory acidosis are important markers of deterioration. A differential white cell count is indicated, especially if the patient is pyrexial or producing purulent sputum. High dose β_2-agonist therapy is associated with hypokalaemia and hypomagnesaemia. The ECG may reveal signs of right heart strain, but this usually resolves quickly with effective therapy. Trend measurements of heart rate, respiratory rate, peak expiratory flow rate and oxygen saturation should be recorded.

Progress

The decision to intubate the asthmatic patient is based mainly on clinical judgement, taking into account developing fatigue and asthmatic history. If intubation and ventilation become necessary, a ventilatory regimen that does not worsen the underlying dynamic hyperinflation should be chosen. Permissive hypercapnia, small tidal volumes and a long expiratory time may reduce the risk of barotrauma and hypotension. Mechanical ventilation supports gas exchange and unloads the respiratory muscles until aggressive medical treatment is effective.

Close monitoring of lung mechanics and experience are necessary to identify the appropriate time for weaning. The intensive care management of acute severe asthma is discussed in *Anaesthesia and Intensive Care Medicine* **2:9** 353. A full review of the patient's asthma management needs to be undertaken before discharge, in anticipation of subsequent asthma attacks.

Inhalation injury

All patients with a history of exposure to smoke or fumes in an enclosed space should be considered at risk of inhalation injury, even if the initial signs and symptoms do not suggest it. Component factors include direct thermal injury, toxic gas inhalation and the later development of a chemical pneumonitis.

Thermal injury to airway mucous membranes happens immediately and causes upper airway erythema and oedema, generally developing during the first 6–24 hours. Severe injury results in ulceration and haemorrhage. It is most common in flame burns patients with extensive (> 30%) surface area injuries who develop a generalized loss of vascular endothelial integrity, resulting in soft tissue oedema.

Intubation

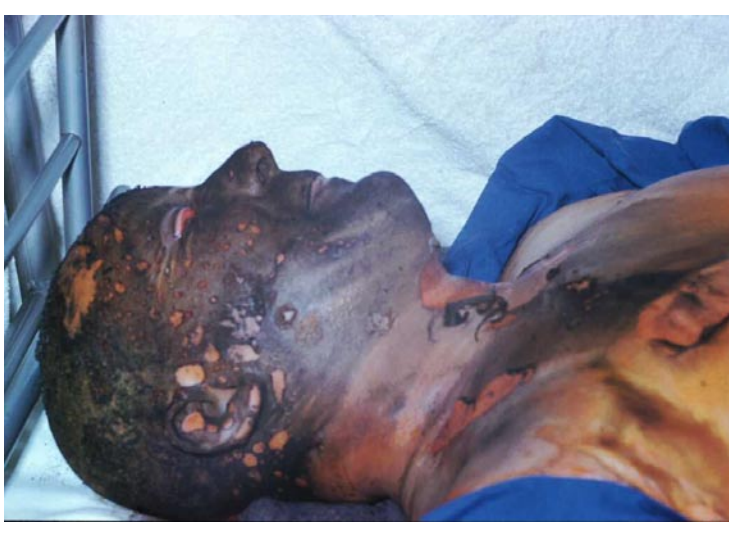
The requirement for urgent airway intervention should be judged on the pattern of the presenting history and examination findings. Any combination of the following signs and symptoms indicates prophylactic tracheal intubation, especially if transfer to a specialist burns centre is required:

- prolonged entrapment at the scene of the fire
- obtunded conscious level
- combination of facial and oral burns
- voice changes
- coughing productive of carbonaceous sputum.

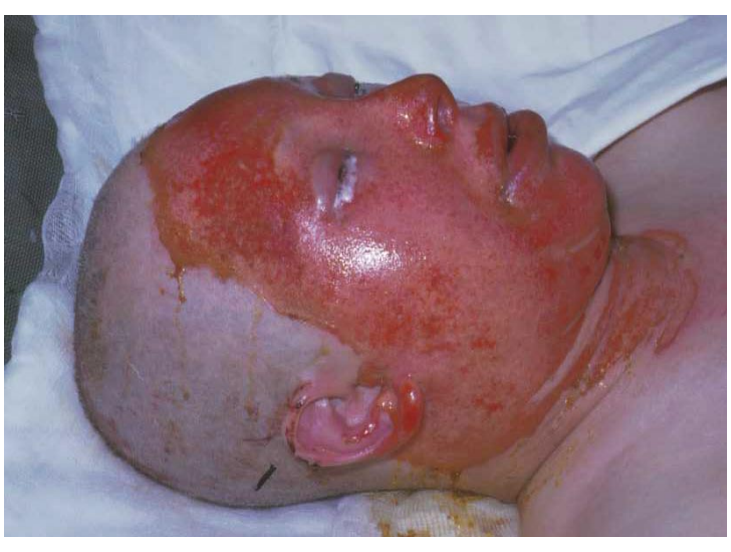
Protocol-based resuscitation procedures and delays in accessing a bed in a specialist burns centre have led to a low threshold for tracheal intubation. This is a safe approach in an adult major flame burn patient, even those with with equivocal degrees of severity of facial burns, in whom progressive swelling will still develop over 24–36 hours. Early examination may be falsely reassuring and the dynamic nature of the evolving injury must be appreciated. The history should be considered, to assess the risk of cervical spine injury, but otherwise the approach to intubation should be routine with rapid sequence induction where necessary.

Early management
Early management of patients with significant inhalation injury is symptomatic; high doses of analgesics and sedatives may be required. There is no need for pro-phylactic antibiotics. Early tracheal toilet, humidified gases and nebulized saline solution help to mobilize secretions. Fibre-optic bronchoscopy is generally performed soon after arrival at the specialist centre to assess the inital damage and enable bronchoalveolar lavage.

Scalding injuries
Scalding injuries are most common in young children and account for 80% of the burns seen in those under 5 years. Facial involvement is common but intubation is seldom necessary. The charred appearance of a major facial flame burn (Figure 2) can be compared with that of a facial scald, managed without intubation (Figure 3).



2 Full thickness burns to head and neck from a house fire.



3 Extensive facial scalds resulting from an assault.

Steam has a much higher specific heat capacity than dry air and can cause thermal injury further down the respiratory tract. In children scalded following ingestion of hot fluids or steam inhalation, thermal injury to the upper airway is rare but should be considered.

Children
Children with inhalation injuries who require intubation are prone to sloughing casts of endobronchial debris, causing sudden onset hypoxic episodes. Aggressive physiotherapy and regularly nebulized solutions possibly including sodium bicarbonate, n-acetyl cysteine and heparin are required to manage episodic airway obstruction and to prevent occlusion of the tracheal tube.

Later management
The possibility of systemic toxicity secondary to carbon monoxide and cyanide toxicity must be considered in burns patients with inhalation injuries. Carbon monoxide binds reversibly to haemoglobin with an affinity 200 times greater than oxygen, forming carboxyhaemoglobin. Oxygen is displaced and the systemic arterial oxygen content reduced. Other toxic effects include impaired cellular metabolism and binding to myoglobin, resulting in myocardial and skeletal muscle dysfunction.

Serial arterial blood samples to measure carboxyhaemoglobin levels are necessary, remembering that displayed oxygen saturation levels on pulse oximetry may be falsely elevated. The clinical presentation of acute carbon monoxide poisoning is variable, but observed symptoms approximately correlate with carboxyhaemoglobin levels (Figure 4).

Effects associated with carboxyhaemoglobin levels

Level	Signs and symptoms
< 10%	Usually asymptomatic
10–20%	Headache
20–40%	Dizziness, confusion and nausea
40–60%	Coma and seizures, cerebral oedema
> 60%	Increasing risk of mortality

4

Treatment for carbon monoxide poisoning is supportive, with supplemental oxygen given by a non-rebreathing circuit, mechanical ventilation and monitoring for cardiac arrhythmias. High inspired oxygen concentrations are necessary to reduce the half-life of carboxyhaemoglobin.

Persistent metabolic acidosis, despite otherwise successful resuscitation end-points, suggests cyanide toxicity. Treatment with sodium nitrite and sodium thiosulphate aims to induce methaemoglobin formation to bind cyanide, thus preserving mitochondrial cytochrome oxidase. Cyanide is detoxified by the hepatic enzyme rhodanase, a process hastened by sodium thiosulphate. This therapy has side-effects including significant methaemoglobinaemia; advice is available from the National Poisons Information Service in the UK.

Referral for hyperbaric oxygen therapy has been advocated, but the logistics of transfer and complications in managing any associated burns injuries leave few cases suitable for this therapy. Its place in patients with severe carbon monoxide toxicity without cutaneous burns is more contentious, but it has been advocated for carbon monoxide toxicity associated with prolonged neurological symptoms or myocardial ischaemia and in pregnancy.

Follow-up
It is important that the lessons learnt from emergency situations are acted upon. Those involved need time to consider the sequence of events and should have an opportunity to reflect and comment.

Critical incident reporting to the risk management process within the hospital helps to identify resource and organizational issues. Good record-keeping is an essential part of the response sequence – record, report and, where necessary, repair. ◆

Respiratory System: Applied Pharmacology

Roseanne Meacher
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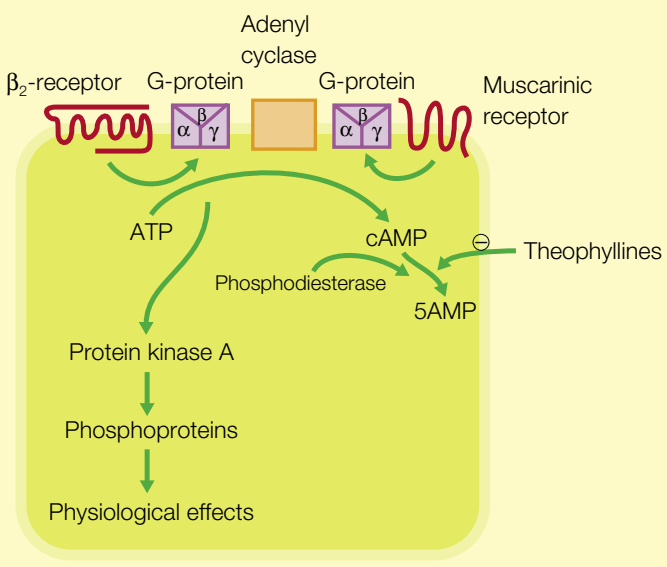
Asthma and chronic obstructive pulmonary disease (COPD) are common and knowledge of respiratory pharmacology is therefore essential for anaesthetists and intensivists.

Respiratory stimulants
Doxapram is a non-specific stimulant that acts on peripheral chemoreceptors and the respiratory centre to increase respiratory rate and tidal volume. In anaesthesia it is used to reverse postoperative respiratory depression without antagonizing opioid analgesia. Doxapram is given as an intravenous bolus of 1–1.5 mg/kg and has a duration of action of 5–12 minutes. For the treatment of type 2 respiratory failure, doxapram is infused at a rate of 1.5–4 mg/minute. It should not be used in patients with acute asthma or upper airway obstruction. Doxapram increases catecholamine release, resulting in tachycardia, hypertension and arrhythmias. This limits its use in patients with ischaemic heart disease, hypertension and thyrotoxicosis. Other important side-effects include agitation, hallucinations and (rarely) convulsions, which precludes its use in epileptics. A recent meta-analysis showed that the use of doxapram in COPD is only marginally superior to placebo in preventing blood gas deterioration and it has largely been superseded by non-invasive ventilation.

Naloxone and flumazenil are competitive antagonists that reverse the respiratory depressant effects of opioids and benzodiazepines, respectively. Both have a short duration of action when given by bolus and may require repeat doses or infusion. Flumazenil is given as boluses of 100 μg up to 1–2 mg. Side-effects include agitation, acute withdrawal, seizures, arrhythmias, hypertension, confusion, nausea, vomiting and raised intracranial pressure. Naloxone is administered in 100 μg increments to a maximum dose of 10 mg (10 μg/kg in children). Side-effects include nausea, vomiting, arrhythmias, tachycardia, reversal of analgesia, pulmonary oedema and cardiac arrest.

Bronchodilators
β_2-agonists such as salbutamol and terbutaline act on the β_2-receptors of airway smooth muscle cells to increase adenyl cyclase activity and raise intracellular levels of cyclic adenosine 3'5' monophosphate (cAMP) (Figure 1). Salbutamol may also inhibit release of histamine and other mast cell mediators. Maximal bronchodilation occurs after 15 minutes and lasts 4–6 hours.

Mechanism of action of bronchodilators



Muscarinic and β_2-receptors are linked to the adenyl cyclase enzyme via a transmembrane G-protein. When these receptors are stimulated, adenyl cyclase is activated and catalyses the conversion of adenosine triphosphate (ATP) to cyclic adenosine 3'5'-monophosphate (cAMP). Cyclic AMP activates protein kinase A which catalyses the phosphorylation of intracellular proteins thus altering their activity. Phosphodiesterase inactivates cAMP and is inhibited by theophyllines

1

At low doses, the β_2 effects of these agents predominate, but at higher doses, β_1 effects occur causing tachycardia, positive inotropy, hypertension and arrhythmias. Non-selective sympathomimetics such as adrenaline (epinephrine) have much greater cardiac effects and their use is reserved for acute emergencies such as anaphylaxis and acute severe asthma. Other important side-effects include tremor, agitation, paradoxical bronchospasm, vasodilatation, hypokalaemia and ketosis. Care should be taken in patients with thyrotoxicosis, heart disease and long QT syndrome. Initial concerns about the adverse effects of regular use of β_2-agonists in chronic asthma have not been confirmed. An increased risk of death reported with the β_2-agonist fenoterol may have been a reflection of increased disease severity. A later meta-analysis showed no association between risk of death in asthma and the use of β_2-agonists. However, it is recommended that to prevent tachyphylaxis β_2-agonists are used on a rescue basis for mild-to-moderate asthma.

β_2-agonists can be administered by inhalation, orally, subcutaneously (e.g. terbutaline) and intravenously. Techniques for inhalation include nebulizers, pressurized metered-dose inhalers, breath-activated aerosols, powder and spacer devices. Newer aerosols use non-chlorofluorocarbon (non-CFC) hydrofluoroalkane (HFA) propellant. Despite good inhaler technique and optimal particle size (2–5 μm) 80–90% of drug is deposited in the mouth and pharynx. Breath-activated devices require an inspiratory effort of 30 litres/minute. Spacer devices can overcome difficulties with inhaler technique and are useful in children under 5 years of age and in the elderly.

Nebulized β_2-agonists remain first-line treatment for acute asthma. Continuous nebulizers are more effective than inter-mittent treatment. High doses (e.g. salbutamol, 2.5–5 mg, terbutaline, 5–10 mg) are required in acute bronchospasm. It is important to use oxygen to nebulize because β_2-agonists may cause hypoxia by inhibiting hypoxic pulmonary vaso-constriction.

In an acute exacerbation of COPD there is often an element of reversible airways obstruction. Therefore, β_2-agonists can be beneficial though they may not be as effective as anticholinergic agents.

Salbutamol and terbutaline can be given intravenously though there is no evidence to support this therapy and side-effects are common. In adults, a bolus of salbutamol, 250 μg, is infused slowly with ECG monitoring.

Ventilated patients have beneficial responses to β_2-agonists given as nebulizers though drug delivery drops to 1–6% of the dose given, depending on respiratory rate and flow. Most drug deposits in the upper airway and on the tracheal tube.

Longer-acting β_2-agonists such as salmeterol and formoterol (eformoterol) are highly lipid soluble and dissolve in smooth muscle cell membranes at high concentration. This acts as a slow-release depot with a duration of action of 12 hours. They are given by inhalation and may improve nocturnal symptoms, poorly controlled asthma and COPD.

Anticholinergic drugs: ipratropium and oxitropium are muscarinic receptor antagonists resulting in vagal inhibition and bronchodilatation. They also block mast cell receptors thus reducing the release of inflammatory mediators. Inhaled ipratropium is given four times daily with maximum effect at 60 minutes and duration of 3–6 hours. Paradoxical bronchospasm can occur. Side-effects are usually local, because little drug is absorbed, and include dry mouth and blurred vision. In patients with glaucoma, the eyes must be protected. Systemic effects include urinary retention, decreased gastric emptying and constipation. Hypoxic pulmonary vasoconstriction is not affected and thus supplemental oxygen need not be given when nebulizing.

There is some evidence that nebulized ipratropium bromide is as effective as β_2-agonists in the treatment of acute asthma and COPD and improves lung function in chronic COPD, but β_2-agonists remain the first-line therapy.

Theophyllines: use is controversial because they are less potent bronchodilators than β_2-agonists but have greater potential for side-effects. Theophylline has several mechanisms of action including phosphodiesterase inhibition, antagonism of presynaptic adenosine receptors, and reduction of calcium influx into smooth muscle cells.

Theophylline, 200–600 mg, is administered orally three times a day. The addition of the salt, ethylenediamine to form aminophylline (86% theophylline), increases water solubility and allows intravenous administration. For intravenous use, a loading dose of aminophylline, 5–7 mg/kg, is given over 20–30 minutes to reduce the incidence of toxic effects. A maintenance infusion is continued at a rate of 0.5 mg/kg/hour with ECG monitoring and daily plasma levels checked. If patients have been on chronic therapy the loading dose should be omitted unless plasma levels are known.

Toxic effects include tachycardia, arrhythmias, agitation, convulsions, altered gut motility and hypokalaemia. Sup-plemental oxygen must be given because hypoxic pulmonary vasoconstriction is inhibited. The therapeutic range is 10–20 mg/litre though beneficial effects can be seen at lower concentrations and adverse effects may occur at concentrations less than 20 mg/litre. Theophylline is metabolized in the liver. Oral absorption is high but subject to varying first-pass metabolism. Changes in hepatic metabolism due to disease, age or induction/inhibition of the cytochrome P450 system (Figure 2) alter clearance and plasma levels. The half-life of theophylline is about 8–12 hours and tolerance does not develop.

Factors affecting clearance of theophylline

Increased	Decreased
• Smoking	• Liver disease
• Alcohol	• Cardiac failure
• Childhood	• Elderly
• Carbamazepine	• Neonates
• Rifampicin	• Viral infection
• Barbiturates	• Sepsis
• Phenytoin	• Cimetidine
	• Ciprofloxacin
	• Erythromycin
	• Fluvoxamine
	• Oral contraceptives

2

Currently, use of theophyllines is limited to acute severe bronchospasm and poorly controlled chronic asthma or COPD. There is no definitive evidence to support intravenous use in acute attacks though some studies have shown a trend in improving lung function and short-term improvements in COPD. Reported symptomatic improvement may be due to effects on diaphragmatic contractility.

Corticosteroids
Corticosteroids are used in the treatment of asthma, COPD, interstitial lung disease and the fibroproliferative phase of acute respiratory distress syndrome (ARDS). Use is restricted by side-effects. With long-term, high-dose corticosteroids, patients may become Cushingoid. Protein catabolism results in striae, thinning and bruising of the skin, and myopathy. Metabolic effects include glucose intolerance, fluid retention, adrenal suppression and osteoporosis. In addition, gastric bleeding, psychosis, cataracts and an increased risk of infection occur including possible reactivation of tuberculosis and chickenpox. In children, higher doses have been shown to suppress growth. A reduction to low-dose inhaled corticosteroids should therefore be achieved as soon as possible because they reduce the rate of growth but do not affect final adult height. Adrenal suppression can occur in any patient who has received more than 2 weeks of oral corticosteroid therapy in the preceding year and may also be seen after high-dose inhaled corticosteroids. Additional corticosteroids may be required during times of additional stress such as surgery or acute illness.

Inhaled corticosteroids have fewer systemic side-effects, but oral candidiasis and reversible vocal cord laxity can occur. Using a spacer device to decrease deposition in the upper airway reduces local adverse effects. Paradoxical bronchospasm is treated using a bronchodilator.

The three corticosteroids available for inhaled use are beclomethasone dipropionate, 0.2–1 mg b.d., budesonide, 0.2–2 mg/day, and fluticasone, 0.1–1 mg b.d. They are available in pressurized metered-dose inhalers and breath-activated aerosol or dry powder devices. There is no evidence that one is better than another. The lowest effective dose should be used. Inhaled corticosteroids should be used if inhaled β_2-agonists are required more than once a day.

A short course of oral corticosteroids can be used to treat acute attacks of asthma, to improve lung function and to reduce the frequency of hospital admission and relapse rates if started early. Prednisolone, 30–60 mg, is usual. Oral prednisone and prednisolone are absorbed well – prednisone is converted by first-pass metabolism to the active prednisolone. Increasing the dose of inhaled corticosteroids may have similar effects. Intravenous hydrocortisone, 400 mg/day in divided doses, can be used if oral corticosteroids cannot be taken or are poorly tolerated. The course can be stopped after 1 week if the patient is stable, but tailed off more slowly if unstable. In chronic asthma, long-term oral corticosteroids have a similar effect to high-dose inhaled corticosteroids but have more adverse effects and therefore patients should be converted to inhaled therapy. Long-term inhaled corticosteroids result in better symptom control, less use of supplemental drugs, improved lung function and decreased bronchial hyper-reactivity. In COPD, oral or high-dose inhaled corticosteroids improve lung function during acute exacerbations with a decreased relapse rate, but evidence of corticosteroid responsiveness during chronic therapy suggests that a diagnosis of reversible airways obstruction should be considered. Corticosteroids do not prevent COPD progression but may reduce the frequency of exacerbations.

Corticosteroids are commonly administered to treat the fibroproliferative phase of ARDS. A common approach is to give methylprednisolone, 2 mg/kg/day reducing over 28 days.

In croup, corticosteroids reduce the requirement for invasive ventilation and should be given early (e.g. dexamethasone, 0.3–0.6 mg/kg orally or by injection).

Newer drugs
Leukotriene receptor antagonists: (e.g. montelukast, zafirlukast) are taken orally as additional therapy for chronic asthma. They have numerous side-effects including hepatitis (zafirlukast) and a risk of Churg–Strauss syndrome. Their role is unclear – they may improve asthma control slightly, but are not yet recommended in place of regular inhaled corticosteroids.

Intravenous magnesium*:* the data do not support the routine use of intravenous magnesium in acute asthma, but it may have a role in severe refractory asthma when 5–10 mmol can be given over 20 minutes. Serum levels must be monitored if repeat doses are given. Magnesium toxicity can cause respiratory muscle weakness.

Effects of anaesthesia on the respiratory system

Induction of general anaesthesia commonly results in respiratory depression and upper airway obstruction due to reduction of pharyngeal tone and posterior displacement of the tongue. Airway reflexes are depressed, increasing the risk of pulmonary aspiration of gastric contents. During emergence, stimulation of the larynx may result in laryngospasm. This occurs more commonly in children and can be life threatening. Tracheal intubation can induce bronchospasm and vagally mediated bradycardia. The presence of a tracheal tube may cause airway oedema that presents only after removal, this is more significant in children

General anaesthesia commonly causes a 20% reduction in functional residual capacity. Atelectasis develops in dependent parts of the lungs resulting in shunting and hypoxia. The reduction in lung volume also leads to increased airway resistance and reduced lung compliance. These effects occur within minutes of induction and atelectasis commonly persists postoperatively. Ventilation is thus increased to non-dependent parts of the lungs. Neuromuscular blocking drugs and positive-pressure ventilation further increase ventilation to poorly perfused areas of lung, increasing physiological dead space. While maintaining alveolar recruitment and reducing shunt, positive-pressure ventilation reduces venous return and cardiac output thus decreasing mixed venous oxygen saturation. These effects are magnified by ventilatory adjustments that increase mean airway pressure such as the addition of positive end-expiratory pressure.

Administration of dry and cold gases is associated with impaired mucociliary function, increased mucus viscosity and decreased surfactant production. This can lead to airway plugging, atelectasis and worsening gas exchange. Thus, it is important to maintain the heat and humidity of inspired gases by using either a heat and moisture exchanger or a heated humidifier.

Volatile anaesthetic agents and gases depress respiration and the ventilatory response to hypercapnoea. Tidal volume is decreased but partially compensated for by increased respiratory rate. Volatile agents are bronchodilators: halothane and isoflurane are used most commonly for this purpose. Halothane and sevoflurane are the least irritant to the airways and are used for gaseous induction of anaesthesia. Nitrous oxide has a blood/gas partition coefficient 35 times that of nitrogen. Therefore, administration of nitrous oxide results in expansion of compliant gas spaces within the body including pneumothoraces. Termination of nitrous oxide causes diffusion hypoxia unless supplemental oxygen is given.

Intravenous induction agents (e.g. propofol, etomidate, thiopental (thiopentone)) cause dose-related respiratory depression and apnoea. Airway reflexes are depressed to a greater degree with propofol than with other agents. This results in a lower incidence of bronchospasm and laryngospasm on induction of anaesthesia. Thiopental (thiopentone) may cause histamine release. In contrast to other anaesthetic drugs, ketamine stimulates ventilation and is depressant only following large doses. Airway patency is usually maintained. Ketamine is a bronchodilator and is occasionally used to treat refractory bronchospasm. Benzodiazepines are also respiratory depressants and may cause apnoea, particularly if used in conjunction with opioids.

Analgesic drugs: morphine depresses the ventilatory response to the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) primarily by reducing respiratory rate rather than tidal volume. Morphine inhibits the cough reflex, can cause bronchoconstriction and should be avoided in asthmatics. Very large doses of opioids can lead to severe muscle rigidity making ventilation impossible. This rigidity is prevented by simultaneous use of a neuromuscular blocking drug. Sufentanil and remifentanil are extremely potent respiratory depressants. Pethidine can cause bronchiolar dilatation via a direct smooth muscle relaxant action and is therefore preferred to morphine for asthmatic patients. Tramadol causes less respiratory depression than morphine. Non-steroidal anti-inflammatory drugs can induce asthma in susceptible patients.

Other drugs used during anaesthesia: neuromuscular blocking drugs produce respiratory muscle paralysis and apnoea. This can be unusually prolonged following the use of suxamethonium in patients with abnormal plasma cholinesterase activity. All the neuromuscular blocking drugs can cause histamine release and bronchospasm but this is uncommon with vecuronium and rocuronium.

Atropine inhibits bronchial glandular secretion, stimulates the respiratory centre and increases anatomical dead space by its bronchodilatory action. The anticholinesterase neostigmine causes increased upper and lower airway secretions and bronchospasm and thus is always administered with an antimuscarinic agent (e.g. atropine, glycopyrrolate). ◆

FURTHER READING

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Allergic Reactions in the Perioperative Period

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The prevalence of major allergic reactions during anaesthesia is poorly defined; estimates range from 1/3,500 to 1/25,000, with little evidence of a true increase in incidence over the last two decades. These figures include anaphylactic and anaphylactoid reactions. Both are associated with mast cell histamine release with its attendant pathophysiological consequences. However, the former is the consequence of interaction of specific antigens with IgE antibody, while the latter are not IgE related. In practice, the mechanisms are of little relevance in the acute stage, and clinical management is governed by the severity of the reaction.

Several drugs used in the perioperative period have been associated with allergic reactions (Figure 1), in particular neuromuscular blocking drugs. Almost every anaesthetic drug has been implicated as a trigger. A previous history of exposure to the relevant drug is often not elicited.

Severe allergic reactions during anaesthesia and surgery are characterized by a different clinical profile from that seen with allergic reactions in the non-operative setting (Figure 2). Cutaneous symptoms and signs are less common, possibly because the skin is covered by drapes, but there is an increase in the percentage of cases presenting as cardiovascular collapse, perhaps because intravenous administration may result in more severe reactions. In the anaesthetized patient, drug-related allergic reactions may also present as angio-oedema (typically facial), unexplained desaturation, arrhythmias, rising airway pressures or an inability to ventilate the lungs. Manifestations usually appear 5–15 minutes after administration of the drug.

Agents commonly implicated in perioperative allergic reactions

- Muscle relaxants (vecuronium, atracurium, suxamethonium, pancuronium)
- Induction agents (barbiturates, etomidate, propofol)
- Opioids (morphine, pethidine, fentanyl)
- Colloids for intravascular volume expansion (particularly gelatins and some dextrans)
- Local anaesthetics
- Antibiotics
- Radiological contrast agents
- Blood and blood products
- Latex

1

Clinical manifestations of serious allergic reactions

Manifestation	Non-operative (n = 1158)	Perioperative (n = 484)	
		Anaphylaxis	Anaphylactoid
Cutaneous	98[1]	75.6	86
Cardiovascular			
Hypotension	21	18.0	20
Cardiovascular collapse	–	49.0	12
Dizziness, syncope	31	–	–
Respiratory			
Wheeze, bronchospasm	53	41.9	25
Death	0	< 1.0[2]	0

[1]All figures are percentages.
[2]May be higher depending on severity. A mortality of 3.5% is often quoted for severe reactions.

2

The treatment of an anaphylactic reaction does not depend on its cause, and standard management algorithms are available in most hospitals (Figure 3). The most important point is to consider the diagnosis and initiate therapy. The diagnosis is essentially clinical, but may be supported by an increase in plasma tryptase levels in a blood sample, ideally obtained 1 hour after the onset of the reaction. Tryptase is one of several neutral serine proteases contained in mast cells, which though not an important mediator, acts as a surrogate marker of other vasoactive substances released during mast cell degradation, because it has a long plasma half-life and it is stable in plasma stored at –20°C. It is important to emphasize that management of the allergic episode beyond the acute stage remains the responsibility of the attending anaesthetist. Comprehensive management should include resuscitation, acute aftercare and arranging for investigation of the patient in an allergy clinic.

Emergency management of perioperative anaphylaxis

The doses specified are for a 70 kg adult if not otherwise specified. Basic monitoring is assumed

Immediate therapy

1 Discontinue administration of the suspect drug
2 Summon help
3 Discontinue surgery and anaesthesia if feasible
4 Maintain airway, 100% oxygen (consider tracheal intubation and intermittent positive-pressure ventilation, if not already instituted)
5 Intravenous adrenaline (epinephrine) especially if bronchospasm present, 50–100 μg (0.5–1.0 ml 1:10,000)
Repeat as necessary for hypotension and bronchospasm
Prolonged therapy may be necessary
6 Start intravascular volume expansion with suitable crystalloid or colloid, 10 ml/kg rapidly
7 Consider formal cardiopulmonary resuscitation, including external cardiac massage

Secondary management

1 Adrenaline (epinephrine)-resistant bronchospasm: consider one of the following
salbutamol, 250 μg i.v. load, 5–20 μg/min maintenance
terbutaline, 250–500 μg i.v. load, 1.5 μg/min maintenance
aminophylline, 6 mg/kg i.v. over 20 min
2 Bronchospasm and/or cardiovascular collapse: corticosteroids
hydrocortisone, 300 mg i.v., or methyl prednisolone, 2 g i.v.
3 Antihistamines
chlorpheniramine, 20 mg i.v. given slowly
4 Measure arterial blood gases. If acidosis is severe after 20 min treatment, consider
sodium bicarbonate, 0.5–1.0 mmol/kg i.v. (0.5–1 ml/kg of 8.4% solution)
5 Catecholamine infusions:
adrenaline (epinephrine), 5 mg in 500 ml saline (10 μg/ml): 10–100 ml/hour
noradrenaline (norepinephrine), 4 mg in 500 ml dextrose (8 μg/ml): 10–100 ml/hour
6 Consider possibility of coagulopathy: clotting screen and blood products if needed
7 Draw 10 ml of venous blood about 1 hour after onset, send sample to laboratory to store plasma at –20°C for tryptase assay

Post-acute care – this is an anaesthetic responsibility

1 Ensure that physiological stability is maintained in recovery
2 Consider admission to ICU
3 Inform patient and warn regarding risks of re-exposure to drug (Need for *Medic-Alert* bracelet?)
4 Arrange for referral to allergy clinic

3

Allergy investigation may involve patch, prick or intradermal testing with low dilutions of the suspect drugs (cutaneous testing). A range of drugs is usually tested. Well-performed cutaneous testing has a high sensitivity and specificity. However, such tests must be conducted in appropriately supervised settings only by qualified people who are able to interpret them. They involve a small risk of serious allergic reactions and must be undertaken only where emergency care is readily available. *Ex vivo* tests for allergy to drugs include radioallergosorbent tests (RAST); enzyme-linked immunosorbent assays (ELISA) are available, but are less sensitive. The patient must be informed of the suspected risk of allergy as soon as possible, and encouraged to wear a *Medic-Alert* bracelet.

Latex allergy

Latex, a natural derivative of the rubber tree, is widely used in medical products because of its physicochemical characteristics and barrier properties. William Halstead introduced latex gloves in 1890, but latex allergy was not recognized until 1979. The epitopes responsible for inducing allergy to latex include native antigens in the rubber and neoantigens that are produced by mechanical and chemical processing of the raw material. Sensitivity to latex is acquired by repeated exposure to latex products. People at high risk of latex allergy include:

- those with repeated or long-term urinary catheterization
- those with spina bifida, myelomeningocele, spinal cord trauma (related to bladder catheterization?)
- healthcare workers (particularly operating theatre and dental staff)
- atopic individuals (risk is 4–5 times greater than general population)
- those with sensitivity to bananas, avocado, chestnuts, kiwi fruit, figs, blue grass, ragweed
- rubber workers.

Measurement of latex antibodies in blood donors or systematic testing in the preoperative period reveals a sensitivity rate of 0.125–2.4% in the general population, but staff in operating theatres and dental surgeries may have sensitivity rates as high as 20%.

Trigger exposure may be from direct contact in the form of latex gloves or equipment (e.g. barium enema catheters, bladder catheters, anaesthetic masks, adhesive tape, tourniquets, electrodes). Mucosal or peritoneal contact is a more effective trigger than cutaneous contact, and may be associated with more severe reactions. Patients may inhale latex from the operating room atmosphere, typically adsorbed on to glove powder. The operating room atmosphere may contain 88–974 ng latex protein/m^3. Such environmental contamination is not significantly attenuated by laminar air systems, but may be substantially reduced by using powder-free gloves.

The stoppers of most injection vials are made of latex, which may leach into the injectate (and result in anaphylactic shock), or be picked up when drugs are reconstituted in solvents that are injected through such stoppers. The latex injection bungs on intravenous access devices and giving sets are also a significant hazard.

Pathogenesis and clinical manifestations: serious clinical reactions are similar to other allergic reactions. However, anaphylactic reactions often manifest later (typically 30–60 minutes after starting surgery) especially if the trigger is surgical glove contact with a mucosal surface rather than reactions to anaesthetic drugs (administered at induction). A reaction to latex contact in the anaesthetic room can manifest earlier, and be difficult to distinguish from a drug-related reaction.

Occupational exposure may present as contact dermatitis or asthma, and may be difficult to identify as latex allergy, especially in the patient with pre-existing atopic disease. Occupational and clinical reactions may be due to Type I (IgE-mediated) or Type IV (T cell-mediated) responses, though serious clinical events are usually associated with the former. Healthcare workers may react to a different antigen (a 20 kDa protein) from that implicated in reactions in children with spina bifida (a 14 kDa protein).

Management: the acute management of an anaphylactic episode remains identical, regardless of the cause. However, specific management is required for the care of a patient known to be at risk of latex allergy, and for the investigation of latex allergy in patients or healthcare workers. The extent to which these guidelines are followed depends on the relative risk posed by a given patient. Patients may be categorized as:

- Group 1: previous anaphylactic reaction to latex
- Group 2: significant allergy to latex (urticaria, angio-oedema, bronchospasm)
- Group 3: at-risk group listed previously.

In general, Groups 1 and 2 are treated identically. Specific precautions are not universally advised in patients in Group 3; practice varies between hospitals.

Preparation and organizational details: preparation for anaesthesia in a patient at risk of latex allergy begins with a careful preoperative assessment and quantification of risk. It is essential to attend to organizational details; patients in Groups 1 and 2 need to be first on the operating theatre list, when the use of latex-free equipment is not negated by a high environmental load of latex from previous cases on the day. If such scheduling is impossible, the theatre must remain unused for at least 2 hours before surgery.

It is essential to ensure that the drugs and equipment required for the treatment of anaphylaxis are available and already drawn up, and an appropriate stock of latex-free anaesthetic and surgical equipment is available (Figure 4), and that latex-containing equipment and disposables are removed from the theatre suite (Figure 5). The anaesthetic machine (including the soda-lime canisters) should not have been contaminated by latex.

Latex-free equipment

• Gloves	Allergard (J & J); Dermaprene, Nitra Topuch, Touch N' Tuff (Ansell); Neoprene (Regent)
• ECG electrodes	3M; Medicotest
• BP cuff	Cover with tape or use J&J Disposa Cuff; Hewlett Packard
• Pulse oximeter	Hewlett Packard
• Pressure transducer	Ohmeda
• Temperature probes	Disposable probes can be used
• Oesophageal stethoscope	Hewlett Packard; Vital Signs
• Operating table	Avoid contact with mattress and trolley by covering with sheet
• Face masks	Rusch; Intersurgical; Vital Signs; Laerdal
• Breathing circuits	Mallinkrodt; Intersurgical; Vital Signs
• Rebreathing bags	Only if specified latex-free
• Guedel airways	Vital Signs; Universal Hospital Supplies
• Nasopharyngeal airways	Portex
• Endotracheal tubes	Portex; Mallinkrodt
• Catheter mounts	Portex
• Suction catheter	Pennine; Yankaeur; Sherwood; Argyle
• Nasogastric tubes	Vygon; Portex; Rusch
• Tape/dressings	Transpore, Tegaderm, Micropore (3M); Hyperfix (Smith & Nephew); Mepore (Molnlycke); SteriStrips (J&J)
• Syringes	B & D; Braun
• Cannulae	Abbott; Abbocath; Venflon; Ohmeda
• Central venous pressure monitor	Arrow
• 3-way taps	Vygon; Ohmeda
• Blood sets	Sangofix Braun
• IV extension	Letrocath, Lectrospiral (Vygon)
• Colloid	Gelofusine in Polyfusor bag
• Epidural catheter	Portex
• Spinal needle	Sprotte (Portex); Whitacre (B&D); Quincke (Vygon)
• Stimuplex	Braun
• Diathermy	3M plate and lead

This table is for guidance only. Any item used in an at-risk patient must be positively identified by the user as safe. Continue the latex-free environment in the recovery unit and on the ward

Equipment containing latex

Do not use the following equipment

• Gloves	Biogel, Diagnostic, Reveal, Super-sensitive (Regent); Nutex, Gammez, latex examination gloves (Ansell)
• Face masks	Rusch; Ohmeda; CDL; WSP
• Rebreathing bags	Ohmeda; Intersurgical; Vital Signs; Mallinkrodt
• Nasopharyngeal airways	Rusch
• Cannulae	Ycan (Wallace); any sets with a latex bung or injection port
• Tapes	Sleek; Elastoplast
• Pulmonary artery catheter	Most manufacturers (balloon is latex)
• Patient-controlled analgesia disposables	Vygon
• Theatre hats	Johnson & Johnson
• Limb exsanguinators	
• Tourniquets	

Use the following with caution

- Anaesthetic machines should be protected with a heat and moisture exchanger at fresh gas outlet and patient circuit
- Gum elastic bougie may be safe if silicone coat intact
- Vials with bungs: remove bung before drug mixing. Do not inject through any latex bungs
- For all regional anaesthesia packs other than those described above, replace syringe with latex-free model
- Pulse oximeter probes: wrap finger in *Tegaderm*

If anaphylaxis occurs, follow the anaphylaxis protocol
Continue to use latex-free anaesthetic and monitoring equipment

Premedication: the drug regimen described here has no proven benefit in preventing reactions but may reduce their severity and delay their onset. Premedication should include:

- methylprednisolone, 1 mg/kg 6 hourly i.v.
- ranitidine, 1 mg/kg 6 hourly i.v.
- chlorpheniramine, 10 mg i.v. 6 hourly (adult dose)
- salbutamol (2 puffs inhaler or 2.5–5 mg by nebulizer) 6 hourly (for patients with asthma).

At least two doses must be given preoperatively, and many protocols prescribe the need for intravenous administration. Diluents should not be added to the drugs via a needle through the bung. The bung should be removed and the solution reconstituted.

Management in theatre should focus on preventing contact between the patient and latex, directly, through exposure to aerosolized particles or through secondary contact.

Postoperative care: precautions should continue in the recovery room and beyond. Some patients may need postoperative critical care; special care is needed in this setting, which is a latex-rich environment. The precautions described above may be difficult to implement because ICUs are multi-patient environments where staff change over the course of the day, and the more prolonged clinical stay may result in vigilance fatigue.

Testing for latex sensitivity: epicutaneous testing provides the best diagnostic yield, and patch testing with 2.5 cm^2 of glove rubber may be useful in establishing contact dermatitis. Well-conducted cutaneous testing with prick or scratch tests has a sensitivity of 100%, a specificity of 99%, a positive predictive value of 79% and a negative predictive value of 100%. RAST and ELISA and Western blot techniques are less sensitive, and may detect only 50–60% of healthcare workers with IgE-mediated sensitivity reactions to latex.

Occasionally, provocative tests may be required to establish or exclude a diagnosis of latex allergy in health workers with negative prick or patch testing and a negative RAST. An inhaled challenge with pulmonary function testing may be useful in those in whom bronchospasm is the primary problem. Such challenge tests are risky, and must not be undertaken lightly. However, they may be essential in healthcare workers in whom latex allergy necessitates a change in occupation or employment, particularly if compensation or retirement issues have to be considered. ◆

FURTHER READING

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Anaesthetic Management of the Transplant Patient

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Few fields in medicine have advanced as rapidly over the past 25 years as organ transplantation. Each year, many thousands of patients with irreversible diseases of the heart, lungs, liver, kidneys and pancreas now receive transplants. Advances in surgical technique, perioperative care and long-term immunosuppression, and increasing use of organs from living donors for renal and hepatic transplants, have created a large population of organ recipients. Up to 30% require surgical intervention after a successful transplant, and many present for surgery outside transplant centres. The anaesthetist may face complex problems related to reduced functional reserve in the graft, effects of the disease originally causing organ failure or complications of immunosuppression.

General considerations

After the immediate postoperative period, transplant recipients are more vulnerable to surgical conditions affecting the abdominal cavity (e.g. bowel perforation, pancreatitis, cholecystitis, peptic ulcer disease, bowel ischaemia and obstruction). Immunosuppressants, particularly corticosteroids, may be implicated, and may mask the signs and symptoms of peritonitis. Malignancy complicates immunosuppression in 2–7% of transplant recipients, most commonly lymphoproliferative disorders and primary carcinomas of skin and colon. These patients may require anaesthesia for diagnostic procedures or surgical intervention. Organ-specific late complications requiring surgical intervention include bronchial stenoses or leaks in lung recipients, uretero-vesical obstruction in kidney recipients, and biliary obstruction or leak in liver recipients.

Chronic rejection

Chronic rejection is the main cause of late, progressive graft dysfunction. Its cause is unknown, but all transplanted organs have intimal thickening in small arteries, which is associated with, and may be the cause of, distinctive lesions in each organ. These are obliterative bronchiolitis in the lung, transplant coronary artery disease in the heart, vanishing bile duct syndrome in the liver and interstitial lymphocytic glomerulopathy in the kidney. They occur more than 3 months after transplantation and are the most common cause of late graft failure and death. Impaired organ function due to chronic rejection is an important consideration when assessing the cause of graft dysfunction and its potential for amelioration.

Assessment of organ function

Assessment of organ function is carried out as for non-transplant patients, with caveats in the case of heart, heart and lung and liver recipients. Renal function is quantified by plasma creatinine or creatinine clearance, plasma potassium and urine output. Liver synthetic function is assessed by plasma albumin and prothrombin time. Raised alanine aminotransferase reflects hepatocellular injury, typically rejection or infarction, and usually before synthetic function is overtly impaired. Increased alkaline phosphatase and bilirubin indicate cholestasis, which may be caused by extrahepatic biliary obstruction, sepsis or chronic rejection. Clinical portal hypertension is uncommon in the long-term liver recipient, but if varices and ascites are present, disease in the graft is regarded as end-stage. Perioperative risk in these patients is increased, because general anaesthesia and surgery may be associated with hepatic decompensation, bleeding and encephalopathy.

Exercise tolerance is the mainstay of the clinical assessment of graft function in heart and lung recipients, supplemented in the presence of any significant limitation by echocardiography in heart and heart and lung patients and pulmonary function tests (spirometry and diffusion capacity) in lung and heart and lung patients. Heart recipients do not experience angina, because the heart is denervated, but have a high incidence of recurrent coronary disease (transplant coronary artery disease), which affects small arteries first and typically presents with global impairment of contractility, arrhythmias or sudden death. Resting electrocardiography may fail to identify advanced disease.

Underlying disease

The disease that originally led to organ failure and transplantation may affect other vital systems. Examples are diabetes mellitus and hypertension (kidney recipients), atherosclerosis, sarcoidosis and amyloidosis (heart recipients), cystic fibrosis (liver, lung and heart and lung recipients), and alcoholism (liver transplantation). Metabolic conditions treated by liver transplantation but potentially affecting other systems include oxalosis, haemophilia and familial amyloid polyneuropathy.

Immunosuppression

The perioperative management of immunosuppression is best discussed with the transplant centre treating the patient. The need for supplemental corticosteroid treatment has been questioned. A study of renal transplant patients taking long-term maintenance corticosteroids showed that clinical adrenal insufficiency associated with major surgery is a rare and readily treatable occurrence, and experience with liver recipients supports this. Higher corticosteroid doses may be detrimental in a carefully managed immunosuppression programme. Maintenance of existing immunosuppression in all but the most ill patients is usual.

Oral absorption is variable postoperatively and immunosuppressants should be given intravenously. Oral prednisolone is replaced with equal doses of intravenous methylprednisolone. Intravenous substitution of azathioprine is also done at equal dosage. Oral ciclosporin (cyclosporin) is only 25–40% absorbed, therefore about one-third of the oral dose is given intravenously, with regular monitoring of plasma concentration.

Antimicrobial prophylaxis for bacterial endocarditis follows guidance applied to non-transplant patients. Heart transplant patients are not considered at increased risk and prophylaxis is not routinely indicated. Postoperative analgesia regimens should generally omit non-steroidal anti-inflammatory drugs (NSAIDs) because of the prevalence of renal impairment and the increased risk of intestinal bleeding accompanying corticosteroid use. If NSAIDs are used, close monitoring of plasma creatinine is important and the addition of a proton-pump inhibitor advisable.

Side-effects of immunosuppressive drugs

Side-effects of immunosuppressive drugs are a substantial cause of clinical and subclinical morbidity in the transplant recipient and are described elsewhere.

Hypertension – the incidence approaches 50% and is commonly multifactorial in origin. Ciclosporin (cyclosporin) and tacrolimus may cause afferent arteriolar vasoconstriction in the kidney, and corticosteroids may induce fluid retention. In renal transplant patients, hypertension may also be related to chronic rejection, renal artery stenosis or the retained native kidney. Treatment, often with more than one agent, is typically with angiotension II receptor antagonists, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists and/or β-blockers. β-blockade and inhibition of the effects of angiotensin improve survival in patients with subclinical or overt cardiac failure, while calcium antagonists blunt ciclosporin (cylcosporin)-induced afferent arteriolar vasoconstriction. These agents may increase the likelihood of and the vulnerability of the kidney to hypotension.

Renal dysfunction – both ciclosporin (cyclosporin) and tacrolimus are nephrotoxic and associated with glomerulosclerosis, tubular atrophy and interstitial fibrosis. Some reduction in renal function is expected in all transplant recipients treated with these agents. Poorly controlled hypertension or hyperglycaemia may aggravate this, and careful attention to maintenance of intravascular volume is important.

Hypercholesterolaemia and coronary atherosclerosis – immunosuppressants, in particular ciclosporin (cyclosporin), tacrolimus and prednisolone, aggravate risk factors for atherosclerosis, including raised low density lipoprotein (LDL) and total cholesterol concentrations. The prevalence of both occult and symptomatic ischaemic heart disease, cerebrovascular and peripheral vascular disease is high in the transplant population, and these processes are accelerated by these effects. Statins and aspirin are often prescribed routinely.

Hyperglycaemia – ciclosporin (cyclosporin) directly inhibits insulin release from pancreatic islet cells and induces glucose intolerance and the incidence of treated diabetes in transplanted patients. Tacrolimus and corticosteroids have a similar effect.

Neurotoxic effects are commonly observed in transplant recipients, usually early in the postoperative period. Side-effects of ciclosporin (cyclosporin) include tremor, seizures, nerve and plexus palsies, impaired consciousness, hemiparesis and psychosis. Corticosteroids in high dose in the setting of acute rejection may also cause acute psychosis. Longer term neuropsychiatric symptoms (e.g. anxiety, depression, impaired memory, emotional lability) have also been attributed to corticosteroids. The possibility of neurotoxicity should always be considered when unexpected neurological symptoms or signs appear in the perioperative period.

Drug interactions

Drug interactions involving immunosuppressants are many, but few affect anaesthetic management. The principal risks are associated with increased or decreased plasma concentrations (toxicity and risk of acute rejection, respectively). Anaesthetic drugs have not been implicated. Ciclosporin (cyclosporin) potentiates atracurium and tacrolimus (also a cytokine inhibitor) is expected to do the same.

There are few published data on the pharmacokinetics and pharmacodynamics of anaesthetic drugs in the transplant population. Clinical experience suggests that the efficacy and side-effects of most agents in routine use are unaffected; the exceptions are described below.

Anaesthetic management

Preoperative assessment and preparation

Preoperative assessment and preparation is guided by the same principles applied to the general population. Elective procedures should be preceded by consultation with the transplant physician responsible for the patient's long-term care, who should advise on evaluation of graft function and on perioperative immunosuppression. Outside normal working hours, the co-ordinator at the transplant centre should be contacted; they can provide or obtain similar expert advice. Intercurrent opportunistic infection (signs of which may be subtle) and acute rejection should be excluded. Clinical and laboratory assessment should focus on graft function, adverse effects of immunosuppression and possible impairment of other organs affected by the underlying disease.

Left ventricular dysfunction and renal impairment both strongly indicate the need for a high-dependency setting after any major procedure. Hypertension, hyperglycaemia, hyperkalaemia, atrial fibrillation, angina, left ventricular dysfunction and gastro-oesosphageal reflux are common clinical features and their management must be optimized. If cannulation is planned, the patency of central veins should be evaluated by ultrasonography because all these patients will have had previous central venous catheters, often many. The patient's blood should be screened; most patients will have had previous blood transfusion and antibody problems may delay the provision of suitable bank blood. The patient's cytomegalovirus (CMV) antibody status should be ascertained and the CMV-negative patient given only CMV-negative products.

Insertion of intravascular catheters should be performed using full sterile precautions and a careful no-touch technique used when they are used for drug and fluid administration or blood sampling. Drug syringes should be kept capped and three-way taps protected from contamination at all times.

Heart recipients

Transplant coronary artery disease is common, typically affecting small peripheral vessels before larger, proximal ones. It presents as heart failure or new arrhythmias, including ventricular fibrillation and complete heart block. Sinus and/or atrio-ventricular (AV) nodal ischaemia leads to persistent bradycardia or AV conduction block in about 10% of patients, who require permanent pacing. Left ventricular contractility should be assessed by echocardiography, and specialist advice about the perioperative management of pacemakers obtained in patients with these devices. The pacemaker should be checked and a programming device made available for elective procedures. In an emergency, an external pacing unit and defibrillator should be immediately to hand. If diathermy must be used, the diathermy plate should be placed on the thigh and a bipolar attachment used.

Cardiac denervation has a fundamental effect on cardiac responses to reduced central blood volume, adrenergic stress and certain drugs (Figure 1).

Effects of cardiac denervation

- The patient does not experience angina
- Resting heart rate is increased 90–110/min, and the electrocardiogram may show atrial activity from the recipient atrial remnant alongside or superimposed on the donor P-wave
- The heart rate response to sympathetic stimuli is delayed and more limited than normal, and is a poor marker of depth of anaesthesia and hypovolaemia
- The chronotropic response to vagolytic drugs (e.g. atropine, glycopyrrolate) is absent
- Vagotonic drugs (suxamethonium, neostigmine) have no effect and the vagally mediated effect of digoxin on atrioventricular conduction is lost
- Denervation supersensitivity amplifies the effects of adenosine, adrenaline (epinephrine) and noradrenaline (norepinephrine); reduced doses are appropriate
- Cardiac output is highly sensitive to preload and to negatively inotropic drugs
- Drug-induced falls in systemic vascular resistance cause exaggerated hypotension, especially when preload is marginal

Anaesthetic technique is guided by the patient's general condition and the scale of the procedure. For a minor or intermediate procedure, spontaneous breathing with a laryngeal mask can be appropriate if left ventricular function is well preserved. In the presence of impaired left ventricular function, intubation and positive-pressure ventilation are advisable. Large-bore venous access, established before induction, is advisable because it allows rapid administration of aliquots of fluid to maintain preload when myocardial depression and reduced systemic resistance occur during anaesthesia. Ephedrine, an indirectly acting sympathomimetic, may be used to provide a modest chronotropic effect if needed; it also exerts positive inotropic and vaso-constricting effects. Cautious doses of adrenaline (epinephrine) also produce all these effects and provide a substitute for isoprenaline (no longer available in the UK) when ephedrine is inadequate. Pure vasoconstrictors (e.g. phenylephrine, metaraminol) may also be used to correct hypotension, but maintenance of intravascular volume usually suffices.

There are few published data to favour the use of any particular maintenance regimen for anaesthesia, but a target-controlled infusion of propofol may be associated with problematic hypotension in patients with limited cardiac reserve, as is remifentanil, and these should be avoided in less fit patients. Spinal and epidural blocks have also been associated with aggravated hypotension in heart recipients and should be used with caution, especially in the postoperative period when supervision must be very close. Peripheral and plexus blocks (e.g. femoral–sciatic, brachial plexus) are well tolerated and a welcome alternative to general anaesthesia in appropriate circumstances.

Lung recipients

As in the general population, routine preoperative tests assessing pulmonary function are typically less informative than the history. Some limitation is expected in virtually all these patients, but their anaesthetic management does not differ from that of other patients with chronic pulmonary disease. Lung denervation reduces the cough reflex distal to the bronchial anastomosis, increasing the importance of postoperative chest physiotherapy. Recipients of single lung transplants may be affected by differential compliance and ventilation–perfusion mismatch during anaesthesia, worsened by the lateral position or some vasoactive infusions. This is normally overcome by increasing the inspired oxygen fraction and/or the addition of modest positive end-expiratory pressure, but occasionally lung isolation and differential ventilation may be needed to alleviate hypoxia or to avoid barotrauma to the grafted lung.

Liver recipients

With good graft function, liver recipients present few anaesthetic problems. Responses to induction agents, relaxants (including suxamethonium) and opiates are typically normal. However, the scale of the liver transplant procedure makes any subsequent operation in the abdomen technically challenging and likely to cause significant bleeding. Prothrombin time, haemoglobin and platelet count are vital routine preoperative tests, and coagulopathy, though rare, should be aggressively corrected before surgery. A prothrombin time prolonged by more than 2 seconds should be treated with fresh frozen plasma, 1–2 units, before any significant procedure. The platelet count for a minor procedure should be above 50,000 (above 100,000 for a major procedure).

Patients with decompensated graft function present a major challenge. They present with coagulopathy and ascites, and both respiratory and renal function may be compromised. Nutritional impairment is usual, accompanied by hypoalbuminaemia and hyponatraemia. Infusion of blood products may be associated with ionic hypocalcaemia, and calcium administration may be needed to maintain haemodynamic stability. Responses to anaesthetic agents are predictable, but the effects of benzodiazepines and pancuronium may be prolonged. Regional techniques are used only when coagulation indices are normal.

Kidney recipients

Diabetes, hypertension and ischaemic heart disease are the most common co-morbidities in kidney recipients and are managed perioperatively as in the general population. In the elective setting, antihypertensives and other cardiovascular drugs are taken on the morning of surgery with the patient's usual immunosuppressants. Most patients continue to have mild-to-moderate renal impairment and should be managed accordingly. Many have limited concentrating ability, therefore prolonged fasting should be avoided and perioperative crystalloid replacement should be generous. Anaemia is common, even in patients treated with erythropoietin. Suxamethonium is safe in the absence of hyperkalaemia, but the effects of non-depolarizing relaxants should be monitored closely. Atracurium and cisatracurium are the most predictable agents but even these may exert a prolonged effect in patients with marginal graft function, particularly in the presence of ciclosporin (cyclosporin) and acidosis.

The need to spare antecubital and lateral forearm veins for possible future arteriovenous fistula formation should be kept in mind, preference being given to the dorsum of the hand and to veins on the medial aspect of the middle third of the forearm. Subclavian vein cannulation should be avoided because subsequent stenosis or thrombosis may render the whole limb incapable of tolerating the high flows produced by a fistula. If central venous access is required, the right internal jugular is the vein of choice. When positioning the patient for surgery, care should be taken to protect any existing fistula from compression or proximal venous obstruction.

Spinal or epidural analgesia is not contraindicated in the kidney recipient, but sustained hypotension, both intraoperatively and postoperatively, must be avoided. NSAIDs (with the exception of low-dose aspirin) are contraindicated.

Pancreas recipients

Pancreas recipients have all the end-organ complications of longstanding insulin-dependent diabetes, including overt and silent ischaemic heart disease, renal impairment, and autonomic and peripheral neuropathy. Gastroparesis and reflux are common, and intubation is more likely to be difficult than in the general population. Blood glucose instability is less common than in other insulin-dependent diabetics, but blood sugars should be monitored at least hourly during surgery. Maintenance of graft perfusion by careful attention to intravascular volume is essential. Peripheral nerve injury and nosocomial infection are common in these patients and every effort should be made to reduce these risks. ◆

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Anaesthetic Problems in Renal Transplantation

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In 2001, in the UK, 1691 kidney-only transplants were performed; of these, 358 (21%) were from living donors. The current UK 1-year graft survival figures are 86% for cadaveric and 95% for living donor grafts. This is associated with a quality of life and long-term survival significantly better than dialysis in most forms of end-stage renal disease. As a result of this success, kidney transplantation is being offered to a wider population of high-risk patients (including those with advanced cardiovascular disease, type II diabetes, morbid obesity, sickle cell disease and various forms of vasculitis). In 2001, in the UK, 4846 patients were on the waiting list, and while the total number of transplants performed per year remains fairly constant, the waiting list continues to grow because the inclusion criteria are being widened. Cadaveric transplants have slowly decreased in number, but living related transplants have tripled since 1992.

Preoperative assessment and preparation

Both the causes (Figure 1) and sequelae (Figure 2) of end-stage renal disease must be considered when assessing the potential transplant patient. Preoperative assessment must include a careful evaluation of hydration status (hypovolaemia risks graft failure), blood pressure control, cardiovascular disease, diabetes management, electrolyte status, magnitude of anaemia and coagulation abnormalities. Preoperative dialysis is routine, with the aim of dialysing the patient to within 0.5 kg of ideal body weight. Sites of any arteriovenous (AV) fistulae should be noted. If there is a history of previous central venous cannulation for monitoring or dialysis, ultrasound examination of the neck veins should be considered because the patient may have narrowed or thrombosed vessels.

Common causes and prevalence of end-stage renal disease

- Types I and II diabetes mellitus (44% and 4%)
- Glomerulonephritides (10%)
- Polycystic kidney disease (6%)
- Pyelonephritis/interstitial nephritis (6%)
- Hypertensive nephrosclerosis (3%)

1

Sequelae of chronic renal disease relevant to anaesthesia

Haematopoiesis and coagulation
Anaemia
- Decreased erythropoietin production
- Reduced red cell half-life
- Reduced red cell production

Platelet dysfunction
- Reduced platelet factor III activity
- Abnormal platelet aggregation

Cardiovascular
Coronary artery disease
- Accelerated atherosclerosis

Congestive heart failure (CHF)
- Primary: uraemic cardiomyopathy
- Secondary: fluid overload

Pericarditis/pericardial effusion (secondary to uraemia)
Dysrhythmias
- Hyperkalaemia
- Hypocalcaemia

Hypertension

Respiratory
Pulmonary oedema (secondary to CHF/fluid overload)
Pleural effusions
- CHF/fluid overload/peritoneal dialysis

Electrolyte disturbances
Hyperkalaemia
- Dysrhythmias

Hypermagnesaemia
- Potentiation of neuromuscular blockade
- Hypotension

Acid–base regulation
Metabolic acidosis

Gastrointestinal
Oesophageal sphincter dysfunction
Diabetic gastroparesis
Gastrointestinal bleeding
- Platelet dysfunction
- Peptic ulcer disease

Hepatic
Hypoalbuminaemia
Cytochrome P450 abnormality

Endocrine
Secondary hyperparathyroidism
- Correct calcium and phosphate abnormalities preoperatively

Diabetic autonomic neuropathy
- Gastroparesis
- Risk of sudden death

Dialysis-related problems
Peritoneal dialysis
- Peritonitis
- Pneumonia, atelectasis, pleural effusion
- Volume overload
- Hypoproteinaemia, hyperglycaemia, hyperlipidaemia
- Pain

Haemodialysis
- Systemic anticoagulation due to residual heparin effect
- Metabolic acidosis
- High output cardiac failure due to shunting through the arteriovenous fistula
- Hypovolaemia, hypotension
- Disequilibrium syndrome (cerebral oedema after acute dialysis)

2

Perioperative morbidity is increased in recipients with diabetes mellitus, generally due to cardiac events. Cardiovascular assessment should be performed carefully and any evidence of ischaemic heart disease investigated. Joint rigidity can occur in patients with longstanding diabetes because of advanced glycosylation of joint tissue; it may affect the temporomandibular joint. Airway evaluation should be carried out with this in mind.

The most common electrolyte abnormality of concern in renal transplant recipients is hyperkalaemia. A preoperative serum potassium of less than 5.5 mmol/litre is desirable in all cases but essential in live donor transplants, which are elective procedures in which all aspects of risk must be minimized. If serum potassium is 5.6–5.9 mmol/litre, acceptability depends on co-morbidity in the recipient. The risk may be prohibitive in the presence of ischaemic heart disease or increased surgical risk (significant blood loss). It should be treated preoperatively. Repeat dialysis is advisable if serum potassium is greater than 5.9 mmol/litre (Figure 3).

All antihypertensive medication should be continued perioperatively with the exception of angiotensin-converting enzyme (ACE) inhibitors, which can exacerbate hypotension at induction of anaesthesia. In addition, ACE inhibitors have been associated with profound hyperkalaemia in uraemic patients, therefore potassium should be closely monitored.

Routine preoperative medication includes immunosuppressive drugs and antibiotic prophylaxis. Consideration should be given to aspiration prophylaxis and an anxiolytic.

Treatment of perioperative hyperkalaemia

Preoperative serum potassium > 5.5 mmol/litre
- Nebulized salbutamol, 10 mg
- Dextrose/insulin, 50 ml D50W, 10 iu insulin

Intraoperative serum potassium > 5.5 mmol/litre
As above plus
- Wash all bank blood using cell saver before transfusion

Intraoperative serum potassium > 6.0 mmol/litre
As above plus
- 8.4% $NaHCO_3$ 50 ml
- Consider 13.4% $CaCl_2$ 10 ml if any ECG changes (increased QRS widening)
- Urgent dialysis/haemofiltration if potassium remains over 6 despite the above

3

Surgical technique

The procedure can be divided into three stages: exposure and preparation of the iliac vessels; revascularization of the donor kidney; and construction of urinary drainage. In living donor transplants, the procedure is complicated by the fact that the renal artery and renal vein are shorter than those in a cadaveric organ and no patches can be taken from the aorta and inferior vena cava, respectively. Revascularization of the kidney is a critical time for the anaesthetist.

Anaesthetic technique

Monitoring and vascular access: central venous pressure (CVP), neuromuscular blockade and temperature are monitored in addition to routine anaesthetic monitoring. CVP is essential for monitoring intravascular volume. Neuromuscular monitoring is important because the extraperitoneal positioning of the graft makes it vulnerable to expression and injury if the abdominal muscles contract before closure of the wound.

When establishing vascular access, the non-fistula arm is used. A large-bore peripheral intravenous cannula is placed in a hand vein if possible, so preserving the forearm and antecubital veins for possible future AV fistula formation. Arterial cannulation is not indicated unless there is overriding concern about intraoperative haemodynamic instability. If direct arterial monitoring is necessary, the dorsalis pedis or femoral artery on the opposite side to the proposed graft site is used. This spares the vessels of the upper limb for possible future AV fistula formation.

Consider placing central venous access in the internal jugular vein on the opposite side to any functioning AV fistula; subclavian venous access is relatively contraindicated because subsequent thrombosis or compression by haematoma may make the entire limb unsuitable for AV fistula formation.

Theatre preparation and positioning: the patient is positioned supine. If an AV fistula is present this arm should be placed on an arm board and the fistula protected from compression. The non-invasive blood pressure cuff should be placed on the arm opposite any AV fistula. Warming devices including a warming mattress, forced air warmer and blood warmer are used. 0.9% saline is standard for initial intravenous infusion.

Anaesthesia: fluid loading before induction may be necessary in patients in whom hypovolaemia is suspected. All patients are intubated and ventilated without exception. Consideration should be given to the need for a rapid sequence induction, in particular for diabetics with autonomic neuropathy who may also have gastroparesis. Anaesthesia may be induced slowly with propofol, thiopental (thiopentone) or etomidate. Suxamethonium causes a rise in serum potassium of up to 0.6 mmol/litre. Fentanyl, atracurium (by infusion), isoflurane or desflurane are used for maintenance. Total intravenous anaesthesia with propofol/remifentanil or alfentanil has also been used successfully.

Sevoflurane can be used for induction but produces inorganic fluoride ions during prolonged use. No evidence of nephrotoxicity has been found, but isoflurane or desflurane are safe alternatives. Enflurane is contraindicated.

Atracurium or cisatracurium are the muscle relaxants of choice because they are metabolized independently of the kidney. Vecuronium and rocuronium are not contraindicated.

Morphine can be given late in the procedure with patient-controlled morphine analgesia planned for postoperative pain control. Epidural analgesia is avoided because of the risks associated with uraemic coagulopathy and difficulties maintaining intravascular volume intraoperatively and postoperatively in the face of marked postoperative polyuria (up to 2 litres/hour).

Specific intraoperative considerations

Graft function: the most important intraoperative measures that improve the likelihood of immediate graft function are the maintenance of adequate intravascular volume and satisfactory perfusion of the transplanted kidney. High blood flow through the graft immediately on clamp release is associated with early renal function, a decreased mortality rate and increased graft survival. Therefore CVP should be maintained at 10–15 mm Hg (if pulmonary artery pressure is being monitored the mean value should be 15–20 mm Hg) from immediately before reperfusion.

Urine output: early onset of urine output is associated with a significantly increased likelihood of graft survival. Furosemide (frusemide), 80–250 mg, mannitol, 20–50 g, and dopamine, 2.5 μg/kg/min, are used to stimulate urine output. Albumin, calcium channel blockers and dopexamine have also been used successfully. Most centres have their own cocktail of drugs to be given at the time of revascularization of the transplanted kidney. Intraoperative anuria or oliguria must be aggressively investigated and both mechanical and non-mechanical factors excluded and treated. Prerenal mechanical factors include arterial or venous stenosis or thrombosis; postrenal mechanical factors include outflow tract obstruction, leakage of urine at the uretovesicle junction or external compression of the kidney, its vessels or ureter. Non-mechanical factors include hypovolaemia, hypotension, acute tubular necrosis or acute rejection.

Perioperative hyperkalaemia is common, particularly in diabetics and patients taking ACE inhibitor or β-blockers. A treatment protocol is suggested in Figure 3.

Postoperative care

Most patients can be extubated soon after surgery is completed. Early postoperative management focuses on adequate renal perfusion and urine output. Continuous CVP monitoring and hourly urine output measurement are standard, aiming for a CVP of 8–12 mm Hg and output of 200 ml/hour. The major concerns at this time are of renal artery or vein thrombosis and allograft failure due to rejection. Renal thrombosis is a particular risk because of the decreased activity of coagulation inhibitors and the fibrinolytic system and the effects of immunosuppression on the vascular endothelium.

Immunosuppression

In the UK, methylprednisolone, ciclosporin (cyclosporin) A and tacrolimus are the immunosuppressants most commonly used for renal transplants. They are associated with few perioperative concerns. Interleukin-2 (IL-2) and the IL-2 receptor have a predominant role in the immunogenic reaction to transplantation. The IL-2 receptor includes three protein chains: α (CD25), β (CD122) and γ (CD132). Stimulation of T lymphocytes by antigen induces expression of CD25. CD25 is responsible for the rapid association of IL-2 with the β and γ chains, which in turn triggers proliferation of T lymphocytes and therefore acute rejection. Selective CD25 monoclonal antibody preparations including the mouse monoclonal antibody OKT3 have been introduced as an effective part of the immunosuppression regimen. However, OKT3 can cause a severe cytokine release syndrome and is used only in severe cases of resistant rejection in the UK. Newer CD25 monoclonal antibody preparations are being introduced into practice in which mouse constant regions have been replaced with human counterparts, resulting in minimal immunogenicity. Trials have shown no cytokine response syndrome to these newer agents.

Management of kidney donors

Perioperative management of the kidney donor plays an important part in the viability of the transplanted kidney.

Living donors – in 2001, 21% of donated kidneys came from living donors. In the USA, 50% of transplanted kidneys come from live donors. Living donors must be in excellent health with no evidence of hypertension, diabetes or other chronic illness that increases the risk to the donor. Donor nephrectomy is performed with the patient in the acutely flexed lateral decubitus position. Pressure points must be carefully padded and excessive stretch on peripheral nerves avoided. During anaesthesia, particular attention is paid to forcing a diuresis of 2–4 ml/min to reduce the incidence of acute tubular necrosis in the transplanted kidney. Therefore, all donors receive large volumes of fluid, mannitol and furosemide (frusemide). Postoperative analgesia is usually provided using an epidural because the flank incision is extremely painful. Increasingly, this operation is being performed laparascopically to reduce morbidity and mortality in the donor.

Cadaveric donors – most kidney recipients receive organs from cadaveric donors. However, the incidence of acute tubular necrosis is much higher in cadaveric kidneys. Absolute contraindications to kidney procurement are prolonged hypotension and hypothermia, metabolic disorders, generalized bacterial or viral infections, malignancies, systemic collagen disorders. Relative contraindications include older age, diabetes mellitus, severe vascular diseases, high serum creatinine before procurement and use of vasopressors. Intraoperative management of the cadaveric donor includes ensuring adequate haemodynamics and urine output. Intraoperative use of vasopressors (i.e. high dose dopamine, adrenaline (epinephrine) and noradrenaline (norepinephrine)) is associated with a significantly lower incidence of immediate renal allograft function and an increased incidence of acute tubular necrosis. ◆

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Inflammation: Cellular Responses and Cytokine Production

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Sepsis is commonly seen in all areas of medical practice. It is the most common cause for admission to ICU, and has a high mortality, especially in the setting of multi-organ dysfunction syndrome (MODS) and septic shock. Non-infective conditions may lead to inflammatory physiological changes similar to those seen in sepsis. The terms used in the inflammatory process (systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock) are clearly defined and should be applied accurately in the clinical setting (Figure 1). Over the last 20 years, the mortality rates in sepsis have decreased, probably as a result of earlier and better resuscitation. However, continued awareness of the pathogenesis of sepsis, the controversies in research and rationale of treatment will ensure greater understanding of this condition and thus optimal care.

Criteria for defining sepsis and the systemic inflammatory response syndrome (SIRS)

SIRS
Inflammation, for example caused by:
- Infection
- Pancreatitis
- Ischaemia
- Trauma
- Haemorrhage

Plus two or more of the following:
- Temperature > 38ºC, < 36ºC
- Heart rate > 90 beats/min
- Tachypnoea (respiratory rate > 20 breaths/min, partial pressure of carbon dioxide in arterial blood ($PaCO_2$) < 4.25 kPa)
- White blood cells > 12 x 10^9/litre, < 4 x 10^9/litre with > 10% immature neutrophils

Sepsis
- SIRS criteria resulting specifically from infection

Severe sepsis
- Sepsis with evidence of organ dysfunction (there are specific definitions for each organ; see Bone in Further Reading)

Septic shock
- Sepsis with hypotension (systolic blood pressure < 90 mm Hg or fall of > 40 mm Hg from baseline systolic pressure despite adequate intravascular filling)

1

Cellular inflammatory process

Leukocyte activation: leukocytes normally circulate in the quiescent state, though they can be activated rapidly to aid clearance of pathogens. The agents most commonly responsible for initiating an inflammatory response are bacterial cell-wall components from Gram-positive bacteria (teichoic acid and peptidoglycans) and potently, Gram-negative bacteria (lipopolysaccharide (LPS) endotoxins). It would be impossible to maintain leukocytes in a state of persistent activation without inducing uncontrolled leukocyte plugging, free radical release, high metabolic demand, with consequent tissue damage and MODS. One consequence of this activation system is the risk of underperformance or overperformance. Underperformance would lead to failure to clear the pathogens and overwhelming sepsis, while overperformance would lead to an overwhelming pro-inflammatory response, killing the bacteria, but also threatening the survival of the host (Figure 2).

Different pathways for the inflammatory response

Overperformance	Balanced	Underperformance
• Overwhelming proinflammatory response • Leukocyte plugging • Excessive enzyme and free radical release • Metabolic derangement	Signs of sepsis: • Calor • Rubor • Dolor • Tumour	• Overwhelming sepsis • Bacterial proliferation
Consequences		
• Hypoxia • Hypotension • Acidosis	• Retained organ function	• Progressive organ dysfunction from bacterial invasion
Outcome		
• Shock • Multi-organ dysfunction syndrome (MODS) • Death	• Resolution	• Shock • MODS • Death

2

Leukocyte influx: the inflammatory and immune responses to triggers such as sepsis, trauma and burns may be widespread, though regulated inflammatory cell activation and mechanisms for the attachment of leukocytes provide specificity and focus to the cellular response. Pro-inflammatory cytokines and chemotactic agents drive local endothelial activation and, through functional adhesion molecule upregulation, promote leukocyte adhesion and subsequent transmigration from vascular into extravascular compartments, where the foci of infection usually lie. These adhesion molecules include the selectins, expressed on both leukocytes and endothelial cells, which bind weakly and lead to slowing of the white cells as they flow through the vessels. This slowing allows more formal adhesion to occur through integrin-mediated events and finally transmigration into the tissues, which requires the function of other key molecules including very late antigen (VLA)-4 and platelet endothelial adhesion molecule (PECAM)-1.

Inflammatory mediators: concurrently with leukocyte activation, potent inflammatory mediator cascade systems are activated, leading to many of the typical features of inflammation (calor, rubor, tumour, dolor). This response may remain compartmentalized or can become systemic. These mediators include the complement, kinin and coagulation proteolytic cascades. In addition, there is release of lipid mediators such as platelet activating factor (PAF), peptide mediators including the chemokines, cytokines and soluble receptors and release of free radicals. Leukocyte degranulation can lead to release of numerous enzymes including elastase, myeloperoxidase, proteases, collagenase and plasminogen activator. Key pro-inflammatory cytokines include tumour necrosis factor (TNF)-α and interleukin (IL)-1 and IL-8. These are all produced early in the inflammatory response and are essential for survival. TNF-α and IL-1 are vital to the upregulation of many pro-inflammatory mechanisms including adhesion molecule expression, leukocyte activation, chemotaxis and degranulation. IL-8 is a particularly powerful neutrophil chemotactic agent. Although these responses are fundamental to the clearance of invading pathogens, they are also responsible for tissue damage. Many of the features of severe sepsis, including severe hypotension, fever and acute lung injury, may be mimicked in animal models by exogenous administration of TNF-α or IL-1. Antibodies that block these cytokines can dramatically prevent death in these models. IL-8 is also present in high concentration in the lungs of patients at risk of acute respiratory distress syndrome (ARDS) before the development of respiratory problems. These cytokines may therefore be directly involved in the disease processes.

Anti-inflammatory response: to protect against unopposed inflammation, the body also mounts an endogenous compensatory anti-inflammatory response syndrome. A number of cytokines have some anti-inflammatory properties, including IL-1 receptor antagonist (IL-1ra), IL-4, IL-10 and IL-13. These cytokines are produced as part of the normal response, for example IL-1ra is found in high concentrations in the urine of patients with sepsis. An excessive anti-inflammatory response may be as dangerous as a pro-inflammatory one. It is now recognized that with persisting inflammation the immune system can become anergic with a reduced ability to respond. Also well recognized for host survival is the importance of the endocrine system, including the cortisol stress response as well as other less well-characterized mediators such as macrophage migration inhibitory factor.

Resolution of inflammation: as inflammation progresses, the nature of the cellular response changes. Initially the main cells are the neutrophils, but over time they are replaced by macrophages and lymphocytes. Finally, with the elimination of bacteria, many of the survival stimuli for the neutrophils wane, leading to local neutrophil apoptosis and subsequent phagocytosis by macrophages. This is an anti-inflammatory process and induces the macrophage to release further IL-10 and other anti-inflammatory mediators thus 'switching off' the inflammatory response, allowing the tissues to return to their normal structure and function.

Fibrosis: if inflammation persists, or is excessive, there may be activation of an aggressive or abnormal fibrotic healing response. Fibrosis is a vital part of normal healing but, when excessive, can lead to severe consequences. This is typified by ARDS but is also a feature of chronic inflammation such as cirrhosis. The fibrotic response begins earlier than previously recognized with profibrotic mediators apparent in lung lavage on the first day of ARDS. A different range of cytokines are traditionally thought of for fibrosis, including transforming growth factor (TGF)-α and TGF-β but other cytokines (e.g. TNF-α) may also have an important role.

Haemodynamic response to sepsis

The main haemodynamic response to sepsis is vasodilatation-induced hypotension. In the early stages there is a compensatory high cardiac output, but this may diminish with time owing to myocardial depression. Hypovolaemia secondary to increased capillary leakage (though there may be a component of direct fluid depletion) also contributes to the hypotension. Blood vessels are normally maintained in a state of partial vasoconstriction by the balance of vasodilator and vasoconstrictor agents. The mechanism of sepsis-induced vasodilatation is complex and incompletely understood.

Normal vasoconstrictor response: agents involved in vasoconstriction include calcium, catecholamines, angiotensin II and endothelin. Vascular smooth muscle contraction is initiated by receptor-mediated release of calcium from intracellular stores and this is added to by calcium influx through voltage-gated calcium channels on the cell surface. This leads to myosin kinase activation and subsequent smooth muscle contraction. The resting membrane potential of the smooth muscle cell is relevant because depolarization enhances the opening of these voltage-gated channels and thereby promotes vasoconstriction. The main mediators for resting membrane potential seem to be ion channels, particularly potassium channels. A key potassium channel is the K_{ATP} channel, which by staying closed, keeps potassium in the cell and the cell depolarized.

Vasodilator response in sepsis: vasodilatation is mainly regulated by nitric oxide (NO), which is synthesized by the action of NO synthases (NOS) on L-arginine. There are several different NO synthases including endothelial NOS (eNOS) and an inducible NOS (iNOS) mainly found in inflammatory cells. In sepsis, iNOS is powerfully induced and this has the ability to generate large quantities of NO. The perceived mechanism by which NO achieves vasodilatation is thought to be via activation of guanylyl cyclase, which in turn leads to the formation of cyclic GMP (cGMP). This activates myosin light chain phosphatase, leading to the dephosphorylation of myosin and subsequent smooth muscle relaxation. Vasodilatation may also be mediated by changes in the function of the voltage-gated calcium channels described above. In contrast to depolarization-mediated vasoconstriction, the hyperpolarized state of the smooth muscle cell leads to the closure of these channels and resistant vasodilatation.

Sepsis and coagulation

The inflammatory response affects coagulation and is thought to have a role in the pathogenesis of MODS. The endothelium, which normally has concurrent anticoagulant and procoagulant properties, develops a predominant procoagulant state in sepsis.

Endothelial anticoagulant mechanisms: in the normal state, a net anticoagulant balance is achieved by activated protein C, antithrombin III and tissue factor pathway inhibitor (TFPI). Thrombomodulin binds thrombin on the endothelial surface, and this increases activation of protein C. The latter binds to protein S, leading to degradation of factors Va and VIIIa, thereby enhancing anticoagulation, especially in the microcirculation. Antithrombin III exerts an anticoagulant action on the endothelial surface by directly inhibiting the activated proteases IXa, Xa and thrombin.

Sepsis-induced procoagulation: in severe sepsis, acquired deficiency of activated protein C (85% of patients), diminished thrombomodulin activity and decreased antithrombin III levels are consistent features. Studies of sepsis in animals have shown that administration of activated protein C, antithrombin III and TFPI have been beneficial, though it is not clear whether the benefits are secondary to anticoagulant or to the potential anti-inflammatory actions of these agents. The latter theory may be strengthened by the recognition that tissue ischaemia secondary to microthrombi may generate IL-8, IL-1 and TNF-α release, and thrombin may lead to increased endothelial adhesion molecule expression with subsequent neutrophil adhesion. The most recognized procoagulant state in sepsis is that of disseminated intravascular coagulation in which widespread intravascular coagulation consumes platelets, increases consumption of coagulation factors, increases production of fibrinogen degradation products and leads to a severe bleeding tendency. Loss of the endothelial anticoagulant state in sepsis is also thought to contribute to the development of MODS because microvascular coagulation may lead to leukocyte and platelet plugs, local shunting and progress to MODS.

Assessment and treatment

Early detection and diagnosis: the evolution of 'outreach' services allied to intensive care potentially enables at-risk patients to be speedily identified and appropriately treated before systemic pro-inflammatory mechanisms have 'taken hold'. The benefits of early oxygen and fluid resuscitation particularly apply to septic patients; for example, hypoxia can lead to enhanced pro-inflammatory cytokine release. Similarly, early detection and treatment of new onset sepsis in the ICU should decrease the duration of stay, though it may be challenging to make this diagnosis in a patient with residual inflammatory features from a recent event. As part of the inflammatory response a fever is a powerful sign, however, severe sepsis may lead to hypothermia, which is a poor prognostic feature. A number of markers of the inflammatory and acute-phase response including C-reactive protein, IL-6 and pro-calcitonin levels may also be used to track the progress of the condition.

Identification and treatment of the infection: the septic or inflammatory focus may be clearly identifiable or completely unknown, though there are usually helpful clinical features. Steps involved in the identification and eradication of the source may include microbiological analysis, imaging, surgical intervention and administration of antibiotics. The advantage of empirical antibiotic therapy and early pathogen elimination may be offset by the development of antibiotic resistance among non-pathogenic organisms, therefore focused prescribing once the pathogen is identified is best practice.

Therapeutic manipulation of the immune response: much time and effort has been spent on developing agents (immunomodulators) that may aid suppression of the inflammatory response and therefore limit tissue damage. Most of these attempts have failed, including the use of agents to block endotoxin, IL-1 and PAF. Limited success has been achieved with anti-TNF therapy, though for other inflammatory conditions including inflammatory bowel disease it is proving more hopeful. These therapies are successful in many animal models, therefore these failures probably represent a failure in our detailed understanding of the pathogenesis of sepsis. The mediators being blocked are part of an adaptive immune response and their complete elimination is probably just as detrimental as when produced in excess. Improved understanding of the septic process may allow us to identify the appropriate timing and degree of suppression required to achieve a balance. This balance will probably be unique for different scenarios and different pathogens.

Corticosteroid treatment should be considered for sepsis and ARDS. A number of large studies had suggested that their use in severe sepsis and ARDS at best held no benefit and at worst was harmful. In these trials, the corticosteroids were prescribed at a high dose, early in the course and for a short duration. Studies within the last 4 years suggest that low dose corticosteroids prescribed for longer may be beneficial in severe sepsis or septic shock and in promoting the resolution of ARDS. Several large studies for sepsis and ARDS are under way. These should help to identify the appropriate dose and timing and whether treatment should depend on the strength of the endogenous stress response, as assessed by a synacthen test, or should be given to all.

Assessment and treatment of haemodynamics

Monitoring: the aims in haemodynamic management are to optimize tissue perfusion and cardiac stroke work, therefore the mainstays of treatment in established sepsis are aggressive fluid management and sympathomimetic therapy. Most agree that central venous pressure monitoring is the bare minimum, while many maintain that additional transoesophageal Doppler or pulmonary artery catheter monitoring is essential. Trans-oesophageal Doppler monitoring provides stroke volume and corrected flow time and allows calculation of cardiac output/index and systemic vascular resistance/index. Pulmonary artery catheter monitoring also incorporates cardiac stroke work, pulmonary capillary wedge pressure and equivalent right heart correlates. Mixed venous oxygen saturation provides an assessment of tissue oxygenation.

Fluid therapy: the large fluid requirement commonly seen in sepsis is the result of intravascular fluid depletion, mainly inflammatory driven capillary leakage, and the expanded intravascular compartment caused by pathological vasodilatation. To improve tissue perfusion and correct this intravascular hypovolaemia requires aggressive, but closely monitored, infusion of fluids. Despite the controversies regarding the choice of fluid (gelatins, starches or crystalloids), it is likely that there are no significant differences in efficacy between them. 'Early filling' may obviate, and should predate, rapid escalation in sympathomimetic therapy, to avoid severe tachycardias. Fluid infusion is maintained until the intravascular compartment is full; this may be manifested by a rapid rate of rise of central venous pressure (or pulmonary capillary wedge pressure) in the absence of a significant rise in mean arterial pressure (or cardiac output/corrected flow time).

Sympathomimetic therapy: the aim is to maximize tissue perfusion, taking into consideration the complications of raised cardiac stroke work. The choice of agent depends on the circulatory state, with vasoconstrictors such as noradrenaline (norepinephrine) being the mainstay of sympathomimetic therapy for septic shock with vasodilatation and a high cardiac output. In late sepsis with myocardial depression there may be a requirement for inotropic agents such as adrenaline (epinephrine). Noradrenaline (norepinephrine) is virtually a pure vasoconstrictor, achieving this by α-receptor agonism; the mild β_1- and β_2-receptor agonism (and hence inotropy and chronotropy) is usually thought not to be clinically significant. Adrenaline (epinephrine), with α-receptor agonism and more potent β_1- and β_2-receptor agonism, is probably as commonly used worldwide, though dopamine with β_1- and β_2-receptor agonism at low doses and α-receptor agonism at higher doses is also used.

Other vasoconstrictors: analogues of antidiuretic hormone (ADH), particularly terlipressin, have been used as rescue therapy for sepsis. Although they have a role in decreasing noradrenaline (norepinephrine) requirements, it is unclear whether they have a beneficial effect on outcome. The same assessment may be made of another vasoconstrictor, intravenous methylene blue, which inhibits guanylate cyclase, eNOS and iNOS. It may be reasonable to reserve ADH analogues and/or methylene blue for occasions when there is rapid escalation in the dose of existing vasoconstrictor(s) without obvious benefit. The only large trial to address NO inhibition in sepsis, using the iNOS inhibitor LNMMA (N^G-monomethyl-L-arginine), caused increased mortality.

Treatment of microvascular coagulation

After long-standing septic insult (or earlier in those with small vessel disease) microvascular hypoperfusion may manifest as digital ischaemia. Cold peripheries with poor capillary refill may lead to permanent pallor and evidence of necrosis. Although the use of vasoconstrictors has been blamed, it should be remembered that the microvasculature is relatively depleted in α-receptors compared with β-receptors. Therefore at least part of the pathogenesis of microvascular ischaemia may be the procoagulant and inflamed state of the vessels, leading to 'sludging'. For therapy, warming blankets, low dose vasodilators (dobutamine, dopexamine, dopamine and nitrates) and prostacyclins are used in various centres, so far with only anecdotal reports of success.

Activated protein C: one important advance has been publication of the recent multicentre phase III, prospective, double-blind trial of activated protein C (drotrecogin-α) in the setting of severe sepsis. This examined 1690 patients with severe sepsis and a significant benefit was seen at 28 days for the treatment group as mortality fell from 30.8% for those receiving placebo to 24.7% for those receiving drotrecogin- α. This equated to a number needed to treat of 16 to save one life. The US and UK regulatory bodies have approved this as the first biological treatment for sepsis. This drug is costly and figures suggest that maximal benefit may be seen in patients with severe sepsis and organ failure. It may be that it should be reserved for those with high APACHE II scores (over 25) or those with several organ failures. A balance needs to be struck because treatment should also be restricted to those in whom the process has not become irreversible. ◆

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Principles and Complications of Immunosuppression

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Organ transplants are allogenic – organs from 'another'. The body's immune system is structured to recognize 'self' and reject 'other'. This rejection of 'other' proteins is mediated by cellular and humoral responses. These responses must be controlled if an allograft is to survive. In some instances, long-term grafts have developed immune tolerance and there is much excitement about finding methods of inducing such tolerance. Until this can be achieved, immune suppression is the mainstay of management.

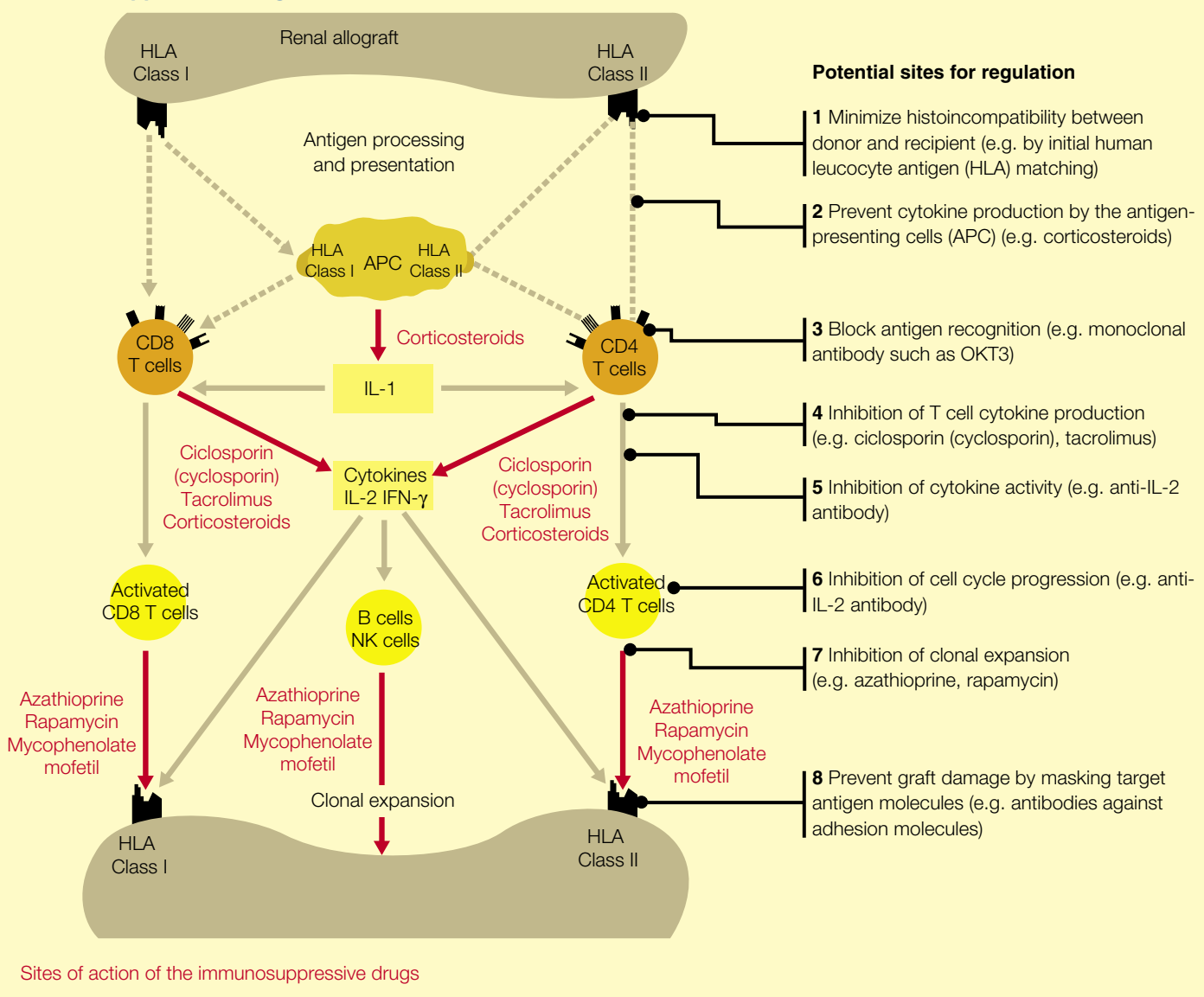
Mechanism of rejection

Cellular response: the main cellular mechanism is the activation of the helper T (thymic) cells. Macrophages scavenge the tissues sampling soluble and particulate matter. When non-self matter is found they act as antigen-presenting cells (APCs). They express high levels of major histocompatibility complex (MHC), which is a glycoprotein on all nucleated mammalian cells and is the root of recognition of self and non-self. MHC class I molecules are expressed on most cells and allow healthy cells to be recognized as 'self'. When cells are diseased (e.g. infected by viruses) these molecules display non-self peptides, allowing clearance by the immune system. MHC class II molecules are displayed exclusively by antigen-presenting cells. They present foreign antigen to immune cells and stimulate the proliferation of antigen-specific T helper cells which further amplify the inflammatory response by stimulating macrophages, B cells (blood lymphocytes becoming plasma cells), cytotoxic T cells and natural killer cells (the latter two are responsible for final cytotoxicity). In the process, many different cytokines, such as interleukins IL-1 and IL-2, are produced. Cytokines are soluble proteins that facilitate communication between cells and may be stimulatory or inhibitory.

Humoral response: lymphocytes recognize non-self antigen fragments and, by a mechanism involving helper T cells, MHC and cytokines IL-4 and IL-5, they proliferate and create antibodies. These antibodies can lead to cell-mediated cytotoxicity and to vascular occlusion. One mechanism of vascular injury is the change of endothelial cells from a non-adhesive to an adhesive state, binding platelets and inflammatory cells. This is mediated by up-regulation of adhesion molecules.

Control of the immune response: Figure 1 shows some of the pathways involved in the immune response and how they can be blocked.

Allograft immune response pathway specifying the sites and mechanisms of action of various immunosuppressive drugs



Sites of action of the immunosuppressive drugs

APC, antigen-presenting cell; CD, lymphocyte surface antigen coding; HLA, human leucocyte antigen; IFN-γ, interferon-γ; IL, interleukin; NK, natural killer

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Complications of immune suppression

Apart from the specific side-effects of the immunosuppressive agents used in transplantation (see below), three main side-effects of current non-specific immunosuppression are infection, cancer and cardiovascular disease.

Infection: immunosuppression weakens the ability to fight against microorganisms and consequently over 80% of transplant recipients have at least one clinical infective episode postoperatively. During the first month after transplant the usual postoperative infections predominate, as do infections from any organisms present in the graft. The level of immunosuppression is usually at its highest during months 1–6 and opportunistic viral and fungal infections (e.g. cytomegalovirus, *Candida*, *Aspergillus*) predominate. Thereafter, common bacterial infections and slow-developing fungal and mycobacterial infections predominate.

Rapid diagnosis is essential, and patients with fever, hypoxia and whose radiographs show pneumonic signs should receive aggressive treatment. Diagnostic bronchoscopy should be considered in the absence of an early response. In the presence of unexplained fever, central vascular and urinary catheters should be removed and cultured. Antibiotic treatment is usually started empirically pending culture and sensitivity results. Infectious complications can be difficult to diagnose in the immunocompromised patient and a high index of suspicion is essential. The temperature may not rise in a patient taking corticosteroids or in a neutropenic patient. White cell count is an unreliable sign of infection because of the effects of azathioprine (reduced count) and/or corticosteroids (elevated count). Infection must always be suspected if the patient's condition deteriorates.

Aseptic techniques must be strictly adhered to during instrumentation and intravascular cannulation. Pathogens that are relatively innocuous in non-immunocompromised patients may cause severe infections in transplant patients because of their altered immune system.

Tumours: transplantation and consequent immunosuppression increases the incidence of several malignancies. This increase is particularly evident in cancers with a putative viral aetiology (e.g. non-Hodgkin's lymphoma, squamous cell cancers of the skin, Kaposi's sarcoma and cervical cancer in women). However, there is an increased risk of all cancers, lymphomatous (often called post-transplant lymphoproliferative disease) or otherwise. Overall, the rate of malignancies is increased 3–4-fold, varying with the severity of immunosuppression used. Surveillance for these complications is an integral part of post-transplant management and simple advice, such as avoiding excessive exposure to sun, can cut down the risk in the case of photosensitive skin cancer. Lymphomas respond favourably to reduced immunosuppression and anti-viral agents, though traditional chemotherapy may also be required. Other tumours may require radical excision. Preoperative chest radiographs may reveal undiagnosed intrathoracic malignancy that might affect cardiopulmonary function or airway patency.

Cardiovascular disease: aggressive atheromatous disease occurs in many transplant recipients. It is usually associated with an increased incidence of hypertension and hyperlipidaemia, which are side-effects of many immunosuppressive drugs. However, it may also be a consequence of non-specific immunosuppressive therapy *per se* through mechanisms currently obscure. In heart transplant recipients, the incidence of coronary atherosclerosis increases about 10–15% each year after transplantation, the reported incidence at 5 years being 40–67%. Cytomegalovirus infection accelerates the coronary artery disease. Owing to graft denervation, coronary ischaemia may be painless in cardiac allografts and may manifest as fatigue and dyspnoea. Silent myocardial ischaemia is also common in kidney transplant recipients. A history revealing poor exercise tolerance is important in determining the extent of further investigations required for anaesthetic assessment.

Specific complications of immunosuppressant drugs

The immunosuppressants in current use are relatively non-specific, in the sense that they inhibit many lymphocyte subsets other than those directed against donor-specific alloantigens. To minimize side-effects almost all the anti-rejection regimens use combinations of several drugs in relatively lower doses. The main groups of drugs are:

- calcineurin inhibitors (ciclosporin (cyclosporin), tacrolimus (FK 506))
- antiproliferative drugs (azathioprine, mycophenolate mofetil (MMF))
- corticosteroids
- polyclonal antibodies (antilymphocyte globulin (ALG), monoclonal antibodies (OKT3)).
- mTOR inhibitors (rapamycin (sirolimus), everolimus (mTOR – mammalian target of rapamycin kinase))
- other agents (leflunomide (FTY 720)).

Apart from the non-specific side-effects of immunosuppression discussed above, these drugs also have specific side-effects (Figure 2). The commonly used drugs are discussed below.

Common immunosuppressive drugs and their main side-effects

Group	Principal relevant side-effects
• Corticosteroids (e.g. prednisolone, methylprednisolone)	Glucose intolerance, hypertension, psychosis
• Calcineurin blockers (e.g. ciclosporin (cyclosporin), tacrolimus)	Hypertension, nephrotoxicity, hepatotoxicity, confusion, fits
• Antiproliferatives (e.g. azathioprine, mycophenolate mofetil)	Leucopenia, thrombocytopenia, anaemia, pancreatitis, gastro-intestinal upset, cholestatic jaundice Azathioprine slightly potentiates muscle relaxant drugs
• Antilymphocyte antibodies (e.g. OKT3, Campath)	Fever, serum sickness, leucopenia, thrombocytopenia, hypotension, pulmonary oedema

2

Ciclosporin (cyclosporin) is a cyclic peptide molecule derived from a soil fungus. It is highly lipid soluble and diffuses passively through cell membranes where it binds to intracellular proteins. It became the mainstay of immunosuppression after the recognition that its use promoted transplant survival among unrelated subjects comparable with that achieved between identical twins. Together with azathioprine and prednisolone, ciclosporin (cyclosporin) forms the ubiquitous 'triple therapy' immunosuppression regimen.

Its major actions are thought to be inhibiting activated macrophages from producing IL-1 (3 in Figure 1), inhibiting T lymphocytes from secreting the key lymphokine IL-2, and blocking activation of helper (CD4) T lymphocytes (4 in Figure 1). Ciclosporin (cyclosporin) has significant side-effects, the most serious of which, in all forms of organ transplantation, is nephrotoxicity.

Nephrotoxicity – the effects of ciclosporin (cyclosporin) on the kidney are acute and chronic. Acute functional nephrotoxicity presents as various features with otherwise functional kidneys. The usual findings are hyperkalaemia with an inappropriately raised creatinine concentration. This responds rapidly to a decrease in the plasma concentration of ciclosporin (cyclosporin). The aetiology may be related to an alteration in the cortical and medullary blood flow. Chronic nephrotoxicity is a major clinical problem. Its cause is unknown and may be related to a generalized sympathetic overactivity that may also account for the hypertension found in patients taking ciclosporin (cyclosporin). About 10% of patients have chronic renal impairment, which is shown on renal histology by vascular sclerosis, interstitial fibrosis and thickened tubular and basement membranes.

Hypertension is the other main complication occurring in 50–70% of patients. It is associated with an increase in systemic vascular resistance and is relieved following withdrawal of the drug. The current treatment is administration of calcium channel blockers.

Hepatotoxicity following ciclosporin (cyclosporin) manifests as a rise in transaminases and plasma alkaline phosphatase.

Other side-effects of ciclosporin (cyclosporin) include gingival hypertrophy, hirsutism, hypertrichosis and, at higher serum levels, tremors or seizures.

Tacrolimus (FK 506) is a potent immunosuppressive macrolide antibiotic. It has a similar mechanism of action to ciclosporin (cyclosporin) but is a very dissimilar molecule. On a weight-to-weight basis it is 10–100 times more potent than ciclosporin (cyclosporin). In trials, it reduces acute and refractory rejection in humans and the need for OKT3. However, the side-effects are similar to those of ciclosporin (cyclosporin) including nephrotoxicity and neurotoxicity. Diabetes requiring insulin therapy may be precipitated by ciclosporin (cyclosporin) or tacrolimus but is probably more common with the latter.

Azathioprine is a purine analogue. It is an antiproliferative agent and inhibits DNA and RNA synthesis by preventing the synthesis of adenylic and guanylic acid from inosinic acid. As a result, T and B cell proliferation is inhibited. Production of other formed elements in bone marrow is also suppressed leading to anaemia, thrombocytopenia and leucopenia. Careful monitoring of white cell count is an important method of monitoring the dose. Hepatotoxicity and dysfunction of any other organ system that has a high rate of cell proliferation (e.g. gastrointestinal, skin) also occurs. Azathioprine increases non-depolarizing relaxant requirements modestly by presynaptic inhibition of the motor nerve terminal.

Mycophenolate mofetil (MMF) is a powerful new immunosuppressant. It is an antiproliferative drug that inhibits the enzyme in a key step in the *de novo* pathway of purine synthesis. It has a specific effect on T and B lymphocytes. In contrast to azathioprine, MMF inhibits a single enzyme in DNA synthesis and does not interfere with repair of DNA or become incorporated into it. It is expected to be less mutagenic to DNA. In clinical trials, MMF has reduced the incidence of biopsy-proven renal allograft rejection to 50%. It also reduces the need for ALG/OKT3 to treat corticosteroid-resistant rejection. Its main side-effects are gastrointestinal and haematological (e.g. diarrhoea, abdominal pain, dyspepsia, leucopenia, anaemia, thrombocytopenia). It is not nephrotoxic or hepatotoxic. Thus, in renal transplantation, MMF has achieved a role of prime adjunct to ciclosporin (cyclosporin) and tacrolimus, in place of azathioprine.

Corticosteroids are potent anti-inflammatory drugs and are widely used immunosuppressive agents. They alter lymphocyte function and decrease the number of circulating lymphocytes. This action is via direct cell lysis and by redistribution of lymphocytes throughout the body. The degree of lymphopenia is dose dependent; a high dose can reduce lymphocyte numbers by a maximum of 50–75%. They also block the production and release of a number of inflammatory cytokines, prostaglandins and leukotrines. Major side-effects are adrenal suppression, glucose intolerance, peptic ulceration, aseptic osteonecrosis, hypertension and integumental necrosis. There may also be fluid retention, psychological disturbance, hypokalaemia and myopathy. Nevertheless, glucocorticoids are a vital component of maintenance and rejection/rescue immunosuppression regimens.

Antibodies (polyclonal and monoclonal)

Polyclonal or antilymphocyte globulin (ALG) preparations are derived from animals immunized with human lymphocytes. Most often T lymphocytes obtained from the thymus are used because they play a predominant role in graft rejection. The active immunoglobulin is largely in the IgG fraction. After injection, ALG attaches to circulating lymphocytes and a complement-dependent process lyses them. The antibodies may also bind to the antigen receptor sites on lymphocytes and thus ‘blind’ the lymphocyte to its targets. ALG may cross-react with antigens other than T lymphocytes, producing marked leukopenia and thrombocytopenia. Systemic symptoms (e.g. fever, pruritus) can also occur, as can frank serum sickness.

Monoclonal antibodies have been developed to reduce the toxicity of the polyclonals and to increase efficacy in preventing rejection. OKT3 is a monoclonal mouse antibody directed against the CD3 protein complex, specific to human T cells. OKT3 binds to CD3, blocking recognition of MHC antigens on foreign cells and the subsequent immune response. OKT3-bound T cells are then removed from circulation and destroyed by the reticulo-endothelial system. The initial dose of OKT3 is usually accompanied by mild systemic symptoms (e.g. fever, hypotension, tachycardia) and occasionally by pulmonary oedema and aseptic meningitis. Patients receiving these antibodies are pretreated with diphenhydramine and corticosteroids. The use of polyclonal antibodies has decreased because OKT3 is less toxic and comparably effective in reversing rejection. ◆

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Trauma

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Assessment and Management of Adult Trauma Patients

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Since the introduction of the Advanced Trauma Life Support (ATLS) programme in the UK in 1988, there have been major improvements in educating healthcare professionals in the principles of assessment and management of the traumatized patient.

In-hospital preparation: each hospital should ensure that an adequately equipped area is available to receive the patient. A 'trauma team', including members of the accident and emergency, anaesthetic/ICU, orthopaedic and surgical departments, should attend all major trauma cases and team members should be aware of their roles. When arriving at the accident and emergency department with the patient, para-medics should give a detailed handover to hospital staff. This should include the mechanism of injury, because this is important in anticipating likely injuries.

Primary survey: assessment and resuscitation

Life-threatening injuries must be identified and treated simultan-eously in order of clinical priority using the ABCDE sequence.

A Airway maintenance with cervical spine control
Recognizing the high risk of cervical spine injury associated with multisystem trauma (especially in patients with blunt trauma or altered consciousness), airway patency should be confirmed while the cervical spine is immobilized manually or using a correctly sized hard collar, lateral supports and fixation (see page 282).

Interventions such as removing foreign bodies, chin lift or jaw thrust or the institution of a definitive airway (tracheal intubation or surgical airway) may be required.

High concentration oxygen should be administered to all traumatized patients. Loosening the cervical collar to avoid rises in intracranial pressure may follow spine stabilization using head blocks and tape.

B Breathing with ventilation
Assessment of breathing must exclude simple or tension pneumothorax, flail chest, pulmonary contusion and haemo-thorax. Needle decompression is a temporary measure for tension pneumothorax; tube thoracocentesis is the definitive therapy. Inadequate ventilation should be assisted.

C Circulation with haemorrhage control
The degree of hypovolaemia should be assessed using capillary refill, peripheral temperature, blood pressure and the conscious level. Blood pressure cannot be predicted accurately merely by the presence or absence of particular peripheral pulses.

The most common aetiology of shock in trauma is haemorrhagic hypovolaemia. External haemorrhage should be managed by direct manual pressure and elevation of the affected part. If peripheral intravenous access is impossible, femoral vein cannulation or surgical cut-down can be life saving.

Limited evidence suggests that crystalloid solutions may be better than colloids; whichever are chosen, they are best administered warm. O negative blood should be available immediately to maintain the haemoglobin level above 8.0 g/dl, but full cross-matching should also be undertaken.

Non-haemorrhagic causes for shock should be identified and treated. For instance, cardiac tamponade requires pericardio-centesis or pericardiotomy.

Specific manoeuvres may be required for pregnant trauma patients. For instance, the gravid uterus should be displaced laterally, using a wedge or blankets under the left hip, to avoid hypotension associated with aorto-caval compression. If the patient requires immobilization on a spinal board, the wedge should be placed underneath the board.

Occasionally the patient has to undergo salvage surgery (i.e. laparotomy for exsanguinating abdominal haemorrhage) as part of the primary survey.

D Disability
A rapid assessment of neurological status, using the AVPU (see *Anaesthesia and Intensive Care Medicine* **3:7:** 235) or Glasgow Coma Score (GCS; see *Anaesthesia and Intensive Care Medicine* **3:4:** 132) systems, capillary size and reaction should be performed as part of the primary survey. An altered conscious level may indicate hypoxaemia or shock. Therefore, the 'ABCs' should be re-evaluated before ascribing the neurological state to CNS trauma. Regular re-evaluation of disability is essential to monitor trends.

A comatose patient (GCS < 8) requires intubation. Secondary brain injury is minimized by ensuring adequate oxygenation (patent airway), adequate ventilation (to prevent cerebral vasodilation caused by hypercapnia) and normotension to ensure adequate cerebral perfusion. Timely consultation with a neurosurgeon is recommended, particularly in patients who have clinical or radiographic evidence of expanding space-occupying lesions.

E Exposure and environment control
The patient's clothing should be removed to allow a complete examination. Log roll the patient and examine the back. Hypothermia is common and can be minimized by warming the room, warming inspired gases and intravenous fluids, using blankets and warmed-air devices (e.g. BairHugger®).

Adjuncts to the primary survey
- All trauma patients should be monitored using ECG, blood pressure, pulse oximetry, temperature and capnography.
- A gastric tube should be placed in all patients with life- threatening injuries, but the nasal route is contraindicated in those with basal skull fracture (risks of intracerebral migration via fractured cribriform plate).
- Urinary catheters permit accurate measurement of urine output, but urethral injury should be excluded before catheterization (suspected by blood at penile meatus, perineal bruising, scrotal haematoma or a high-riding prostate on rectal examination).
- Plain anteroposterior radiographs of chest, pelvis and lateral cervical spine should be taken in the resuscitation area. They may provide information to guide resuscitative efforts (e.g. pelvic fracture can explain hypotension resistant to fluid infusion).
- Diagnostic peritoneal lavage and abdominal ultrasonography may reveal occult abdominal haemorrhage.

Transfer: depending on the patient's injuries and the local facilities, intra- or inter-hospital transfer may be required. This can be facilitated by administrative staff, but the patient should be stable before being moved. Occasionally, transfer of a patient to salvage surgery (i.e. laparotomy for exsanguinating abdominal haemorrhage) may form part of the primary survey.

Secondary survey

The secondary survey, a meticulous head-to-toe evaluation (including log-roll), should not commence until the primary survey is complete. It is also a useful time to re-evaluate injuries identified in the primary survey and to arrange targeted radiological and laboratory tests.

History: the important aspects of patient history are covered by the mnemonic AMPLE (Allergies, Medications, Past illness/pregnancy, Last meal and Events/environment related to injury).

Physical examination: clinical examination should be systematic. All injuries should be documented for clinical and medico-legal reasons.

Head and skull – the entire head and scalp should be examined for lacerations, contusions and fractures. Eyes should be examined early, in case eyelid oedema precludes subsequent examination. Auditory canals should be examined for CSF leak, tympanic membrane integrity and haemotympanum.

Maxillofacial – facial burns and trauma can lead to airway obstruction or major blood loss. Patients with mid-face fractures should be assessed for nasal CSF leak and ocular mobility (entrapment of extraocular muscles may occur with orbital fractures).

Cervical spine and neck – patients with injuries above the clavicles should be assumed to have an unstable cervical spine injury. Immobilization should continue until the spine has been cleared of bony, ligamentous and neurological injury. Patients who have suspected trauma to neck vasculature may require angiographic examination.

Thoracic and lumbar spine – examine for deformity, tenderness and neurological signs. The mechanisms of injury are important clues.

Chest – repeated evaluation is required to ensure a patent airway and adequate ventilation. Any deterioration of the patient should trigger a repeat of the primary survey. Positive-pressure ventilation may rapidly convert a small simple pneumothorax into a life-threatening tension pneumothorax. Plain chest radiography does not always detect rib fractures. An apparently widened mediastinum is common in portable, supine chest radiographs, but should trigger suspicion of an aortic injury; contrast aortography is required to exclude the diagnosis.

Abdomen – early surgical assessment is vital to identify and manage covert intra-abdominal injury. Bleeding from the liver and spleen can be predicted from the mechanism of injury and bruising patterns, but remains under-recognized, especially in unconscious patients who are unable to complain of pain. Diagnostic peritoneal lavage and ultrasonography can be performed at the bedside; more complex radiological evaluation (e.g. angiography) should be reserved for stable patients. Exploratory laparotomy may be required as a diagnostic procedure in some patients.

Perineum (including rectal and vaginal examination) – rectal examination is required before urethral catheterization and may provide information about pelvic fractures, integrity of the rectal wall and anal tone (spinal injury). A pregnancy test should be undertaken in women of childbearing age.

Musculoskeletal – a 'look, feel, move' approach is required for every bone and joint. Neurovascular assessment of extremities should be performed and repeated after any manipulation. Pelvic mobility should be assessed once only. Injuries to the extremities are often overlooked, but remain a major source of litigation; the secondary survey is the time to discover them.

Neurological – early consultation with a neurosurgeon is required in all patients with neurological injury. The most important measures to minimize secondary brain injury are the maintenance of adequate oxygenation, ventilation and cerebral perfusion. The management of acutely raised intracranial pressure and convulsions is best discussed locally, because neurosurgical preferences differ.

Adjuncts to the secondary survey
The specialized diagnostic tests indicated by the findings of the secondary survey (e.g. CT, angiography, bronchoscopy) involve transfer of the patient away from the resuscitation area. As a general rule, the patient should be stable and should be accompanied by a team and equipment that permits continuing resuscitation.

Post-resuscitation monitoring and re-evaluation
The successful management of trauma depends on frequent re-evaluation. Invasive blood pressure monitoring may be a useful adjunct to the monitoring previously described. Intravenous opiates (e.g. morphine, 2 mg increments) should be titrated to effect. An anti-emetic should also be administered.

Definitive care
Definitive care usually involves early surgery or admission to ICU. Control of haemorrhage and optimization of oxygen delivery to all organs is vital in minimizing mortality and morbidity from major trauma. ◆

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Burns and Smoke Inhalation

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In the UK, there are 250,000 burn injuries annually, resulting in 16,000 hospital admissions. About 1000 of these are severe burn injuries requiring fluid resuscitation (500 are children) and 300 deaths result. The size of the burn injury affects patient outcome – those with a 75% total burn surface area (TBSA) have a 60% mortality.

Pathophysiology

The skin represents 15% of body mass and tolerates temperatures up to 40°C without risk of injury.

Thermally injured skin consists of three parts, a central area of coagulation and necrosis, a surrounding zone of stasis and an outer zone of hyperaemia. Within these, capillary endothelial destruction occurs causing an increase in permeability. This is the result of direct thermal destruction and indirect release of inflammatory mediators.

Loss of epidermal integrity increases evaporative water loss from the burn site (up to 200 ml water/m^2/hour). Increased heat loss results causing hypothermia. Gram-negative bacterial colonization occurs rapidly, even if strict asepsis is enforced. Plasma fluid accumulates within the interstitial tissue spaces causing hypoalbuminaemia and hypovolaemic shock. This tissue swelling may compromise the airway, cause compartment syndromes or increase skin necrosis. Systemic oedema occurs through loss of plasma oncotic pressure (low plasma albumin concentrations) and this may contribute to a further decline in organ function.

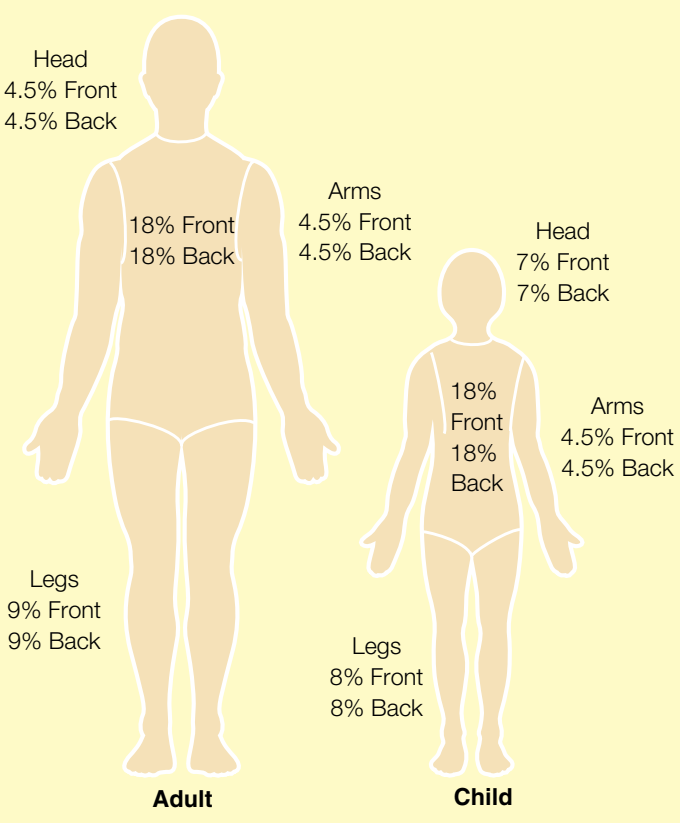
Initially, the haematocrit rises, but after 24–48 hours, anaemia occurs owing to increased haemolysis and reduced red cell haemoglobin content. Anaemia persists as a result of surgical blood loss, sepsis-induced bone marrow suppression and malnutrition.

Following burn injury, the metabolic rate increases which persists until wound closure is established. This is mediated by increased glucagon, cortisol, catecholamines and cytokines. As a consequence, carbon dioxide excretion and oxygen consumption increase coupled with protein catabolism and hyperglycaemia.

Assessment of burn injury

The extent of any burn-injured site is measured in terms of the depth of injury and the area of body surface involved. The total burnt surface area can be assessed using the rule of nines (Figure 1), mapping out the areas of partial- and full-thickness injury. An alternative means of assessment is based on the assumption that the palm of the patient's hand corresponds to 1% of their body surface area.

Calculation of total burn surface area



1

Superficial burns (first degree) involve only the epidermal layer and are characterized by erythema, redness and blistering. They are painful but desquamate and heal quickly.

Partial-thickness burns (second degree) involve the entire epidermis and upper dermal layer. They are always associated with blisters, are painful and take longer to heal (10–14 days). Because epidermal islands (hair follicle and sweat glands) remain intact, these burns may not require grafting to achieve wound closure. If deeper dermal destruction has occurred, the injury is less painful (because nerve endings have been destroyed), takes longer to heal and may require excision and grafting.

Full-thickness burns (third degree) involve total destruction of the epidermis and dermis. They are painless and the wound has a black, brown or pale waxy appearance. Early excision and grafting is required to reduce infection and preserve limb function.

Inhalational thermal injury

Inhalational thermal injury adds up to 50% to the expected burn mortality. From the history and clinical examination, thermal injury to the airway is expected in association with:

- facial burns and burnt eyebrows
- dysphagia, drooling, dysphasia
- carbon present within oropharynx
- carbon in sputum
- fire within a confined space
- history of an explosion
- history of loss of consciousness.

Airway trauma and respiratory failure can result from several processes (Figure 2).

Mechanisms of thermal injury to the airway and respiratory system

Heat
Direct thermal trauma caused by inhalation of hot gases often confined to the upper airway (glottis protects lower airway). Steam injuries often destroy distal lung tissue owing to higher specific heat capacity than dry gases

Blast
Shockwave (velocity 220 m/s) causes pulmonary barotrauma, lung contusion and blunt chest injuries

Chemical poisoning

- *Choking agents*

Aldehydes, nitrogen oxides, chlorine, sulphur oxides, carbon cause bronchospasm, ciliary dysfunction, epithelial necrosis, mucus secretion and pulmonary atelectasis

- *Carbon monoxide*

Over 20% carboxhyhaemoglobin is significant and causes metabolic acidosis or coma
Treat with high inspired oxygen fraction and consider hyperbaric oxygen

- *Cyanides*

Toxic over 50 ppm. Generated by partial combustion of plastics (polyurethane, polyacrilonitryl and acrocyanates). May present as a metabolic acidosis or coma, associated with high venous oxygen saturation
Treatment includes high fraction of oxygen in inspired air ($FiO_2$1.0) and ventilation

Asphyxia
Oxygen consumption by combustion (firestorms) or displacement by other gases (carbon dioxide or other fire extinguisher agents within a confined space)

2

Management

Patients should be removed from the source of trauma and decontaminated. Assessment and initial management should follow Advanced Trauma Life Support (ATLS) guidelines.

Airway management

The airway should be maintained, protected and high concentration oxygen administered via a non-rebreathing bag and face mask. A high index of suspicion of cervical spine injury is required.

Where indicated, tracheal intubation is best performed early, because evolving swelling of the lips, tongue, palate, epiglottis or arytenoids may make this impossible later. Fibre-optic nasendoscopy may assist in confirming the presence of airway injury. Absolute indications for tracheal intubation include the presence of stridor, respiratory failure, circumferential or full-thickness burns to the face or neck and a reduced conscious level.

Unless airway obstruction is suspected, a rapid sequence induction should be performed. Reliable intravenous access should be obtained and hypovolaemia corrected. Suxamethonium, 1–1.5 mg/kg i.v., is safe to use in the first 24 hours following a burn injury and an appropriate induction agent should be administered (ketamine, 2 mg/kg, is ideal in the presence of hypovolaemic shock). If airway obstruction is suspected or oedema of the airway is present, then awake fibre-optic intubation, inhalational induction or an emergency surgical airway may be required.

A tracheal tube of sufficient length should be inserted, because subsequent airway oedema may 'draw' the tube out of the trachea. The tube should be secured, avoiding further trauma to the face. The tracheal tube should be of adequate diameter because bronchoalveolar lavage may be required to clear mucus and debris (a nasotracheal tube may prove too narrow). While securing the airway, it is vital to site a nasogastric tube to decompress the stomach and permit early feeding. Often, a tracheostomy is contraindicated because burnt tissue adjacent to the proposed stoma site increases the risk of infection and haemorrhage. Therefore, the tracheal tube may be required for an extended period with extubation possible only after airway and facial oedema have resolved.

Respiratory support

Respiratory function should be monitored and hypoxaemia corrected. Chest radiography detects most blunt chest injuries or areas of lung collapse. Owing to skin tissue destruction and oedema, or the presence of carbon monoxide, pulse oximetry may be unreliable and intermittent arterial blood gas sampling allows determination of oxygenation and adequacy of ventilation. In addition, co-oximetry provides accurate measurement of any carboxyhaemoglobin. Inhalational thermal injuries, and the likely development of acute respiratory distress syndrome, may require advanced respiratory support. Such techniques may include pressure control, inverse ratio, prone ventilation, high frequency oscillation, therapeutic paralysis and use of inhaled pulmonary vasodilators (prostacyclin or nitric oxide). In addition, the use of nebulized N-acetyl cysteine and heparin have been described.

High levels of carboxyhaemoglobin (> 30%) are treated by administration of 100% oxygen. Several hours therapy with an FiO_2 of 1.0 may be required to disassociate carbon monoxide from its haemoglobin binding sites. Hyperbaric oxygen therapy has a role in severe carbon monoxide poisoning (if a suitable facility is available that is capable of managing a critically ill patient).

Significant cyanide poisoning occurs following partial combustion of plastics (Figure 2). It may present as a severe metabolic acidosis that is out of proportion to the degree of hypovolaemic shock present. Treatment with 100% oxygen accelerates inactivation of the cyanide anion to thiocyanate.

Circulatory support
Restoration of the blood volume and maintenance of organ perfusion are crucial to patient survival and often difficult to achieve. Reliable intravenous access is required for resus-citation and is best sited away from burnt tissue. In patients with extensive burns there may be few cannulation sites available, though the femoral triangle is often spared.

Cardiovascular monitoring may be complicated by tissue destruction with sites being unavailable for placement of ECG electrodes or blood pressure cuffs. Adequacy of cardiovascular function may be assessed by placement of a urethral catheter and monitoring urine production and composition. Often central venous or pulmonary arterial occlusion pressure measurement is required. Oesophageal Doppler may also have a role in guiding fluid therapy to correct hypovolaemic shock. Temperature monitoring is essential.

There are various fluid resuscitation formulas for calculating early fluid requirements following thermal injury (Figure 3). These serve as a guide and do not account for daily fluid maintenance or other fluid requirements. ATLS guidelines suggest the use of a crystalloid-based regimen, though many UK burns centres still use colloid resuscitation (often with albumin). Whether to use crystalloid or colloid has yet to be resolved, and advantages and disadvantages are well described for each.

Initially when they present in the Accident and Emergency Department, patients are seldom hypovolaemic, but significant fluid loss occurs within the first few hours after the burn. Septic shock often develops after several days.

Burn injury fluid resuscitation formulas

Parkland (crystalloid)
- 24-hour fluid replacement following injury
- (ml) Hartmann's solution = 4 x body weight (kg) x TBSA[1] (%)
  50% given over 8 hours
  50% given over next 16 hours

Muir and Barclay (colloid)
- 36-hour fluid requirement following injury
- (ml) 4.5% albumin = 0.5 x body weight (kg) x TSBA[1] (%)
  This volume to be administered over six time periods:
  three periods of 4 hours
  two periods of 6 hours
  one period of 12 hours

Renal support
Acute renal tubular necrosis is associated with extensive burn injuries and is often caused by pre-renal failure secondary to hypovolaemia. However, myoglobin and free haemoglobin may further contribute to acute renal failure. If myoglobinaemia is suspected, urinary alkalinization may preserve renal function, but is notoriously difficult to achieve. If required, renal support is best undertaken using continuous veno-venous haemofiltration or dialysis. The development of acute renal failure is a bad prognostic sign.

Surgical care and infection
Early surgical excision and grafting of partial- and full-thickness burns reduces muscle catabolism, encourages early healing, decreases the incidence of sepsis and reduces mortality. Complete surgical excision of these burns is limited by the extent of intra-operative blood loss, ability to maintain patient core temperature and availability of donor sites to provide tissue coverage. To provide temporary coverage, cadaveric or artificial skin substitutes are available to facilitate wound closure after extensive injuries. Compartment syndromes may develop (associated with circumferential burns) and should be sought and decompressed as required.

Infection and sepsis are common causes of mortality in burn injury. Silver sulphadiazine, which reduces Gram-negative bacterial infection, is incorporated in standard burn dressings. Systemic antibiotics are best given in response to accurate culture and sensitivity rather than prophylactically.

Gastrointestinal support
Nutrition should be commenced early in any burn exceeding 10% TBSA. This reduces infection, preserves body mass and protects against bacterial translocation. Enteral nutrition especially protects against stress ulceration. Parenteral nutrition should be avoided, unless the enteral route has failed. Individual nutritional requirements are extensive. As a guide, 1 g of nitrogen may be required per 100 kcal of energy provided. Owing to catabolism, up to 60 kcal/kg energy may be required daily and is best provided by part lipid and carbohydrate (to minimize carbon dioxide production).

Exogenous glucagon and insulin may encourage protein sparing, preserve immunological function and promote wound healing. However, long-chain and polyunsaturated triglycerides may preferentially encourage synthesis of proinflammatory mediators; hence medium-chain triglycerides may have more value. Certain non-essential amino acids can become supply-dependent and leucine, isoleucine, valine, arginine and glutamine may require supplementation.

Electrical injury
Electrocution injuries often occur in the workplace and in the USA result in 1000 deaths per year. Electrocution is often associated with injury to the head, spinal cord or chest. The victim becomes part of the electrical circuit, with current flowing through the path of least resistance (muscle or vasculature). Current flows of 10 mA generate local muscle spasm; higher currents cause generalized spasm, which may throw the patient some distance. At flows in excess of 30 mA, cardiac arrhythmia may occur. The current path is unpredictable and small wounds often conceal extensive and remote damage.

These injuries are always underestimated and invasive monitoring should be instituted early. Immediate surgical debridement is required and often locates further tissue injury. Muscle necrosis often causes rhabdomyolysis requiring renal support.

Anaesthesia for the burned patient
After the initial resuscitation period, patients with burns have to return to theatre daily for dressing changes or further grafting. Many will have been discharged from the ICU and will be nursed on conventional wards.

Suxamethonium causes acute hyperkalaemia, owing to extra-junctional migration of acetylcholine receptors following a burn injury. It is safe within the first few hours of injury, but, subsequently, should not be used for the following 12 months. Burned patients also develop resistance to non-depolarizing relaxants, which persists for up to 10 weeks. Ketamine is often used for induction in the early phase of burns management, but is best avoided once the patient is more stable because it causes emergence phenomena. Propofol is a good alternative.

Requirements for sedation and opioid analgesia may be vast owing to tolerance and they should be given intravenously to avoid unpredictable absorption. Once the patient is awake, patient-controlled analgesia (PCA) devices work well, provided hand injuries are not extensive. Oral analgesia can be added, when feeding is established, but care should be taken with non-steroidal anti-inflammatory drugs because of the increased risk of gastric ulceration.

Burns patients have high calorific requirements and repeated trips to theatre interfere with their ability to meet daily nutrition targets. It has been suggested that preoperative fasting times may be reduced to 1 hour without increased risk of aspiration. Intubated patients do not need to have feeding discontinued before and during surgery.

Fluid balance should be corrected preoperatively, because blood and evaporative water loss during burn debridement is extensive. Reliable intravenous access, availability of blood products and fluid-warming devices are essential. ◆

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Chest Injuries

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In the UK, chest injuries are mainly caused by blunt trauma. One in four trauma deaths is attributed to chest trauma; 10% of patients with chest injuries die at the scene, mainly from damage to the great vessels or heart, and 5% die within 1 hour of reaching hospital from airway obstruction or cardiac tamponade. Of the remainder, only 15% require surgical intervention.

Primary survey
The primary survey includes the application of high concen-tration oxygen, maintenance of the airway, stabilization of the cervical spine and identification and treatment of immediately life-threatening injuries.

Tension pneumothorax: reduced chest movement, reduced breath sounds, and a resonant percussion note on the affected side, along with respiratory distress, hypotension and tachy-cardia, indicate a tension pneumothorax. Deviation of the trachea to the opposite side is a late sign, and neck veins may not be distended if the patient is hypovolaemic. Treatment involves immediate large-bore needle thoracocentesis in the second intercostal space, in the mid-clavicular line on the affected side. Once intravenous access has been obtained, a large chest drain (36 F) should be inserted in the fifth intercostal space in the anterior axillary line, and connected to an underwater seal drain (Figure 1).

Indications for chest drain insertion

- Simple or tension pneumothorax (following immediate decompression)
- Open pneumothorax
- Haemothorax
- Severe lung injury together with the need to transfer by ground or air
- Suspected significant lung injury (multiple rib fractures or expanding surgical emphysema) in patients requiring general anaesthesia and/or positive-pressure ventilation

1

Open pneumothorax should be sealed on three sides with an occlusive dressing; tube thoracocentesis should follow.

Massive haemothorax is present when there is more than 1500 ml of blood in a hemithorax; it results in reduced chest movement, a dull percussion note, hypoxaemia and hypo-volaemia. Tube thoracocentesis should be undertaken once volume resuscitation has begun.

Cardiac tamponade: neck vein distension in the presence of hypotension may indicate cardiac tamponade, though these signs may also occur in patients with myocardial contusion or tension pneumothorax. If tamponade is suspected, and the patient is deteriorating despite treatment, pericardiocentesis should be performed. In the presence of a suitably experienced surgeon, open pericardiotomy is more effective.

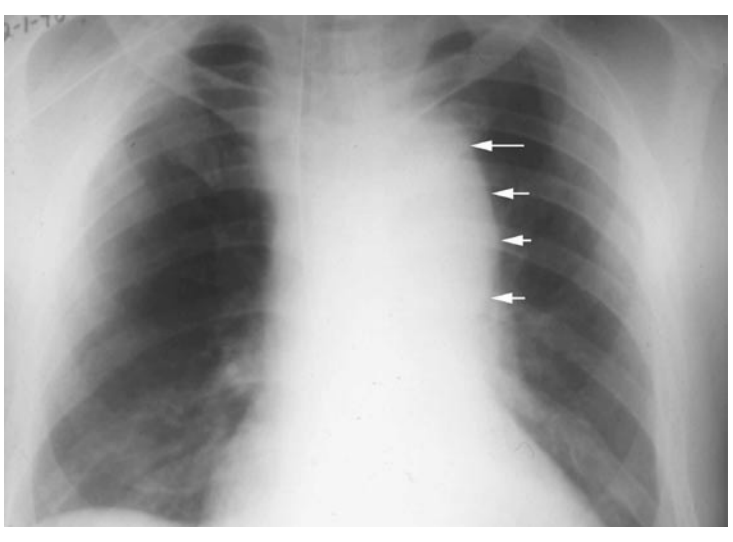
Flail chest: multiple fractures in adjacent ribs cause a segment of the chest wall to lose bony continuity with the thoracic cage. Although this flail segment moves paradoxically with inspiration, the life-threatening consequence is underlying lung contusion, which can cause severe hypoxaemia. Assisted ventilation, via a tracheal tube or by a non-invasive technique, is required if hypoxaemia persists despite supplemental oxygen and adequate analgesia.

Secondary survey
The following potentially life-threatening injuries may be identified during the secondary survey.

Pulmonary contusion: inspection of the chest may reveal signs of a deceleration injury, (e.g. seat-belt bruising). Pulmonary contusion is the most common, potentially lethal, chest injury – young adults and children have compliant ribs and considerable energy can be transmitted to the lungs without fracturing them. The earliest indication of pulmonary contusion is hypoxaemia (reduced PaO_2:FiO_2 ratio). The radiograph may be normal initially, but eventually shows patchy infiltrates over the affected area. Patients may require a high FiO_2 and mask continuous positive airway pressure (CPAP), or tracheal intubation and intermittent positive-pressure ventilation (IPPV). During IPPV, the use of small tidal volumes (5–7 ml/kg), a low peak inspiratory pressure (< 35 cm H_2O) and low FiO_2 ($\leq$ 0.5) are advised. The patient requires adequate fluid resuscitation, but fluid overload compounds the lung contusion.

Cardiac contusion should be suspected in any patient with severe, blunt chest trauma, particularly if there is a sternal fracture. Cardiac arrhythmias and ST changes on the ECG may be present but are non-specific. The right ventricle is most often injured, but it is not well evaluated by a 12-lead ECG. An elevated creatine kinase isoenzyme of cardiac muscle (CK-MB) is insensitive for diagnosing myocardial contusion; serum troponin I is better. Echocardiography confirms the diagnosis of cardiac contusion. Patients with severe cardiac contusion are likely to require inotropic support and tend to have other injuries that require ICU admission.

Blunt aortic injury: the thoracic aorta is at risk in any patient sustaining a significant decelerating force (e.g. fall from a height or high-speed crash). Only 10–15% of patients with blunt aortic injury reach hospital alive. The most common site for injury is just distal to the origin of the left subclavian artery. Intimal and medial tears may involve either part or the entire circumference of the aorta. In survivors, the haematoma is contained by an intact aortic adventitia and mediastinal pleura. Patients sustaining traumatic aortic rupture usually have multiple injuries and may be hypotensive at presentation. However, upper extremity hypertension is present in 40% because the haematoma compresses the true lumen. The chest radiograph shows a widened mediastinum in most cases (Figure 2). Although this is a sensitive sign of aortic rupture, it is non-specific – in 90% of cases it is caused by venous bleeding. Other radiological signs suggesting possible blunt aortic injury include pleural capping, a left-sided haemothorax, deviation of the trachea or nasogastric tube to the right and depression of the left main stem bronchus.



2 Chest radiograph showing widening of the aorta (arrows) in a patient with blunt aortic injury.

The definitive investigation is helical CT and/or arteriography. Once a rupture of the thoracic aorta is suspected, the systolic blood pressure should be maintained at 80–100 mm Hg using a β-blocker (e.g. esmolol, 0.5 mg/kg over 1 min then 50–200 μg/kg/min as an infusion; under anaesthesia these doses need to be reduced). Pure vasodilators (e.g. nitroprusside) increase the pulse pressure and shear forces on the aortic wall.

Rupture of the diaphragm occurs in 5% of patients sustaining severe blunt trauma; 75% occur on the left. The stomach or colon commonly herniates into the chest. Signs and symptoms include ipsilateral diminution in breath sounds, chest pain and respiratory distress. The chest radiograph may show an elevated hemidiaphragm, gas bubbles above the diaphragm, and a nasogastric tube in the chest. The diagnosis is confirmed by instilling contrast media through the nasogastric tube and repeating the radiograph.

Oesophageal rupture: a severe blow to the upper abdomen may result in a torn lower oesophagus as gastric contents are forcefully ejected. The conscious patient will complain of severe chest and abdominal pain. Mediastinal air may be visible on the chest radiograph and gastric contents may appear in the chest drain. The diagnosis is confirmed by contrast study of the oesophagus or endoscopy. Urgent surgery is essential because accompanying mediastinitis carries a high mortality.

Tracheobronchial injury: laryngeal fractures are uncommon. Signs of laryngeal injury include hoarseness, subcutaneous emphysema and crepitus. Transections of the trachea or bronchi proximal to the pleural reflection cause massive mediastinal and cervical emphysema. Injuries distal to the pleural sheath lead to pneumothoraces that do not resolve after chest drainage. Most bronchial injuries occur within 2.5 cm of the carina and the diagnosis is confirmed by bronchoscopy. Tracheobronchial injuries require urgent repair through a thoracotomy.

Rib fractures
Up to 10% of blunt trauma victims have rib fractures. Fractures of the lower ribs are associated with hepatosplenic injury. Multiple rib fractures in elderly patients and those with co-morbidity often cause death. The pain caused by fractured ribs impairs respiratory function. Adequate analgesia is essential. The options include:

- simple, regular, oral analgesia (paracetamol and non-steroidal anti-inflammatory drugs)
- intercostal analgesia (provides pain relief for up to 6 hours)
- intrapleural analgesia using bupivacaine infused through an epidural catheter inserted into the pleural space
- opiates (using intramuscular or intravenous patient-controlled analgesia; PCA)
- thoracic epidurals (provide better analgesia than PCA and may reduce pulmonary morbidity).

Anaesthesia
Anaesthesia for chest-injured patients may include use of a double lumen tube and one lung ventilation, bronchial blockers and extracorporeal support. Anaesthesia for a multiply injured patient with chest trauma follows that for any critically ill patient (e.g. adequate volume resuscitation, avoidance of hypothermia), but the following points should be noted.

- Myocardial contusion is common yet often unrecognized; during anaesthesia it may present with volume resistant hypotension and arrhythmias.
- Portable, supine chest radiographs miss small haemothoraces and anterior pneumothoraces.
- 10% of pulmonary contusions are not visible on the initial radiograph. They may develop insidiously with increasing oxygen requirements and may require advanced ventilatory modes.
- Up to 33% of occult pneumothoraces progress and about 15% will tension. A low threshold should be adopted for tube thoracocentesis before general anaesthesia in patients suspected of having a significant lung injury.
- Nitrous oxide should be avoided because it may double the volume of a pneumothorax in 10 minutes. ◆

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Hormonal and Metabolic Responses to Trauma

Grainne Nicholson

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The neuroendocrine and inflammatory aspects of trauma and surgery are part of the overall stress response and similar changes are found with haemorrhage, burns and severe exercise. Surgery serves as a useful model of the stress response because the changes that occur can be observed from a well-defined starting point. These result in substrate mobilization, muscle protein loss, and sodium and water retention. Such changes may have evolved to aid survival in a more primitive environment, when fluid retention together with glucose, lipid and protein mobilization would be beneficial to the organism. In modern surgical practice, such physiological disturbances may be easily prevented or rapidly corrected, therefore the benefits of the stress response are less obvious. It has been argued that attenuating the metabolic and endocrine changes associated with surgery may improve patient outcome, though no accepted definitions of outcome or recovery exist.

Initiation of the response

Management of the hormonal and metabolic changes following trauma demands an understanding of the causative factors and their interactions. The magnitude of the metabolic response is proportional to the severity of injury. Afferent neuronal input, both somatic and autonomic from the site of trauma, activates the hypothalamic–pituitary axis and the sympathetic nervous system. In addition to a marked increase in catabolic hormone secretion there is suppression of the anabolic hormones insulin and testosterone, and the normal negative feedback controls no longer prevail. Release of cytokines also plays an important role.

Hormonal aspects – increased pituitary hormone secretion results in secondary effects on hormonal output from target organs (Figure 1). A significant feature of the hormonal response to trauma is the failure of normal feedback mechanisms that control secretion. Cortisol release by the adrenal gland fails to inhibit further output of adrenocorticotrophin (ACTH) by the pituitary, and similarly hyperglycaemia fails to inhibit growth hormone secretion.

Summary of hormonal changes associated with metabolic response to trauma

	Secretion increased	Secretion increased/decreased	Secretion decreased
Pituitary	• Growth hormone • Adrenocorticotrophic hormone • β-endorphin • Prolactin • Arginine vasopressin	• Thyroid-stimulating hormone • Luteinizing hormone • Follicle-stimulating hormone	
Adrenal	• Catecholamines • Cortisol • Aldosterone		
Pancreas	• Glucagon		• Insulin
Other organs	• Renin		• Testosterone • Oestrogen • Triiodothyronine

1

Cortisol has both glucocorticoid and mineralocorticoid effects. It increases blood glucose concentrations by stimulating protein catabolism and promoting glucose production in the liver by gluconeogenesis. It reduces peripheral glucose utilization by an anti-insulin effect. Cortisol promotes lipolysis, which increases the production of gluconeogenic precursors from the breakdown of triglyceride into glycerol and fatty acids. It also has well-recognized anti-inflammatory effects mediated by inhibition of the accumulation of macrophages and neutrophils into areas of inflammation, a decrease in production of inflammatory mediators (e.g. leukotrienes, prostaglandins) and inhibition of cytokine synthesis.

Growth hormone has diabetogenic and protein anabolic effects. It promotes lipolysis and has an anti-insulin effect. It is unlikely that the values achieved following trauma have significant effects on glucose metabolism; however, interest has focused recently on its potential for preventing muscle protein breakdown and promoting tissue repair. The anabolic effects of growth hormone are mediated via polypeptides synthesized in the liver. These are termed somatomedins or insulin-like growth factors (IGFs). The main protein is somatomedin C or IGF-1 and attempts have been made to use human recombinant growth hormone and/or IGF-1 to reduce muscle catabolism and improve wound healing in severely catabolic patients. At present, experience is limited.

Arginine vasopressin is released by the posterior pituitary. In addition to its antidiuretic role, it also has important vasopressor and haemostatic effects. It also promotes the release of ACTH via secretion of C reactive protein from the hypothalamus.

Insulin is the key anabolic hormone. It is usually secreted in response to hyperglycaemia and promotes glucose uptake and storage as glycogen, inhibits lipolysis and decreases muscle protein loss. There is a failure of insulin secretion in response to the hyperglycaemia associated with trauma. Absolute values of insulin may vary but are inevitably low relative to the blood glucose value. The reduction in insulin secretion is due, primarily, to α-adrenergic inhibition of insulin secretion. Significantly lower insulin values are found in patients receiving β-blockade therapy during surgery. Failure of the usual cellular response to insulin, the so-called 'insulin resistance' following trauma may also contribute to hyperglycaemia. This resistance results from a defect of the insulin receptor, but the exact mechanism has yet to be elucidated.

Catecholamines – hypothalamic activation of the sympathetic nervous system results in increased secretion of catecholamines from the adrenal medulla and release of noradrenaline (norepinephrine) from presynaptic nerve terminals. The increased sympathetic activity results in tachycardia and hypertension. Renin is released from the kidney in response to sympathetic stimulation and promotes conversion of angiotensin I to angiotensin II. Angiotensin II stimulates secretion of aldosterone from the adrenal cortex resulting in sodium resorption from the distal convoluted tubule of the kidney. Sympathetic stimulation of the pancreas results in an increase in glucagon secretion and inhibition of insulin secretion. Other metabolic effects of catecholamines include breakdown of glycogen in liver and muscle resulting in increased plasma concentrations of glucose and lactate, as well as mobilization of free fatty acids from lipid stores.

Cytokines are a heterogeneous group of low molecular weight glycoproteins. They are released locally in response to tissue injury and act locally and systemically via specific receptors. The term cytokine includes the interleukins (IL-1–17), the interferons and tumour necrosis factor. They are synthesized mainly by cells of the macrophage/monocyte series, but are also produced by other cell types such as fibroblasts, endothelial cells and glial cells. Cytokines have a major role in the inflammatory response to surgery and trauma. They mediate and maintain the inflammatory response to tissue injury and initiate some systemic changes.

IL-6 is the main cytokine released after routine surgery. Changes occur 2–4 hours after the start of surgery, with peak values occurring after 6–12 hours. Laparoscopic techniques lead to smaller increases than those following conventional, open surgery. IL-6 is a prime inducer of acute phase protein synthesis in the liver. These proteins include C reactive protein, fibrinogen, proteins of the complement system, serum amyloid A, α_1-antitrypsin and ceruloplasmin. They limit tissue damage and promote haemostasis, repair and regeneration. Their synthesis usually occurs at the expense of decreased production of other proteins (e.g. albumin, transferrin). Concentrations of circulating cations (e.g. zinc, iron) decrease, partly as a result of changes in the production of transport proteins.

Acute phase response

The acute phase response is characterized by changes in metabolic, immunological and haematological functions. It comprises a complex series of reactions:

- acute phase protein synthesis in the liver
- hepatic sequestration of iron and zinc
- pyrexia
- neutrophil leucocytosis
- increased muscle proteolysis
- changes in vascular permeability
- activation of the hypothalamic–pituitary axis (*in vitro*)
- lymphocyte differentiation.

The acute phase response prevents further tissue damage, isolates and destroys infective organisms, activates the repair processes necessary to return the organism to normal function and is considered an integral part of wound healing and repair.

The immune system and the neuroendocrine system are interconnected because cytokines IL-1 and IL-6 stimulate secretion from isolated pituitary cells *in vitro*. In surgical patients, cytokines may augment pituitary ACTH secretion and subsequently increase the release of cortisol. Glucocorticoids inhibit cytokine production in a negative feedback system. It has been suggested that the cytokines are responsible for the hypercortisolaemia that persists in burns patients.
Metabolic consequences of substrate mobilization

Carbohydrate metabolism hyperglycaemia is a prominent feature of the metabolic changes after trauma and the increase in blood glucose is approximately proportional to the severity of injury. Glucose production in the liver, by glycogenolysis and gluconeogenesis, is increased and glucose utilization is impaired. Major surgery can result in a marked elevation of blood glucose. Further iatrogenic increases may be caused by administration of glucose infusions or as blood or blood products. Deleterious effects of sustained hyperglycaemia (blood glucose > 12 mmol/litre) include increased risk of infection and impaired wound healing, water and electrolyte loss, as well as exacerbation of ischaemic damage to the nervous system and myocardium.

Protein metabolism – a major effect of trauma is an increase in muscle protein loss. Following major abdominal surgery, losses of up to 0.5 kg/day lean body mass can occur. The amino acids released by proteolysis, especially glutamine and alanine, are used for gluconeogenesis and for synthesis of acute phase proteins by the liver. Concomitantly, albumin synthesis is decreased. More recently the cytokines, particularly IL-1 and IL-6, have been implicated in promoting muscle breakdown and stimulating acute phase protein synthesis.

Lipid metabolism after trauma has received little attention compared with glucose. In general, there are few changes in lipid mobilization unless starvation becomes a major factor postoperatively. Lipolysis of triglycerides to free fatty acids is promoted by adrenaline and glucagon, potentiated by cortisol and inhibited by insulin. The oxidation of free fatty acids to acetyl CoA is promoted by high glucagon concentrations and low insulin concentrations. Acetyl CoA is converted in the liver, via acetoacetyl CoA, to the ketone bodies acetoacetate, β-hydroxybutyrate and acetone. These can be utilized as energy sources by tissues other than the liver. Dramatic increases in free fatty acid concentrations are seen during cardiac surgery because heparinization activates lipoprotein lipase, but less so with the newer 'cleaner' heparins.

Management of endocrine and metabolic responses

Preoperative factors that can affect the metabolic response include personality and preoperative mental status, anxiety and fear, dehydration and partial starvation. During surgery, haemorrhage and hypothermia may alter the metabolic response while postoperative immobilization, infection, hypoxia and alterations in normal diurnal rhythms may cause metabolic changes.

It is common to view the stress response as an inevitable consequence of trauma, but many approaches to decreasing the metabolic sequelae have been tried. It is important to prevent the sympathetically-mediated cardiovascular responses of tachycardia and hypertension to surgical stress or trauma, particularly in patients with ischaemic heart disease. Modern anaesthetic practice strives to maintain physiological homeo-stasis by using techniques that prevent, or obtund, the stress response to surgery but no single anaesthetic or surgical technique is wholly successful in achieving this aim. Effective pain control and nutrition have not significantly improved postoperative recovery. Reducing postoperative catabolism may improve perioperative morbidity and hasten recovery.

Anaesthesia – many investigators have studied the effects of anaesthesia and different anaesthetic techniques on the neuroendocrine response to surgery. The intravenous induction agent etomidate is a potent inhibitor of adrenal steroidogenesis. It is no longer licensed for long-term sedation because it causes increased mortality in critically ill patients.

Analgesics – morphine inhibits the hypothalamic–pituitary–adrenal axis. Intravenous fentanyl, > 50 μg/kg, can abolish the hormonal response to pelvic surgery and higher doses (> 100 μg/kg) prevent catabolic hormone secretion to upper abdominal surgery. However, the consequence is profound and prolonged respiratory depression, which precludes its use in routine surgery. High-dose fentanyl is widely used in cardiac surgery where patients routinely need postoperative ventilatory support.

Regional anaesthesia provides excellent pain relief and prevents the response to surgery in pelvic and lower limb surgery by preventing afferent neuronal input. However, cytokine-mediated responses, which occur as a consequence of tissue trauma, are not altered. For upper abdominal and thoracic procedures, regional anaesthesia has less effect on the neuroendocrine response. Although regional anaesthesia has well-documented beneficial effects on thromboembolic complications, pulmonary function, cardiac and gastrointestinal function, it has not been proved to reduce postoperative morbidity and length of stay in hospital.

Laparoscopic surgery – obtunding the inflammatory response, rather than the neuroendocrine response, may improve recovery after major surgery or trauma. Laparoscopic surgery causes less tissue injury than conventional open procedures and thus the increase in inflammatory mediators (e.g. IL-6, C reactive protein) is less. For many intra-abdominal and intra-thoracic procedures, there is improved outcome and enhanced recovery compared with laparotomy and open thoracotomy. In general, laparoscopic techniques reduce perioperative immunosuppression and infection risks, and lead to an earlier hospital discharge.

Parenteral nutrition does not reduce muscle protein loss, except in severely malnourished patients. Enteral feeding is beneficial because it maintains the integrity of the gastrointestinal mucosa and reduces the incidence of bacterial translocation and septic complications. Recent attention has focused on the addition of arginine, glutamine, nucleotides and omega-3 fatty acids to enteral feeds because they appear to act as immunomodulators.

Glutamine, an amino acid used by lymphocytes and rapidly dividing cells of the gut mucosa, acts as a precursor for renal production of ammonia. Plasma glutamine values decline rapidly following surgery or injury. Glutamine supplementation of parenteral nutritional regimens improves nitrogen balance, but an overall improvement in outcome has not been demonstrated. Arginine stimulates the secretion of several hormones, including insulin and growth hormone. It may also be involved in the local regulation of tissue blood flow because it is a precursor of nitric oxide. The omega-3 fatty acids were thought to enhance immune defences through increased production of prostaglandin E3, but they also have effects on the release of thromboxane A_2 and prostacyclin and inhibit a variety of cellular and humoral immunological mechanisms. The administration of RNA or synthetic polynucleotides may enhance cell-mediated immunity and T lymphocyte function but convincing evidence is lacking.

Research into recovery after surgery is important for information, planning and economic reasons. A clear definition of recovery must be found together with an effective method of measuring this variable. ◆

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Hypovolaemic Shock

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Hypovolaemic shock is present when a reduced circulating volume causes tissue perfusion to be inadequate for its metabolic requirements. True hypovolaemia is caused by loss of blood, plasma, intracellular fluid or extracellular fluid (Figure 1). Relative hypovolaemia may occur if there is pooling of a normal blood volume; this occurs in sepsis, after spinal anaesthesia or due to the effect of venodilating drugs (Figure 1). Fluid loss as a result of internal haemorrhage or redistribution of the circulating volume may not always be apparent. However, identification of the cause of hypovolaemia is fundamental to its reversal. The remainder of this article considers hypovolaemic shock caused by acute haemorrhage.

Causes of hypovolaemia

	Common causes
True hypovolaemia	
Blood loss	Surgery Trauma Leaking abdominal aortic aneurysm Haematemesis Massive haemoptysis
Plasma loss	Burns Toxic epidermal necrolysis
Loss of extracellular or intracellular fluid	Vomiting Diarrhoea Pyrexia Diabetic ketoacidosis Haemodialysis or haemofiltration Diuretics Sepsis Anaphylaxis
Relative hypovolaemia	Anaphylaxis Drugs (e.g. nitrates, loop diuretics) Spinal or epidural anaesthesia Sepsis

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Physiological response to acute blood loss
The physiological response to acute blood loss involves several processes described in *Anaesthesia and Intensive Care Medicine* **2:1**: 17; **2.4**: 149; **2.4**: 155. Compensatory mechanisms produce the following effects that attempt to increase cardiac output.

Increased heart rate and cardiac contractility involves baroreceptor reflex, adrenal secretion of catecholamines and stimulation of the peripheral chemoreceptors.

Sodium and water retention involves reduced glomerular filtration, alterations in Starling's forces in capillaries, increased sodium reabsorption from distal convoluted tubules (aldosterone) and reduced water loss from distal convoluted tubules and collecting ducts.

Vasoconstriction involves baroreceptor reflex, adrenal secretion of catecholamines, stimulation of the peripheral chemoreceptors, renin-angiotensin system and circulating catecholamines.

Increased circulatory volume – splenic contraction injects 'stored' blood into the circulation.

Prevention of further blood loss is mediated by the coagul-ation cascade and platelets.

Signs and symptoms
The signs and symptoms of haemorrhagic shock are attributable to the underlying physiological responses described above. They include:

- skin pallor
- peripheral cyanosis
- cool digits, nose and ears
- prolonged capillary refill time
- tachycardia or a rising pulse rate
- absent peripheral pulses
- systolic hypotension or a falling systolic blood pressure
- low jugular venous pressure or central venous pressure
- reduced pulse pressure
- thirst
- irritability, confusion, low Glasgow Coma Score (GCS) and coma
- oliguria
- coronary ischaemia
- tachypnoea
- diaphoresis
- mydriasis.

Often, the only early sign of haemorrhage is a rising pulse rate, because compensatory vasoconstriction can maintain blood pressure. However, elderly patients have little physiological reserve and are prone to rapid, cardiovascular decompensation. Children often maintain normal blood pressure despite severe volume depletion, until they suffer a sudden, life-threatening circulatory collapse. Athletes have low heart rates; a pulse of 80 beats/minute may indicate significant shock. β-adrenergic receptor antagonist therapy, the presence of a fixed rate pacemaker, high spinal injury and spinal or epidural local anaesthesia may limit or prevent a compensatory tachycardia during haemorrhage.

Classification of haemorrhagic shock
The classification of haemorrhagic shock (Figure 2) emphasizes that the response to continuing blood loss is a dynamic process.

Classification of hypovolaemic shock

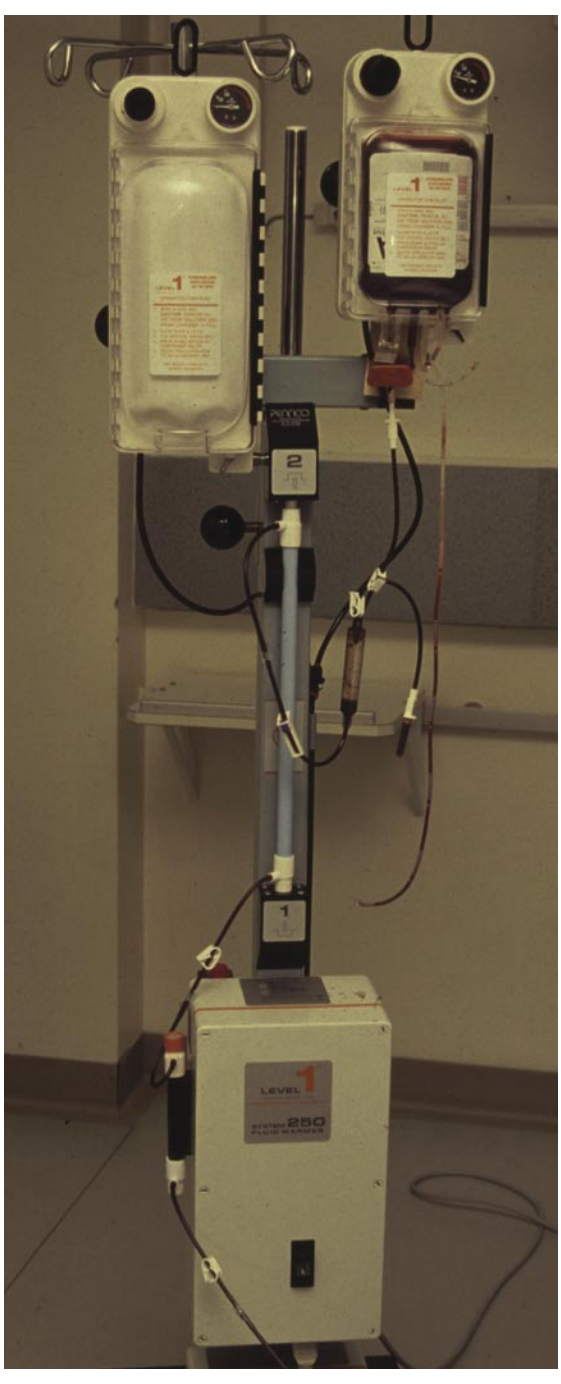
	Class I	Class II	Class III	Class IV
Blood loss (ml)	Up to 750	750–1500	1500–2000	> 2000
Blood loss (%)	Up to 15%	15–30%	30–40%	> 40%
Pulse rate	< 100	> 100	> 120	> 140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	> 35
Capillary refill	≤ 2 s	> 2 s	> 2 s	> 2 s
Urine output (ml/hour)	> 30	20–30	5–15	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious and confused	Confused and lethargic
Fluid replacement	Crystalloid	Crystalloid: colloid 2:1	Crystalloid/ colloid + blood	Crystalloid/ colloid + blood

2

Treatment
It is essential to ensure airway patency and the adequacy of respiration, before attending to control of haemorrhage. All bleeding patients should receive 100% oxygen.

The goal of treatment is to improve cardiac output and tissue perfusion by increasing cardiac preload. Consequently, the main aim is replenishment of the circulating volume; vasopressors should not be used. Peripheral haemorrhage can often be controlled by simple elevation of the limb and local pressure; pneumatic antishock garments may be required to control haemorrhage from the lower limbs, pelvis and abdomen. In general, limb tourniquets are not advised. Severe haemorrhage requires the rapid infusion of fluid via large bore cannulas placed in large veins. In practice, the easiest sites for venous access include the antecubital, femoral and saphenous veins and for central access the internal jugular or subclavian veins. For central access, a cannula with a single, large lumen should be used, because flow is related to the fourth power of the radius of the cannula. Venous access may be difficult in hypovolaemic children; the interosseous route is potentially the quickest and easiest alternative. Occasionally, surgical cut-down onto the long saphenous vein is necessary in adults and children.

Although blood replacement is required in many cases, the choice of initial fluid is usually immaterial. Suitable fluids include isotonic electrolyte solutions (e.g. Hartmann's, normal saline) or colloid solutions (e.g. gelofusine). Each ml of blood loss requires replacement with 3 ml of crystalloid because it distributes in the interstitial and extracellular spaces. Colloids are probably better retained within the circulation. An initial rapid infusion (i.e. over 15 minutes) of 1000–2000 ml fluid in an adult, or 20 ml/kg in a child, is appropriate for most circumstances, but the infused volume should be tailored to the clinical circumstances and the observed response. All infusion fluids should be warmed before infusion (Figure 3).



3 Devices such as the Level 1 warmer (SIMS) permit the rapid infusion of large volumes of warmed infusion fluid or blood.

If blood has been lost, the ideal replacement fluid is blood. However, correct cross-matching takes time and, in critical situations, uncross-matched O negative blood may be given. In elective surgery, previously donated and stored autologous blood may be used; alternatively, blood lost during surgery can be recovered and, after processing, re-infused as part of 'blood salvage'.

If large volumes of blood are used (e.g. 5 units within 1 hour) the potential effects of massive transfusion should be considered, including:

- impaired oxygen delivery
- impaired coagulation
- hypothermia
- hypocalcaemia
- hyperkalaemaia
- metabolic acidosis
- fluid overload
- adult respiratory distress syndrome.

During volume resuscitation, the underlying cause of shock should be sought and reversed. Occasionally, this is achieved only by surgical intervention (e.g. laparotomy).

Monitoring and end-points of successful resuscitation

Regular evaluation of physiological parameters and the effects of interventions, using simple measures (e.g. capillary refill time, pulse rate, blood pressure, GCS, urine output, central venous pressure) is essential. However, the end-points of successful resuscitation are not always easy to determine. Return of cardiovascular parameters, such as heart rate and blood pressure, to normal probably gives the best indication of adequate fluid replacement. However, these may be influenced by other factors, for example pain, and normovolaemia may exist despite a high heart rate. Other factors such as end organ perfusion are useful indicators. For instance, a urine output greater than 0.5 ml/kg suggests normal renal perfusion and a normal GCS indicates normal cerebral perfusion. If the cardiovascular system is monitored using a central venous pressure catheter, normal values may be obtained despite inadequate fluid replacement. This may be due to myocardial depression (e.g. ischaemia or cardiac tamponade), raised intrathoracic pressure (e.g. tension pneumothorax, haemothorax) or a high venous tone. Monitoring acid–base status may also give a guide to the adequacy of the circulation, because a persistent acidosis may reflect inadequate replacement or continuing haemorrhage. ◆

Major Incident Management Outside Hospital

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An incident is classified as major when the number of casualties or the severity of their injuries requires that special arrangements be made inside and outside hospital. Major incidents can be subdivided into:

- compensated incidents, which can be managed simply by mobilizing extra resources
- uncompensated incidents in which the number of casualties exceeds the maximum that can be treated.

In compound (rather than simple) major incidents the infrastructure (e.g. communications, roads, healthcare systems) is affected as part of the event. Most major incidents are simple, compensated and man-made (e.g. a train or aeroplane crash).

The effective management of a major incident scene involves the close coordination of all the emergency services (police, fire, ambulance), the voluntary services (e.g. Red Cross and St John's Ambulance), medical teams from local hospitals and doctors from the British Association for Immediate Care (BASICS). One of the biggest problems, and a challenge for all those managing a major incident, is effective communication between these groups at the scene and the receiving hospitals and other support services.

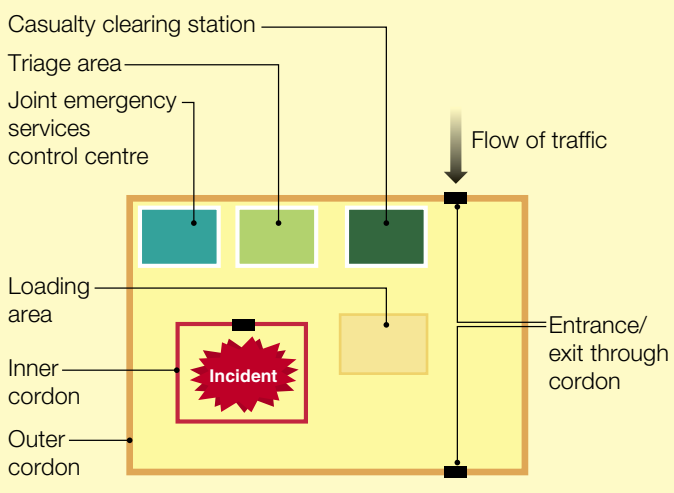
Advance preparation for major incidents, comprising theoretical and practical exercises, and carefully agreed plans and operating protocols, is vital. Specially designed courses (e.g. the Major Incident Medical Management and Support (MIMMS)) can give excellent additional training.

This article concentrates on the aspects of major incident management of particular importance to those providing a medical response out of hospital.

Command and control structure

At the scene of a major incident, areas are cordoned off and controlled by the police. The inner cordon encompasses the heart of the incident and includes areas that remain hazardous. The outer cordon encloses all other areas involved in the incident management (Figure 1).

Command and control layout of a typical major incident



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All emergency services adopt a gold/silver/bronze hierarchy of command. Gold control is usually located at the headquarters of the emergency service. Silver control is located at the joint emergency services control centre inside the outer cordon. Bronze control usually comprises specific individuals directly controlling rescue activity.

Each emergency service has its own role in a major incident. The police remain in overall control, unless the incident involves fire, chemicals or nuclear material when the fire service is in command. The responsibility of the ambulance service and on-site medical teams is to assess patients, perform any early treatment required and then to facilitate transfer to receiving hospitals.

Communication within and between emergency services at the scene is vital for an effective coordinated response. It is equally important that good communication lines are established with gold control, receiving hospitals and other supporting services.

Safety

It is important that the rescuers do not become victims. Personal safety involves the use of good quality, protective, high visibility clothing and previous appropriate training in major incident management. The presence of any potential hazards at the scene should be considered in consultation with the fire service; special precautions (e.g. for chemical spillage or nuclear leakage) may be required. The safety of casualties should also be maintained.

The Medical Incident Officer (MIO)

The duties of the MIO include:

- obtaining information on the potential hazards present
- determining the number of casualties and the severity of their injuries (via the forward medical incident officer/triage doctor)
- liaison with the ambulance incident officer
- liaison with receiving hospitals.

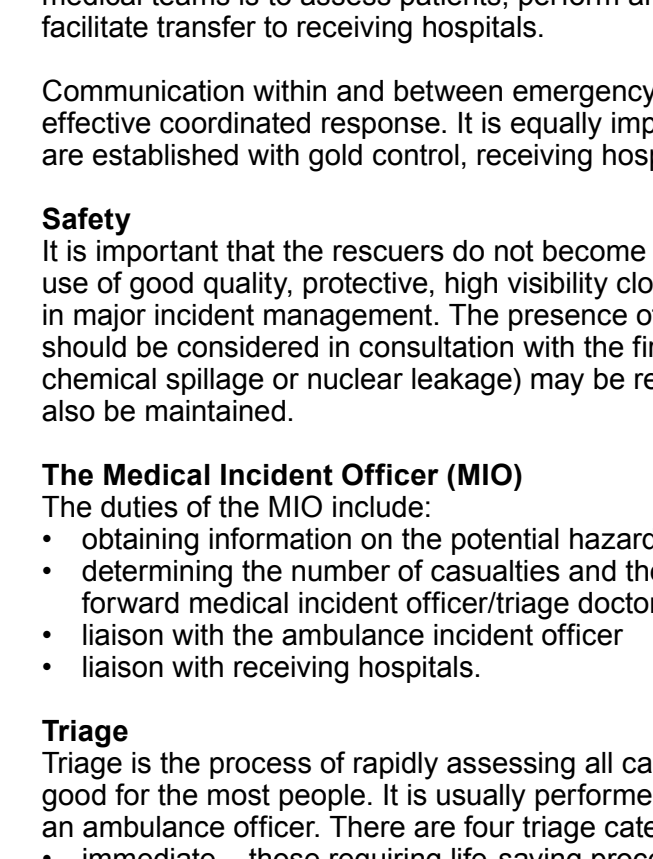
Triage

Triage is the process of rapidly assessing all casualties with the aim of doing the most good for the most people. It is usually performed by the triage doctor in conjunction with an ambulance officer. There are four triage categories:

- immediate – those requiring life-saving procedures (e.g. intubation, limb amputation)
- urgent – those who will require some form of early intervention within a few hours of the incident
- delayed – those who can wait for treatment
- dead/expectant (likely to die regardless of intervention).

These categories are often colour coded to aid identification with cards such as that in Figure 2.

The initial triage (triage sieve) is followed by a 'triage sort' at the casualty clearing station. A triage sieve may simply assess whether the patient can walk (delayed priority), whether they are not ambulant but have a normal respiratory rate and capillary refill (urgent priority), or abnormal respirations or capillary refill, in which case they become immediate priority. The triage revised trauma score (TRTS) can been used to perform a triage sort, by assigning a variable from 0–4 for values of respiratory rate, Glasgow Coma Score (see *Anaesthesia and Intensive Care Medicine* **3:4:** 132) and systolic blood pressure. The total TRTS can then be used to assign treatment priority, but should also be used in conjunction with the available information on anatomical injury.



2 Cruciate triage label. The label can be folded to display the triage category.

Treatment

The MIO should not be directly involved in the treatment of casualties; these duties should be delegated to the ambulance service and medical teams. Generally, procedures should be performed in the casualty clearing station, away from the hazards of the incident. However, occasionally medical teams have to provide treatment in the inner cordon of the incident site (e.g. trapped casualties). This should be done only after permission from the service in charge of site safety.

Treatment at the scene should largely be confined to securing the airway (with adequate spinal stabilization), ensuring adequate breathing and oxygenation, controlling major external haemorrhage and initiating circulatory support. Excessive treatment at the scene delays definitive care and risks hypothermia.

Anaesthesia may be required to allow the performance of amputations, extrications or for securing the airway in the major trauma patient. The exact conduct of anaesthesia in these circumstances is not as important as the general principles of maintaining adequate oxygenation and perfusion of the patient at all times. It should always be remembered that although anaesthesia may have an important role in the management of casualties with major trauma, the prerequisites of triage often preclude its use in a major incident.

Transport

The safe mobilization of casualties away from the incident scene to appropriate hospitals is the responsibility of the ambulance incident officer in consultation with the MIO. Decisions on the type of transport to be used depend on local circumstances, including the availability and capacity of the different modalities, as well as individual suitability. Usually, casualties are transferred in order of their triage category with the most seriously injured going first, but there may be circumstances in which this is not the most efficient way of using resources.

In some incidents there are large numbers of dead casualties. A temporary mortuary is usually set up close to the incident site, away from areas that are accessible to the media and public. Bodies are usually transferred there after the pronouncement of death (usually by a designated member of the medical team) and as soon as any relevant forensic evidence has been gathered.

Aftermath

Involvement in the management of a major incident can be emotionally traumatic. De-briefing of staff is essential to assist them in coming to terms with what they have witnessed and also allows the system and individuals to learn from the experience. The MIO is required (with the other service team leaders) to provide a formal report of the incident; careful and accurate documentation during the incident is therefore essential. ◆

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Managing the Airway in Trauma Patients

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David A Gabbott

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Emergency airway management in trauma victims is a challen-ging situation, with limited time for preparation. Some patients with blunt or penetrating injuries to the head and neck have obvious, extensive disruption of normal anatomy. Others may have an apparently normal airway, which can prove unexpectedly difficult. Therefore, it is essential to plan the initial approach to securing the airway and develop a fail-safe back-up strategy.

Airway obstruction may occur because of oedema, blood, debris or foreign bodies (e.g. teeth). A flail maxilla or mandible may also cause obstruction if there is posterior displacement of a mobile fracture. Such patients may adopt positions (e.g. lateral or prone) in which they can best maintain their own airway, but these may make orotracheal intubation difficult. If the patient is agitated, because of hypoxaemia, pain, cerebral injury or drugs, the use of techniques that require patient cooperation can be challenging. Trauma patients almost inevitably have a full stomach, risking pulmonary aspiration; many also have a suspected cervical spine injury that requires immobilization with a collar and lateral supports. These make laryngoscopy difficult. Normal manoeuvres to open the airway (e.g. chin lift, head tilt or oral airway insertion) may be contraindicated, cause further trauma or fail to help.

In the cooperative patient with stable injuries and a patent airway, fibre-optic intubation, an inhalational induction or tracheostomy under local anaesthetic may be appropriate to secure the airway. However, these techniques may prove impossible owing to bleeding or poor patient cooperation; inhalational induction also risks regurgitation and may not prevent airway obstruction at lighter planes of anaesthesia. If immediate airway control is required, a rapid sequence induction of anaesthesia with bimanual cricoid pressure, manual in-line stabilization of the neck and orotracheal intubation is preferred. The cervical collar should be undone, because it increases the chance of successful laryngoscopy and permits the application of cricoid pressure.

Nasotracheal intubation is contraindicated if a basal skull fracture is suspected, because intracranial penetration may occur via a fractured cribriform plate.

Rapid sequence induction in trauma patients

Many components of rapid sequence induction present problems in trauma patients.

- Pre-oxygenation may be impossible in an agitated patient though oxygenation may improve cooperation if hypoxaemia is the cause.
- Trauma victims often have a combination of hypoxaemia, a reduced cardiac output and anaemia. Therefore, it is often necessary to ventilate patients after induction of anaesthesia, before attempting orotracheal intubation.
- Cricoid pressure is contraindicated in cases of laryngeal trauma.
- If a cervical fracture is suspected, bimanual cricoid pressure should be used, with one hand supporting the posterior spine.

Improving the chances of successful intubation

A number of devices and techniques can be used to increase the chances of a successful orotracheal intubation.

- The gum elastic bougie is particularly useful if the neck must be maintained in a neutral position
- A number of laryngoscopes are available to help make laryngoscopy easier, including the McCoy blade. It consists of a standard Macintosh blade, with a hinged tip and is useful in Cormack and Lehane grades 3 and 4 laryngeal views (see *Anaesthesia and Intensive Care Medicine* **1:1:** 32) when the neck is in a neutral position. It also requires less force to expose the laryngeal inlet and this reduces the haemodynamic response to intubation and the force applied to the cervical spine.
- A dental mirror, positioned on the posterior pharyngeal wall may provide a reflected view of the laryngeal inlet and can guide the passage of a bougie.
- If normal laryngeal anatomy cannot be identified at laryn-goscopy, gentle pressure on the chest may force air bubbles out of the laryngeal inlet, indicating the position of the trachea.

Management of failed intubation in trauma patients

There must be a contingency plan for failed orotracheal intubation. Multiple attempts at intubation result in hypoxaemia and can lead to progressive airway oedema. The priority is to oxygenate the patient adequately, using techniques such as two-person, bag-mask ventilation. A number of airway adjuncts (e.g. laryngeal mask airway (LMA), Combitube) can be used in the emergency situation. Ideally, they should be easy to insert, be reliable in the presence of an abnormal airway and provide some protection against aspiration.

Laryngeal masks

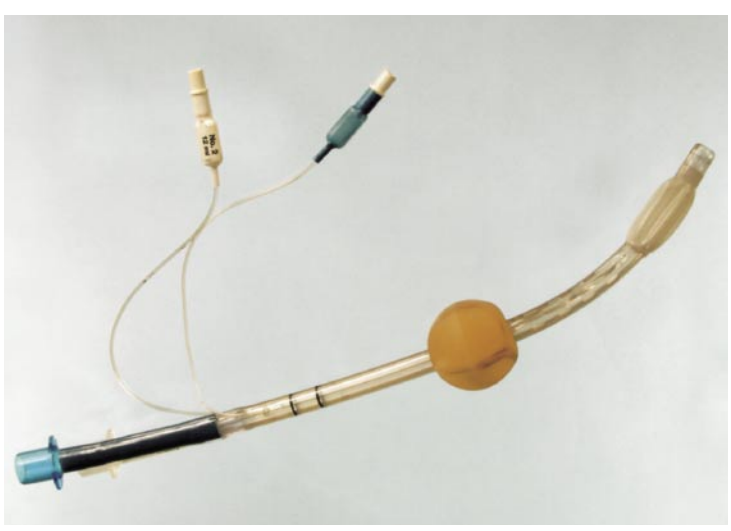
The LMA offers the overwhelming advantage of familiarity in a stressful situation. It is available in several sizes and can be placed rapidly, blindly and with the neck in a neutral position. Airway pressures up to 20 cm H_2O are easily generated, and it provides some, but not complete, protection of the lower airway from soiling. After placement, it may act as a conduit for intubation via a fibre-optic scope. However, the use of cricoid pressure significantly impairs the insertion and function of the LMA, to the extent that pressure must usually be relaxed or released. Furthermore, because it is a supraglottic device, the LMA cannot overcome laryngospasm.

In recent years, the intubating laryngeal mask (ILMA) has become available. It consists of a rigid metal tube, anatomically curved to fit the airway, and incorporates a laryngeal mask head with an epiglottic elevator bar. A flexible tracheal tube with a uniquely shaped tip is passed blindly or with the aid of a lighted stylet through the ILMA and enters the trachea, usually within a few attempts. It provides the least traumatic of all blind insertion techniques and has been used successfully for awake orotracheal intubation with topical anaesthesia. It is easier to insert than a standard LMA with the neck in a neutral position, reduces the haemodynamic stress of intubation and can be used for ventilation, generating pressures up to 30 cm H_2O. Like the LMA, the ILMA is functionally impaired by cricoid pressure and there is concern about the amount of force imparted to the cervical spine by the metal component of the device.

The Proseal LMA, which has an additional oesophageal lumen running in parallel with the airway lumen, is a further development. An extra posterior cuff significantly improves airway sealing and permits ventilation pressures in excess of 40 cm H_2O in a number of patients. The oesophageal lumen allows venting of stomach contents and the passage of an orogastric tube.

The Combitube

The Combitube (Figure 1) is a double lumen device with eight supraglottic tracheal apertures, a single distal oesophageal aperture and two cuffs, each with an independent pilot balloon. It is passed blindly into the pharynx where, although it almost always enters the oesophagus, it still allows ventilation of the lungs. There are two sizes, but 37 F is appropriate for all adults.



1 The Combitube.

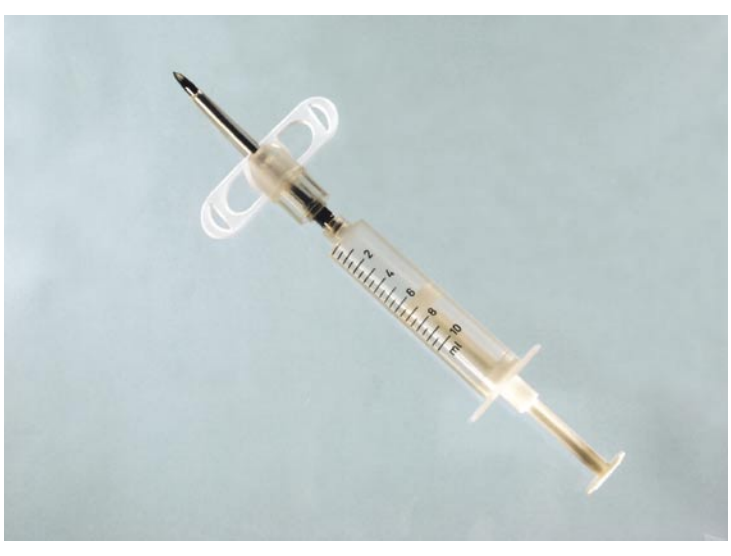
The Combitube has a number of potential advantages. It can be inserted with the head in a neutral position and can generate airway pressures up to 30 cm H_2O. Aspiration is usually prevented, because the small volume distal cuff occludes the oesophagus and the stomach contents can be drained via one of the lumens. In addition, the oesophageal balloon can remain inflated, protecting the airway, while attempts are made to intubate the trachea. Arterial oxygenation may also be improved because the small exhalation apertures of the Combitube create a positive end-expiratory pressure.

Problems occur because the Combitube is a bulky device that requires reasonable mouth opening for insertion. It can also cause pharyngeal and laryngeal trauma, often because of over-distension of the large volume pharyngeal cuff. Other problems include an inability to suction the trachea and difficulty with insertion in the presence of a hard cervical collar. The Combitube is a single-use device, making it an expensive option for teaching and clinical use.

Newer airway adjuncts, such as the Airway Management Device and Laryngeal Tube have not been evaluated in trauma patients.

Cricothyrotomy

If adequate ventilation and oxygenation cannot be achieved by other means, it is essential to gain access to the trachea at a point below the larynx. The cricothyroid membrane is the most suitable anatomical site because it is relatively avascular, requires minimal neck extension for exposure and has some protection posteriorly from the cricoid cartilage. The techniques available for cricothyrotomy each have advantages and disadvantages, though a formal surgical airway has the highest complication rate. The use of a simple needle and cannula technique requires a high pressure oxygen source and does not permit adequate exhalation. The best compromise is to use a purposely designed large bore trocar and cannula (e.g. Quicktrach VBM Medical (Figure 2), Melker cricothyroidotomy cannula Cook Critical Care) that allows exhalation, permits suction and to which an anaesthetic circuit can be attached. Cricothyrotomy should not be deferred until the patient is moribund and should be used early to secure the airway in those who have severely disrupted anatomy. ◆



2 Quicktrach (VBM Medical).

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Near Drowning and Hypothermia

Giles Morgan

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Drowning is death from asphyxiation in water. In near drowning, the victim survives the initial immersion but may suffer complications related to associated physical injuries or caused by hypoxaemia, hypothermia or the inhalation of water.

Outcome from near drowning depends on the severity of the injuries. Initial cardiovascular and cerebral dysfunction are unreliable in predicting death or disability, because of the effects of hypothermia. In general, a favourable outcome is expected in patients who have not lost consciousness and survival is more likely if bystander resuscitation is performed. In over 300 incidents from Cornwall, only three deaths occurred in patients who had not suffered a cardiac arrest before hospital admission. A poor outcome is expected in patients who have a Glasgow Coma Score of 5 or less, or who are asystolic on arrival at hospital. If neurological function remains poor 24 hours after restoration of a stable circulation, death or severe neurological impairment is likely. 20% of children who require cardiopulmonary resuscitation sustain permanent neurological damage.

In the UK, more than 500 people die by drowning each year. It is the second most common cause of accidental death in children. In the USA, 50% of deaths from drowning occur in children below the age of 4 years. The incidence is higher in men than in women. There is an association with intoxication with alcohol and other recreational drugs. Disorders that could potentially render a patient unconscious such as epilepsy, heart disease and cerebrovascular accident are relatively rare associations. The incidence of near drowning is six to ten times more common than drowning and many cases are not documented.

Pathophysiology of drowning

Early events: asphyxiation is central to the early stages of drowning. The temperature of the water influences the initial physiological behaviour of the patient and may influence survival. The composition of the water is of less importance than the temperature. Sudden immersion submits the victim to substantial hydrostatic pressure that increases venous return, pulmonary blood volume, cardiac output and stimulates a diuresis. Pressure on the abdominal wall increases the work of breathing by 65%. Three reflexes may be activated.

Airway irritation – aspiration of water into the pharynx leads to swallowing, coughing, glottic closure and, when water is eventually aspirated into the airway, laryngospasm and bronchospasm.

Cold shock – in response to sudden total body immersion in cold (< 25°C) water, the victim first takes a large gasp and then begins to hyperventilate. Breath holding time may be reduced to less than 10 s. The effect increases as water temperature falls to a maximum at 10°C.

Diving reflex – cold water in contact with the face and eyes causes bradycardia, peripheral vasoconstriction and apnoea. The effect is more marked in children.

Drowning without aspiration of water (dry drowning) occurs in less than 10% of cases, but is more likely to occur in thermo-neutral water when cold-stimulated reflexes are minimal. The larynx remains closed during submersion until the victim loses consciousness. Aspiration may be minimal. A rapid fall in the partial pressure of oxygen in arterial blood, and subsequent loss of consciousness, may occur as alveolar oxygen is utilized.

Drowning with aspiration of water: 90% of drowning victims have aspirated significant volumes of water. In cold water, the cold shock response leads to hyperventilation and aspiration. In thermoneutral water, glottic closure is either overcome by the victim or occurs when the victim becomes unconscious, leading to aspiration and bronchospasm.

Nature of the water: aspiration of fresh water causes a reduction in pulmonary surfactant rendering the lungs inelastic and poorly compliant. Absorption of water and alveolar collapse causes ventilation–perfusion abnormalities, pulmonary shunting and hypoxaemia. Neurogenic pulmonary oedema may occur if cerebral hypoxaemia ensues. Absorption of fresh water into the circulation can cause haemodilution and haemolysis, but about 800 ml is required to produce a significant effect in adults. Usually only small quantities of water are inhaled and haemolysis and dangerous electrolyte changes are rare.

Sea water is hypertonic and has an osmolality about three times that of blood. It tends to draw water into the alveoli from the blood, but this is of little clinical significance. Its effect on surfactant is less than that of fresh water. Vomit and particulate matter suspended in water are also likely to be inhaled and may cause infection.

Hypothermia

The highest sea temperature round the UK is about 15°C during the summer and about 5°C during the winter. Hypothermia (33–36°C) is usual in immersion victims. At 35°C victims may become unaware of danger. Loss of consciousness occurs at about 32°C. Ventricular fibrillation or asystole occur at about 28°C.

Management

All patients who have been rescued from an immersion incident resulting in near drowning should be taken to hospital. Widespread organ system dysfunction may occur as a result of hypoxaemia, but the onset may be delayed by several hours. To aid management, patients are categorized into four groups.

- Group 1: Conscious and breathing adequately with no clinical evidence of aspiration.
- Group 2: Conscious and breathing adequately with clinical evidence of aspiration.
- Group 3: Conscious or unconscious with inadequate ventilation.
- Group 4: Not breathing and no cardiac output.

The principles applicable to the management of general trauma patients should be applied to the management of immersion victims because head, spinal and other injuries may have been sustained during the near-drowning incident.

Group 1 patients may display reluctance to accept medical attention because of moderate hypothermia or a feeling of relief that they have had a lucky escape. However, in 3% of cases, ventilatory distress may supervene several hours after the incident. Patients in this group should be monitored for at least 6 hours and discharged only if pulmonary function is normal.

Group 2: aspiration of water is indicated by tachypnoea, wheeze, paroxysmal cough, retrosternal pain and the production of grey sputum. Chest radiography may show areas of patchy consolidation. Blood gas analysis may show hypoxaemia or a metabolic acidosis. Electrolyte abnormalities are unusual and there is unlikely to be haematological evidence of haemolysis. Hypo-thermia may be evident. Patients in this group should be admitted to hospital until their temperature is normal. They may be discharged after 6 hours, only if examination of the respiratory system reveals no abnormalities and their arterial oxygen saturation is normal when breathing air.

Group 3 patients may have evidence of poor tissue oxygenation and organ dysfunction. Admission to a critical care area is mandatory.

Respiratory system – aspiration of water leads to broncho-spasm, reduced compliance, increased shunting and ventilation–perfusion mismatch. Initial treatment includes high concentration oxygen therapy and continuous positive airway pressure. Patients with minor breathing difficulties plus evidence of hypoxaemia may deteriorate and require ventilation. Ventilation should be commenced using strategies to prevent alveolar overdistension and barotrauma.

Cardiovascular system – cardiovascular instability is common. Initially, patients may have profound vasoconstriction, a low cardiac output and prolonged capillary refill time. Intravenous access may be difficult and in children intra-osseous access may be the best option. Chest radiography shows bilateral infiltrates suggestive of pulmonary oedema due to the acute respiratory distress syndrome, rather than myocardial dysfunction. Measurement of cardiac output and pulmonary artery occlusion pressure can be a useful adjunct to intravascular volume resuscitation and the use of inotropic drugs. Pulse oximetry is unreliable in cold vasoconstricted patients.

CNS – cerebral injury from hypoxaemia can occur in as little as 5 minutes at normothermia, but hypothermia may provide protection for periods as long as 1 hour. Cerebral hypoxaemia is associated with cerebral oedema; raised intracranial pressure (ICP) should be expected. There is no evidence that measurement of ICP has a positive impact on outcome, but this may be related to the poor outcome in patients who have sustained a significant hypoxic brain injury. Other causes of a reduced level of consciousness must be excluded, including head trauma, cerebrovascular accident, drugs and metabolic causes such as hypo- and hyperglycaemia. Standard measures for the management of hypoxic brain injury (e.g. 15° head elevation, mild hyperventilation, sedation to obtund coughing) should be implemented. If no improvement can be demonstrated within 24 hours of the incident, the outcome is likely to be poor for patients who were admitted unconscious and normothermic.

Renal and metabolic – common metabolic abnormalities include a profound metabolic acidosis and hyperkalaemia. These may be associated with hypothermia, rhabdomyolysis and reperfusion injury. A persistent metabolic acidosis, despite adequate circulatory resuscitation and treatment with intra-venous sodium bicarbonate, should raise suspicions of liver or bowel ischaemia. Specific measures to reduce plasma potassium should be introduced if levels are greater than 5.5 mmol/litre (i.e. 50% glucose, 50 ml, with soluble insulin, 15 units intravenously over 30 minutes). Intravenous calcium chloride (10%) should be given to treat dysrhythmias associated with hyperkalaemia. A urinary catheter should be inserted. Haemo-filtration should be commenced if renal failure occurs.

Prophylaxis against sepsis – it is common to withhold the use of antibiotics until there is clinical or laboratory evidence of sepsis, because unusual organisms may be cultured.

Group 4 patients appear to be dead. Hypothermia causes unconsciousness at temperatures below 33°C and ventricular fibrillation or asystole may occur at or below 30°C. Peripheral pulses may not be palpable. The carotid pulse should be palpated continuously for at least 60 s and an ECG recorded to exclude profound bradycardia or pulseless ventricular fibrillation. Recovery is possible, therefore the danger of assuming death from cardiac arrest in the presence of hypothermia cannot be overestimated. Prolonged submersion in very cold water is compatible with recovery.

Restoration of body temperature – warming the victim is difficult because resuscitative measures require the patient to be undressed. Resuscitation should be continued until the core temperature has reached 32°C. This may take 2–3 hours. Below 32°C, attempts to restart the heart are likely to be unsuccessful. All wet clothing should be removed and the patient dried. Room temperature should be increased and doors and windows closed. Whenever possible, the patient's body should be covered and warmed using warm-air devices (e.g. BairHugger). Further warming can be achieved by warming inspired gases and intravenous fluids to 35°C. The stomach, urinary bladder and peritoneal cavity can be irrigated using warmed fluids. Extracorporeal circuits, in particular those used in cardiac surgery, have been used effectively to warm patients in a more controlled environment. ◆

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Spinal Cord Injury

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Spinal cord injury is an uncommon but devastating event. Patient management is complex, long term and requires a team approach. In the UK, there are 12 spinal injuries units, therefore initial management is usually in a non-specialist hospital. This article concentrates on three areas of particular concern for anaesthesia and intensive care.

In the UK, there are 500–700 spinal cord injuries each year. Most are caused by road traffic accidents and falls. Any trauma patient is potentially at risk of vertebral and/or spinal cord injury. The aim of management is to identify spinal injuries early to prevent further damage and to commence treatment. Diagnosis of spinal cord injury is based on the presence of spinal pain, sensory disturbance and weakness. Abnormalities are difficult to determine in an unconscious patient in whom a high index of suspicion must be maintained and injury assumed until proved otherwise. In conscious patients, it is important to establish the level of injury and whether it is complete or incomplete because this affects the prognosis. The presence of any 'distracting' injury should be noted. Neurological examination must include assessment of sensation to pinprick (spinothalamic tracts), fine touch and joint position (posterior columns), muscle power (corticospinal tracts), reflexes (including anal) and cranial nerve function. Signs that do not fit a classic pattern must not be dismissed because injuries can be caused by impaired vascular supply and affect only some areas of the cord.

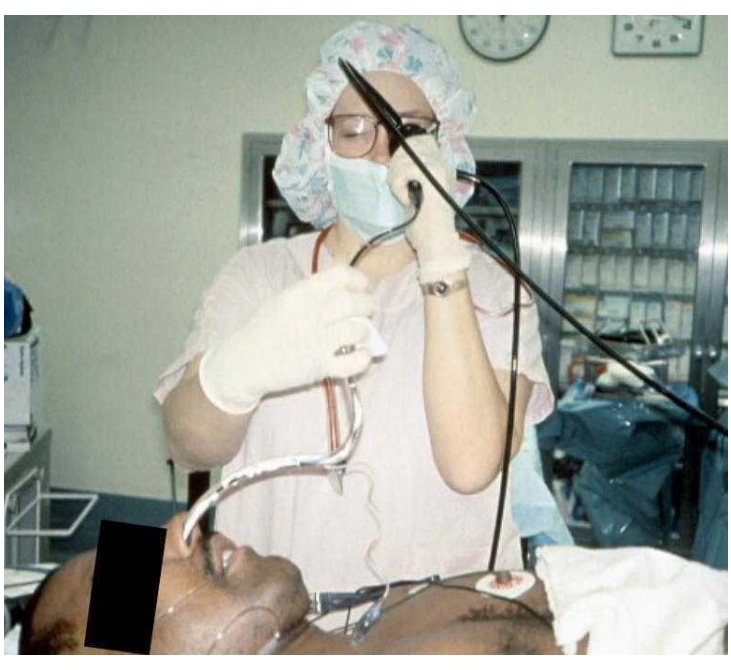
The cervical spine is at particular risk because of its mobility in relation to the relatively fixed thoracic cage: 44% of spinal injuries involve the cervical region and up to 3% of major trauma cases have a cervical spine injury. 10% of patients with a cervical spine injury have another vertebral injury.

Airway management

Immediate: patients with spinal injuries have often sustained multiple trauma and may require intubation and ventilation urgently. Most evidence supports the use of rapid sequence induction using manual in-line immobilization to minimize neck movement and cord damage during laryngoscopy. Suxamethonium can be used safely for up to 48 hours following injury but can produce a hyperkalaemic response subsequently. Patients with spinal cord injury above the level of the cardiac sympathetic supply (T1–T4) should be pretreated with atropine or glycopyrollate before any airway manoeuvre to avoid a profound bradycardia/asystole associated with unopposed vagal action.
A lateral cervical spine radiograph may miss up to 10% of injuries. Consequently, radiographs cannot exclude cervical spine injury, do not alter airway management and are not essential before intubation. The neck must be immobilized at all times either using manual in-line immobilization or '3-point fixation' of collar, headblocks and tape; collars alone are insufficient.

Emergent: patients with spinal cord injury who do not require immediate anaesthesia should have the level and stability of their injury determined by clinical and radiological investigation. They may subsequently require intubation for operative procedures (including spinal stabilization) or if ventilation becomes compromised by ascending cord oedema, diaphragm fatigue or sputum retention. The choice for airway control in these patients depends on individual factors and operator expertise. The options include:

- awake fibre-optic intubation (Figure 1)
- standard induction/laryngoscopy
- the intubating laryngeal mask airway (LMA)
- blind nasal intubation.



1 Patient in head calipers undergoing awake fibre-optic intubation.

In all cases the cervical spine should be stabilized either by the prior application of callipers under local anaesthetic or by manual in-line stabilization. Particular care is required on induction to avoid hypotension in cases of high spinal cord injury with sympathetic block and bradycardia.

Preventing secondary cord injury

Secondary cord injury occurs after further mechanical disruption or ischaemic necrosis following vasospasm and oedema. A complex biological cascade is initiated involving lipid peroxidation and elevations in intracellular calcium, oxygen-free radicals and proteolytic enzymes, which propagate injury. The mainstays of management from the time of injury are therefore to treat hypoxia and hypotension and maintain spinal stability. Although high spinal cord injury may cause hypotension, trauma victims must be assumed to be hypovolaemic until proved otherwise. Evidence is lacking about the ideal target mean arterial pressure required to optimize spinal cord perfusion but it should probably be at least 'normal' for that patient.

The role of steroids: neuroprotection and limitation of cord oedema by administration of methylprednisolone for 24 hours has been widely promoted for acute non-penetrating spinal cord injury since the publication of the National Acute Spinal Cord Injury Study (NASCIS 2) trial results in 1990 and 1992. The NASCIS 3 trial (1997/1998) recommended the 24-hour infusion of methylprednisolone for those presenting within 3 hours of injury and a 48-hour infusion for those presenting within 3–8 hours of injury. The use of methylprednisolone is under debate given other level 1 evidence suggesting no benefit and an increased incidence of pneumonia, sepsis and gastrointestinal bleeding in those treated for 48 hours. In March 2002, the American College of Neurosurgeons stated that use of methylprednisolone should not be considered a 'standard of care' but as an option in acute spinal cord injury. Local policies should be discussed with the regional spinal unit. Other neuroprotective agents have shown promise in animal studies only.

'Clearing' the cervical spine in unconscious patients

The normal conditions required to 'clear' a cervical spine are:

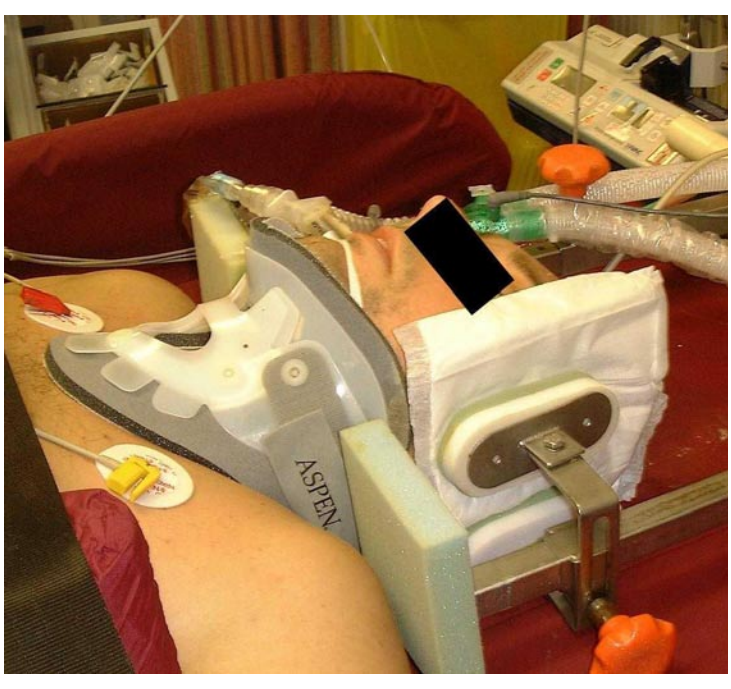
- a conscious patient, not under the influence of drugs or alcohol
- no neck pain
- no abnormal neurological signs
- no distracting injury (e.g. long bone fracture).

These are impossible to achieve in most ICU patients. Failure to 'clear' the cervical spine and having to maintain immobilization are associated with the following problems:

- cervical collars cause pressure sores and may raise intracranial pressure
- positioning patients for chest physiotherapy, prone ventilation and pressure area care is difficult
- the inability to extend the neck impedes tracheostomy
- weaning 'irritable' patients is hampered by spinal immobilization.

Pressure areas can be minimized by switching rigid, pre-hospital collars to fitted, semi-rigid collars (e.g. the Aspen). The use of kinetic beds (Figure 2) aids chest physiotherapy, pressure area care and oxygenation.

There is considerable benefit in 'clearing' the cervical spine in unconscious patients especially those likely to be ventilated for more than 48 hours. A survey by Gupta and Clancy showed a woefully inadequate and variable approach to the cessation of spinal immobilization in unconscious ICU patients. The following imaging should be considered.



2 Kinetic bed therapy with spinal immobilization.

Radiography and CT: three complete views of the cervical spine (lateral, anterioposterior and odontoid peg) reviewed by a specialist exclude about 95% of injuries. CT scanning of higher risk (C1/C2) and difficult-to-visualize areas in conjunction with radiographs detects about 98% of injuries (i.e. 2% of cervical spine injuries may not be identified by three radiographs with CT supplementation (EAST report)). Further imaging is required for patients in whom the mechanism of injury is associated with a high risk of spinal cord injury (e.g. road traffic accidents at over 35 mph; deaths at scene; falls over 10 feet).

MRI and dynamic fluoroscopy: MRI is superior at delineating ligament and cord damage particularly in the first 48 hours. MR angiography has shown that vascular injury occurs in up to 40% of patients with cervical spine injury. However, access to MRI is limited in some hospitals and even with appropriate MRI-compatible equipment the process is labour intensive. High-risk patients should undergo dynamic flexion/extension views under image-intensifier control to assess spinal stability before removing immobilization. This can be performed on ICU if patients cannot be moved. These further imaging techniques should be undertaken in daylight hours in conjunction with orthopaedic/radiology specialists. ◆

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Vascular

Anaesthesia
and intensive care medicine
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Anaesthesia for Abdominal Vascular Surgery

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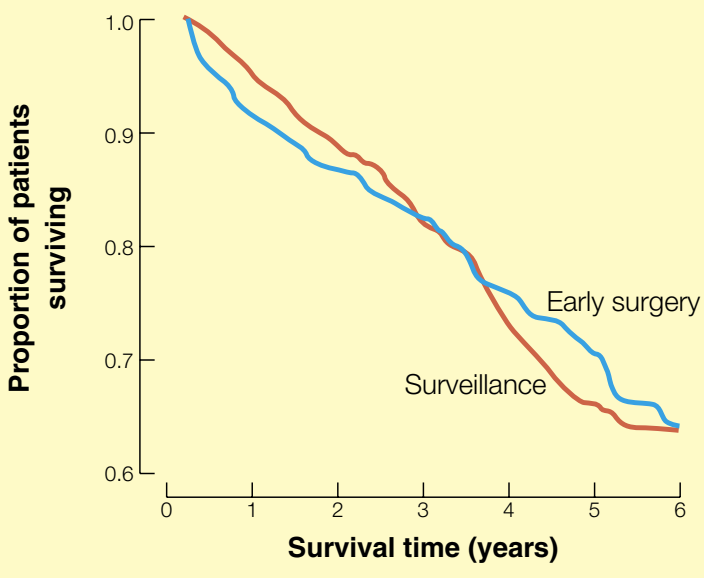
Surgery on the abdominal aorta may be required for aneurysmal dilatation or for symptomatic occlusive atherosclerosis.

The risks of non-surgical management of aortic aneurysm depend on aneurysm diameter. Aneurysms greater than 6 cm carry a risk of rupture within 1 year of about 25%. In addition, larger aneurysms expand more rapidly, further increasing the risks. In patients with smaller aneurysms (< 5 cm), it may be thought appropriate to operate early when the patient is younger and fitter, but there seems to be no benefit to long-term survival from early surgical intervention (Figure 1). The operative mortality figures for elective aortic surgery are 2–10%, reflecting the higher incidence of associated risk factors:

- ischaemic heart disease
- renal impairment
- increasing age
- diabetes mellitus
- obstructive pulmonary disease
- hypertension
- smoking.

The principal causes of perioperative morbidity and mortality are myocardial ischaemia or infarction, organ failure and respiratory complications. Although improvements in perioperative monitoring and management have reduced morbidity and mortality in elective surgery, the mortality from emergency surgery remains high at about 70%.

Overall survival of patients given early surgery compared with ultrasound surveillance in the management of small aneurysms



Number at risk

Surveillance	527	497	468	412	229	125	52
Early surgery	563	513	489	450	302	187	63

Source: UK Small Aneurysm Trial Participants. Mortality Results for Randomised Controlled Trial of Early Elective Surgery or Ultrasonographic Surveillance for Small Abdominal Aortic Aneurysms. *Lancet* 1998; **352 (9141):** 1649–55.

Abdominal aortic surgery

Preoperative assessment and optimization

Assessment of patients for abdominal vascular surgery is aimed at identifying the risk factors outlined above, and ameliorating them when possible. The most significant factor affecting outcome is perioperative myocardial ischaemia and failure. In addition to baseline ECG and chest radiography, most patients warrant further evaluation of cardiac function (e.g. echocardiography and/or stress testing). Close liaison with the cardiology department helps to optimize the medical management of hypertension, ischaemia or failure before surgery. There is evidence that patients with ischaemic heart disease benefit from perioperative β-blockade, which results in reduced perioperative silent myocardial ischaemia and adverse events.

General anaesthetic considerations

Most patients will be taking cardiac medication, and this should be continued up to and including the day of surgery. Admission to a high-care area for invasive monitoring and optimization of oxygen delivery in high-risk patients has been shown to improve outcome, but few units have the capacity to achieve this and the benefits probably apply only to those in high-risk groups.

The aims of anaesthesia are to avoid exaggerated responses to surgical stimulation, reduce myocardial work and therefore oxygen demand, and maintain cardiac output and oxygen delivery to the tissues. Additional goals include attenuation of the stress response to surgery, preservation of renal function and the provision of postoperative analgesia.

Various general anaesthetics can be used, most having some benefits appropriate to aortic surgery (Figure 2), however, many units employ a combination technique of opioid, oxygen, air and low-dose volatile agent to optimize the beneficial effects while minimizing side-effects.

The addition of regional anaesthesia in the form of a thoracic epidural has several beneficial effects. There is a reduction in haemodynamic instability, the stress response to surgery, and general anaesthetic requirement. There is an increase in endocardial blood flow, and the high-quality analgesia in the postoperative period reduces the incidence of respiratory and other complications.

The main problem related to the use of a thoracic epidural in vascular surgery is the requirement for heparinization for cross-clamping, and therefore the potential risk of spinal haematoma. Reports from large numbers of patients suggest that the technique is safe and that the potential benefits outweigh the risks. Some units advocate insertion of the catheter the day before surgery, but most accept insertion on the day of surgery, allowing at least 1 hour between catheter insertion and heparin administration. Most patients also receive thromboprophylaxis with low molecular weight heparin (LMWH) during their admission. It is recommended that an epidural should not be placed less than 2 hours before or 12 hours after administration of LMWH.

General anaesthesia for use in aortic surgery

Agent	Advantages	Disadvantages
Opioids	• Cardiovascular system stability • Analgesia • Reduced stress response	• Prolonged postoperative respiratory depression
Volatile agents	• Reduced afterload (vasodilator) • Reduced myocardial oxygen consumption • Titratable	• Reduced myocardial contractility • Reduced diastolic pressure/coronary blood flow • Coronary steal at higher minimum alveolar concentration
Nitrous oxide	• Rapid onset and offset • Analgesia	• Myocardial depression
Propofol (total intravenous anaesthesia, target-controlled infusion)	• Titratable • Reduced afterload (vasodilator) • Postoperative sedation	• Reduced myocardial contractility

Monitoring

Usual baseline monitoring is required, with the addition of invasive arterial and central venous blood pressure, core temperature and urine output. A five-lead ECG, displaying leads II and V5, is more sensitive than a standard three-lead ECG for the detection of myocardial ischaemia.

Pulmonary artery flotation catheters are not beneficial for routine use in abdominal vascular surgery. Their use is associated with an increase in fluid administration with no improvement in outcome, and it may increase the morbidity associated with excessive fluid. However, these catheters provide additional information in patients with poor left ventricular filling which guides fluid management and the use of inotropic agents to improve cardiac output.

Transoesophageal echocardiography is a relatively non-invasive real-time monitoring technique. Ventricular filling can be assessed rapidly, and ejection fraction and cardiac output calculated. Ventricular segmental wall motion abnormalities can be visualized and are more sensitive markers of ischaemia than ECG changes. However, the equipment is expensive and requires a trained operator to interpret the images. If an anaesthetist performs the echocardiography, another is needed to deliver the anaesthetic safely.

Oesophageal Doppler monitoring is a relatively non-invasive technique for assessing cardiac output. However, the results are variable if used by an inexperienced operator, and are difficult to interpret when the aortic clamp is in place. In this situation, trends can give valuable information but absolute figures may be inaccurate.

Blood preservation

Blood loss during abdominal vascular procedures increases with the complexity of the surgery and with surgery involving a more proximally sited aortic cross-clamp. Transfusion is often recommended if the haematocrit falls below 30% (0.30), and there is some evidence that levels below 28% (0.28) are associated with a higher incidence of myocardial ischaemia in patients with vascular disease. Regular sampling from the arterial line for estimation of the haematocrit allows for logical transfusion of blood products. Other ways to minimize the use of homologous blood transfusion include pre-donation, haemodilution and intraoperative cell salvage. Cell salvage allows for the re-infusion of fresh RBCs with normal concentrations of 2,3-diphosphoglycerate, and without anticoagulant, acid–base or electrolyte disturbance.

Wide-bore cannulae, either peripheral or central, are required to allow rapid transfusion of blood and other fluids, preferably warmed. If severe haemorrhage is anticipated, rapid infusion systems capable of delivering large volumes of warmed fluids should be available.

Large-volume blood loss and transfusion results in coagulopathy, requiring fresh frozen plasma and platelet transfusion. Further coagulopathy may occur following gut ischaemia in supra-coeliac clamping, especially if the ischaemic time exceeds 30 minutes. Laboratory coagulation tests, bench-top activated clotting time and thromboelastography can all be used to guide appropriate use of clotting factors. Fibrinolysis may be a problem in complicated or supra-coeliac cases, requiring the use of antifibrinolytic agents (e.g. aprotinin, tranexamic acid).

Temperature control

Mild hypothermia has been thought of as protective in abdominal aortic surgery, but it is associated with vasoconstriction, tachycardia, hypertension and increased myocardial oxygen requirement. In addition, blood viscosity is increased and coagulation adversely affected. Maintenance of normothermia is associated with less biochemical disturbance, improved clinical variables and less myocardial ischaemia. Warming is achieved more effectively by forced-air warming devices than by a circulating mattress, and all infused fluids should be warmed. The area below the cross-clamp is not actively warmed while the clamp is in place.

Fluid management

In addition to blood loss, there is excessive evaporation from abdominal contents, and also third-space fluid loss, especially into the retroperitoneal space. Replacement with crystalloid or colloid is titrated against central venous or pulmonary artery occlusion pressure, and regular electrolyte analysis is required to detect and correct disturbances of potassium, calcium and magnesium.

Aortic cross-clamp

The placement of an aortic cross-clamp has significant effects on the cardiovascular and neuroendocrine system, the severity increasing the more proximally the clamp is placed. In addition, blood flow to vital structures including the kidneys, spinal cord and gastrointestinal tract may be interrupted if supra-renal or supra-coeliac clamping is required. The cardiovascular effects of cross-clamping are less severe in occlusive aortic disease owing to the development of collateral circulation.

Cardiovascular effects and management: following placement of an aortic cross-clamp, systemic vascular resistance rises causing an increase in mean arterial pressure and left ventricular afterload. An increase in left ventricular end systolic pressure and wall tension, and a reduction in ejection fraction and cardiac output of up to 40% accompany this. The reduction in cardiac output is greater in patients with inadequate intravascular volume, and the cardiovascular changes in general are more severe in supra-coeliac clamping when the splanchnic circulation is interrupted. Patients with normal coronary arteries and myocardial function tolerate these changes and maintain cardiac contractility reasonably well. However, in patients with ischaemic heart disease the combination of increased myocardial workload and greater intraventricular pressures inhibiting subendocardial blood flow may lead to myocardial ischaemia. This further affects cardiac contractility, central venous and left atrial pressures rise, and left ventricular failure and dysrhythmias may ensue.

Before placing the clamp, the patient requires adequate intravascular filling. Afterload reduction is usually achieved by increasing the depth of anaesthesia with a volatile agent. Nitrates, including glyceryl trinitrate and sodium nitroprusside, are generally required only in compromised or emergency patients in whom the additional preload reduction and improved coronary blood flow are beneficial. Inotropic agents may be required if cardiac output is not improved with normalized preload and afterload.

During cross-clamping the period of ischaemia causes vasodilatation distal to the clamp, and the accumulation of H^+, lactate and other vasoactive metabolites. The release of these agents into the circulation on reperfusion in combination with vasodilatation results in low systemic vascular resistance, reduced venous return and reduced cardiac output. Acidosis and metabolites may directly depress the myocardium and, if hypotension is severe, low coronary blood flow exacerbates the problem. A combination of adequate filling to a central venous pressure above 10 cm H_2O or pulmonary artery wedge pressure of 12–15 before de-clamping, and the use of vasoconstrictors and inotropes help to reduce cardiovascular instability. Surgical techniques that minimize the effects are short cross-clamp times and careful, slow release of the clamp.

Renal preservation: renal impairment is a significant cause of perioperative morbidity and mortality in abdominal aortic surgery. Up to 10% of patients have preoperative renal impairment, and the overall rate of perioperative renal failure in aortic surgery is of the order of 3%. Mortality associated with renal failure exceeds 25%.

Risk factors for the development of renal failure are shown in Figure 3. Although suprarenal clamping is associated with much higher rates of renal complications (up to 50%), all levels of cross-clamp impair renal blood flow. The combination of increased vascular resistance, reduced cardiac output, activation of the renin-angiotensin system and sympatho-adrenal stimulation all serve to impair renal blood flow even with infra-renal cross-clamp. There may also be intra-renal blood flow redistribution away from the medulla, increasing the risk of medullary ischaemia.

Risk factors for perioperative renal failure

Preoperative renal impairment
- Renal artery atherosclerosis
- Hypertension
- Diabetes mellitus
- Contrast toxicity
- Heart failure

Age

Dehydration
- Osmotic diuresis from intravenous contrast
- Preoperative starvation

Operative factors
- Suprarenal cross-clamp
- Hypotension
- Hypovolaemia
- Large-volume blood transfusion

3

Oliguria is a poor predictor of renal dysfunction, because many patients demonstrate a reduction in urine output without developing renal impairment. Similarly, maintaining urine output has not been shown to improve outcome. However, it is the only perioperative monitor of renal function available. The most important factors in the prevention of renal impairment are the maintenance of adequate intravascular volume (pulmonary artery wedge pressure 12–15) and cardiac output, and the avoidance of hypotension. If oliguria persists despite these precautions, various agents are used to re-establish or maintain urine output (Figure 4). Although these agents increase urine output, and have theoretical benefits, they have not been shown to improve renal function or outcome when compared with volume expansion alone. Most units employ one or more of these techniques to augment urine output during surgery, especially if a supra-renal clamp is required.

Beneficial effects of drugs affecting renal function

Mannitol
- Plasma expansion
- Improved cortical blood flow
- Osmotic diuresis
- Free-radical scavenging

Loop diuretic (e.g. frusemide)
- Diuresis
- Sodium excretion

Dopamine
- Decreased systemic vascular resistance, increased cardiac output, β-adrenergic effects
- Increased renal blood flow, dopaminergic effects
- Increased glomeruler filtration rate and urine output

4

Spinal cord ischaemia: normally the spinal cord receives most of its blood supply via the anterior spinal artery. This artery receives blood from the aorta via medullary branches, the most important being the artery of Adamkiewicz, which generally arises between T8 and T12, but may arise anywhere between T1 and L1. Distal supply is via the iliac vessels. Interruption to this blood supply may result in spinal cord ischaemia and a flaccid paralysis, which may be transient or develop into long-term paraplegia. The overall incidence is low (about 0.25%) in aortic aneurysm surgery, but increases in supra-renal or thoraco-abdominal procedures, and in emergency surgery.

The most important factors in the preservation of spinal cord function are avoiding prolonged periods of cross-clamp (over 30 minutes), and the identification, preservation and re-implantation of critical vessels. Anaesthetic considerations are principally the maintenance of adequate blood pressure proximal to the clamp to optimize anterior spinal artery perfusion, and the avoidance of hyperglycaemia. Various techniques have been advocated for higher-risk supra-renal surgery including:
- somatosensory evoked potentials for the early detection of ischaemia
- cord cooling via an epidural catheter
- CSF drainage to improve spinal artery perfusion pressure
- corticosteroid administration to reduce cord oedema
- magnesium administration as a free-radical scavenger.

However, there is no clear evidence of improved outcome.

Endovascular aortic stent procedures

The technique of endovascular stent repair of aortic aneurysm via the femoral artery was first described in 1991. If the procedure is technically possible, it is associated with less physiological disturbance, morbidity and mortality than open procedures. Mortality in those thought fit for open repair is reported as 2.3% in the Eurostar database, and in those unfit for open repair as 12.5%. Rate of conversion to open repair is low (5%), but conversion is associated with a high mortality. There is no clear evidence of the long-term effectiveness of stent procedures, and they are generally limited to patients considered unfit for conventional surgery, or to those included in randomized controlled trials.

Anaesthetic considerations
Patients tend to be in the high-risk group for anaesthesia and surgery, therefore careful consideration must be given to preoperative assessment and optimization of medical problems.

Site: the procedure can be performed in a theatre suite with portable imaging, but about half of the units in the UK prefer to use the higher-quality imaging available in the radiology department. This results in the problems associated with anaesthesia in a distant site not primarily designed for general anaesthesia. The most important consideration is to anticipate everything that could be required, and have it available. A trolley specially set up with all the appropriate drugs and equipment makes the situation less stressful for the anaesthetist. The area is often cramped, with large numbers of staff and bulky equipment. The temperature is usually kept low for optimal equipment function, but too low for optimal patient function, and therefore warming with a forced-air warmer will be required because warming mattresses under the patient interfere with the imaging. The table on which the patient lies will not tip, therefore anaesthesia must be established before transfer from a theatre trolley or bed. In addition, the mattress is thinner than that on an operating table, and because procedure times can be prolonged, pressure areas need protection.

Anaesthesia and analgesia: general and epidural anaesthesia are possible for stent procedures, however, because heparin is administered during the procedure, the timing of the epidural is important. In addition, if epidural anaesthesia is to be used without general anaesthesia, sedation may be required to help the patient to tolerate prolonged procedures. Overall, the choice of anaesthetic technique depends on the general physical state of the patient.

Monitoring: baseline monitoring is principally the same as for open repair. Although there is not the same potential for third- space or evaporative fluid losses there is usually a continual, and occasionally brisk, blood loss from the femoral arteriotomy. In addition, though the aorta is occluded for only short periods of time during graft deployment, one femoral artery is occluded for most of the procedure. This may cause significant cardiovascular effects on reperfusion. Urine output also needs careful monitoring, especially if large volumes of potentially nephrotoxic radiological contrast are required. Carbon dioxide may be used as an alternative contrast agent, but the image quality is adversely affected.

Recovery: following an uneventful stent procedure, most patients can be woken up and transferred to a recovery area with appropriate monitoring. Most patients are in the high-risk group, therefore 24 hours in a high-dependency area are usually indicated.

Anaesthesia for Patients with Haemoglobinopathies

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It is estimated that 4.5% of the world population carries a haemoglobinopathy trait. Haemoglobinopathies result from the formation of an abnormal globin. The most common and clinically significant are sickle cell haemoglobin (HbS) and the thalassaemias. Patients may be heterozygous (HbAS), homozygous (HbSS) or a compound heterozygote for the sickle gene and an interacting abnormal haemoglobin such as HbC or β thalassaemia. The presence of HbS produces clinical symptoms of varying severity. Sickle cell trait (HbAS) is benign, requiring extremely hypoxic or acidotic conditions before sickling occurs. Homozygous (HbSS) or doubly heterozygous (HbSC or HbS β thalassaemia) forms produce chronic incurable illness. In children less than 6 months, HbF is protective but under adverse conditions sickling can occur in the newborn.

Sickle cell disease affects all organ systems (Figure 1). The abnormal haemoglobin shortens the survival time of RBCs and causes anaemia. Patients with thalassaemia present with anaemia or complications from repeated transfusion, such as iron overload manifesting as damage to the heart, liver and endocrine organs, or infection. There is no cure for these diseases, though a number of therapies have been tried including bone marrow transplantation. In these patients, careful preoperative preparation and perioperative manage-ment contribute to improved outcome, and a multidisciplinary approach is essential.

Complications of sickle cell disease

- Anaemia
- Jaundice
- Reticulocytosis
- Hepatosplenomegaly
- Autosplenectomy
- Hand–foot syndrome
- Enlarged skull and long bones
- Dactylitis
- Pulmonary infarcts
- Vitreous haemorrhages
- Stroke
- Leg ulcers
- Avascular necrosis of bone
- Priapism
- Acute chest syndrome
- Ischaemic pain crisis
- Haemolytic crisis
- Aplastic crisis
- Sequestration syndrome

1

Preoperative preparation

It is recommended that all patients of non-European origin are screened for variant haemoglobins preoperatively. Sickle forms, even in small numbers, are diagnostic on blood film but specific haemoglobin type and percentage can be confirmed only by electrophoresis. The sickle solubility test (*Sickledex*) does not identify low levels of HbS and false-negative results are common before the age of 6 months. Above this age, a negative *Sickledex* renders clinical problems with sickling unlikely.

Preoperative assessment should focus on signs and symptoms of end-organ damage, including pulmonary hypertension and cor pulmonale from pulmonary infarction, liver disease and renal dysfunction. Patients with sickle cell trait can be regarded as healthy before surgery, though sickling can occur in exceptional circumstances. Prolonged fasting and dehydration should be avoided.

Preoperative transfusion

Transfusion reduces the proportion of HbS and improves the oxygen-carrying capacity of the blood, which may improve microvascular perfusion. Its use to terminate acute crises is controversial. In general, preoperative transfusion should be undertaken to reduce HbS to less than 30% of total Hb without increasing haematocrit above 36%. This may require partial exchange. However, raising the haemoglobin to 10 g/dl may be as effective in preventing perioperative complications and result in fewer transfusion-associated complications.

Perioperative management

The mainstay of anaesthesia is to avoid factors likely to precipitate sickling such as dehydration, acidosis or hypothermia. The anaesthetic technique is less important than the care with which it is administered. General and regional techniques have been used successfully, though there is evidence that complications related to sickle cell disease are more common in patients with HbSS receiving regional anaesthesia. Adequate fluid replacement is essential and hypotension should be treated with fluids in preference to pressor agents, which produce vasoconstriction and stasis. Maintenance of normothermia using warming devices and increasing ambient temperature is essential.

Oxygenation should be optimized. Preoxygenation is advisable and postoperative oxygen therapy should be continued for 24 hours after major surgery. Patients with sickle cell disease are at high risk of postoperative pulmonary complications and chest physiotherapy should be routine. Sickle crisis may manifest postoperatively as the acute chest syndrome, a serious complication with 10% mortality. Features include severe chest wall pain, fever, cough, hypoxia and pulmonary infiltrates. High-dependency care is necessary and ventilatory support is occasionally required. Good analgesia is essential, together with rehydration and treatment of infection. Sickle crises can occur during surgery and symptoms are masked by anaesthesia and postoperative analgesia.

Tourniquets may be used, provided the patient is adequately hydrated and periods of inflation are limited. Hyperventilation may be useful. Pregnant women with HbSS, HbSC or HbS β thalassaemia may pose particular problems. Severe anaemia and sickling in intrauterine blood vessels may cause intrauterine growth retardation, abortion or stillbirth. Labour and delivery can precipitate crises. Meticulous management of regional anaesthesia with regard to hydration, blood transfusion, oxygen supplementation and postoperative analgesia is required. The effect of haemoglobinopathies on the outcome of cardiac surgery is uncertain. Cardiopulmonary bypass imposes a major physiological insult but profound hypothermia may protect against sickling. If adequate perfusion and oxygenation are ensured, using vasodilators and crystalloids to reduce viscosity, low temperature may be beneficial. Recommended levels of HbS before cardiopulmonary bypass are less than 30% in adults and less than 5% in children. Timing of transfusion is controversial because it may precipitate fluid overload and pulmonary oedema in susceptible patients.

Pain management

Sickle crises cause severe pain, which is often underestimated. Precipitating causes should be identified and treated. Pain control requires opiates, and patient-controlled analgesia devices have been widely used. Non-steroidal anti-inflammatory drugs are a useful adjunct in the treatment of bone pain. Regional blocks have been used successfully for localized pain, but many patients suffer repeated crises and chronic pain syndromes can develop.

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Anaesthesia for Vascular Surgery on Extremities

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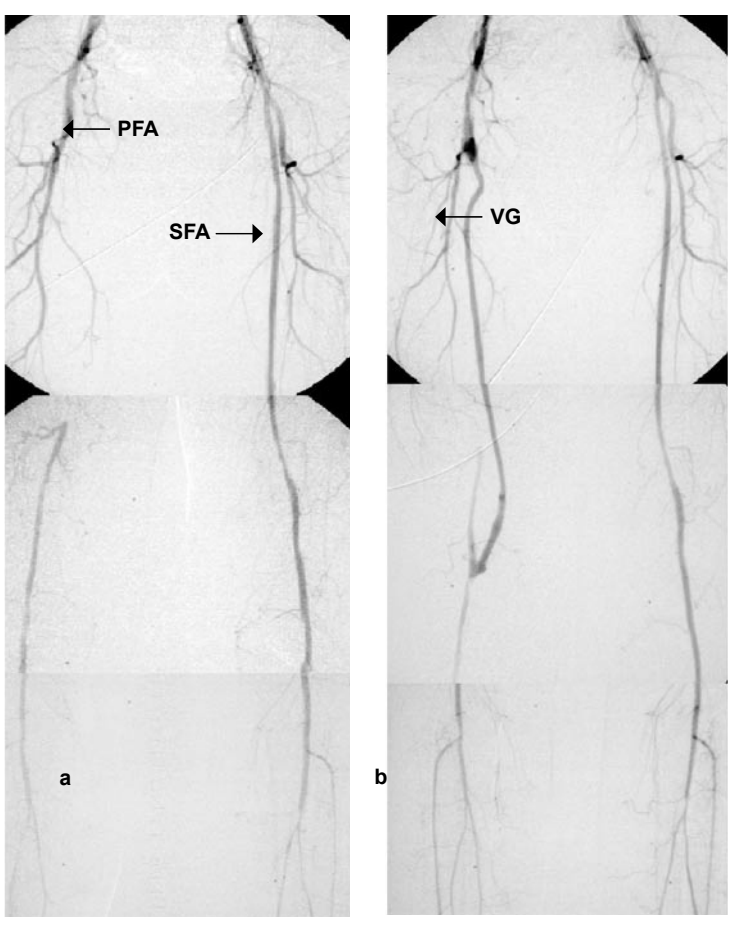
Lower limb surgery

Most patients presenting with lower limb ischaemia are elderly, often with concomitant medical disease. Early symptoms include intermittent claudication and leg ulcers, progressing to critical ischaemia (rest pain) or acute ischaemia (white leg) and gangrene. Patients commonly have widespread atherosclerosis involving coronary, cerebral and renal vasculature, and 10-year mortality in these patients is 45%, mainly as a result of coronary and cerebral events. Revascularization of the leg normally involves bypass of the diseased arterial segment with either synthetic tube grafts or vein. Figure 1 shows arteriograms before and after revascularization.

Medical treatment of lower limb ischaemia includes cessation of smoking, exercise programmes, aspirin and control of diabetes mellitus and hypertension. With these simple measures many patients with intermittent claudication improve spontaneously, but 20% of patients progress to critical ischaemia or gangrene within 6 years and require surgery. Smoking increases the risk of surgical intervention to 80% in 6 years.

Perioperative mortality for lower limb revascularization is 2–6%, increasing with age and more distal bypass surgery. Causes of death are cardiac complications, cerebrovascular accidents or multi-system failure in equal numbers. Morbidity is more common and includes myocardial ischaemia and infarction, and less often heart failure, respiratory and renal complications.



1 Angiograms before and after revascularization.
a Preoperative angiogram. The superficial femoral artery (SFA) is occluded at its origin, but reconstitutes in the mid-thigh region via collaterals from the profunda femoris artery (PFA).
b Postoperative angiogram showing reversed vein bypass graft (VG) between the common femoral and above-knee popliteal arteries.

Anaesthetic technique

Recent studies suggest that the mortality and cardiovascular morbidity of surgery is similar with a regional or general anaesthetic technique. Figure 2 shows the advantages and disadvantages of each technique. Prolonged surgery and potential harvesting of arm veins are important surgical factors in the choice of anaesthetic technique.

Advantages and disadvantages of general and regional anaesthesia

General

Advantages
- 100% reliable
- Cardiovascular control easier during surgery
- No patient discomfort during long procedures

Disadvantages
- Postoperative cardiovascular instability
- Unpredictable postoperative analgesic requirement
- Nausea and vomiting
- Hypercoagulable state postoperatively
- Respiratory complications

Regional

Advantages
- Patient self-monitors for cardiovascular and respiratory problems
- Vasodilatation improves graft blood flow and tissue perfusion
- Reduced stress response to surgery
- Good respiratory function and analgesia postoperatively
- Reduced incidence of deep vein thromboses

Disadvantages
- Technical difficulties in elderly population
- Vasodilatation and hypotension require careful fluid management
- Patient agitation if used alone for long procedures
- Risk of post-dural puncture headaches
- Rare neurological complications

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General anaesthesia: induction of anaesthesia is usually with an intravenous agent followed by a short-acting opioid, and a non-depolarizing muscle relaxant to facilitate intubation and ventilation. Maintenance is achieved with inhaled anaesthetic or intravenous infusions. For both induction and maintenance, care must be taken to administer appropriate doses of anaesthetic agents in elderly patients with poor cardiovascular reserve. Longer-acting opioids (e.g. morphine) may be used for analgesia during maintenance, the effects of which will continue into the postoperative period, but more commonly analgesia is achieved by the simultaneous use of a regional technique.

Regional anaesthesia: the sympathetic blockade associated with regional anaesthesia improves graft blood flow and reduces thrombotic tendency, and therefore may reduce the incidence of early graft failure. Aspirin, low molecular weight heparin (LMWH), and intravenous heparin during surgery all contribute to a theoretical increase in the risk of spinal haematomas with the use of regional anaesthesia in vascular patients. To minimize this risk, the following guidelines should be followed.
- Epidural catheters should only be sited or removed more than 12 hours after LMWH is administered.
- Intravenous heparin should not be given within 60 minutes of an epidural or spinal injection.
- Activated clotting time should be monitored during surgery.
- Appropriate neurological monitoring should be performed following surgery, usually in a high-dependency area.

Technical difficulties with regional techniques are common owing to degenerative disease of the spine. The level of epidural insertion is usually middle to high lumbar, depending on the proposed surgery. A test dose is given to detect subarachnoid or intravenous injection. Epidural regimens vary, but in the authors' unit 0.5% bupivacaine is used for regional anaesthesia alone, or 0.25% bupivacaine if combined with general anaesthesia. Postoperatively, low-concentration infusions are used (e.g. 0.1% bupivacaine) to minimize motor block while maintaining adequate analgesia and sympathetic blockade. Epidural opiates are not normally required for peripheral vascular surgery.

In this group of patients, cardiovascular compromise should be limited by:
- avoiding excessive preoperative dehydration
- aggressive fluid replacement
- appropriate depth of anaesthesia
- invasive monitoring
- gradual achievement of regional blockade
- the use of vasopressors when adequate intravenous volume is achieved.

Monitoring

In addition to standard monitoring, consider the following.

Cardiovascular: ECG using either a five-lead or CM_5 configuration is useful to detect rhythm and ST segment changes more reliably than a standard three-lead system. Invasive blood pressure measurement is normally used – a radial arterial line sited under local anaesthetic provides accurate monitoring during the potential cardiovascular instability of induction with minimum discomfort for the patient. A multi-lumen central venous catheter is often required, using either the internal jugular or subclavian veins. Patients with poor left ventricular function, poorly controlled heart failure, pulmonary oedema or severe valvular cardiac disease may require a pulmonary artery flotation catheter. Oesophageal Doppler monitoring can be used as an estimation of cardiac output in the absence of a pulmonary artery flotation catheter. In patients at high risk, transoesophageal echocardiography is useful for detecting ventricular segmental wall motion abnormalities during ischaemia or infarction.

Temperature: central temperature should be monitored and heat loss minimized by ensuring adequate theatre air temperature, a warming mattress under the patient, warming intravenous fluids and blood products, and using a circle breathing system to warm and humidify inspired gases. The use of forced-air warming blankets has facilitated the prevention of hypothermia but these devices should not be used over body areas with poor or absent arterial blood supply.

Renal: urine output is a valuable monitor of renal function, adequate renal perfusion and intravascular fluid status.

Haematology, blood gases and coagulation: the arterial catheter allows convenient access to sampling of blood for haemoglobin concentration, biochemical analysis, calcium, acid–base status and coagulation studies. Activated clotting time monitoring is easily performed in the operating theatre and, in patients with normal coagulation preoperatively, provides a useful measure of *in vivo* heparin activity during surgery. The activated clotting time should be maintained at about 200 seconds during arterial clamping, compared with a normal value of 70–110 seconds.

Intraoperative management

Vein harvesting: veins are harvested for graft formation from the same or contralateral leg, but previous venous surgery, such as varicose vein or coronary artery bypass surgery, may necessitate the harvest of arm veins. The operative arm should then be avoided for intravenous access and monitoring.

Anticoagulation: intravenous heparin is given before clamping of the arterial supply to the limb. Usually, 3000–5000 iu are required, and the effects monitored by activated clotting time. A degree of anticoagulation is beneficial postoperatively for graft patency, and therefore protamine is not normally required.

Reperfusion: during clamping, ischaemic vasodilatation occurs and, following clamp release, there is a drop in systemic vascular resistance, venous return and left ventricular end diastolic pressure. Lactic acid and anaerobic metabolites influx into the systemic circulation, causing hypotension, myocardial dysfunction, renal vasoconstriction and a metabolic acidosis. Reperfusion effects can be minimized by increasing fluid replacement before clamp release, keeping clamp time short, and sequential release of the profunda and superficial femoral arteries. Pharmacological correction of reperfusion effects may be required, including vasopressors and calcium.

Hyperaemia of the limb may continue for over 24 hours postoperatively and predisposes to the development of systemic inflammatory response syndrome and multi-system failure.

Fluid management: a balance must be achieved between normal to increased intravascular volume and fluid overload, left heart failure and pulmonary oedema. Continuous monitoring of central venous pressure, arterial blood pressure and urine output is therefore useful.

Crystalloid and colloid solutions should be administered early to replace preoperative dehydration and insidious blood loss. Haemoglobin estimation provides an indication of blood loss and haemodilution. A haemoglobin level of 10–12 g/dl provides a balance between adequate oxygen delivery to the tissues and reduction of viscosity to improve graft blood flow.

Amputation

Amputation may be a primary procedure for overwhelming sepsis or intractable pain, or secondary to failed revascularization procedures. Amputation represents a huge reduction in the quality of life for the patient and an increase in dependency on carers and the rehabilitation services, but may be the only option to offer some relief from pain.

The morbidity and mortality following amputation of the lower limb is high. Mortality rates range from a median survival of 2 years for unilateral below-knee amputation to 6 months for bilateral above-knee amputations.

Phantom limb pain: continuing perception of pain from the leg following amputation is common. Three-quarters of amputees experience some pain in the phantom limb within the first few weeks after surgery and, in about 10%, this persists in a severe form. The incidence is increased if chronic pain was present preoperatively, or severe pain occurred immediately before surgery (e.g. in trauma victims). Two small studies, involving 49 patients, have suggested a benefit from preoperative epidural anaesthesia in reducing the long-term incidence of phantom limb pain. The risks of epidural analgesia in this group of patients and logistical difficulties with providing preoperative epidurals preclude universal use of the technique. However, in patients at high risk of phantom limb pain, such as those with significant ischaemic pain preoperatively, early establishment of epidural analgesia should be considered.

Anaesthetic technique: patients requiring amputation often have multi-system disorders and require optimization preoperatively, and should be managed in a high-dependency area throughout the perioperative period.

The choice of anaesthetic technique is general, regional or selective nerve blockade. Unilateral spinal blocks provide excellent analgesia with minimal cardiovascular compromise.

A regional anaesthetic alone usually requires a degree of sedation to reduce the psychological stress from the noise of surgery. When general anaesthesia is used, this may be supplemented with an epidural, nerve or plexus block and/or opiates to provide analgesia into the postoperative period. If regional techniques are contraindicated, a perineural catheter may be placed during surgery directly into the sciatic nerve sheath (for above-knee amputations) or the anterior tibial nerve (for below-knee amputations). Postoperative perineural infusion of local anaesthetic (e.g. 0.5% bupivacaine, 3–5 ml/hour) may reduce opiate requirements.

Upper limb surgery

Thoracic outlet syndrome

Thoracic outlet syndrome is caused by compression of the subclavian vessels or brachial plexus between the clavicle, first rib and scalene muscles. Symptoms include severe pain and paraesthesia usually in the distribution of C8–T1, and occasionally muscle wasting and weakness. Surgery is indicated in 5% of patients. Techniques vary from partial to full resection of the first rib, scalenectomy, subclavian aneurysm repair and major vessel reconstruction.

Anaesthetic considerations: the potential for major blood loss is high, and blood should be cross-matched if arterial surgery is proposed, and invasive monitoring instituted. The non-operative arm is used for cannulation, induction of anaesthesia and invasive monitoring. Rib resection is painful postoperatively and opioid analgesia is usually required, often in the form of a patient-controlled analgesia system.

Thoracoscopic sympathectomy

Thoracoscopic sympathectomy is performed for palmar hyper-hidrosis. It involves gas insufflation into the pleural space and division of the cervical sympathetic chain between T2–T5.

Anaesthetic considerations: patients are usually young and fit, and may require only a baseline chest radiograph for preoperative investigations. The airway is maintained with an endobronchial tube to allow ventilation of one lung. After carbon dioxide insufflation of the pleural space by the surgeon, the thoracoscope is inserted to check lung deflation, and the insufflation pressure limit set to a maximum of 5 mm Hg. Excessive pressures or volumes can cause physiological changes consistent with a tension pneumothorax (i.e. hypotension, hypoxia, bradycardia). Immediate release of carbon dioxide volume from the chest cavity should reduce the intrathoracic pressure and re-establish cardiovascular stability.

Complications include cardiac arrhythmias (owing to the partial sympathetic denervation of the heart by division of the T2 to T4 fibres) and hypoxaemia due to one-lung ventilation and a large pulmonary shunt. Following nerve destruction, the lung is fully re-expanded under direct vision of the thoracoscope. A chest drain is not usually required, though a postoperative chest radiograph often reveals a small apical pneumothorax which usually resolves spontaneously. Pain may be severe following thoracoscopy and perceived as lower neck and back pain. Methods to alleviate pain include opiates, NSAIDs, which are effective for pleuritic pain, and intrapleural local anaesthetic.

Anaesthetic Techniques for Carotid Surgery

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Carotid endarterectomy is performed for patients with embolic or ischaemic symptoms (e.g. transient ischaemic attack, cerebrovascular accident or amaurosis fugax) who have 70% or more internal carotid artery stenosis. The fundamental problem is maintenance of cerebral oxygenation during carotid cross- clamping. The perioperative mortality rate from stroke and myocardial infarction approaches 5%, thus there is considerable interest in improving surgical and anaesthetic techniques to reduce this risk.

Regional or general anaesthesia may be used. A multi-centre, randomized, controlled comparison of general and local anaesthesia is under way in the UK (GALA (General Anaesthesia versus Local Anaesthesia) trial). Non-randomized studies have suggested that regional anaesthesia gives better cerebral perfusion monitoring and, perhaps, reduces cardiovascular, pulmonary and neurological complications. However, there are strong advocates for general anaesthesia the advantages of which include:

- a reduction in the cerebral metabolic rate for oxygen
- an increase in cerebral blood flow by isoflurane
- absolute control of the airway
- tight control of partial pressure of carbon dioxide in arterial blood
- patient comfort.

Cerebral perfusion monitoring

Techniques used for cerebral perfusion monitoring during general anaesthesia include:

- carotid artery stump pressure measurement
- EEG processing
- somatosensory evoked potential monitoring
- transcranial Doppler ultrasound of the middle cerebral artery (which gives audible indication of particulate embolization during dissection around the carotid artery)
- near infrared spectroscopy.

These techniques may be used to indicate which patients have inadequate collateral circulation. A shunt may then be used to bypass the internal carotid during cross-clamping. However, the poor sensitivity and specificity of these techniques mean that some surgeons use a shunt on all patients. Alternatively, blood pressure may be augmented pharmacologically to maintain cerebral perfusion.

Using regional anaesthesia, changes in speech, cerebration or motor power following carotid cross-clamping provide a more direct monitor of cerebral perfusion. The requirement for shunting is thereby reduced to 10%.

General anaesthetic techniques

The prerequisites for general anaesthetic techniques are maintenance of haemodynamic stability, reduction in cerebral oxygen consumption and rapid emergence to allow immediate postoperative neurological assessment. A conventional technique might include preoxygenation, intravenous induction with propofol or thiopental (thiopentone), supplemented by fentanyl, 2−5 μg/kg and neuromuscular relaxation to facilitate tracheal intubation and ventilation with a suitable gas mixture. Monitoring includes five-lead ECG, invasive and non-invasive arterial pressure, pulse oximetry, capnography, and the usual oxygen and pressure alarms. Central venous access is unnecessary − indeed inadvertent contralateral carotid puncture may lead to cancellation of the surgery.

Most anaesthetists control partial pressure of carbon dioxide in arterial blood and oxygenation with intermittent positive-pressure ventilation (IPPV). Spontaneous ventilation may cause hypercapnia, leading to an undesirable steal effect. The drawback of IPPV is the need for intubation and extubation, which may cause hypertensive crises. At extubation, the brain is no longer protected by the tight carotid stenosis against sudden increases in perfusion pressure. Remifentanil may be used to prevent such hypertensive crises, permitting intubation and ventilation without muscle relaxation and, when used in conjunction with superficial cervical block, allows rapid recovery with excellent postoperative analgesia. Another way of reducing this risk is to replace the tracheal tube with a laryngeal mask airway (LMA) before emergence. The LMA has been used as sole airway control during carotid endarterectomy, but cerebral blood flow is decreased by the LMA cuff. The significance of this in patients with carotid stenosis is unknown.

Regional anaesthetic techniques

Cervical epidural anaesthesia

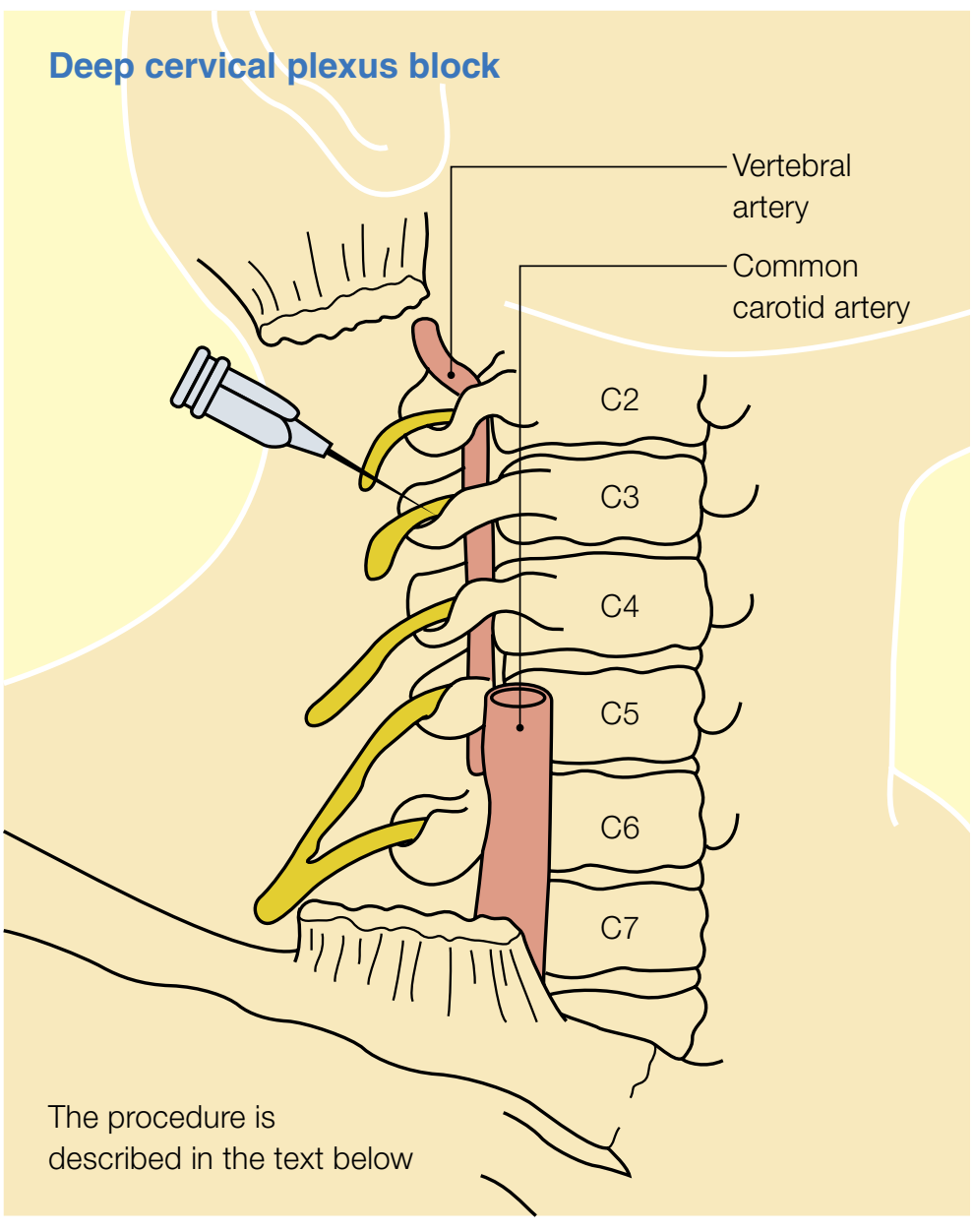
Cervical epidural anaesthesia is used infrequently in the UK and USA, though there are large case series reporting its simplicity and success, particularly in France. However, as all cervical and upper thoracic nerve roots bilaterally are affected, there is a high incidence of side-effects, including hypotension and bradycardia, respiratory failure, dural puncture and bloody tap.

Cervical plexus block

Cervical plexus block is easier to perform, affects unilateral nerve roots only and has fewer side-effects than epidural anaesthesia. Deep and/or superficial cervical plexus block is commonly used.

Deep block may be performed at C3 or C4 (Figure 1). The patient lies supine, slightly sitting up, with the head turned contralaterally. After skin disinfection, the cervical transverse processes are palpated 1 cm behind the posterior border of sternocleidomastoid. The third cervical transverse process is located by counting up from the sixth (Chassaignac's) tubercle at the level of the cricoid cartilage. After intradermal infiltration of 1% lidocaine (lignocaine), a 1" 25 G needle is introduced at C3 perpendicular to the skin, but aiming slightly caudad to avoid intrathecal injection. The transverse process is located 1−2 cm under the skin.

The patient may report paraesthesia in the distribution of the cervical plexus. 0.375% bupivacaine, up to 20 ml, is then injected after careful aspiration by a second operator,



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Superficial block is a simpler technique. With the patient similarly positioned, an intradermal 'bleb' of 1% lidocaine (lignocaine) is raised at the midpoint of the posterior border of the sternocleidomastoid. 0.375% bupivacaine, 10−20 ml, is injected in the subcutaneous plane along the posterior body of the sternocleidomastoid in cranial and caudal directions from this point.

Complications

Deep block is more difficult to perform than superficial block and may have more serious complications, though it is more reliable and gives better postoperative analgesia. Serious potential complications include:

- intravascular injection producing immediate unconsciousness or seizures
- subarachnoid injection producing total spinal anaesthesia
- phrenic nerve palsy.

Phrenic nerve palsy occurs in 60% of deep block recipients, but is tolerated well, except in patients with underlying respiratory disease, who should receive superficial block alone.

Other potential side-effects of cervical plexus block include local haematoma, hoarseness, dysphagia, stellate ganglion block and Horner's syndrome. Aspiration of blood during placement of cervical plexus blocks is common, occurring in up to 30% of patients. Frequent aspiration is therefore vital to avoid intravascular injection of local anaesthetic, which may cause immediate epileptic seizure.

Regional techniques for carotid endarterectomy are seldom perfect. In some patients, the carotid disease extends so high that the incision needs to be extended into tissues innervated by cranial nerves. Additionally, despite apparently having good surgical anaesthesia, patients sometimes complain of pain from the carotid sheath. This may reflect sympathetic afferent carotid innervation. Half the patients will require local anaesthetic supplementation, which is not a failure of the technique. Patients occasionally complain of pain referred to the jaw, molar teeth or the ear, which may be relieved by moving the surgical retractor, by local anaesthetic supplementation or by mandibular nerve block.

Sedation A target-controlled infusion of propofol, 0.2−2 μg/ml provides reversible, predictable sedation during block placement and dissection to enhance patient cooperation. During carotid cross- clamping, constant neurological assessment is vital, therefore sedation must be minimal at this stage.

If the patient complains of pain, sedation is no substitute for augmentation of the block by the surgeon with supplemental local anaesthetic.

Perioperative management

Oxygen is administered via a standard face mask. Monitoring consists of five-lead ECG, invasive arterial pressure measured from the contralateral radial artery, non-invasive blood pressure cuff, pulse oximetry and capnography, estimated by sampling within the oxygen face mask.

The patient's head must be readily accessible. Verbal communication and grip strength are tested before block placement and regularly throughout the operation, particularly following carotid cross-clamping. Slurring of speech, altered grip strength or an alteration in conscious level are indicators for shunt insertion to maintain ipsilateral carotid flow.

The patient's normal cardiovascular medications are administered on the morning of surgery to help maintain haemodynamic stability. Blood pressure is maintained within 20% of awake values, provided absolute systolic values are 120−180 mm Hg. Ephedrine, phenylephrine, metaraminol, labetalol and intravenous nitrates should all be available for close haemodynamic control as appropriate. Significant blood loss is uncommon, therefore minimal fluids are administered to avoid the problem of a patient needing to void during surgery.

Postoperative problems

Haemodynamic complications such as hypertension, hypotension, arrhythmias and myocardial ischaemia are common, therefore invasive arterial pressure and ECG monitoring are continued in recovery. Analgesia is not usually required following regional anaesthesia, however, patients recovering from general anaesthesia without regional block may require small doses of morphine titrated against their pain. If patients are haemodynamically stable after 4 hours, they are discharged to the ward. There is some evidence that patients who develop neurological dysfunction after cross-clamping are at greater risk of permanent postoperative deficit. These patients may benefit from closer observation on a high-dependency unit.

Compromise of the airway as a result of oedema or haematoma is not uncommon. Wounds are observed carefully for signs of swelling and, if required, opened in recovery and explored immediately in the operating theatre. This may be done without additional local anaesthetic supplementation following a regional technique. Neurological deficit developing postoperatively requires immediate surgical consultation because it may indicate developing cerebral ischaemia due to haemorrhage, embolus or obstruction to blood flow.

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Blood Groups, Cross-matching and Haemovigilance

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Blood groups

RBCs have antigens on their surface, the most important of which are the carbohydrate 'ABO' type antigens (Figure 1). The next most important antigen class is the Rhesus polypeptide type (antigen present = Rh positive). There are over 50 Rhesus antigen types but five (D, C, E, c, e) are involved in 99% of Rh-system antibody–antigen reactions. Of these five, the Rh(D) antigen is the most important. Rh(D) matching of donor and recipient is important but is essential if the recipient is:

- an Rh(D) negative woman who may have had prior Rh(D) exposure during pregnancy and childbirth
- an Rh(D) negative woman in the reproductive years who may subsequently be exposed to Rh(D) antigens during pregnancy and childbirth
- Rh(D) negative but may have been exposed to Rh(D) antigen in previous transfusion episodes
- young and may therefore be exposed to future transfusion episodes.

There are over 200 other non-ABO/Rh antigens, and they are often classified as either common (e.g. Kell, Duffy, Kidd) or uncommon (e.g. Diego, Lutheran, Y1). Antibody reactions to most of the non-ABO/Rh antigens, though rare, can cause both immediate and delayed haemolytic transfusion reactions.

Typically about 70% of unmatched RBC transfusions are compatible purely by chance. Statistically, about 30% of unmatched transfusions are incompatible and then as little as 10 ml of incompatible blood may trigger a serious haemolytic reaction involving intravascular destruction of RBCs, activation of coagulation and inflammatory cascades and disseminated intravascular coagulation. This is fatal in 10% of cases.

ABO blood groups defined by RBC antigens and plasma antibodies

Blood group	UK population (approximate %)	RBC antigens (ABO)	Plasma antibodies (ABO type)	Can donate RBCs to	Can receive RBCs from
A	42	A	Anti-B (IgM)	A or AB	A or O
B	9	B	Anti-A (IgM)	B or AB	B or O
AB	3	A + B	None	AB	Any
O	46	None	Anti-A (IgG) Anti-B (IgG)	Any	O

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Cross-matching and screening

ABO typing is determined *in vitro* with direct agglutination of RBCs with anti-A and anti-B reagents. Rh(D) grouping is determined routinely as is an antibody screen against the common non-ABO RBC antigens (incidence is 0.3% in donor population). The incidence of uncommon non-ABO antigens is less than 0.01% and screening for them is not performed routinely. Cross-matching requires incubation of recipient and donor blood *in vitro* to check for potential reactions not predicted by the ABO grouping and antibody screen. This takes about 45 minutes and is responsible for a significant proportion of the delay between the blood sample arriving in the transfusion laboratory and the issue of the cross-matched blood. Where blood is required in an extreme emergency non-cross-matched but group-specific blood may be issued. There is obviously a risk that an important Rh or non-ABO incompatibility may result but this has to be weighed against the clinical urgency of the recipient's situation. In some cases, such as massive haemorrhage where the victim is in extremis, or during major incidents involving multiple casualties, it may be appropriate to start the resuscitation using Group O Rh(D) negative blood. However, full group testing and compatibility matching should be achieved whenever possible, minimizing the antigen exposure of the recipient and conserving this valuable resource for real need.

Donated blood is screened for a number of pathogens that may be responsible for transfusion transmitted infection (TTI). Confidential screening questions are used to detect and defer potential blood donors who have 'at risk' behaviour patterns. There is an understandable trend to introduce more and more sensitive screening tests to further improve the detection of these pathogens but with the risk of TTI already so low (< 1/500,000 transfusion episodes), there is not likely to be a great improvement in safety. However, the cost of blood products has increased substantially as a result.

Haemovigilance

The true incidence of complications of transfusion and the frequency and nature of human and systematic errors can only be derived from a national haemovigilance system. In the UK, Serious Hazards of Transfusion (SHOT) was launched as a voluntary reporting scheme run by healthcare professionals in 1996 and has produced an annual report every year. Over 80% of UK hospitals have taken part, accounting for about 90% of all the blood product usage during the period (about 3 million individual blood products per year). All suspected or definite transfusion-related errors or complications are collated, followed up and reported by the SHOT team. Successive reports have highlighted the importance of human error resulting in incorrect blood component transfused as the most common serious hazard of transfusion (more than 50% of all SHOT events and accounting for four deaths between 1996 and 1999). Inadequate labelling of cross-match sample tubes and deviation from mandatory recipient identity checks are factors. These accidents typically occur in the context of other clinical pressures such as haemodynamic instability of the transfusion recipient. However, urgency of the need for the transfusion is no excuse for reduction in the care of the identity checks.

Figure 2 shows the importance of transfusion errors and the relatively low importance of TTI. The incidence of transfusion- related acute lung injury (TRALI) was higher than would have been predicted before SHOT and has been shown to be associated with serious morbidity (i.e. almost 100% associated with ICU admission and ventilation) and significant mortality (about 25%). TRALI is distinct from other causes of respiratory distress such as trauma, cardiac dysfunction and volume overload. It is thought to result from interaction between antigranulocyte antibodies in the transfused product with corresponding antigens in the recipient, leading to neutrophil aggregation and trapping in the lungs with complement activation and other inflammatory mechanisms setting up severe acute lung injury. This is usually in the context of another event such as hypoxia, massive transfusion, major surgery, infection and inflammation or cytokine therapy. Cases of TRALI may be unrecognized and some non-specific pulmonary complications may be wrongly attributed to TRALI, but careful investigation of suspected cases clarifies the situation. Follow-up by the transfusion service is extremely important, because it may be necessary to defer donors found to have been the source of the antigranulocyte antibodies in confirmed TRALI episodes.

Blood is a limited resource and transfusion carries significant risk. Therefore every clinical decision concerning blood transfusion must consider whether the benefit of transfusion outweighs the risk of complications and the costs involved. A number of strategies have been described to safely reduce the frequency of blood transfusion. The simplest is the strict application of indications for transfusion of blood or products. It is generally accepted that RBC transfusion is not indicated when the haemoglobin concentration is above 8 g/dl, provided that the patient is not actively bleeding, is adequately volume resuscitated and is otherwise stable. Dependence on donor blood can be reduced or eliminated by collection of the patient's own blood before or during surgery in one of the following ways.

- Autologous predeposit, which requires strict planning well before scheduled surgery.
- Normovolaemic haemodilution where blood is collected at the start of surgery with appropriate volume replacement and returned later in place of, or in addition to, donor blood.
- Intra-operative blood salvage where shed blood may be salvaged from the operating field, filtered and centrifuged to remove debris and suspended in heparinized saline for re-infusion.

Artificial oxygen carrying blood substitutes show promise but have enjoyed little clinical application. There is no substitute for careful surgical technique that avoids unnecessary blood loss.

Summary of incidents reported to SHOT from 1996 to 1999

	1996/97	1997/98	1998/99
Incorrect blood component transfused (IBCT)	81	121	144
Acute transfusion reaction (ATR)	27	30	34
Delayed transfusion reaction (DTR)	27	27	34
Post-transfusion purpura (PTP)	11	13	10
Transfusion-associated graft versus host disease (TA-GVHD)	4	4	3
Transfusion-related acute lung injury (TRALI)	11	16	16
Transfusion-transmitted infection (TTI)	8	4	7
Unclassified	7		
Total	169	215	252

All data taken from Table 2 of the Serious Hazards of Transfusion (SHOT) Report for 1998–1999. http// www.shot.demon.co.uk

■ Most important transfusion-related complications.

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Coagulopathies

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Haemostasis

Disorders of haemostasis may be congenital or acquired (including drug treatment aimed at inhibiting normal coagulation), and may involve platelets, clotting factors or both.

Congenital platelet disorders
Inherited platelet disorders are uncommon. Von Willebrand's disease is the most common hereditary bleeding disorder in humans (incidence > 1/10,000). It is caused by the defective production of von Willebrand factor, which is required for platelet adhesion and as a vehicle for factor VIII transport (there is no primary platelet defect). Blood products are seldom required for treatment and levels of von Willebrand factor may be increased to normal in the more common autosomal dominant variant with preoperative 1-deamino-8-D-arginine vasopressin (DDAVP). The severe autosomal recessive variant may require treatment with purified plasma products under haematological guidance.

Congenital factor deficiencies
Haemophilia A is caused by a deficiency of factor VIII (incidence 10/100,000) and haemophilia B (Christmas disease) by a deficiency of factor IX (incidence 2/100,000). Both are X-linked recessive, and can be classified as mild, moderate or severe. Treatment in the past has been based on purified, pooled plasma factors, exposing patients to blood-borne viruses (e.g. hepatitis C, human immunodeficiency virus). Perioperative management is aimed at increasing factor levels to 50% of normal for minor procedures and 100% of normal for major operations. In the milder form, this may be achieved with DDAVP, but moderate and severe variants and/or major surgery require synthetic factor concentrates.

Haemophilia C is a deficiency of factor XI (autosomal dominant or recessive) and is common in Ashkenazi Jews (5%). Factor XI concentrate may be required, but often fresh frozen plasma is adequate. There are many other rare congenital factor deficiencies, but they are beyond the scope of this review.

Acquired platelet disorders
Dysfunction: the most common cause of platelet dysfunction is the use of non-steroidal anti-inflammatory drugs (NSAIDs). The subsequent reduction in platelet thromboxane A_2 reduces platelet activation and aggregation. Systemic conditions such as renal or liver failure may alter the biochemical environment sufficiently to affect normal platelet function.

Thrombocytopenia is defined as a platelet count below 150 x 10^9/litre. There may be excessive consumption of platelets (owing to tissue injury or platelet activation), dilution caused by massive transfusion, reduced production from bone marrow, or increased destruction in the spleen. Pregnancy commonly induces thrombocytopenia (Figure 1). Extracorporeal circuits for cardiopulmonary bypass activate platelets and retain them within the circuit – others are damaged by the mechanical nature of the circuit and are removed from the circulation by the spleen.

There are many autoimmune thrombocytopenias; they may be primary (idiopathic) or secondary (Figure 1). Treatment involves immunosuppression and often splenectomy.

Prolonged heparin administration can lead to heparin-induced thrombocytopenia. An antibody to platelet factor 4 is formed after 5–10 days of heparin therapy. It precipitates platelet aggregation, leading to widespread thrombosis and a fall in the platelet count. Thrombus formation in large vessels may render limbs ischaemic and carry the risk of amputation. Heparin-induced thrombocytopenia may recur on subsequent exposure to heparin. Treatment includes the immediate cessation of heparin and continued anticoagulation with hirudin or danaparoid while warfarin is commenced.

Secondary thrombocytopenias

Autoimmune
Malignancy
- Carcinoma
- Non-Hodgkin's lymphoma
- Chronic lymphocytic leukaemia

Immunosuppressive
- Human immunodeficiency virus
- Radiotherapy
- Chemotherapy
- Transplantation

Systemic autoimmune diseases
- Thyroid
- Systemic lupus erythematosus

Pregnancy
- Benign gestational thrombocytopenia
- Pre-eclampsia
- HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome
- Disseminated intravascular coagulation
- Autoimmune (as above)

1

Acquired factor disorders
Drugs: heparin binds to antithrombin III, markedly accelerating the rate of inactivation of factors IIa (thrombin), VIIa, Xa, IXa and XIa. Warfarin inhibits vitamin K-epoxide reductase, reducing the carboxylation (and therefore activation) of factors II, VII, IX and X.

Consumption: disseminated intravascular coagulation (DIC) is the most common consumptive coagulopathy. It results in the formation of multiple thrombi throughout the vascular tree. Usually an underlying condition (Figure 2) triggers uncontrolled coagulation, overwhelming the normal mechanisms of clot localization. This may be from acute or chronic (prolonged) stimulation of the coagulation system, which consumes and depletes the factors controlling normal coagulation. In addition to thrombocytopenia, excessive fibrinolysis causes hypofibrinogenaemia, elevating levels of fibrin degradation products and D-dimers. Fibrin degradation products have anticoagulant properties in high concentrations and inhibit the normal cross-linking of fibrin monomers, as well as platelet aggregation.

Therapies involve treating the precipitating disease process and haematological support with blood products. Further measures have been advocated, and include antithrombin III and protein C concentrate, prostacyclin, heparin and aprotinin.

Aetiology of disseminated intravascular coagulation

Pregnancy
- Pre-eclampsia
- Placental abruption
- Placenta praevia
- Septic abortion
- Amniotic fluid embolus

Infection
- Systemic sepsis
- Viraemia
- Protozoa

Shock
- Trauma
- Burns

Malignancy
- Haematological
- Metastatic

Extracorporeal circulation

Liver disease

Transplantation

2

Dilution: massive transfusion of crystalloid, colloid or stored blood dilutes endogenous coagulation factors. Packed RBCs have little plasma and few functional platelets, and about 60 ml of every unit of blood is anticoagulant citrate solution.

Liver disease: most of the clotting factors (except factor VIII) are synthesized in the liver, as are the anticoagulants antithrombin III, proteins C and S and plasminogen. The liver also clears activated clotting factors and fibrin degradation products. Therefore, liver disease causes significant disruption to the normal clotting pathways.

Vitamin K deficiency leads to the abnormal synthesis of factors II, VII, IX, and X, as well as proteins C and S. Vitamin K is present in leafy vegetables, and absorption requires the presence of bile salts in the jejunum. Deficiency occurs with malabsorption syndromes, biliary and gastrointestinal obstruction, and liver and pancreatic insufficiency.

Extracorporeal blood circulation: cardiopulmonary bypass, renal dialysis and intraoperative cell salvage lead to dilution of clotting components and expose platelets to a large surface area of inert material. Platelet activation occurs and some are consumed (see thrombocytopenia above).

Prothrombotic states

There are many underlying causes of hypercoagulable states in addition to those related to lifestyle (obesity, smoking, immobility).

Genetic causes include deficiencies of endogenous anti-coagulants such as antithrombin III and proteins C and S, and the presence of abnormal factor V (factor V Leiden). All predispose to venous thromboembolism. Hyperhomocysteinaemia has been linked to arterial thrombosis.

Acquired causes include the synthetic female hormones in oral contraceptive and hormone replacement preparations which predispose to a prothrombotic state. Malignancy and polycythaemia are implicated in venous thromboembolism, as is perioperative immobility.

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Management of Vascular Emergencies

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Patients usually have emergency vascular surgery because of acute arterial bleeding, acute arterial occlusion or trauma.

Ruptured abdominal aneurysm repair

Presentation and diagnosis
Emergency repair of an abdominal aortic aneurysm is performed either because bleeding has occurred from the aneurysm (ruptured or leaking aneurysm) or because the aneurysm has become acutely painful and tender and there is considered to be a high risk of rupture (symptomatic aneurysm).

Ruptured aneurysm usually occurs in patients older than 60 years and is more common in men. Many patients die before reaching hospital, and of those who reach hospital typically 50% survive.

Classically, the patient presents with abdominal or lower back pain associated with shock or collapse and a pulsatile abdominal mass. However, the presentation may be atypical. An abdominal ultrasound scan can show if the patient has an abdominal aneurysm but cannot reliably tell if the patient has bled from it. Without surgery, death is inevitable, so repair of a ruptured aneurysm is attempted in most cases.

Preoperative assessment and preparation for surgery
Once the diagnosis and decision to operate have been made, the patient should be transferred immediately to the operating room. Catastrophic further haemorrhage may occur at any moment and there is no place for prolonged resuscitation or investigation in the accident and emergency department or for the use of an anaesthetic induction room.

When faced with a shocked, hypotensive patient, the natural instinct is to give large amounts of intravenous fluid rapidly to correct the hypovolaemic state. However, after initial bleeding from the aneurysm, clot formation together with retroperitoneal tamponade and hypotension may limit further bleeding. Fluid resuscitation before aortic cross-clamping may raise blood pressure, dislodge clot and result in further haemorrhage. The authors' practice is not usually to give intravenous fluid before induction of anaesthesia. Fluids are reserved for the patient showing signs of myocardial or cerebral ischaemia. In these patients, urgent cross-clamping of the aorta is required.

Oxygen should be given by face mask and two large intravenous cannulae (14 G) should be inserted. Blood samples should be taken for blood grouping and antibody screening, a full blood count, coagulation screening, urea and electrolyte assessment and a blood glucose test. 10 units of blood; plus fresh frozen plasma and platelets should be requested urgently.

A brief history should be taken from the patient or the relatives, asking about previous health, current medications and allergies. A brief examination should take place with particular regard to heart rate, blood pressure, peripheral perfusion and conscious level. The blood pressure may differ between the arms (usually because of subclavian artery stenosis) and the higher pressure should be regarded as being correct. Assess the airway, noting the presence of dentures and any likely difficulty in tracheal intubation. Surgery should not be delayed to wait for the result of blood tests. While an ECG and chest radiograph are useful investigations, surgery should not be delayed significantly to get them, and on no account should the patient be transferred to the radiography department.

Preparation for anaesthesia
Satisfactory management of a patient with a ruptured aneurysm requires two anaesthetists. Anaesthesia should be induced in the operating room with the abdomen already disinfected and draped and the surgeons ready to begin. Before induction, the patient is connected to the ECG, non-invasive blood pressure monitoring and oxygen saturation monitors. Both blood and clear fluids should be connected to the patient via large-bore cannulae using a pressure-infusion and warming system. If no grouped blood is available, group O blood may be used.

Drugs (including vasopressors) should be prepared. The suggested drugs are listed in Figure 1.

Invasive arterial pressure monitoring during induction is useful but surgery should not be delayed by prolonged attempts at arterial cannulation. It is not necessary to insert a central venous catheter before induction unless a large peripheral intravenous cannula cannot be inserted. In that case, a large-gauge central line should be used. Place one or both arms out on arm boards to permit access to intravenous and arterial cannulae. A urethral catheter is usually inserted.

Suggested drugs to draw up for anaesthesia in a patient with ruptured anaeurysm

- Etomidate, 20 mg
- Suxamethonium, 100 mg
- Fentanyl, 500 μg
- Muscle relaxant (e.g. atracurium, 50 mg)
- Ephedrine, 30 mg in 10 ml
- Methoxamine, 20 mg in 10 ml
- Adrenaline (epinephrine) 1:100 000, 10 ml
- Atropine, 0.6 mg
- Calcium gluconate, 10% 10 ml
- Glyceryl trinitrate infusion, 1 mg/ml in a 50 ml syringe
- Adrenaline (epinephrine) infusion, 3 mg in a 50 ml syringe

1

Induction of anaesthesia
A rapid sequence induction is used; etomidate and suxamethonium are suitable agents. Surgery may start as soon as the patient is anaesthetized. A non-depolarizing relaxant should be given after intubation.

At induction, there is a reduction in sympathetic drive and circulating catecholamines. Anaesthetic drugs may cause vasodilatation and myocardial depression. Positive-pressure ventilation causes reduced venous return and muscle relaxation may result in a reduction in tamponade and further haemorrhage. These factors combined may produce a catastrophic drop in blood pressure, which can lead to cardiac arrest. If blood pressure is not being monitored invasively, some indication of changes in blood pressure and of cardiac output may be given by an assistant with a finger on a pulse and by observing the pulse oximeter and capnography waveforms.

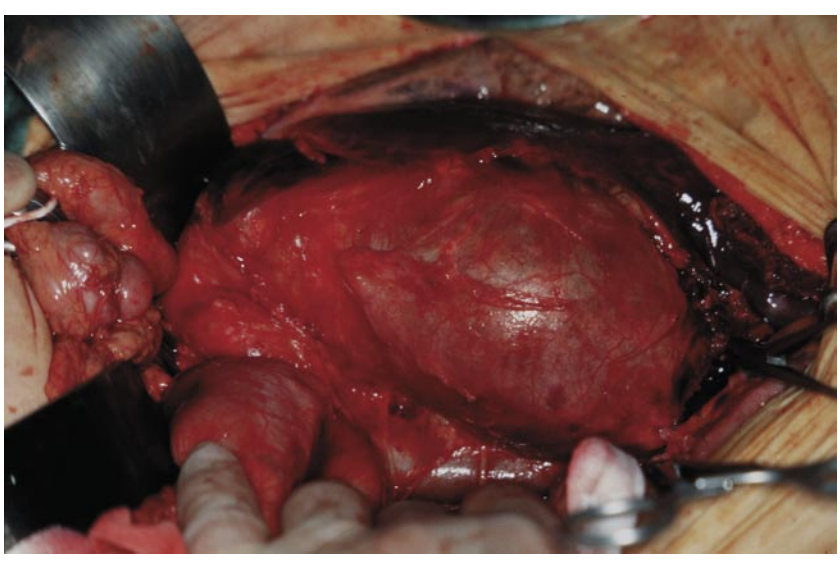
It is essential to be able to prevent or treat an excessive fall in blood pressure on induction by infusing fluids rapidly and giving pressor agents. It is important to give both RBCs and clear fluids or a severe dilutional anaemia may rapidly occur. Rapidly infused blood can produce a dangerous temporary hyperkalaemia. If this is suspected, intravenous calcium should be given. Remember that vigorous ventilation of the lungs reduces venous return. Head-down tilt may help raise blood pressure. Before clamping the aorta, however, the aim should be to prevent severe hypotension that might lead to cardiac arrest or cardiac or cerebral ischaemia – not to restore normal blood pressure. On the other hand, laryngoscopy and surgery may result in hypertension with the risk of further bleeding and myocardial ischaemia. To attenuate this response, an opioid such as fentanyl or alfentanil should be given before induction unless the patient is moribund or already drowsy because of previous opioids.

Conduct of anaesthesia following induction
Anaesthesia may be maintained with a volatile agent or a propofol infusion. Nitrous oxide should be avoided because it causes bowel distension and may contribute to postoperative raised intra-abdominal pressure. Morphine is best avoided because postoperative renal impairment is common and accumulation of morphine metabolites may occur. Boluses of fentanyl or an alfentanil infusion can be used. Adequate muscle relaxation should be maintained.

The surgeon will dissect and cross-clamp the (usually infra-renal) neck of the aneurysm (Figure 2). There is a risk of tearing the left renal vein or its tributaries during the dissection and the resulting venous bleeding may be impossible to control. After clamping the aneurysm neck, the iliac arteries are clamped. Intravenous heparin is not usually given.

Cross-clamping may cause the patient to become hypertensive and this may be treated by deepening anaesthesia and or by infusing glyceryl trinitrate. The latter should also be used if signs of cardiac ischaemia develop and the blood pressure is normal or raised. After the aorta is cross-clamped, the following should be inserted:

- a central venous catheter (and/or a PA catheter)
- an arterial cannula (if not already in place)
- a nasogastric tube
- a temperature probe.



2 A large ruptured abdominal aortic aneurysm. The patient's head is to the left of the picture. The aneurysm had ruptured posteriorly and to the patient's left (top of picture). The aortic clamp is on the left of the picture and two iliac clamps on the right. Blood clot is seen around the left side of the aneurysm at the top of the picture.

Cardiovascular goals and fluid management
After aortic clamping, the aim is to maintain blood pressure and central venous pressure close to normal levels. Haemoglobin, arterial gases and plasma electrolyte levels should be measured, preferably by near-patient analysers situated in or close to the operating room. Haemoglobin should be maintained above 80 g/litre (90 g/litre in patients with cardiac disease).

Coagulopathy is usually present. After cross-clamping, fresh frozen plasma and platelets should be given. It is not practical to wait for laboratory coagulation results at this stage. Further blood product administration should be guided by laboratory results and clinical assessment of bleeding. Ideally, near-patient coagulation testing should be available in the operating room.

Renal function
Patients undergoing emergency aortic surgery are at risk of renal failure because of haemorrhagic shock, aortic cross-clamping, trauma or emboli to the renal arteries and postoperative hypotension and low cardiac output. The risk of renal failure may be reduced by minimizing the duration of any period of supra-renal aortic clamping; avoiding hypotension and a low cardiac output during and after surgery; and avoiding the use of nephrotoxic drugs (e.g. NSAIDs). There is no convincing evidence that mannitol, frusemide or dopamine preserve renal function. Sometimes an infusion of an inotrope is required to maintain an acceptable blood pressure level during or after surgery but it is important to correct hypovolaemia, if present, and to remember that inotropes may cause myocardial ischaemia.

Temperature maintenance
Hypothermia is associated with impaired coagulation and increased blood loss, postoperative vasoconstriction and myocardial ischaemia, and more infections. However, warming ischaemic lower limbs is harmful. The chest, upper limbs and head should be warmed (e.g. by forced-air warming), and intravenous fluids should be warmed.

Clamp release and completion of surgery
When the iliac artery clamps are released, reperfusing the pelvis and lower limbs, hypotension and myocardial depression occur. This results from the refilling of empty dilated vessels, anastomotic blood loss, myocardial depression secondary to the release of metabolites from the ischaemic limbs and pelvis, and pulmonary hypertension caused by microemboli. The surgeon should warn the anaesthetist that the clamps are about to be released. In anticipation of release, the patient should be well filled with fluid (central venous pressure of at least 10 mm Hg). Any vasodilator such as glyceryl trinitrate should be discontinued a few minutes before unclamping. Suitable vasopressors (e.g. ephedrine) should be immediately to hand. Each leg should be reperfused in turn. Significant hypotension should be treated with fluid and or vasopressors. It may be necessary for the surgeon to reclamp or manually compress the artery if the fall in blood pressure is excessive. The filling pressure of the heart should be watched closely. A rising filling pressure in the face of falling blood pressure indicates myocardial dysfunction, which may require the use of an inotrope.

It is usual for a rise in end tidal carbon dioxide, a transient fall in oxygen saturation and a metabolic acidosis to occur following clamp release. Minute ventilation may be increased provided that the patient is not unduly hypotensive. If there is no drop in blood pressure following clamp release, the reason may be that the leg has not been reperfused because there is thrombus or embolus present. Reperfusion also results in lung injury.

The patient should be transferred to the ICU after surgery and ventilation continued until he is warm and normovolaemic, metabolic acidosis has resolved, and pulmonary gas exchange is satisfactory. Although postoperative complications are common, typically 50% or more of the patients undergoing surgical repair of a ruptured abdominal aortic aneurysm will be discharged from hospital alive and their long-term survival and quality of life is little different from that of an age- and sex-matched control population.

Symptomatic non-ruptured aneurysm

A symptomatic but non-ruptured aneurysm can be difficult to distinguish from a small contained rupture (which may bleed further at any moment). The anaesthetist can consider managing the anaesthetic as for an elective abdominal aortic aneurysm repair if the patient has not been hypotensive at any time, has not suffered an episode of collapse or blackout, has no signs of shock (including no otherwise unexplained tachycardia) and the surgeon thinks it unlikely that a contained rupture has already occurred. Otherwise, the patient should be treated as having a ruptured aneurysm.

Acute limb ischaemia

Acute limb ischaemia typically presents with pain, pallor, pulselessness, paraesthesia and paralysis. It may be caused by thrombosis, usually in patients with pre-existing peripheral vascular disease, or by embolism – most commonly from the heart (e.g. as the result of atrial fibrillation). Ischaemia thought to be caused by thrombosis may be treated by the administration of a thrombolytic agent directly into the affected artery and/or by surgical reconstruction. Embolic occlusion of an artery is treated surgically using a Fogarty balloon embolectomy catheter.

Anaesthesia for acute lower limb ischaemia

Embolectomy may be performed under infiltration with local anaesthesia. However, the patients are usually frail and elderly and an anaesthetist should oversee monitoring and any sedation that is required. A low dose propofol infusion is suitable for sedation, being easily titratable and not resulting in prolonged drowsiness after surgey.

If embolectomy or thrombolysis is unsuccessful, a bypass graft may be required. If muscle damage has occurred, fasciotomies may be performed to prevent compartment syndrome. Amputation is sometimes necessary. General or regional anaesthesia may be used for these procedures. However, spinal and epidural analgesia are contraindicated if a thrombolytic agent has been given before surgery or is likely to be given intra-operatively, and are usually avoided if anticoagulant administration has resulted in an international normalized ratio (INR) above 1.5 or an activated partial thromboplastin time more than 1.5 times normal at the time of surgery.

Anaesthesia for acute upper limb ischaemia

Acute ischaemia of the upper limb is less common than acute ischaemia of the lower limb. It occurs more often in women than in men and is often the result of embolism. Embolectomy may be carried out following local infiltration of anaesthetic. Alternatively, a brachial plexus block or general anaesthesia may be used.

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Postoperative Care and Pain Relief in Vascular Surgery

L D Caldicott

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Postoperative care of vascular surgical patients involves the same principles as the care of any surgical patient and includes:
- oxygenation
- maintenance of a stable cardiovascular system
- fluid balance and urine output
- pain relief
- deciding on the appropriate level of postoperative care.

Many vascular operations are prolonged and may involve large blood losses. When combined with the generally poor medical condition of the average vascular patient, this predisposes to a high rate of postoperative complications. Meticulous attention to detail in the postoperative management of surgical patients can help to avoid the slow decline in which one complication follows another leading to admission to ICU, multi-organ failure and death.

Specific problems

Postoperative myocardial infarction (MI) is the greatest cause of death after vascular surgery and occurs in 2–5% of patients. It has a number of clinical features.
- Mortality is 50–75%
- It occurs on day 1–3 postoperatively.
- Presentation is often 'silent' due to opioid administration, diabetes and altered perioperative pain thresholds.
- It presents as low blood pressure, heart failure, sudden death, unstable angina or ventricular arrhythmia.
- It can be diagnosed clinically by sequential ECGs, and measurement of myocardial bound creatine kinase and cardiac troponin 1 levels.
- Treatment is as for MI in medical patients except that thrombolysis cannot be used.

Possible explanations for the occurrence of MI in the postoperative period include:
- increased myocardial oxygen demand perioperatively
- increased coagulability of blood postoperatively
- hypoxaemia at night and with opiates.

Thrombosis: most vascular patients are hypercoagulable and the coagulability of the blood increases postoperatively. Prevention of deep vein thrombosis (DVT) and graft occlusion is important. Standard regimens of low molecular weight heparin and thromboembolic disease stockings, when appropriate, should be used, but despite their use an incidence of DVT after vascular surgery of 3–8% has been reported. Conversely, patients being treated with aspirin and heparin may suffer postoperative bleeding at the site of surgery.

Compartment syndrome: restoration of blood flow to ischaemic tissue can cause oedema, release of free radicals and rhabdomyolysis. If the swelling occurs in tight fascial compartments, the pressure can rise to such an extent that capillary blood flow is stopped. Subsequently, muscle cell death releases myoglobin and creatine kinase. Clinically, the limb is extremely tender and the urine is low in volume and dark in colour. Myoglobin will precipitate in the renal tubules producing renal failure if the urine is acidic. Treatment includes fasciotomies and forced alkaline diuresis using sodium bicarbonate, mannitol and large volumes of crystalloid to maintain urinary pH above 6.5 and a urine volume of 300 ml/hour.

Sites of postoperative care

Intensive care is defined as 'a service for patients with potentially recoverable conditions who can benefit from more detailed observation and invasive treatment than can safely be provided on the general wards or high-dependency areas'. These patients usually have respiratory failure and require mechanical ventilation, and often have other system failure requiring support. In ICU, the nurse:patient ratio is usually 1:1, and 24-hour dedicated medical cover is available.

High-dependency unit (HDU) is an area that can provide a greater level of care and monitoring than can be provided on the ward. Patients on the HDU have actual or impending single organ failure (not respiratory), and invasive central or arterial pressure monitoring can be performed. The nurse:patient ratio is usually 1:2. Most postoperative vascular patients are cared for in HDU.

Peripheral vascular surgery

Arterial surgery below the umbilicus can be prolonged, but does not usually involve large blood losses. The use of perioperative epidural analgesia in these patients is controversial, but has a number of advantages including:
- excellent analgesia
- sympathetic paralysis and improved blood flow to the limb
- reduced stress response to surgery with possible reduction in postoperative hypercoagulability and improved graft flow
- a possible reduction in DVTs postoperatively
- less impairment of respiratory function postoperatively.

Although many studies have been conducted, consistent advantages in terms of patient or graft survival are difficult to demonstrate and the real difference is likely to be small. It is therefore reasonable to limit epidural analgesia to patients at highest risk of early graft failure (femoral distal grafts or redo surgery). If the decision to use epidural analgesia is taken, potential problems should be anticipated.
- Patients should be nursed only in a ward where the nursing staff are able to look after the epidural properly.
- Vasodilatation requires careful fluid management to avoid hypotension.
- Bilateral motor block hinders mobilization and surgeons often want the epidural removed 24–48 hours postoperatively.
- Neurological complications, though rare, may occur, especially if the patient is taking anticoagulants, and appropriate monitoring is necessary.

Lumbar plexus blocks: posterior insertion of a lumbar plexus block, either with a nerve stimulator to evoke contraction of the quadriceps or a loss of resistance to saline, may have advantages over lumbar epidural. In unilateral surgery, it is illogical to block both legs because this increases the risk of hypotension and severely hinders mobility. Lumbar plexus block is essentially a lumbar paravertebral block and reliably produces unilateral blockade of the femoral nerve. This maximizes analgesia to the area of surgery and minimizes hypotension. Mobility is also improved.

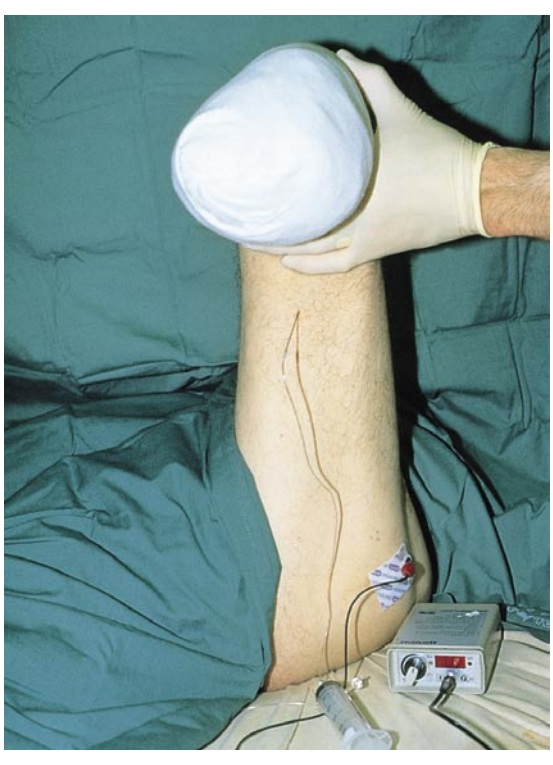
Other analgesic techniques: femoral nerve block from the front can be performed, either preoperatively or perioperatively by the surgeon under direct vision, with insertion of a catheter for postoperative pain relief if desired. Patient-controlled analgesia is popular, but is often used only overnight after which oral paracetamol, codeine or morphine can be started.

Amputations

Patients undergoing amputations are among the most severely ill vascular patients. Cardiac, respiratory and renal failure are common, and infection and dead tissue lead to the development of systemic inflammatory response syndrome or progress to multi-organ failure.

All blocks of the lower limb can be used to produce analgesia, often for up to 12 hours, including sciatic and/or femoral nerve block by all the available routes (Figure 1). Amputation of toes can easily be managed under ankle block or metatarsal block, taking care not to inject too much local anaesthetic to avoid compressing the blood vessels. Otherwise morphine, administered intravenously, intramuscularly or orally and combined with paracetamol, dihydrocodeine or diclofenac (if not contraindicated) can be used.

The role of anaesthetic technique in cases of chronic pain in the 'phantom' limb has been well documented. After early reports of good results with preoperative epidural analgesia, more recent reports seem to suggest that anaesthetic technique does not alter the incidence of phantom limb pain. It does seem illogical to assume that abolishing central neural input with spinal or epidural anaesthesia at the time of surgery will abolish the chronic pain pathways that have built up in the preceding days or weeks. Ketamine, an N-methyl-D-aspartate receptor antagonist, has been shown to reduce phantom limb pain and may have a role in the management of severe postoperative phantom limb pain.



1 Block of the sciatic nerve in the popliteal fossa, using nerve stimulation, in a patient undergoing trimming of stump.

Carotid endarterectomy

Carotid endarterectomy takes 1–3 hours and is not usually associated with severe postoperative pain. An oral or intramuscular opiate, or codeine and paracetamol, is usually all that is required. Mortality and major morbidity are due to MI and stroke.

Cardiovascular problems: baroreceptor function is altered postoperatively for up to 24 hours and low blood pressure is common as the full force of the systolic blood pressure distends the carotid sinus. Increased firing of the carotid sinus nerve follows, together with reflex vagal-mediated bradycardia and hypotension. This can be treated with glycopyrrolate and fluids, but occasionally inotropic support is required (e.g. ephedrine or low-dose dopamine infusion). If this occurs perioperatively, surgeons can instil local anaesthetic to numb the nerve. Some surgeons leave a viral filtered epidural catheter *in situ* for local anaesthetic to be instilled postoperatively if severe hypotension associated with bradycardia occurs.

Hypertension may be due to pain or preoperative essential hypertension. Unexplained hypertension is possible and may be due to cerebral renin and/or noradrenaline release, or cerebral oedema. Both increases or falls in blood pressure can cause strokes and, after carotid endarterectomy, patients should receive invasive blood pressure monitoring and rapid correction of abnormalities for at least 4–6 hours postoperatively. Any appropriate drug can be used in small titrated doses; for example, β-blockers or hydralazine to reduce blood pressure and dopamine infusions to raise blood pressure. Ideally, the patient should be cared for in an HDU, but if a place is unavailable prolonged monitoring in the post-anaesthetic care unit is acceptable. After 24 hours, the baroreceptors have usually 'reset' themselves and the frequency of monitoring can be reduced.

Neurological problems: 60–70% of strokes occur peroperatively and most of these are a result of embolic events. Post-operatively, neurological observations should be carried out every 15 minutes. Any deterioration should prompt urgent Doppler ultrasound because urgent surgical removal of a carotid thrombosis can reverse a developing hemiplegia and allow total recovery. Patients suffering a stroke and loss of consciousness or bulbar palsies and airway problems may need to be ventilated and admitted to ICU.

Cranial nerve palsies may occur, but usually resolve in the first 6 months postoperatively.
- Recurrent laryngeal palsy causes hoarseness, difficulty coughing and vagal damage to the fibres on the surface.
- In hypoglossal nerve palsy, the tongue deviates to the side of the lesion.
- Palsy of the mandibular branch of the facial nerve causes the corner of the mouth to droop, which may be confused with a stroke.
- Spinal accessory nerve palsy results in weakness and aching of the shoulder.
- Superior laryngeal nerve palsy leads to difficulty with high-pitched sounds, and is not usually noticed by the patient.

Hyperperfusion syndrome: rarely, blood flow through the newly endarterectomized artery can be excessive and produce headaches, facial pain, seizures, confusion, cerebral oedema or haemorrhage, probably caused by precapillary cerebral spasm from unaccustomed flow. This usually occurs 5–7 hours postoperatively and hypertension is commonly present. Treatment is aimed at reducing blood pressure, and mannitol and dexamethasone are sometimes used if cerebral oedema is present. Transcranial Doppler ultrasound, which will show high intracerebral blood flow velocities, can be used in diagnosis.

Airway: bleeding around the site can be due to hypertension, aspirin use or a residual effect of heparin. The haematoma does not usually obstruct the airway directly, but causes venous and lymphatic obstruction, and leads to oedema. This can present as life-threatening airway obstruction. Emergency evacuation of the clot (after gas induction and intubation) is indicated and a period of postoperative ventilation is needed until the oedema has resolved. A surgeon should be standing by to perform urgent tracheostomy if needed.

GALA (General Anaesthesia versus Local Anaesthesia) trial: there is no definitive evidence that carotid endarterectomy (or any other type of surgery) results are better when performed under local anaesthesia compared with general anaesthesia, though some studies suggest the incidence of cardiac events is lower under local anaesthetic. The GALA trial, which is a large multi-centre trial that is hoping to recruit 400–600 patients, is under way in the UK to answer this question.

Elective aortlc aneurysm surgery

Site of postoperative care: many centres advocate the availability of an ICU bed before starting elective aneurysm surgery. The unpredictable nature of the surgery, the potential for prolonged surgery with large blood loss and the need for postoperative ventilation cannot be excluded. If the surgery proceeds without problems, the level of postoperative care can be downgraded to HDU.

Epidural: most vascular anaesthetists elect to insert a low thoracic epidural (T7–T9) for aortic anaeurysm surgery, because of the intraoperative stability and postoperative analgesia they provide. Postoperative analgesia regimens usually include an infusion of 0.1–0.25% bupivicaine with or without fentanyl or diamorphine at a rate of 6–12 ml/hour, which can be continued for 2–4 days postoperatively. In addition to the excellent analgesia and a low level of sedation compared with a patient-controlled analgesia (PCA) pump, there is also a shorter duration of ileus. If epidural analgesia is contraindicated, morphine via a PCA pump is used instead.

Fluid balance: after aortic aneurysm repair, there are large fluid losses into the gut (third space) and central venous pressure monitoring is useful to guide fluid replacement, which may be many litres in the first postoperative day. Haemoglobin levels should be measured and, if there is pre-existing cardiac disease, it is safest to maintain the level at about 10 g/dl. Hourly urine measurement is essential to ensure adequate renal perfusion; low urine output is usually due to hypovolaemia not frusemide deficiency.

Enteral feeding: there is some evidence that stomach emptying is relatively normal 18 hours after aortic aneurysm surgery and enteral feeding should be started early, perhaps on day 2, because this stimulates blood flow to the gut.

Ischaemic colitis presents as left-sided abdominal pain and diarrhoea. Infarcted bowel can ensue, and a metabolic acidosis and septic shock result. Emergency laparotomy and bowel resection is needed, but carries a high mortality.

Emergency abdominal aortic surgery

Patients undergoing emergency abdominal aortic surgery have a high mortality due to the severity of the preoperative insult and, if they survive surgery, the development of multi-organ failure. Poor prognostic factors include:

- age over 80 years
- low blood pressure or cardiac arrest preoperatively
- acidosis
- transfusion of more than 15 units of blood.

Postoperatively, patients are always admitted to ICU for care, which includes the following.

- Management of a large blood transfusion, with clotting factors, platelets and more blood as required to normalize haemoglobin levels and clotting times.
- Warming the patient.
- Maintaining an adequate cardiac output and cardiovascular system; inotropic support to the myocardium may be needed.
- A period of ventilation and possibly prolonged weaning if respiratory function is poor.
- Optimizing renal function, including the insertion of a pulmonary artery catheter and maintaining adequate urine output (renal failure is associated with a poor prognosis); dopamine, mannitol or dopexamine can also be used.

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Preoperative Assessment of Vascular Patients

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Vascular surgical patients are usually elderly and have a high incidence of significant medical problems. Preoperative history and examination should mainly address the functional capacity and integrity of the following systems and diseases:
- cardiovascular
- respiratory
- renal
- diabetes.

Cardiovascular system

Vascular surgical patients have a high incidence of symptomatic and asymptomatic coronary artery disease. This is responsible for the relatively high postoperative cardiac morbidity and mortality of this type of surgery (5–10%). Adverse cardiac events (ACE) in the postoperative period are due to thrombus formation on a ruptured atheromatous plaque leading to a Q-wave myocardial infarction (MI), or long-duration subendocardial ischaemia causing a non Q-wave infarction. This can present in the early postoperative period as:
- sudden death
- sudden onset of low blood pressure/cardiogenic shock
- acute left heart failure/pulmonary oedema
- onset of severe ventricular arrhythmias.

Preoperative assessment of these patients involves history, examination and simple tests in order to:
- identify and optimize cardiac conditions medically, radiologically and occasionally surgically, to reduce postoperative cardiac problems
- decide when, how and in which patients further testing (possibly invasive) is justified
- quantify the risk of surgery to allow the risk:benefit ratio to be calculated and to decide on the level of intraoperative monitoring and postoperative care required.

Many factors that predispose to an ACE in the postoperative period have been identified and many scoring systems have been described for cardiac risk assessment (Figure 1); high scores indicate patients at high risk. In general, most of the information needed can be gained from details of the history and examination, and a few simple tests. More invasive investigation is seldom necessary, but occasionally coronary angiography and coronary artery or valve surgery may be indicated. Preoperative cardiovascular factors that can be optimized include coronary artery disease, cardiac failure, valve disease and hypertension.

Cardiac risk indices

Cardiac condition	Goldman Index (points)	Detsky Index (points)	Eagle Index (present or absent)
Third heart sound	11		
History of pulmonary oedema	5		
Pulmonary oedema in the last week	10		
Unstable angina within 6 months	10		
Angina (CCSC III)[1]		10	
Angina (CCSC IV)[1]		20	
Angina (any)			✓
Preoperative myocardial infarction < 6 months	10	10	
Q wave on ECG			✓
Preoperative myocardial infarction > 6 months		5	
More than five ventricular ectopic beats per minute at any time	7	5	
Important aortic stenosis	3	20	
Ventricular arrhythmias			✓
ECG not sinus rhythm	7	5	
Age > 70 years	5	5	✓
Intraperitoneal, aortic or intrathoracic operation	3		
Poor medical condition	3	5	
Diabetes			✓
Emergency operation	4	10	
High risk score	> 12	> 15	3 or more

[1]In Canadian Cardiovascular Society Classification (CCSC) of heart disease, III is marked limitation of activity (i.e. walking 100–200 metres on the level) and IV represents an inability to do anything without pain, which may even occur at rest.

Angina
Symptomatic myocardial ischaemia, perhaps surprisingly, has not consistently been found to predict postoperative ACE. It is now known that myocardial ischaemia is often silent and can be detected only by ST-segment analysis of a 24-hour ECG. Myocardial ischaemia is a risk factor in the development of a perioperative ACE. Symptomatic angina therefore represents only a small proportion of the total myocardial ischaemia that occurs. In general, increasing severity of angina is related to increased risk. Low-grade chronic stable angina conveys a small added risk, but unstable angina occurring at minimal activity, at reduced exercise tolerances or at rest is a medical emergency and must be treated before any operation other than in exceptional circumstances. The degree of activity needed to provoke symptoms is the most important part of the history; the frequency of angina attacks is less important because people vary in their willingness to provoke the pain.

Exercise tolerance in vascular patients is difficult to judge because of the high rate of claudication, strokes and amputations. In these patients, more invasive tests may be warranted to clarify the situation before major surgery. Tests for myocardial ischaemia or coronary artery disease are sensitive but not very specific; a large number of patients test positive, only a few of whom will have a postoperative ACE. Thus, a negative test is a good sign, in that it is extremely unlikely that the patient will suffer a perioperative ACE.

Many vascular procedures are also relatively urgent (e.g. critical limb ischaemia, tight carotid stenosis with transient ischaemic attacks, large abdominal aneurysm), and often only a short time is available for optimization.

Further testing and treatment: studies have shown that aggressive investigation and surgical treatment of coronary artery lesions before vascular surgery does not influence the overall mortality in the short term, because of the deaths associated with coronary artery bypass grafting (CABG). This route should be followed only if the angina is severe and not responding to maximal medical treatment. Angina should be investigated and treated if it warrants further investigation and treatment in itself, and not just because the patient is facing an operation.

Advances in angioplasty techniques and practice may alter the future treatment of angina preoperatively as more difficult lesions become accessible, stent design improves and complication rates decrease. It may be possible to provide quick and relatively safe treatment of coronary lesions preoperatively without recourse to CABG.

Dobutamine stress echocardiography – the heart rate is increased by the administration of dobutamine, 20–40 μg/kg/minute and or atropine, 0.6 mg, and the function of the heart observed using ultrasound to detect wall motion abnormalities induced by ischaemia.

Dipyridamole–thallium scanning – dipyridamole is a vasodilator that reduces blood pressure and causes a reflex tachycardia. Normal coronary arteries dilate and the myocardium they supply shows a large uptake of thallium (a potassium analogue). Narrowed or blocked coronaries show little uptake. In the 4 hours after the dipyridamole, the thallium is redistributed to all the viable myocardium leaving irreversible defects in areas of infarction. Ischaemic areas show up as reversible defects in thallium uptake.

Ambulatory ECG is carried out preoperatively and can show the presence of silent myocardial ischaemia. Patients without silent myocardial ischaemia are at a very low risk of perioperative cardiac complications.

Coronary angiography is the gold standard in the assessment of coronary artery anatomy and allows measurement of intraventricular pressures, ventricular function and gradients across valves.

CABG is indicated for the treatment of angina refractory to medical treatment, left main stem disease and triple vessel disease, especially if there is poor ventricular function.

Coronary angioplasty is a developing area. It allows percutaneous treatment of coronary artery lesions, avoiding the need for cardiac surgery.

Medical treatment includes:
- nitrates (long-acting)
- β-blockers (cardioselective, atenolol or metoprolol)
- calcium antagonists (diltiazem or amlodipine)
- aspirin.

In practice, cardiological referral for medical optimization is common, while referral for invasive investigation, coronary angiography and CABG is relatively rare.

Previous MI
In patients with a history of a previous MI, the risk of perioperative infarction during subsequent surgery is 5–6%. Earlier studies suggested that this risk was much higher if surgery was carried out less than 3 months after the initial infarction (Figure 2). Later studies, however, have failed to show such a relationship (Figure 2). This may be due to an increase in invasiveness of perioperative monitoring and general improvements in postoperative care and management. Nevertheless, it is still recommended that truly elective surgery should be postponed for 6 months after a MI.

Risk of perioperative reinfarction

Study	Number of patients	Reinfarction risk from time of myocardial infarct (%)		
		0–3 months	4–6 months	> 6 months
Tarhan 1972	422	37	16	5-6
Steen 1978	587	27	11	4-5
Rao 1973–76	364	36	26	5
Rao 1977–82	733	5.7	2.3	< 2
Shah 1990	275	4.3	0	5.7

Cardiac failure
Cardiac failure indicates severe myocardial dysfunction, carries a poor long-term prognosis and places the patient at high risk of ACE. Like angina, the degree of failure is related to the operative risk. Frank cardiac failure with a third heart sound and pulmonary oedema is an extremely high-risk situation, and the need for surgery should be carefully considered. Preoperative echocardiography can provide qualitative measurement of myocardial contractility and an estimation of ejection fraction. A low (< 50%) ejection fraction does not necessarily predict perioperative ACE, but will indicate those patients in whom more invasive monitoring, inotropes and postoperative ICU management are indicated. Pulmonary artery catheterization may be useful to allow logical selection of inotropic agents. Symptoms should be optimized preoperatively by treatment with:
- diuretics
- digoxin
- angiotensin converting enzyme inhibitors
- β-blockade under cardiological supervision.

Aortic stenosis
A pressure gradient of more than 50 mm Hg across the aortic valve is considered severe. On induction of anaesthesia, vasodilatation and myocardial depression cause a drop in blood pressure that reduces coronary artery blood flow. This is already compromised due to the high intraventricular pressures and myocardial oxygenation is reduced, cardiac output drops and blood pressure spirals downwards until cardiac arrest occurs. Blood pressure must be maintained in the perioperative period. If possible, severe stenosis may need to be corrected surgically before vascular surgery.

Hypertension
Hypertensive patients are prone to extreme rises and falls in blood pressure in the perioperative period. Although not identified as a factor for the development of ACE in all studies, it is generally accepted that surgery in untreated hypertensive patients with a diastolic blood pressure greater than 110 mm Hg should be cancelled and the hypertension treated to reduce operative risk. Patients with a diastolic blood pressure above 110 mm Hg are at risk of:
- myocardial ischaemia/MI
- dysrhythmias
- neurological events
- renal failure.

Ideally, blood pressure should be controlled according to general medical guidelines and be less than 160/100 mm Hg. Treatment is gradually increased until blood pressure is satisfactory, though the optimal period for blood pressure stabilization before surgery is unclear. Treatment includes:
- diuretics
- β-blockers
- calcium channel blockers
- angiotensin converting enzyme inhibitors
- β-blockers (doxazocin).

In the elderly (> 80 years), the treatment of high blood pressure is associated with more morbidity than if the patient had been left untreated.

Arrhythmias
Frequent ventricular ectopics are a significant risk factor for postoperative ACE but, following the results of large trials, suppression of these ectopics with antiarrhythmic drugs is contraindicated because it increases mortality.

Atrial fibrillation (AF) is common and should be investigated fully. In long-term AF, the ventricular rate should be slowed to below 90 beats/minute with digoxin, and anticoagulation should be considered if the patient has another medical problem or is between 60 and 80 years old. Cardioversion can be considered if the patient is young, has no medical problems or the AF is of short duration. This can be achieved either pharmacologically with amiodarone or flecainide, or electrically after a period of 4 weeks of anticoagulation to prevent embolus.

Preoperative pharmacological optimization
In recent years, two seemingly contradictory regimens for managing high-risk patients have been proposed and both purport to show impressive improvements in outcome.

- The concept of 'preoptimization' of patients presenting for major surgery uses preoperative insertion of a pulmonary artery catheter to measure cardiac output and oxygen delivery to the tissues, and careful fluid and inotrope therapy to raise this to predetermined 'goals'. In high-risk patients presenting for major surgery, this has been shown to produce impressive reductions in mortality and morbidity.
- The use of preoperative β-blockers for 1 week before vascular surgery has, in studies in the USA, shown a significant reduction in mortality which, surprisingly, was maintained for a long time after the surgery.

These two totally different philosophies seem to produce significant improvements on standard 'best care' management, but it is not easy to explain how. Which option to chose in an individual patient is also unclear. It would be foolish to choose to fluid load, give inotropes and seek to achieve large increases in cardiac output in a patient with angina on minimal exertion for whom a 'cardioprotective' β-blocker would be more appropriate. However, this approach may be justified in a patient without significant coronary artery disease presenting for aortic aneurysm surgery. Carotid artery and peripheral vascular surgery are probably not sufficiently 'major' to justify invasive monitoring and inotrope therapy, and β-blocker therapy is more appropriate. Patients should be approached individually after consideration of their cardiac status.

Respiratory system

Many vascular patients have been (or still are) lifelong smokers and have varying degrees of chronic obstructive airway disease. Alveoli that have been destroyed cannot be recreated, but various measures can be taken to ensure the patient is in optimal condition preoperatively.

- If the chest condition is seasonal, try to perform the operation at the best time of year.
- Encourage the patient to stop smoking for 6–8 weeks preoperatively to allow ciliary function to return to normal.
- Provide physiotherapy and breathing exercises for 2–3 days preoperatively so that the patient can practise and become familiar with the routine.
- Help the patient to lose any excess weight.
- Bronchodilators and corticosteroids may be used if it is thought there is a reversible component to the airway disease.
- Signs of active chest infection should be excluded (e.g. pyrexia, radiographic changes, sputum culture).

The severity of the lung disease is best assessed by pulmonary function testing. A forced expired volume in 1 second (FEV_1) is a good measure of ventilatory capacity. An FEV_1 below 1 litre indicates severely impaired function, which will cause difficulty in coughing postoperatively and predicts an increased risk of postoperative mechanical ventilation. Forced vital capacity indicates the severity of diffuse parenchymal disease. It is easy to measure and should be compared with standard nomograms derived from healthy people of the same height, weight and sex. A value less than 50% of expected is considered high risk and arterial blood gases should be measured. This can prove useful as a baseline and detect hypoxaemia, but may also identify the occasional patient who is retaining carbon dioxide and relying on hypoxic drive – the so-called 'blue bloater'. In these patients it is difficult to resume breathing postoperatively and a period of ventilation in ICU is almost inevitable.

A preoperative chest radiograph is useful to detect anatomical abnormalities, such as pneumothorax and bronchial carcinoma, but is an extremely poor indicator of lung function. It can be useful, however, in detecting the cardiomegaly of heart failure and, if there is evidence of pulmonary oedema (i.e. Kerley B lines, upper lobe diversion), the patient is likely to be at high risk.

Renal function

Many studies have shown a greatly increased morbidity and mortality in patients developing renal failure in the perioperative period. Vascular patients may have hypertensive or diabetic renal damage, or renal artery stenosis, and care must be taken to preserve existing renal function and prevent new damage. Maintenance of renal function depends on:

- avoiding drugs that are nephrotoxic
- maintaining renal perfusion by ensuring a normal circulating blood volume, and maintaining a normal blood pressure for that patient
- monitoring urine output closely and acting quickly with appropriate treatment to prevent the development of acute renal failure. Nephrotoxicity induced by contrast media can occur in response to the high osmolality and increased intrarenal production of adenosine. This is due to a reduction in renal perfusion and damage to the tubular cells and is thought, in part, to be due to the release of free radicals during the breakdown of adenosine. Risk factors for renal impairment after administration of contrast media include:
- pre-existing renal impairment (especially diabetic nephropathy)
- dehydration
- congestive cardiac failure
- type and amount of contrast media given; contrast media with lower osmolalities are safer.

Patients should be well hydrated (with intravenous fluids overnight if necessary) and administration of the adenosine antagonist, theophylline, before angiography helps prevent deterioration in renal function. Carbon dioxide angiography, involving the injection of 50 ml of carbon dioxide gas into the vessels to displace blood, produces good pictures after digital subtraction. It is absorbed very quickly into the tissues with no renal side-effects.

Fenoldopam is a new dopamine agonist which shows promise as a drug able to offer 'renal protection' in the perioperative period. Exact clarification of its role is awaited.

Diabetes

Diabetes is common in the vascular patient population. As well as the associated medical problems (e.g. ischaemic heart disease, renal failure, neuropathy), there are specific anaesthetic considerations. Furthermore, myocardial ischaemia is often silent in these patients.

Blood glucose control: most hospitals have their own regimen for perioperative blood sugar control. This usually takes the form of an insulin and glucose/potassium infusion in which the insulin component is varied according to a standard sliding scale and the results of frequent blood glucose sugar readings. Blood sugar should be measured peroperatively to exclude hypoglycaemia.

Perioperative management: autonomic neuropathy can lead to an unstable cardiovascular system during the operation. The patient is unable to tolerate induction of anaesthesia and positive pressure ventilation, and large drops in blood pressure and heart rate can occur, which are difficult to treat. The sweating and tachycardia of hypoglycaemia may be absent. There have also been reports of sudden death in patients with autonomic neuropathy, which can be due to sudden cardiac or respiratory arrest in the perioperative period or an abnormal response to hypoxia. Gastric stasis, with the increased risk of aspiration, is also possible and a rapid sequence induction with cricoid pressure may be wise. Autonomic neuropathy can be identified by the loss of sinus arrhythmia. There is usually a difference in heart rate on deep breathing of 15 beats/minute, though in these patients it is usually less than 5 beats/minute. The lack of the normal tachycardic response to a bedside Valsalva manoeuvre and postural hypotension of more than 30 mm Hg can also be useful.

FURTHER READING

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